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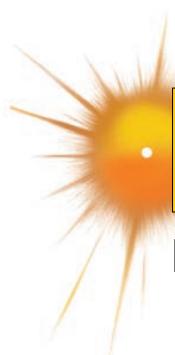
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## Section 1 Introduction to Cardiovascular Disorders

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### Approach to the Patient with Possible Cardiovascular Disease

Joseph Loscalzo



#### THE MAGNITUDE OF THE PROBLEM

Cardiovascular diseases comprise the most prevalent serious disorders in industrialized nations and are a rapidly growing problem in developing nations (Chap. 238). Age-adjusted death rates for coronary heart disease have declined by two-thirds in the past four decades in the United States, reflecting the identification and reduction of risk factors as well as improved treatments and interventions for the management of coronary artery disease, arrhythmias, and heart failure. Nonetheless, cardiovascular diseases remain the most common causes of death, responsible for one-third of all deaths, >800,000 deaths each year. Approximately one-fourth of these deaths are sudden. In addition, cardiovascular diseases are highly prevalent, diagnosed in nearly half of the adult population. The growing prevalence of obesity (Chap. 402), type 2 diabetes mellitus (Chap. 403), and metabolic syndrome (Chap. 408), which are important risk factors for atherosclerosis, now threatens to reverse the progress that has been made in the age-adjusted reduction in the mortality rate of coronary heart disease.

For many years, cardiovascular disease was considered to be more common in men than in women. In fact, cardiovascular disease is the leading cause of all deaths among women and men (Chap. 398). In addition, although the absolute number of deaths secondary to cardiovascular disease has declined over the past decades in men, this number has actually risen in women. Inflammation, obesity, type 2 diabetes mellitus, and the metabolic syndrome appear to play more prominent roles in the development of coronary atherosclerosis in women than in men. Coronary artery disease (CAD) is more frequently associated with dysfunction of the coronary microcirculation in women than in men. Exercise electrocardiography has a lower diagnostic accuracy in the prediction of epicardial obstruction in women than in men.

#### NATURAL HISTORY

Cardiovascular disorders often present acutely, as in a previously asymptomatic person who develops an acute myocardial infarction (Chap. 275), or a previously asymptomatic patient with hypertrophic cardiomyopathy (Chap. 259) or with a prolonged QT interval (Chap. 252) whose first clinical manifestation is syncope or even sudden death. However, the alert physician may recognize the patient at risk for these complications long before they occur and often can take measures to prevent their occurrence. For example, a patient with acute myocardial infarction will often have had risk factors for atherosclerosis for many years. Had these risk factors been recognized, their elimination or reduction might have delayed or even prevented the infarction. Similarly, a patient with hypertrophic cardiomyopathy may have had a heart murmur for years and a family history of this disorder. These findings could have led to an echocardiographic examination, recognition of the condition, and appropriate therapy long before the occurrence of a serious acute manifestation.

Patients with valvular heart disease or idiopathic dilated cardiomyopathy, by contrast, may have a prolonged course of gradually increasing dyspnea and other manifestations of chronic heart failure that is punctuated by episodes of acute deterioration only late in the course of the

disease. Understanding the natural history of various cardiac disorders is essential for applying appropriate diagnostic and therapeutic measures to each stage of the condition, as well as for providing the patient and family with the likely prognosis.

#### CARDIAC SYMPTOMS

The symptoms caused by heart disease result most commonly from myocardial ischemia, disturbance of the contraction and/or relaxation of the myocardium, obstruction to blood flow, or an abnormal cardiac rhythm or rate. Ischemia, which is caused by an imbalance between the heart's oxygen supply and demand, is manifest most frequently as chest discomfort (Chap. 14), whereas reduction of the pumping ability of the heart commonly leads to fatigue and elevated intravascular pressure upstream of the failing ventricle. The latter results in abnormal fluid accumulation, with peripheral edema (Chap. 41) or pulmonary congestion and dyspnea (Chap. 37). Obstruction to blood flow, as occurs in valvular stenosis, can cause symptoms resembling those of myocardial failure (Chap. 257). Cardiac arrhythmias often develop suddenly, and the resulting symptoms and signs—palpitations (Chap. 43), dyspnea, hypotension, and syncope (Chap. 21)—generally occur abruptly and may disappear as rapidly as they develop.

Although dyspnea, chest discomfort, edema, and syncope are cardinal manifestations of cardiac disease, they occur in other conditions as well. Thus, dyspnea is observed in disorders as diverse as pulmonary disease, marked obesity, and anxiety (Chap. 37). Similarly, chest discomfort may result from a variety of noncardiac and cardiac causes other than myocardial ischemia (Chap. 14). Edema, an important finding in untreated or inadequately treated heart failure, also may occur with primary renal disease and in hepatic cirrhosis (Chap. 41). Syncope occurs not only with serious cardiac arrhythmias but in a number of neurologic conditions as well (Chap. 21). Whether heart disease is responsible for these symptoms frequently can be determined by carrying out a careful clinical examination (Chap. 239), supplemented by noninvasive testing using electrocardiography at rest and during exercise (Chap. 240), echocardiography, roentgenography, and other forms of myocardial imaging (Chap. 241).

Myocardial or coronary function that may be adequate at rest may be insufficient during exertion. Thus, dyspnea and/or chest discomfort that appear during activity are characteristic of patients with heart disease, whereas the opposite pattern, that is, the appearance of these symptoms at rest and their remission during exertion, is rarely observed in such patients. It is important, therefore, to question the patient carefully about the relation of symptoms to exertion.

Many patients with cardiovascular disease may be asymptomatic both at rest and during exertion but may present with an abnormal physical finding such as a heart murmur, elevated arterial pressure, or an abnormality of the electrocardiogram (ECG) or imaging test. It is important to assess the global risk of CAD in asymptomatic individuals, using a combination of clinical assessment and measurement of cholesterol and its fractions, as well as other biomarkers, such as C-reactive protein, in some patients. Since the first clinical manifestation of CAD may be catastrophic—sudden cardiac death, acute myocardial infarction, or stroke in previous asymptomatic persons—it is mandatory to identify those at high risk of such events and institute further testing and preventive measures.

#### DIAGNOSIS

As outlined by the New York Heart Association (NYHA), the elements of a complete cardiac diagnosis include the systematic consideration of the following:

1. *The underlying etiology.* Is the disease congenital, hypertensive, ischemic, or inflammatory in origin?
2. *The anatomic abnormalities.* Which chambers are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?

**TABLE 236-1** New York Heart Association Functional Classification

<b>Class I</b>	Marked limitation of physical activity
No limitation of physical activity	Less than ordinary activity causes symptoms
No symptoms with ordinary exertion	Asymptomatic at rest
<b>Class II</b>	Inability to carry out any physical activity without discomfort
Slight limitation of physical activity	Symptoms at rest
Ordinary activity causes symptoms	
<b>Class IV</b>	

Source: Data from The Criteria Committee of the New York Heart Association.

3. **The physiologic disturbances.** Is an arrhythmia present? Is there evidence of congestive heart failure or myocardial ischemia?
4. **Functional disability.** How strenuous is the physical activity required to elicit symptoms? The classification provided by the NYHA has been found to be useful in describing functional disability (**Table 236-1**).

One example may serve to illustrate the importance of establishing a complete diagnosis. In a patient who presents with exertional chest discomfort, the identification of myocardial ischemia as the etiology is of great clinical importance. However, the simple recognition of ischemia is insufficient to formulate a therapeutic strategy or prognosis until the underlying anatomic abnormalities responsible for the myocardial ischemia, for example, coronary atherosclerosis or aortic stenosis, are identified and a judgment is made about whether other physiologic disturbances that cause an imbalance between myocardial oxygen supply and demand, such as severe anemia, thyrotoxicosis, or supraventricular tachycardia, play contributory roles. Finally, the severity of the disability should govern the extent and tempo of the workup and strongly influence the therapeutic strategy that is selected.

The establishment of a correct and complete cardiac diagnosis usually commences with the history and physical examination (**Chap. 239**). Indeed, the clinical examination remains the basis for the diagnosis of a wide variety of disorders. The clinical examination may then be supplemented by five types of laboratory tests: (1) ECG (**Chap. 240**); (2) noninvasive imaging examinations (chest roentgenogram, echocardiogram, radionuclide imaging, computed tomographic imaging, positron emission tomography, and magnetic resonance imaging) (**Chap. 241**); (3) blood tests to assess risk (e.g., lipid determinations, C-reactive protein) or cardiac function (e.g., brain natriuretic peptide [BNP] [**Chap. 257**] or cardiac function (e.g., brain natriuretic peptide [BNP] [**Chap. 257**]); (4) occasionally, specialized invasive examinations (i.e., cardiac catheterization and coronary arteriography [**Chap. 242**]); and (5) genetic tests to identify monogenic cardiac diseases (e.g., hypertrophic cardiomyopathy [**Chap. 259**], Marfan's syndrome [**Chap. 413**], and abnormalities of cardiac ion channels that lead to prolongation of the QT interval and an increase in the risk of sudden death [**Chap. 246**]). These genetic tests are becoming more widely available.

### FAMILY HISTORY

In eliciting the history of a patient with known or suspected cardiovascular disease, particular attention should be directed to the family history. Familial clustering is common in many forms of heart disease. Mendelian transmission of single-gene defects may occur, as in hypertrophic cardiomyopathy (**Chap. 259**), Marfan's syndrome (**Chap. 413**), and sudden death associated with a prolonged QT syndrome (**Chap. 252**). Premature coronary disease and essential hypertension, type 2 diabetes mellitus, and hyperlipidemia (the most important risk factors for CAD) are usually polygenic disorders. Although familial transmission may be less obvious than in the monogenic disorders, it is helpful in assessing risk and prognosis in polygenic disorders, as well. Familial clustering of cardiovascular diseases not only may occur on a genetic basis but also may be related to familial dietary or behavior patterns, such as excessive ingestion of salt or calories and cigarette smoking.

### ASSESSMENT OF FUNCTIONAL IMPAIRMENT

When an attempt is made to determine the severity of functional impairment in a patient with heart disease, it is helpful to ascertain the

level of activity and the rate at which it is performed before symptoms develop. Thus, it is not sufficient to state that the patient complains of dyspnea. The breathlessness that occurs after running up two long flights of stairs denotes far less functional impairment than do similar symptoms that occur after taking a few steps on level ground. In addition, the degree of customary physical activity at work and during recreation should be considered. The development of two-flight dyspnea in a well-conditioned marathon runner may be far more significant than the development of one-flight dyspnea in a previously sedentary person. The history should include a detailed consideration of the patient's therapeutic regimen. For example, the persistence or development of edema, breathlessness, and other manifestations of heart failure in a patient who is receiving optimal doses of diuretics and other therapies for heart failure (**Chap. 257**) is far graver than are similar manifestations in the absence of treatment. Similarly, the presence of angina pectoris despite treatment with optimal doses of multiple antianginal drugs (**Chap. 273**) is more serious than it is in a patient on no therapy. In an effort to determine the progression of symptoms, and thus the severity of the underlying illness, it may be useful to ascertain what, if any, specific tasks the patient could have carried out 6 months or 1 year earlier than he or she cannot perform at present.

### ELECTROCARDIOGRAM

(See also **Chap. 240**) Although an ECG usually should be recorded in patients with known or suspected heart disease, with the exception of the identification of arrhythmias, conduction abnormalities, ventricular hypertrophy, and acute myocardial infarction, it generally does not establish a specific diagnosis. The range of normal electrocardiographic findings is wide, and the tracing can be affected significantly by many noncardiac factors, such as age, body habitus, and serum electrolyte concentrations. In general, electrocardiographic changes should be interpreted in the context of other abnormal cardiovascular findings.

### ASSESSMENT OF THE PATIENT WITH A HEART MURMUR

(Fig. 236-1) The cause of a heart murmur can often be readily elucidated from a systematic evaluation of its major attributes: timing, duration, intensity, quality, frequency, configuration, location, and radiation when considered in the light of the history, general physical examination, and other features of the cardiac examination, as described in **Chap. 239**.

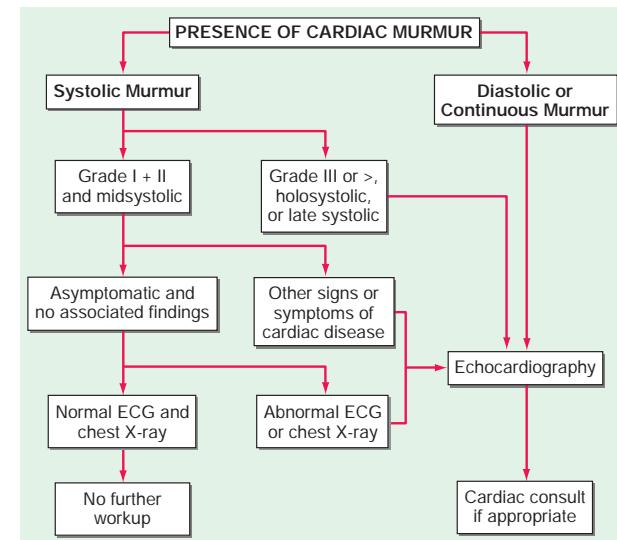


FIGURE 236-1 Approach to the evaluation of a heart murmur. ECG, electrocardiogram. (Reproduced with permission from E Braunwald, L Goldman (eds): Primary Cardiology, 2nd ed. Philadelphia, Saunders, 2003.)

The majority of heart murmurs are midsystolic and soft (grades I–II/VI). When such a murmur occurs in an asymptomatic child or young adult *without* other evidence of heart disease on clinical examination, it is usually benign and echocardiography generally is not required. By contrast, two-dimensional and Doppler echocardiography (**Chap. 241**) are indicated in patients with loud systolic murmurs (grades III/VI), especially those that are holosystolic or late systolic, and in most patients with diastolic or continuous murmurs.

### PITFALLS IN CARDIOVASCULAR MEDICINE

Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences. Examples include the following:

- Failure by the *noncardiologist* to recognize important cardiac manifestations of systemic illnesses. For example, the presence of mitral stenosis, patent foramen ovale, and/or transient atrial arrhythmia should be considered in a patient with stroke, or the presence of pulmonary hypertension and *cor pulmonale* should be considered in a patient with scleroderma or Raynaud's syndrome. A cardiovascular examination should be carried out to identify and estimate the severity of the cardiovascular involvement that accompanies many noncardiac disorders.
- Failure by the *cardiologist* to recognize underlying systemic disorders in patients with heart disease. For example, hyperthyroidism should be considered in an elderly patient with atrial fibrillation and unexplained heart failure, and Lyme disease should be considered in a patient with unexplained fluctuating atrioventricular block. A cardiovascular abnormality may provide the clue critical to the recognition of some systemic disorders. For example, an unexplained pericardial effusion may provide an early clue to the diagnosis of tuberculosis or a neoplasm.
- Overreliance on and overutilization of laboratory tests, particularly invasive techniques, for the evaluation of the cardiovascular system. Cardiac catheterization and coronary arteriography (**Chap. 242**) provide precise diagnostic information that may be crucial in developing a therapeutic plan in patients with known or suspected CAD. Although a great deal of attention has been directed to these examinations, it is important to recognize that they serve to *supplement*, not *supplant*, a careful examination carried out with clinical and noninvasive techniques. A coronary arteriogram should not be performed in lieu of a careful history in patients with chest pain suspected of having ischemic heart disease. Although coronary arteriography may establish whether the coronary arteries are obstructed and to what extent, the results of the procedure by themselves often do not provide a definitive answer to the question of whether a patient's complaint of chest discomfort is attributable to coronary atherosclerosis and whether or not revascularization is indicated.

Despite the value of invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on medical facilities. Therefore, they should be carried out only if the results can be expected to modify the patient's management.

### DISEASE PREVENTION AND MANAGEMENT

The prevention of heart disease, especially of CAD, is one of the most important tasks of primary health care givers as well as cardiologists. Prevention begins with risk assessment, followed by attention to lifestyle, such as achieving optimal weight, physical activity, and smoking cessation, and then aggressive treatment of all abnormal risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus (**Chap. 403**).

After a complete diagnosis has been established in patients with known heart disease, a number of management options are usually available. Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:

- In the absence of evidence of heart disease, the patient should be clearly informed of this assessment and *not* be asked to return at

intervals for repeated examinations. If there is no evidence of disease, such continued attention may lead to the patient's developing inappropriate concern about the possibility of heart disease.

- If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart disease (**Chap. 273**), a plan for their reduction should be developed and the patient should be retested at intervals to assess compliance and efficacy in risk reduction.
- Asymptomatic or mildly symptomatic patients with valvular heart disease that is anatomically severe should be evaluated periodically, every 6–12 months, by clinical and noninvasive examinations. Early signs of deterioration of ventricular function may signify the need for surgical treatment before the development of disabling symptoms, irreversible myocardial damage, and excessive risk of surgical treatment (**Chap. 261**).
- In patients with CAD (**Chap. 273**), available practice guidelines should be considered in the decision on the form of treatment (medical, percutaneous coronary intervention, or surgical revascularization). Mechanical revascularization may be employed too frequently in the United States and too infrequently in Eastern Europe and developing nations. The mere presence of angina pectoris and/or the demonstration of critical coronary arterial narrowing at angiography should not reflexively evoke a decision to treat the patient by revascularization. Instead, these interventions should be limited to patients with CAD whose angina has not responded adequately to medical treatment or in whom revascularization has been shown to improve the natural history (e.g., acute coronary syndrome or multivessel CAD with left ventricular dysfunction).

### FURTHER READING

Benjamin EJ et al: Heart disease and stroke statistics – 2019 update: A report from the American Heart Association. *Circulation* 139:e56, 2019.

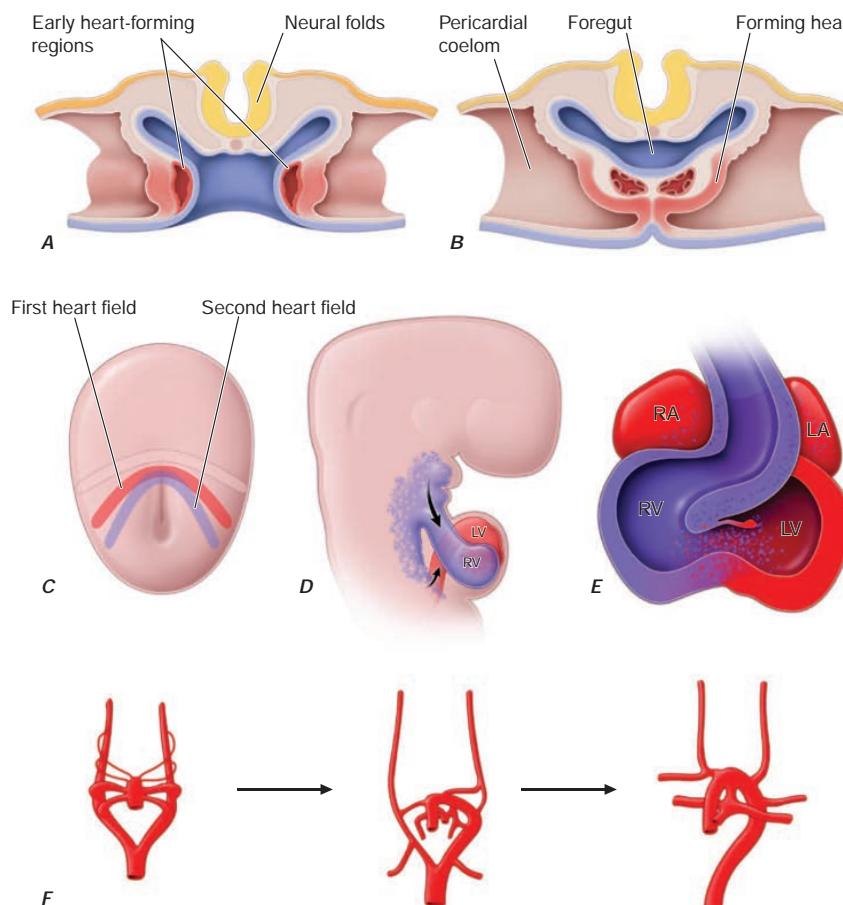
## 237 Basic Biology of the Cardiovascular System

Joseph Loscalzo, John F. Keaney, Jr., Calum A. MacRae

### DEVELOPMENTAL BIOLOGY OF THE CARDIOVASCULAR SYSTEM

The heart forms early during embryogenesis (**Fig. 237-1**), circulating blood, nutrients, molecular signals, and oxygen to the other developing organs while continuing to grow and undergo complex morphogenetic changes. Early cardiac progenitors arise within crescent-shaped fields of lateral splanchnic mesoderm under the influence of multiple cues and migrate to the midline to form the linear heart tube: a single layer of endocardium and a single layer of primitive beating cardiomyocytes.

The linear heart tube undergoes chamber specification and asymmetric looping, coordinated with linear and concentric growth of different regions of the heart tube, to produce the presumptive atria and ventricles. Cells continue to migrate into the heart at both ends from later, or second, heart fields in adjacent pharyngeal mesoderm as looping and growth occur. These cells exhibit distinctive gene expression (e.g., Islet-1) and distinctive physiology (e.g., calcium handling), contributing to discrete areas of the adult heart, including the right atrium and the right ventricle. Different embryonic origins of cells within the right and left ventricles help explain why some forms of congenital and adult heart diseases affect discrete regions of the heart.



**FIGURE 237-1** **A.** Schematic depiction of a transverse section through an early embryo depicts the bilateral regions where early heart tubes form. **B.** The bilateral heart tubes subsequently migrate to the midline and fuse to form the linear heart tube. **C.** At the early cardiac crescent stage of embryonic development, cardiac precursors include a primary heart field fated to form the linear heart tube and a second heart field fated to add myocardium to the inflow and outflow poles of the heart. **D.** Second heart field cells populate the pharyngeal region before subsequently migrating to the maturing heart. **E.** Large portions of the right ventricle and outflow tract and some cells within the atria derive from the second heart field. **F.** The aortic arch arteries form as symmetric sets of vessels that then remodel under the influence of the neural crest to form the asymmetric mature vasculature. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

After looping and chamber formation, a series of morphogenetic events divide the left and right sides of the heart, separate the atria from the ventricles, and fashion the aorta and pulmonary artery from the truncus arteriosus. Cardiac valves form between the atria and the ventricles and between the ventricles and the outflow vessels. Early in development, myocardial cells secrete an extracellular matrix rich in hyaluronic acid, or “cardiac jelly,” which accumulates within the endocardial cushions, precursors of the cardiac valves. Signals from overlying myocardial cells trigger migration, invasion, and phenotypic changes in underlying endocardial cells, which undergo an epithelial-mesenchymal transformation to invade and populate the endocardial cushion matrix with cells. Mesenchymal cells then proliferate and form the mature valve leaflets.

The great vessels form as a series of bilaterally symmetric aortic arch arteries that remodel asymmetrically to define the mature central vasculature. Migrating neural crest cells from the dorsal neural tube orchestrate this process and are necessary for aortic arch remodeling and the septation of the truncus arteriosus. The smooth-muscle cells within the tunica media of the aortic arch, the ductus arteriosus, and the carotid arteries all derive from neural crest. By contrast, smooth-muscle within the descending aorta arises from lateral plate mesoderm, and smooth-muscle of the proximal outflow tract arises from the second heart field. Neural crest cells are sensitive to both vitamin A

and folic acid, and congenital heart disease involving abnormal remodeling of the aortic arch arteries is observed with maternal deficiencies of these vitamins. The shared embryonic origins of different cardiovascular cell types lead to syndromic associations between various congenital heart diseases and a range of extracardiac abnormalities.

Coronary artery formation requires the addition of yet another cell population to the embryonic heart. Epicardial cells arise in the proepicardial organ, a derivative of the septum transversum, which also contributes to the fibrous portion of the diaphragm and to the liver. Proepicardial cells contribute smooth muscle to the coronary arteries and are required for proper coronary patterning. Other cell types within the heart (e.g., fibroblasts) also can arise from the proepicardium.

The cardiac conduction system, which generates and propagates electrical impulses, differentiates from cardiomyocyte precursors. The conduction system is composed of slow-conducting (proximal) components, such as the sinoatrial (SA) and atrioventricular (AV) nodes, as well as fast-conducting (distal) components, including the His bundle, bundle branches, and Purkinje fibers. Precursors within the sinus venosus give rise to the SA node, whereas those within the AV canal mature into heterogeneous cell types that compose the AV node. So-called decremental conduction through the AV node delays the electrical impulses between atria and ventricles, whereas the distal conduction system rapidly delivers the impulse throughout the ventricles. Each compartment within the conduction system expresses distinct gap junction proteins and ion channels that characterize the discrete cell fates and electrical properties. Developmental

defects in the conduction system can lead to clinical electrophysiologic disorders, such as congenital heart block or pre-excitation (Wolff-Parkinson-White syndrome) ([Chap. 246](#)).

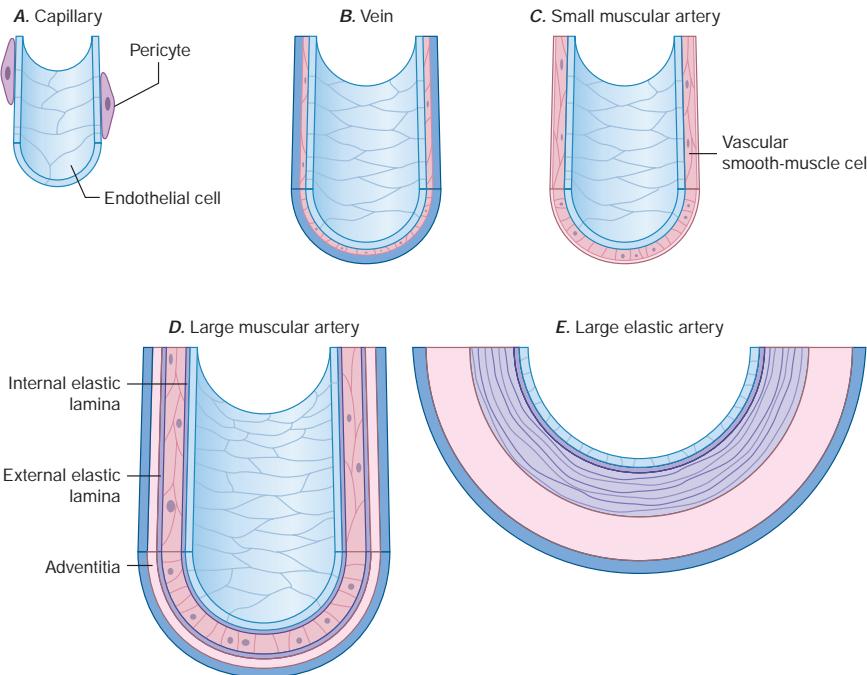
## ORIGIN OF VASCULAR CELLS

Smooth-muscle cells are of varied origin. Some upper-body arterial smooth-muscle cells derive from the neural crest, whereas lower-body arteries develop smooth-muscle cells from neighboring mesodermal structures. Bone marrow-derived endothelial progenitors may aid repair of damaged or aging arteries. With the latter, bone marrow clonality, increasingly prevalent in aging, may impart significant clonality into endothelial cell populations. Vascular stem cells resident in vessel walls may give rise to some smooth-muscle cells in injured or atherosomatous arteries ([Chaps. 96 and 484](#)).

## THE BLOOD VESSEL

### VASCULAR ULTRASTRUCTURE

Blood vessels participate in physiologic function as well as disease biology in virtually every organ system. The smallest blood vessels—capillaries—consist of a monolayer of endothelial cells on a basement membrane, adjacent to a discontinuous layer of smooth-muscle-like



**FIGURE 237-2** Schematics of the structures of various types of blood vessels. **A.** Capillaries consist of an endothelial tube in contact with a discontinuous population of pericytes. **B.** Veins typically have thin medias and thicker adventitias. **C.** A small muscular artery features a prominent tunica media. **D.** Larger muscular arteries have a prominent media with smooth-muscle cells embedded in a complex extracellular matrix. **E.** Larger elastic arteries have cylindrical layers of elastic tissue alternating with concentric rings of smooth-muscle cells as well as *vasa vasorum* to facilitate tissue blood supply.

cells known as *pericytes* (Fig. 237-2A). Arteries typically have a trilaminar structure (Fig. 237-2B–E). The *intima* consists of a monolayer of endothelial cells continuous with those of the capillaries. The middle layer, or *tunica media*, consists of smooth-muscle cells and, in veins, consists of just a few layers of smooth-muscle cells (Fig. 237-2B). The outer layer, or *adventitia*, consists of extracellular matrix with fibroblasts, mast cells, and nerve terminals. Larger arteries require nourishment of the tunica media that is accomplished via their own vasculature, the *vasa vasorum* (Fig. 237-2E).

Arterioles are small muscular arteries (Fig. 237-2C) that regulate blood pressure and flow through arterial beds. Medium-size muscular arteries also contain prominent smooth-muscle layers (Fig. 237-2D) that participate in atherosclerosis. Larger elastic arteries have a highly structured tunica media with concentric bands of smooth-muscle cells, interspersed with strata of elastin-rich extracellular matrix (Fig. 237-2E). Larger arteries form an internal elastic lamina between intima and media, while an external elastic lamina partitions the media from surrounding adventitia.

## VASCULAR CELL BIOLOGY

**Endothelial Cell** The endothelium forms the interface between tissues and the blood compartment, regulating the passage of molecules and cells. This function of endothelial cells as a selectively permeable barrier fails in vascular diseases, including atherosclerosis, hypertension, and renal disease, as well as in pulmonary edema, sepsis, and other situations exhibiting “capillary leak.”

The endothelium also participates in the local regulation of vascular tone and blood flow. Endogenous endothelium-derived substances, such as prostacyclin, endothelium-derived hyperpolarizing factor, nitric oxide (NO), and hydrogen peroxide ( $H_2O_2$ ), provide tonic stimulation of endothelial homeostatic properties under physiologic conditions *in vivo* (Table 237-1). Impaired production or excess catabolism of these substances can mediate dysfunctional properties of the endothelium. A major homeostatic influence on the endothelium

is laminar blood flow, and the measurement of flow-mediated dilatation can assess endothelial vasodilator function in humans (Fig. 237-3). Endothelial cells also produce potent vasoconstrictor substances such as endothelin. Excessive production of reactive oxygen species, such as superoxide anion ( $O_2^-$ ), by endothelial or smooth-muscle cells under pathologic conditions (e.g., excessive exposure to angiotensin II) can promote local oxidative stress and inactivate NO.

Endothelial cells also regulate leukocyte traffic through tissues. Normal endothelium exhibits limited interaction with circulating leukocytes, but bacterial products such as endotoxin or proinflammatory cytokines can induce endothelial cells to express an array of adhesion molecules that selectively bind various classes of leukocytes in different pathologic conditions. The adhesion molecules and chemokines generated during acute bacterial infection tend to recruit granulocytes, while in chronic inflammatory diseases such as tuberculosis or atherosclerosis, the adhesion molecules expressed favor monocyte recruitment. Endothelial cell injury participates in the pathophysiology of many immune-mediated diseases. For example, complement-mediated lysis of endothelial cells contributes to tissue

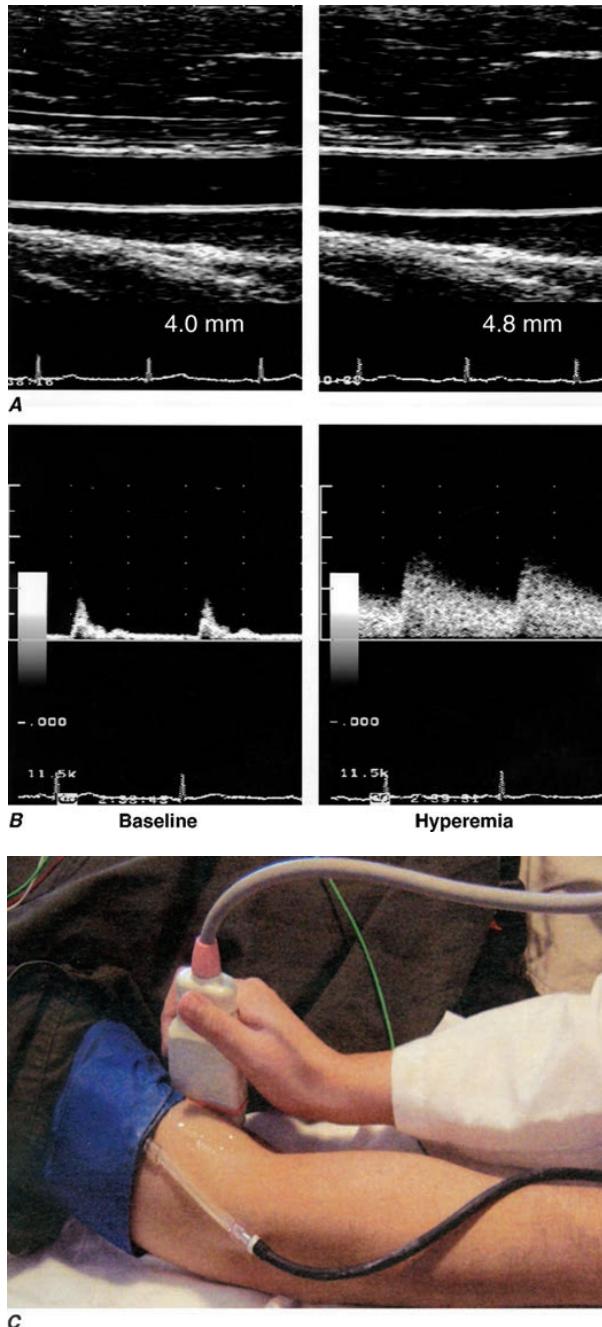
injury. The foreign histocompatibility complex antigens on endothelial cells in solid-organ allografts can promote allograft arteriopathy, while immune-mediated endothelial injury also plays a role in thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome.

The endothelium also regulates the balance between thrombosis and hemostasis through a highly tuned set of regulatory pathways. For example, inflammatory cytokines, bacterial endotoxin, or angiotensin II can activate endothelial cells to produce substantial quantities of plasminogen activator inhibitor 1 (PAI-1), the major inhibitor of fibrinolysis. Inflammatory stimuli also induce endothelial expression of the potent procoagulant tissue factor, a contributor to disseminated intravascular coagulation in sepsis. Thus, in pathologic circumstances, endothelial dysfunction tends to promote local thrombus accumulation rather than combat it.

Endothelial cells regulate the growth of subjacent smooth-muscle cells by elaborating heparan sulfate glycosaminoglycans that inhibit smooth-muscle proliferation. In the setting of vascular injury, endothelium-derived growth factors and chemoattractants (e.g., platelet-derived growth factor) induce the migration and proliferation of vascular smooth-muscle cells. Dysregulation of these growth-stimulatory molecules may promote smooth-muscle accumulation in atherosclerotic lesions.

**TABLE 237-1** Endothelial Functions in Health and Disease

HOMEOSTATIC PROPERTIES	DYSFUNCTIONAL PROPERTIES
Optimize balance between vasodilation and vasoconstriction	Impaired dilation, vasoconstriction
Antithrombotic, profibrinolytic	Prothrombotic, antifibrinolytic
Anti-inflammatory	Proinflammatory
Antiproliferative	Proproliferative
Antioxidant	Prooxidant
Selective permeability	Impaired barrier function



**FIGURE 237-3** Assessment of endothelial function *in vivo* using blood pressure cuff occlusion and release. Upon deflation of the cuff, an ultrasound probe monitors changes in diameter (**A**) and blood flow (**B**) of the brachial artery (**C**). (Courtesy of Joseph A. Vita, MD.)

**Vascular Smooth-Muscle Cell** Contraction and relaxation of vascular smooth-muscle cells in muscular arteries determine blood pressure, regional flow, and the afterload experienced by the left ventricle (see below). Venous tone regulates venous tree capacitance and, thus, influences ventricular preload. Smooth-muscle cells in the adult vessel seldom replicate in the absence of arterial injury or inflammatory activation, but proliferation and migration of arterial smooth-muscle cells contribute to arterial stenoses in atherosclerosis, arteriolar remodeling in hypertension, and the hyperplastic response of arteries to injury. In the pulmonary circulation, smooth-muscle

migration and proliferation underlie the vascular disease that occurs in sustained high-flow states such as left-to-right shunts in congenital heart disease.

Smooth-muscle cells secrete the bulk of vascular extracellular matrix. Excessive production of collagen and glycosaminoglycans contributes to the remodeling, altered biomechanics, and physiology of arteries affected by hypertension or atherosclerosis. In larger elastic arteries, such as the aorta, the ability to store the kinetic energy of systole promotes tissue perfusion during diastole. Arterial stiffness associated with aging or disease, evident in a widening pulse pressure, increases left ventricular afterload and portends a poor outcome.

Like endothelial cells, vascular smooth-muscle cells not only respond to paracrine stimuli from other cells, but can themselves serve as a source of such stimuli. For example, proinflammatory stimuli induce smooth-muscle cells to elaborate cytokines and other mediators that drive thrombosis and fibrinolysis as well as proliferation.

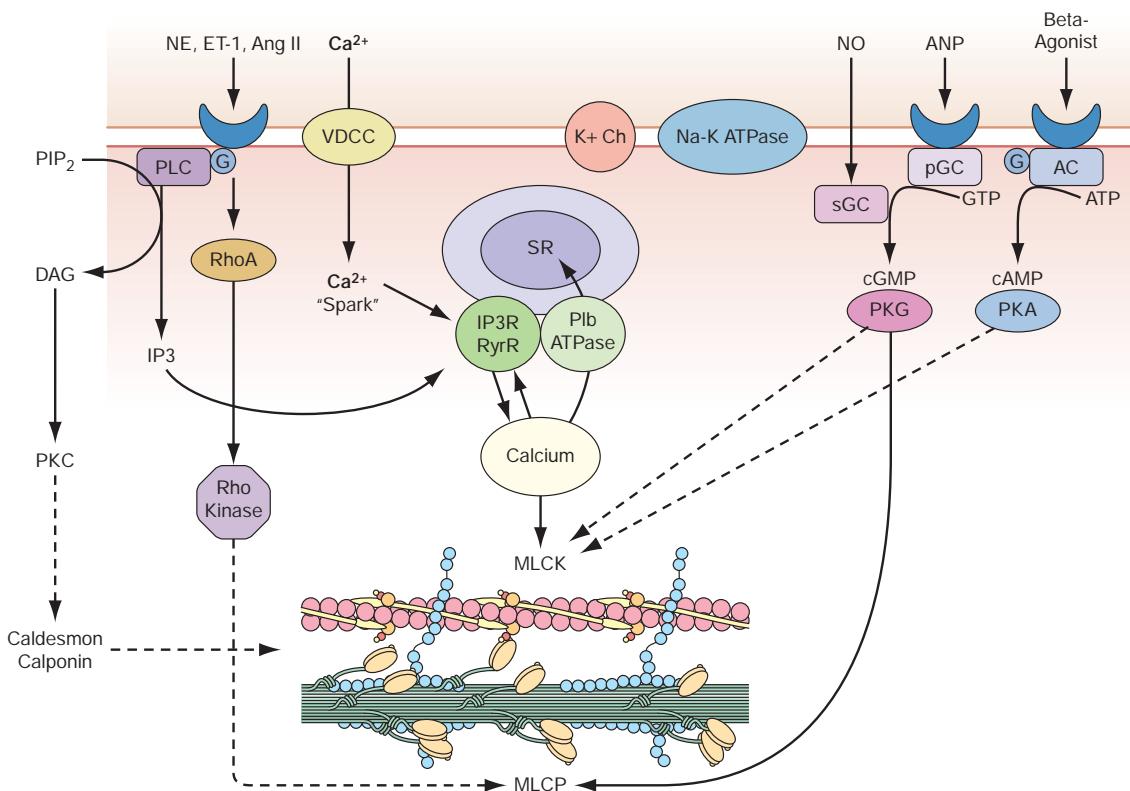
**Vascular Smooth-Muscle Cell Contraction** The principal mechanism for vascular smooth-muscle cell contraction is increased cytoplasmic calcium concentration due to transmembrane influx and triggered release from intracellular calcium stores (Fig. 237-4). In vascular smooth-muscle cells, voltage-dependent L-type calcium channels open with membrane depolarization. Local influx of calcium, termed *calcium sparks*, can trigger release from intracellular stores, which results in more contraction and increased vessel tone (see below). Opposing currents balance the effects of individual ionic fluxes, promoting homeostasis, which is tightly regulated by neural and metabolic influences.

Vasoconstricting agonists also increase intracellular  $[Ca^{2+}]$  by various mechanisms including receptor-dependent phospholipase C activation producing hydrolysis of phosphatidylinositol 4,5-bisphosphate to generate diacylglycerol (DAG) and inositol 1,4,5-trisphosphate ( $IP_3$ ). These membrane lipid derivatives, in turn, activate protein kinase C and increase intracellular  $[Ca^{2+}]$ . In addition,  $IP_3$  binds specific sarcoplasmic reticulum (SR) receptors to increase calcium efflux from this storage pool into the cytoplasm.

Vascular smooth-muscle cell contraction depends on myosin light chain phosphorylation that reflects the balance between the activity of relevant kinases and phosphatases. Calcium activates myosin light chain kinase via calmodulin, augmenting myosin ATPase activity and enhancing contraction. Conversely, myosin light chain phosphatase reduces myosin ATPase activity and contractile force. Other kinase/phosphorylase combinations result in a complex regulatory network that refines vascular tone and links it to physiologic requirements.

**Control of Vascular Smooth-Muscle Cell Tone** The autonomic nervous system and endothelial cells modulate vascular smooth-muscle cells through similar convergent pathways. Autonomic neurons enter vessel media and modulate vascular smooth-muscle cell tone in response to baroreceptors and chemoreceptors within the aortic arch or carotid bodies and to thermoreceptors in the skin. Rapidly acting reflex arcs modulated by central inputs respond to multiple sensory inputs as well as emotional stimuli through three neuronal classes: *sympathetic*, whose principal neurotransmitters are epinephrine and norepinephrine; *parasympathetic*, whose principal neurotransmitter is acetylcholine; and *nonadrenergic/noncholinergic*, which include two subgroups—*nitriergic*, whose principal neurotransmitter is NO, and *peptidergic*, whose principal neurotransmitters are substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and the nonpeptide, adenosine triphosphate (ATP).

Each of these neurotransmitters acts through specific receptors on the vascular smooth-muscle cell to modulate intracellular  $Ca^{2+}$  and, consequently, contractile tone. Norepinephrine activates adrenergic receptors, and epinephrine activates both  $\alpha_1$  and  $\beta_1$  receptors. In most blood vessels, norepinephrine activates postjunctional  $\alpha_1$  receptors in large arteries and  $\alpha_2$  receptors in small arteries and arterioles, leading to vasoconstriction. Most blood vessels express  $\beta_2$ -adrenergic receptors on their vascular smooth-muscle cells and respond to agonists by cyclic AMP-dependent relaxation. Acetylcholine released from



**FIGURE 237-4** Regulation of vascular smooth-muscle cell calcium concentration and actomyosin ATPase-dependent contraction. AC, adenylyl cyclase; Ang II, angiotensin II; ANP, atrial natriuretic peptide; DAG, diacylglycerol; ET-1, endothelin-1; G, G protein; IP<sub>3</sub>, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NE, norepinephrine; NO, nitric oxide; pGC, particulate guanylyl cyclase; PIP<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; sGC, soluble guanylyl cyclase; SR, sarcoplasmic reticulum; VDCC, voltage-dependent calcium channel. Solid lines depict stimulatory interaction, and dashed lines represent inhibition. (Reproduced with permission from B Berk, in *Vascular Medicine*, 3rd ed. Philadelphia, Saunders, Elsevier, 2006.)

parasympathetic neurons may bind to muscarinic receptors on either vascular smooth-muscle cells, causing vasoconstriction, or endothelial cells, causing NO-dependent vasorelaxation. Nitrergic neurons release NO, which relaxes vascular smooth-muscle cells via the cyclic GMP-dependent and –independent mechanisms outlined, and other peptidergic inputs that regulate vascular tone. **For the detailed molecular physiology of the autonomic nervous system, see Chap. 440.**

The release of endothelial effectors of vascular smooth-muscle cell tone integrates the smooth-muscle response to mechanical (shear stress, cyclic strain, etc.) and biochemical stimuli (purinergic agonists, muscarinic agonists, peptidergic agonists). In addition to these local paracrine modulators, a complex system of circulating modulators ranging from norepinephrine to the natriuretic peptides also modulates vascular smooth-muscle cell tone.

### ARTERIOGENESIS AND ANGIOGENESIS

Recruitment and growth of blood vessels (arteriogenesis) and new capillaries (angiogenesis) can occur in response to conditions such as chronic hypoxemia and tissue ischemia. Growth factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), can activate a signaling cascade that stimulates endothelial proliferation and tube formation, defined as *angiogenesis*. Guidance molecules, including members of the semaphorin family of secreted peptides, direct blood vessel patterning by attracting or repelling nascent endothelial tubes. The recruitment and expansion of preexisting collateral vascular networks in response to a blocked artery, an example of arteriogenesis, can result from selective activation of both growth factors and, perhaps, local or circulating endothelial progenitor cells. True vascular regeneration, or the development of a new blood

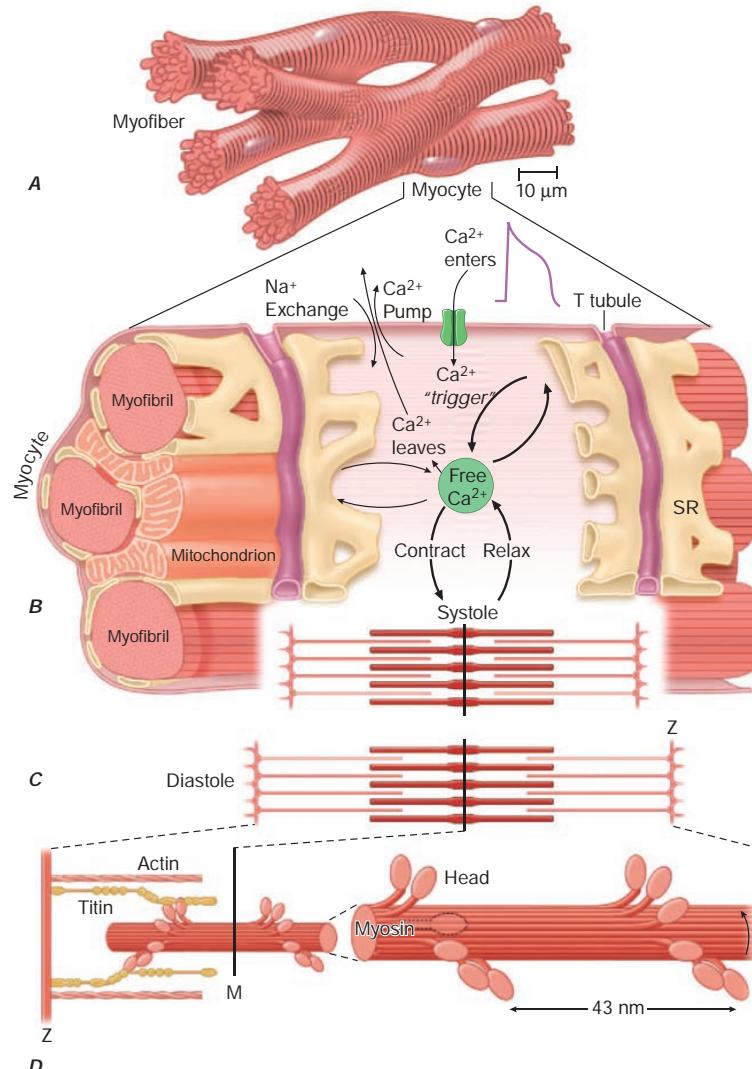
vessel that includes all three cell layers, normally does not occur in adult mammals, but recent scientific advances might help obviate such limitations ([Chaps. 96 and 484](#)).

## CELLULAR BASIS OF CARDIAC CONTRACTION

### CARDIAC ULTRASTRUCTURE

Most of the ventricular mass is composed of cardiomyocytes, normally 60–140 µm in length and 17–25 µm in diameter ([Fig. 237-5A](#)). Each cell contains multiple myofibrils that run the length of the cell and are composed of series of repeating sarcomeres. The cytoplasm between the myofibrils contains other cell constituents, including a single centrally located nucleus, mitochondria, and the intracellular membrane system, the SR.

The sarcomere, the structural and functional unit of contraction, lies between adjacent Z lines, which on transmission electron microscopy are seen as dark repeating bands. The distance between Z lines varies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 µm. At the center of the sarcomere is a dark band of constant length (1.5 µm), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, consists of interdigitating thick and thin myofilaments. Thicker filaments, composed principally of the protein myosin, traverse the A band; they are about 10 nm (100 Å) in diameter, with tapered ends. Thinner filaments, composed primarily of actin, course from the Z lines through the I band into the A band; they are ~5 nm (50 Å) in diameter and 1.0 µm in length. Thus, thick



**FIGURE 237-5** **A** shows the branching myocytes making up the cardiac myofibers. **B** illustrates the critical role played by the changing [Ca<sup>2+</sup>] in the myocardial cytosol. Ca<sup>2+</sup> ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca<sup>2+</sup> ions “trigger” the release of more calcium from the sarcoplasmic reticulum (SR) and thereby initiate a contraction-relaxation cycle. Eventually the small quantity of Ca<sup>2+</sup> that has entered the cell leaves predominantly through an Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, with a lesser role for the sarcolemmal Ca<sup>2+</sup> pump. The varying actin-myosin overlap is shown for (**B**) systole, when [Ca<sup>2+</sup>] is maximal, and (**C**) diastole, when [Ca<sup>2+</sup>] is minimal. **D**, The myosin heads, attached to the thick filaments, interact with the thin actin filaments. (Courtesy of L.H. Opie.)

and thin filaments overlap only within the (dark) A band, whereas the (light) I band contains only thin filaments. On electron-microscopic examination, bridges extend between the thick and thin filaments within the A band; these are myosin heads (see below) bound to actin filaments.

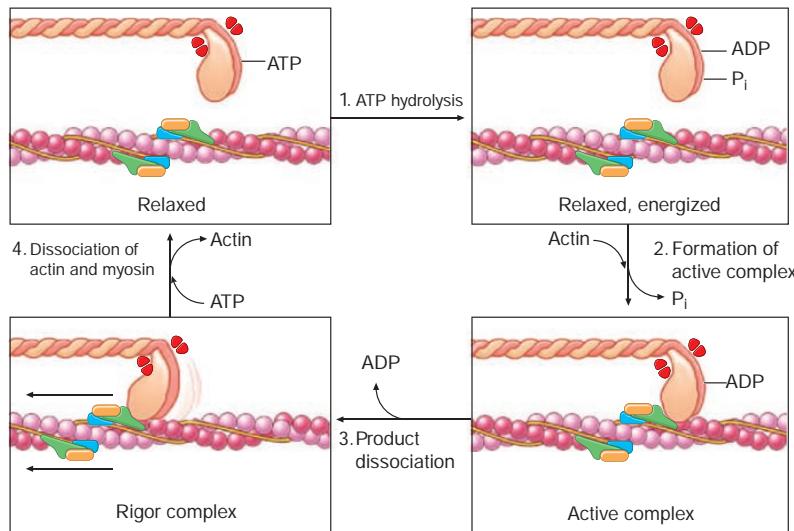
### THE CONTRACTILE PROCESS

The sliding filament model for muscle contraction rests on the central observation that both the thick and the thin filaments are constant in length during both contraction and relaxation. With activation, the actin filaments are propelled farther into the A band. In the process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another.

The myosin molecule is a complex, asymmetric protein with a molecular mass of about 500,000 Da; it has a rod-like portion that is about 150 nm (1500 Å) in length with a globular portion (head) at its end. The globular portions of myosin form the bridges to actin and are the site of ATPase activity. In thick myofilaments, composed of

~300 longitudinally stacked myosin molecules, the rod-like segments of myosin assume an orderly, polarized orientation, with outwardly projecting globular heads interacting with actin to generate force and shorten (Fig. 237-5B).

Actin has a molecular mass of about 47,000 Da. Thin filaments consist of a double helix of two chains of actin molecules wound about each other on a larger molecule, tropomyosin. A group of regulatory proteins—troponins C, I, and T—localize at regular intervals on this filament (Fig. 237-6). In contrast to myosin, actin lacks intrinsic enzymatic activity, but combines reversibly with myosin in the presence of ATP and Ca<sup>2+</sup>. Calcium activates the myosin ATPase, which breaks down ATP to supply the energy for contraction (Fig. 237-6). The activity of myosin ATPase determines the rate of actomyosin cross-bridge formation and breakdown and ultimately determines contraction velocity. In relaxed muscle, tropomyosin inhibits this interaction. Titin (Fig. 237-5D) an enormous, flexible, myofibrillar protein, connects myosin to the Z line; its elasticity contributes to the passive mechanical characteristics of the heart. Dystrophin, a cytoskeletal protein that



**FIGURE 237-6** Four steps in cardiac muscle contraction and relaxation. In relaxed muscle (upper left), ATP bound to the myosin cross-bridge dissociates the thick and thin filaments. **Step 1:** Hydrolysis of myosin-bound ATP by the ATPase site on the myosin head transfers the chemical energy of the nucleotide to the activated cross-bridge (upper right). When cytosolic  $\text{Ca}^{2+}$  concentration is low, as in relaxed muscle, the reaction cannot proceed because tropomyosin and the troponin complex on the thin filament do not allow the active sites on actin to interact with the cross-bridges. Therefore, even though the cross-bridges are energized, they cannot interact with actin. **Step 2:** When  $\text{Ca}^{2+}$  binding to troponin C has exposed active sites on the thin filament, actin interacts with the myosin cross-bridges to form an active complex (lower right) in which the energy derived from ATP is retained in the actin-bound cross-bridge, whose orientation has not yet shifted. **Step 3:** The muscle contracts when ADP dissociates from the cross-bridge. This step leads to the formation of the low-energy rigor complex (lower left) in which the chemical energy derived from ATP hydrolysis has been expended to perform mechanical work (the "rowing" motion of the cross-bridge). **Step 4:** The muscle returns to its resting state, and the cycle ends when a new molecule of ATP binds to the rigor complex and dissociates the cross-bridge from the thin filament. This cycle continues until calcium is dissociated from troponin C in the thin filament, which causes the contractile proteins to return to the resting state with the cross-bridge in the energized state. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase. (Reproduced with permission from AM Katz, in WS Colucci [ed]: Heart failure: Cardiac function and dysfunction, in *Atlas of Heart Diseases*, 3rd ed. Philadelphia, Current Medicine, 2002.)

binds to the dystroglycan complex at membrane adherens junctions, tethers the sarcomere to the cell membrane at these regions of tight coupling to adjacent myocytes. Mutations in multiple sarcomeric and cytoskeletal proteins cause different Mendelian disorders involving the heart and skeletal muscle and also sensitize individuals to toxic cardiomyopathies (e.g., due to alcohol or chemotherapy).

During activation of the cardiac myocyte,  $\text{Ca}^{2+}$  binds the heterotrimer troponin C, resulting in regulatory conformational changes in tropomyosin and exposing actin cross-bridge interaction sites (Fig. 237-6). Repetitive interaction between myosin heads and actin filaments is termed *cross-bridge cycling* and results in sliding of the actin along the myosin filaments, with muscle shortening and/or the development of tension. The splitting of ATP then dissociates the myosin cross-bridge from actin. In the presence of ATP (Fig. 237-6), actin and myosin filaments bind and dissociate cyclically if sufficient  $\text{Ca}^{2+}$  is present; these processes cease when  $[\text{Ca}^{2+}]$  falls below a critical level, and the troponin-tropomyosin complex once more inhibits actin-myosin interactions (Fig. 237-7).

Cytoplasmic  $[\text{Ca}^{2+}]$  is a principal determinant of the inotropic state of the heart. Most agents that stimulate myocardial contractility (positive inotropic stimuli), including digitalis glycosides and  $\beta$ -adrenergic agonists, increase cytoplasmic  $[\text{Ca}^{2+}]$ , triggering cross-bridge cycling. Increased adrenergic neuronal activity stimulates myocardial contractility through norepinephrine release, activation of  $\beta$ -adrenergic receptors, and, via G<sub>s</sub>-stimulated guanine nucleotide-binding proteins, activation of the adenylyl cyclase, which leads to the formation of the intracellular second messenger cyclic AMP from ATP (Fig. 237-7). Cyclic AMP in turn activates protein kinase A (PKA), which phosphorylates sarcolemmal  $\text{Ca}^{2+}$  channels, thereby enhancing the influx of  $\text{Ca}^{2+}$  into the myocyte.

The SR (Fig. 237-8), a complex network of anastomosing intracellular channels, invests the myofibrils. The transverse tubules, or T system, closely related to the SR, both structurally and functionally, arise as sarcolemmal invaginations that extend into the myofibrillar bundles along the Z lines, i.e., the ends of the sarcomeres.

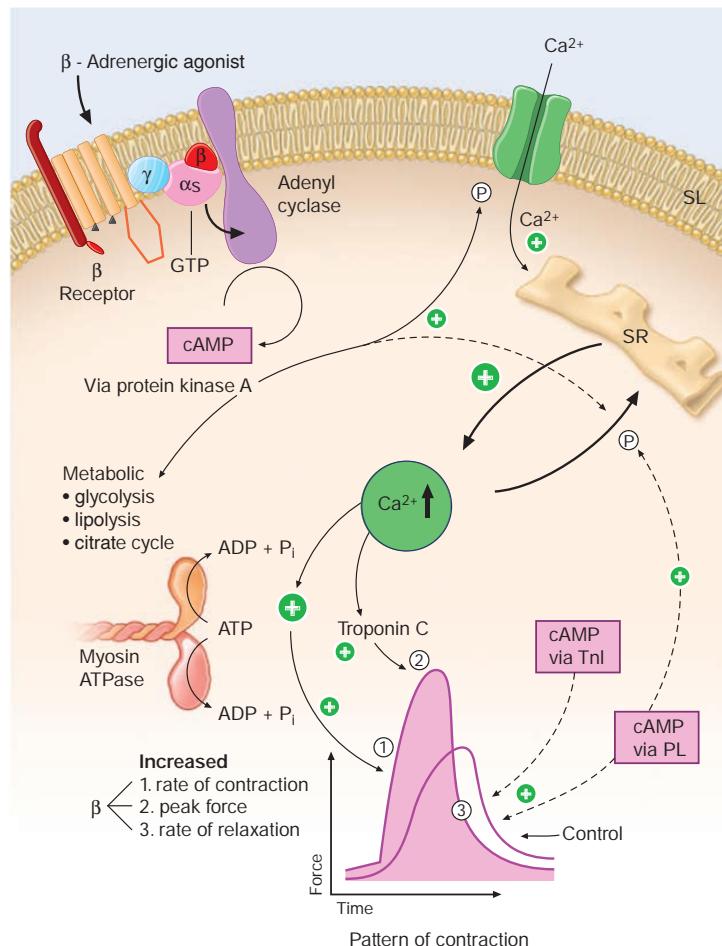
## CARDIAC ACTIVATION

In the inactive state, the cardiac cell is electrically polarized; i.e., the interior has a negative charge relative to the outside of the cell, with a transmembrane potential of  $-80$  to  $-100$  mV (Chap. 243). The sarcolemma, which in the resting state is largely impermeable to  $\text{Na}^+$ , and a  $\text{Na}^+$ - and  $\text{K}^+$ -pump energized by ATP that extrudes  $\text{Na}^+$  from the cell and maintain the resting potential. In this resting state, intracellular  $[\text{K}^+]$  is relatively high and  $[\text{Na}^+]$  is far lower; conversely, extracellular  $[\text{Na}^+]$  is high and  $[\text{K}^+]$  is low. At the same time, extracellular  $[\text{Ca}^{2+}]$  greatly exceeds free intracellular  $[\text{Ca}^{2+}]$ .

The action potential has four phases (see Fig. 243-1B). During the action potential plateau (phase 2), there is a slow inward current through sarcolemmal L-type  $\text{Ca}^{2+}$  channels (Fig. 237-8). Depolarizing current spreads across the cell membrane, penetrating deeply into the cell via the T tubular system. The absolute quantity of  $\text{Ca}^{2+}$  traversing sarcolemmal and T tubular membranes is modest and insufficient to fully activate contraction. However, this initial  $\text{Ca}^{2+}$  current, through  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release, triggers substantial  $\text{Ca}^{2+}$  release from the SR, inducing contraction.

$\text{Ca}^{2+}$  is released from the SR through a  $\text{Ca}^{2+}$  release channel, a cardiac isoform of the ryanodine receptor (RyR2). Several regulatory proteins, including calstabin 2, inhibit RyR2 and thus SR  $\text{Ca}^{2+}$  release. Inherited disorders or exogenous factors affecting the efficiency or stability of SR  $\text{Ca}^{2+}$  handling can impair contraction, leading to heart failure or to ventricular arrhythmias.

The  $\text{Ca}^{2+}$  released from the SR diffuses to interact with myofibrillar troponin C (Fig. 237-7), repressing this protein's inhibition of contraction, and so activating myofilaments to shorten. During repolarization, the activity of the SR  $\text{Ca}^{2+}$  ATPase (SERCA<sub>2A</sub>) leads to  $\text{Ca}^{2+}$  uptake against a concentration gradient into the SR where it complexes with another specialized protein, calsequestrin. The uptake of  $\text{Ca}^{2+}$  is ATP (energy)-dependent and lowers cytoplasmic  $[\text{Ca}^{2+}]$  to a level where actomyosin interaction is inhibited and myocardial relaxation occurs. There is also a sarcolemmal exchange of  $\text{Ca}^{2+}$  for  $\text{Na}^+$  (Fig. 237-8), reducing the cytoplasmic  $[\text{Ca}^{2+}]$ . Additional control of calcium



**FIGURE 237-7** Signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects of  $\beta$ -adrenergic stimulation. When the  $\beta$ -adrenergic agonist interacts with the  $\beta$  receptor, a series of G protein-mediated changes leads to activation of adenyl cyclase and the formation of cyclic adenosine monophosphate (cAMP). The latter acts via protein kinase A to stimulate metabolism (left) and phosphorylate the  $\text{Ca}^{2+}$  channel protein (right). The result is an enhanced opening probability of the  $\text{Ca}^{2+}$  channel, thereby increasing the inward movement of  $\text{Ca}^{2+}$  ions through the sarcolemma (SL) of the T tubule. These  $\text{Ca}^{2+}$  ions release more calcium from the sarcoplasmic reticulum (SR) to increase cytosolic  $\text{Ca}^{2+}$  and activate troponin C.  $\text{Ca}^{2+}$  ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate ( $P_i$ ). Enhanced myosin ATPase activity explains the increased rate of contraction, with increased activation of troponin C explaining increased peak force development. An increased rate of relaxation results from the ability of cAMP to activate as well the protein phospholamban, situated on the membrane of the SR, that controls the rate of uptake of calcium into the SR. The latter effect explains enhanced relaxation (lusitropic effect). P, phosphorylation; PL, phospholamban; TnI, troponin I. (Courtesy of L.H. Opie.)

compartmentalization results from cyclic AMP-dependent PKA phosphorylation of the SR protein *phospholamban*, permitting SERCA<sub>2A</sub> activation, increasing SR  $\text{Ca}^{2+}$  uptake, and so accelerating relaxation rates and loading the SR with  $\text{Ca}^{2+}$  for subsequent cycles of release and contraction.

Thus, the combination of the cell membrane, transverse tubules, and SR, which transmit the action potential, release and then reaccumulate  $\text{Ca}^{2+}$ , controls the cyclic contraction and relaxation of heart muscle. Genetic or pharmacologic alterations of any component can disturb any of the functions of this finely tuned system.

## CONTROL OF CARDIAC PERFORMANCE AND OUTPUT

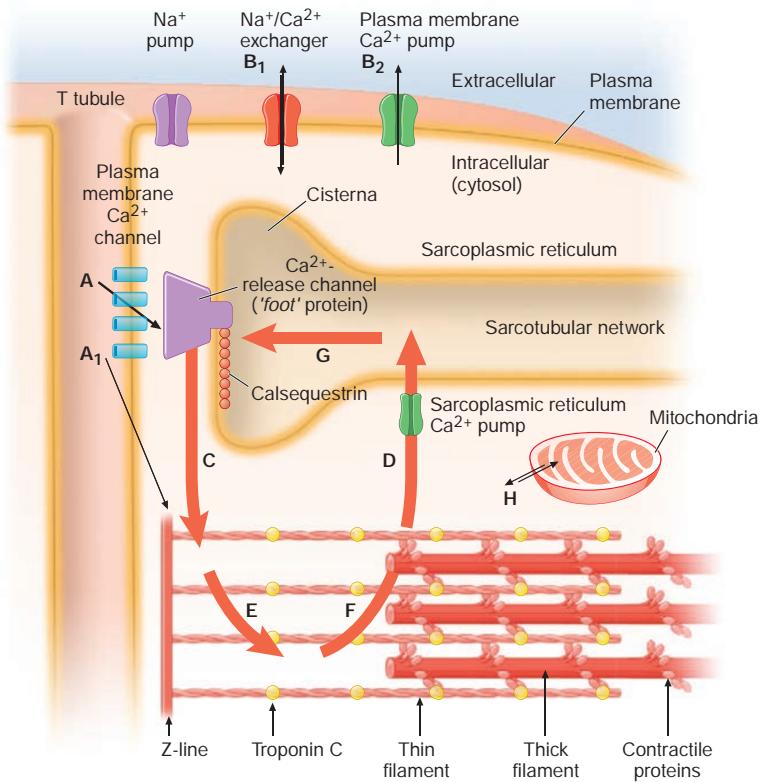
The extent of shortening of heart muscle and, therefore, ventricular stroke volume in the intact heart depends on three major influences: (1) the length of the muscle at the onset of contraction, i.e., the preload; (2) the tension that the muscle must develop during contraction, i.e., the afterload; and (3) muscle contractility, i.e., the extent and velocity of shortening at any given preload and afterload. **Table 237-2** lists the major determinants of preload, afterload, and contractility.

## THE ROLE OF MUSCLE LENGTH (PRELOAD)

Preload determines sarcomere length at the onset of contraction. Contractile force is optimal at specific sarcomere lengths (~2.2  $\mu\text{m}$ ) where both myofilament  $\text{Ca}^{2+}$  sensitivity is maximal and myofilament interactions and activation of contraction are most efficient. The relationship between initial muscle fiber length and the developed force is the basis of Starling's law of the heart, which states that, within limits, the ventricular contraction force depends on the end-diastolic length of the cardiac muscle, which *in vivo* relates closely to the ventricular end-diastolic volume.

## CARDIAC PERFORMANCE

Ventricular end-diastolic or "filling" pressure can serve as a surrogate for end-diastolic volume. In isolated heart and heart-lung preparations, stroke volume varies directly with the end-diastolic fiber length (preload) and inversely with the arterial resistance (afterload), and as the heart fails—i.e., as its contractility declines—it delivers a progressively smaller stroke volume from a normal or even elevated end-diastolic volume. The relation between ventricular end-diastolic pressure and the stroke work of the ventricle (the ventricular function curve)



**FIGURE 237-8** The  $\text{Ca}^{2+}$  fluxes and key structures involved in cardiac excitation-contraction coupling. The arrows denote the direction of  $\text{Ca}^{2+}$  fluxes. The thickness of each arrow indicates the magnitude of the calcium flux. Two  $\text{Ca}^{2+}$  cycles regulate excitation-contraction coupling and relaxation. The larger cycle is entirely intracellular and involves  $\text{Ca}^{2+}$  fluxes into and out of the sarcoplasmic reticulum, as well as  $\text{Ca}^{2+}$  binding to and release from troponin C. The smaller extracellular  $\text{Ca}^{2+}$  cycle occurs when this cation moves into and out of the cell. The action potential opens plasma membrane  $\text{Ca}^{2+}$  channels to allow passive entry of  $\text{Ca}^{2+}$  into the cell from the extracellular fluid (arrow A). Only a small portion of the  $\text{Ca}^{2+}$  that enters the cell directly activates the contractile proteins (arrow A<sub>1</sub>). The extracellular cycle is completed when  $\text{Ca}^{2+}$  is actively transported back out to the extracellular fluid by way of two plasma membrane fluxes mediated by the sodium-calcium exchanger (arrow B<sub>1</sub>) and the plasma membrane calcium pump (arrow B<sub>2</sub>). In the intracellular  $\text{Ca}^{2+}$  cycle, passive  $\text{Ca}^{2+}$  release occurs through channels in the cisternae (arrow C) and initiates contraction: active  $\text{Ca}^{2+}$  uptake by the  $\text{Ca}^{2+}$  pump of the sarcotubular network (arrow D) relaxes the heart. Diffusion of  $\text{Ca}^{2+}$  within the sarcoplasmic reticulum (arrow G) returns this activator cation to the cisternae, where it is stored in a complex with calsequestrin and other calcium-binding proteins.  $\text{Ca}^{2+}$  released from the sarcoplasmic reticulum initiates systole when it binds to troponin C (arrow E). Lowering of cytosolic  $[\text{Ca}^{2+}]$  by the sarcoplasmic reticulum (SR) causes this ion to dissociate from troponin (arrow F) and relaxes the heart.  $\text{Ca}^{2+}$  also may move between mitochondria and cytoplasm (H). (Reproduced with permission from AM Katz: *Physiology of the Heart*, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2005.)

provides a working definition of cardiac contractility in the intact organism. An increase in contractility is accompanied by a shift of the ventricular function curve upward and to the left (greater stroke work at any level of ventricular end-diastolic pressure, or lower end-diastolic volume at any level of stroke work), whereas a shift downward and to the right characterizes reduction of contractility (Fig. 237-9).

### VENTRICULAR AFTERLOAD

In the intact heart, as *ex vivo*, the extent and velocity of shortening of ventricular muscle fibers at any level of preload and of myocardial contractility relate inversely to the afterload, i.e., the instantaneous load opposing shortening. In the intact heart, the afterload may be defined as the tension developed in the ventricular wall during ejection. Afterload is determined by the aortic impedance as well as by the volume of the ventricular cavity and myocardial tissue characteristics including thickness. Laplace's law models the tension of the myocardial fiber as the product of intracavitary ventricular pressure and ventricular radius divided by wall thickness. Therefore, at any given aortic pressure, the afterload on a dilated left ventricle exceeds that on a normal-sized ventricle. Conversely, at the same aortic pressure and ventricular diastolic volume, the afterload on a hypertrophied ventricle is lower than that on a normal chamber. Aortic pressure (and impedance) in turn depends on the peripheral vascular resistance, the biomechanics of the arterial tree, and the volume of blood it contains at the onset of ejection.

Ventricular afterload finely regulates cardiovascular performance (Fig. 237-10). As noted, elevations in both preload and contractility increase myocardial fiber shortening, whereas increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular size determine stroke volume. An increase in arterial pressure induced by vasoconstriction, for example, augments afterload, which opposes myocardial fiber shortening, reducing stroke volume.

When myocardial contractility is impaired and the ventricle dilates, afterload rises (Laplace's law) and limits cardiac output. Increased afterload also may result from neural and humoral stimuli that occur in response to a fall in cardiac output. This increased afterload may reduce cardiac output further, thereby increasing ventricular volume and initiating a vicious circle, especially in patients with ischemic heart disease and limited myocardial  $O_2$  supply. Treatment with vasodilators has the opposite effect; when afterload falls, cardiac output rises (Chap. 257).

Under normal circumstances, the various influences acting on cardiac performance interact in a complex fashion to maintain cardiac output at a level responsive to the requirements of tissue metabolic demands (Fig. 237-10). Interference with a single mechanism may not influence the cardiac output due to homeostatic adjustments. For example, a moderate reduction of blood volume or the loss of the atrial contribution to ventricular contraction can be tolerated without a reduction in resting cardiac output. Under these circumstances,

**TABLE 237-2 Determinants of Stroke Volume****I. Ventricular Preload**

- A. Blood volume
- B. Distribution of blood volume
  - 1. Body position
  - 2. Intrathoracic pressure
  - 3. Intrapercardial pressure
  - 4. Venous tone
  - 5. Pumping action of skeletal muscles
- C. Atrial contraction

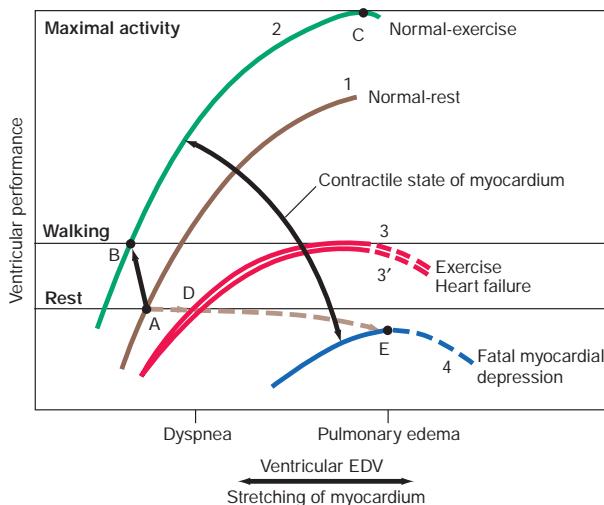
**II. Ventricular Afterload**

- A. Systemic vascular resistance
- B. Elasticity of arterial tree
- C. Arterial blood volume
- D. Ventricular wall tension
  - 1. Ventricular radius
  - 2. Ventricular wall thickness

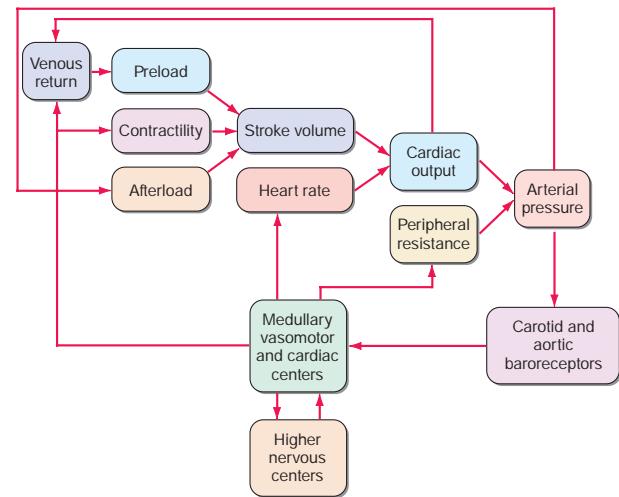
**III. Myocardial Contractility<sup>a</sup>**

- A. Intramycocardial  $[Ca^{2+}] \uparrow\downarrow$
- B. Cardiac adrenergic nerve activity  $\uparrow\downarrow^b$
- C. Circulating catecholamines  $\uparrow\downarrow^b$
- D. Cardiac rate  $\uparrow\downarrow^b$
- E. Exogenous inotropic agents  $\uparrow$
- F. Myocardial ischemia  $\downarrow$
- G. Myocardial cell death (necrosis, apoptosis, autophagy)  $\downarrow$
- H. Alterations of sarcomeric and cytoskeletal proteins  $\downarrow$ 
  - 1. Genetic
  - 2. Hemodynamic overload
- I. Myocardial fibrosis  $\downarrow$
- J. Chronic overexpression of neurohormones  $\downarrow$
- K. Ventricular remodeling  $\downarrow$
- L. Chronic and/or excessive myocardial hypertrophy  $\downarrow$

<sup>a</sup>Arrows indicate directional effects of determinants of contractility. <sup>b</sup>Contractility rises initially but later becomes depressed.



**FIGURE 237-9** The interrelations among influences on ventricular end-diastolic volume (EDV) through stretching of the myocardium and the contractile state of the myocardium. Levels of ventricular EDV associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required when the subject is at rest, while walking, and during maximal activity are designated on the ordinate. The broken lines are the descending limbs of the ventricular-performance curves, which are rarely seen during life but show the level of ventricular performance if end-diastolic volume could be elevated to very high levels. For further explanation, see text. (Reproduced with permission from WS Colucci and E Braunwald, in DP Zipes et al [eds]: *Pathophysiology of heart failure*, in Braunwald's *Heart Disease*, 7th ed. Philadelphia, Elsevier, 2005.)



**FIGURE 237-10** Interactions in the intact circulation of preload, contractility, and afterload in producing stroke volume. Stroke volume combined with heart rate determines cardiac output, which, when combined with peripheral vascular resistance, determines arterial pressure for tissue perfusion. The characteristics of the arterial system also contribute to afterload, an increase that reduces stroke volume. The interaction of these components with carotid and aortic arch baroreceptors provides a feedback mechanism to higher medullary and vasomotor cardiac centers and to higher levels in the central nervous system to affect a modulating influence on heart rate, peripheral vascular resistance, venous return, and contractility. (Reproduced with permission from MR Starling, in WS Colucci and E Braunwald [eds]: *Physiology of myocardial contraction*, in *Atlas of Heart Failure: Cardiac Function and Dysfunction*, 3rd ed. Philadelphia, Current Medicine, 2002.)

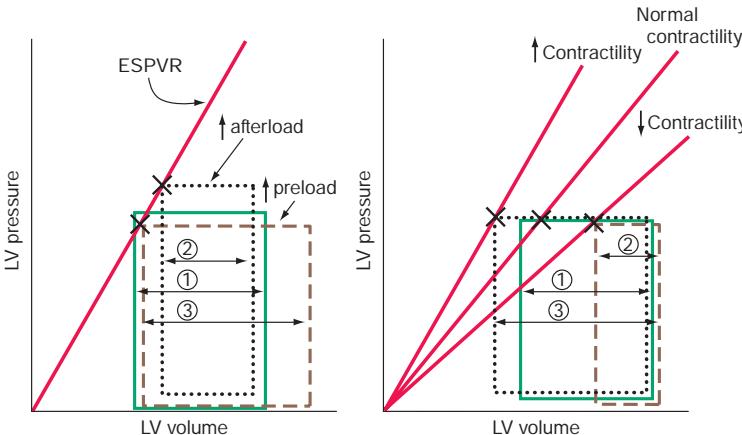
other factors, such as adrenergic neuronal impulses increasing cardiac contractility, heart rate, and venous tone, will serve as compensatory mechanisms and sustain cardiac output in a normal individual. Ultimately, understanding the complex interactions between these different variables requires rigorous models to predict relevant outcomes, and led to the early application of systems engineering principles in medicine.

### EXERCISE

The integrated response to exercise illustrates typical interactions among the three determinants of stroke volume: preload, afterload, and contractility (Fig. 237-9). Hyperventilation, the pumping action of the exercising muscles, and vasoconstriction during exercise all augment venous return and hence ventricular filling and preload (Table 237-2). Simultaneously, the increase in neuronal and humoral adrenergic stimulation of the myocardium and the tachycardia that occur during exercise combine to augment the myocardial contractility (Fig. 237-9, curves 1 and 2), together elevating stroke volume and stroke work, with little or no change in end-diastolic pressure and volume (Fig. 237-9, points A and B). Vasodilation occurs in the exercising muscles, thus limiting the increase in afterload that otherwise would occur as cardiac output rises to levels as high as five times greater than basal levels during maximal exercise. This vasodilation ultimately allows the achievement of elevated cardiac outputs during exercise at arterial pressures only moderately higher than the resting state.

### ASSESSMENT OF CARDIAC FUNCTION

Several techniques can define impaired cardiac function in clinical practice. Cardiac output and stroke volume may decline in the presence of heart failure, but these variables are often within normal limits, especially at rest. A more sensitive index of cardiac function is the ejection fraction, i.e., the ratio of stroke volume to end-diastolic volume (normal value =  $67 \pm 8\%$ ), which is frequently depressed in systolic heart failure even when stroke volume is normal. Alternatively, abnormally elevated ventricular end-diastolic volume (normal value =  $75 \pm 20 \text{ mL/m}^2$ ) or



**FIGURE 237-11** The responses of the left ventricle (LV) to increased afterload, increased preload, and increased and reduced contractility are shown in the pressure-volume plane. **Left.** Effects of increases in preload and afterload on the pressure-volume loop. Because there has been no change in contractility, the end-systolic pressure-volume relationship (ESPVR) is unchanged. With an increase in afterload, stroke volume falls (1 → 2); with an increase in preload, stroke volume rises (1 → 3). **Right.** With increased myocardial contractility and constant left ventricular end-diastolic volume, the ESPVR moves to the left of the normal line (lower end-systolic volume at any end-systolic pressure) and stroke volume rises (1 → 2). With reduced myocardial contractility, the ESPVR moves to the right; end-systolic volume is increased, and stroke volume falls (1 → 3).

end-systolic volume (normal value =  $25 \pm 7 \text{ mL/m}^2$ ) signifies left ventricular systolic impairment.

Noninvasive techniques, particularly echocardiography, radionuclide scintigraphy, and cardiac magnetic resonance imaging (MRI) (**Chap. 241**), have great value in the clinical assessment of myocardial function. They provide measurements of end-diastolic and end-systolic volumes, ejection fraction, and systolic shortening rate, and they allow assessment of ventricular filling (see below) as well as regional contraction, relaxation, and tissue characterization. The latter measurements have particular importance in ischemic heart disease, as myocardial infarction causes regional myocardial damage.

Strong dependence on ventricular loading conditions influences the precision of measurements of cardiac output, ejection fraction, and ventricular volumes as indices of cardiac function. Thus, a depressed ejection fraction and lowered cardiac output may occur in patients with normal ventricular function but reduced preload, as occurs in hypovolemia, or with increased afterload, as occurs in acutely elevated arterial pressure.

The end-systolic left ventricular pressure-volume relationship has particular value as an index of ventricular performance as it does not depend on preload and afterload (**Fig. 237-11**). At any level of myocardial contractility, left ventricular end-systolic volume varies inversely with end-systolic pressure; as contractility declines, end-systolic volume (at any level of end-systolic pressure) rises. Invasive measurement of end-systolic left ventricular pressure-volume loops add rigor to research studies of left ventricular function, and integrated cardiopulmonary exercise testing is now more broadly available, but these techniques are less pragmatic than the more readily assessed indices obtained in routine clinical practice, such as ventricular volumes and ejection fraction. Longitudinal measurements of some aspects of cardiovascular physiology are increasingly feasible with implantable or wearable devices.

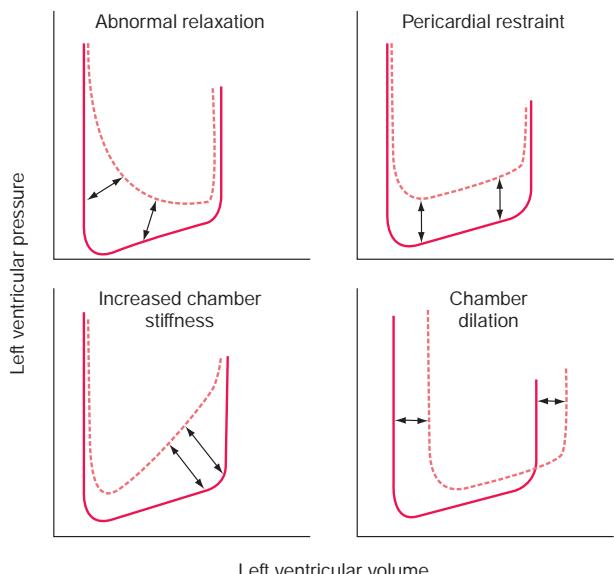
## DIASTOLIC FUNCTION

Ventricular filling is influenced by several characteristics of the myocardium, including (1) the extent and speed of myocardial relaxation and (2) the passive stiffness of the ventricular wall. The former is largely a function of the rate of uptake of  $\text{Ca}^{2+}$  by the SR that may be enhanced by adrenergic activation and reduced by ischemia due to limited ATP available for pumping  $\text{Ca}^{2+}$  into the SR (see above). For the latter, ventricular stiffness increases with hypertrophy, fibrosis, and conditions that infiltrate the ventricle, such as amyloid, or can result from an extrinsic constraint (e.g., pericardial compression) (**Fig. 237-12**).

Ventricular filling can be assessed by measuring flow velocity across the mitral valve using Doppler ultrasound. Normally, inflow velocity is more rapid in early diastole than during atrial systole. However, with mild to moderately impaired relaxation, the rate of early diastolic filling declines as presystolic filling rates rise. With further stiffening, flow is “pseudo-normalized,” as early ventricular filling becomes more rapid with rising left atrial pressure upstream of the left ventricle.

## CARDIAC METABOLISM

The heart requires a continuous supply of energy (ATP) not only to drive mechanical contraction but also to maintain ionic and biochemical homeostasis. The development of tension, the frequency of contraction, and myocardial contractility levels are the principal determinants



**FIGURE 237-12** Mechanisms that cause diastolic dysfunction reflected in the pressure-volume relation. The bottom half of the pressure-volume loop is depicted. Solid lines represent normal subjects; broken lines represent patients with diastolic dysfunction. (Reproduced with permission from JD Carroll et al: The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. *Circulation* 74:815, 1986.)

**1810** of the heart's energy and oxygen requirements, representing ~15% of that of the entire organism.

The heart's ATP production requires the generation of acetyl coenzyme A (acetyl-CoA) that can be derived from (in descending order) free fatty acids (FFAs), glucose, lactate, amino acids, and ketone bodies. Myocardial FFAs derive from circulating FFAs, whereas the cardiomyocyte's glucose derives from plasma as well as from myocardial glycogen stores (glycogenolysis). These two principal sources of acetyl-CoA are metabolized distinctly in cardiac muscle. Glucose is converted in the cytoplasm into pyruvate, which passes into mitochondria for conversion into acetyl-CoA that then undergoes oxidation. FFAs are converted to acyl-CoA in the cytoplasm and acetyl-CoA in the mitochondria. Acetyl-CoA enters the citric acid (Krebs) cycle to produce ATP by oxidative phosphorylation; ATP then enters the cytoplasm from the mitochondrial compartment. Intracellular adenosine diphosphate (ADP), resulting from ATP breakdown, enhances ATP production.

In the fasted, resting state, circulating FFAs furnish most of the heart's acetyl-CoA (~70%). In the fed state, with elevations of blood glucose and insulin, glucose oxidation increases and FFA oxidation subsides. Increased cardiac work, inotropic agents, hypoxia, and mild ischemia all enhance myocardial glucose uptake, production (glycogenolysis), and metabolism to pyruvate (glycolysis). Exercise raises circulating lactate levels and myocardial utilization of acetyl-CoA. By contrast,  $\beta$ -adrenergic stimulation, even from stress, raises the circulating levels and metabolism of FFAs in favor of glucose. Severe myocardial ischemia inhibits cytoplasmic pyruvate dehydrogenase, producing incomplete glucose metabolism to lactic acid (anaerobic glycolysis). Anaerobic glycolysis produces much less ATP than does aerobic glucose metabolism. High concentrations of circulating FFAs, which can occur when adrenergic stimulation is superimposed on severe ischemia, reduce oxidative phosphorylation, and the myocardial content of ATP declines, impairing contraction. In addition, FFA breakdown products may exert toxic or arrhythmogenic effects on cardiac cell membranes.

Myocardial energy is stored as creatine phosphate (CP), which is in equilibrium with ATP, the immediate energy source. In states of reduced energy availability, the CP stores decline first. Cardiac hypertrophy, fibrosis, tachycardia, increased wall tension due to ventricular dilation, and increased intracytoplasmic  $[Ca^{2+}]$  all contribute to increased myocardial energy needs. When coupled with reduced coronary flow reserve, as occurs with obstruction of coronary arteries or abnormalities of the coronary microcirculation, an imbalance in myocardial ATP production relative to demand may occur, and the resulting ischemia can worsen or cause heart failure.

### REGENERATING CARDIAC TISSUE

Adult mammalian myocardial cells are fully differentiated and have little or no regenerative potential; however, there is evidence that the immature mammalian heart has some limited regenerative potential that rapidly becomes constrained with increasing maturity and workload. Considerable current effort is being devoted to evaluating the utility of various approaches to facilitate the transient release of these constraints to enhance cardiac repair after injury. The success of such approaches would offer the exciting possibility of reconstructing an infarcted or failing ventricle (**Chap. 484**).

### Acknowledgment

The authors wish to thank Peter Libby for his contribution to the prior version of this chapter.

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## Epidemiology of Cardiovascular Disease

Thomas A. Gaziano, J. Michael Gaziano



Cardiovascular disease (CVD) is now the most common cause of death worldwide. Before 1900, infectious diseases and malnutrition were the most common causes, and CVD was responsible for <10% of all deaths. In 2017, CVD accounted for 17.8 million deaths worldwide (32%), with the same rate now occurring in both high-income countries and low- and middle-income countries.

### THE EPIDEMIOLOGIC TRANSITION

The global rise in CVD is the result of an unprecedented transformation in the causes of morbidity and mortality during the twentieth century. Known as the epidemiologic transition, this shift is driven by industrialization, urbanization, and associated lifestyle and demographic changes and is taking place in every part of the world among all races, ethnic groups, and cultures. The transition is divided into four basic stages: pestilence and famine, receding pandemics, degenerative and man-made diseases, and delayed degenerative diseases. A fifth stage, characterized by an epidemic of inactivity and obesity, is emerging in some countries (**Table 238-1**).

The *age of pestilence and famine* is marked by malnutrition, infectious diseases, and high infant and child mortality that are offset by high fertility. Tuberculosis, dysentery, cholera, and influenza are often fatal, resulting in a mean life expectancy of about 30 years. CVD, which accounts for <10% of deaths, takes the form of rheumatic heart disease and cardiomyopathies due to infection and malnutrition. Approximately 10% of the world's population remains in the age of pestilence and famine.

Per capita income and life expectancy increase during the *age of receding pandemics* as the emergence of public health systems, cleaner water supplies, and improved nutrition combine to drive down deaths from infectious disease and malnutrition. Infant and childhood mortality also decline, but deaths due to CVD increase to between 10% and 35% of all deaths. Rheumatic valvular disease, hypertension, coronary heart disease (CHD), and stroke are the predominant forms of CVD. Almost 40% of the world's population is currently in this stage.

The *age of degenerative and man-made diseases* is distinguished by mortality from noncommunicable diseases—primarily CVD—surpassing mortality from malnutrition and infectious diseases. Caloric intake, particularly from animal fat, increases. CHD and stroke are prevalent, and between 35% and 65% of all deaths can be traced to CVD. Typically, the rate of CHD deaths exceeds that of stroke by a ratio of 2:1 to 3:1. During this period, average life expectancy surpasses the age of 50. Roughly 35% of the world's population falls into this category.

**TABLE 238-1 Five Stages of the Epidemiologic Transition**

STAGE	DESCRIPTION	DEATHS RELATED TO CVD, %	PREDOMINANT CVD TYPE
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths related to malnutrition and infection; precipitous decline in infant and child mortality rates	10–35	Rheumatic valvular disease, hypertension, CHD, and stroke (predominantly hemorrhagic)
Degenerative and man-made diseases	Increased fat and caloric intake and decrease in physical activity lead to emergence of hypertension and atherosclerosis; with increase in life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious disease	35–65	CHD and stroke (ischemic and hemorrhagic)
Delayed degenerative diseases	CVD and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events; age-adjusted CVD mortality declines; CVD affecting older and older individuals	40–50	CHD, stroke, and congestive heart failure
Inactivity and obesity	Overweight and obesity increase at alarming rate; diabetes and hypertension increase; decline in smoking rates levels off; a minority of the population meets physical activity recommendations	38	CHD, stroke, and congestive heart failure, peripheral vascular disease

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

Source: Data from AR Omran: The epidemiologic transition: A theory of the epidemiology of population change. *Milbank Mem Fund Q* 49:509, 1971; and SJ Olshansky, AB Ault: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. *Milbank Q* 64:355, 1986.

In the *age of delayed degenerative diseases*, CVD and cancer remain the major causes of morbidity and mortality, with CVD accounting for 40% of all deaths. However, age-adjusted CVD mortality declines, aided by preventive strategies (for example, smoking cessation programs and effective blood pressure control), acute hospital management, and technologic advances, such as the availability of bypass surgery. CHD, stroke, and congestive heart failure are the primary forms of CVD. About 15% of the world's population is now in the age of delayed degenerative diseases or is exiting this age and moving into the fifth stage of the epidemiologic transition.

In the industrialized world, physical activity continues to decline while total caloric intake increases. The resulting epidemic of overweight and obesity may signal the start of the *age of inactivity and obesity*. Rates of type 2 diabetes mellitus, hypertension, and lipid abnormalities are on the rise, trends that are particularly evident in children. If these risk factor trends continue, age-adjusted CVD mortality rates that have fallen for decades during the fourth phase could increase in the coming years as suggested by recent data.

## PATTERNS IN THE EPIDEMIOLOGIC TRANSITION

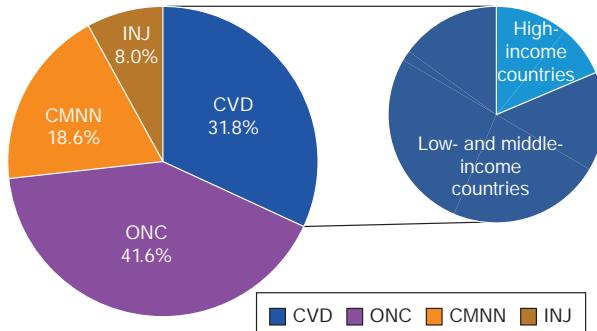
Unique regional features have modified aspects of the transition in various parts of the world. High-income countries experienced declines in CVD death rates by as much as 50–60% over the past 60 years, whereas CVD death rates increased by 15% over the past 20 years in the low- and middle-income range and the rate of change has been faster. However, given the large amount of available data, the United States serves as a useful reference point for comparisons. The age of pestilence and famine occurred before 1900, with a largely agrarian economy and population. Infectious diseases accounted for more deaths than any other cause. By the 1930s, the country proceeded through the age of receding pandemics. The establishment of public health infrastructures resulted in dramatic declines in infectious disease mortality rates. Lifestyle changes due to rapid urbanization resulted in a simultaneous increase in CVD mortality rates, reaching ~390 per 100,000. Between 1930 and 1965, the country entered the age of degenerative and man-made diseases. Infectious disease mortality rates fell to fewer than 50 per 100,000 per year, whereas CVD mortality rates reached peak levels with increasing urbanization and lifestyle changes in diet, physical activity, and tobacco consumption. The age of delayed degenerative diseases took place between 1965 and 2000. New therapeutic approaches, preventive measures, and exposure to public health campaigns promoting lifestyle modifications led to substantial declines in age-adjusted mortality rates and a steadily rising age at which a first CVD event occurs.

Currently, the United States is entering what appears to be a fifth phase. The decline in the age-adjusted CVD death rate of 3% per year through the 1970s and 1980s has tapered off in the 1990s to 2%. However, CVD death rates have declined by 3–5% per year during the first decade of the new millennium. Competing trends appear to be at play. On the one hand, an increase in the prevalence of diabetes and obesity, a slowing in the rate of decline in smoking, and a leveling off in the rate of detection and treatment for hypertension are in the negative column. On the other hand, cholesterol levels continue to decline in the face of increased statin use.

Many high-income countries (HICs)—which together account for 15% of the population—have proceeded through four stages of the epidemiologic transition in roughly the same pattern as the United States. CHD is the dominant form of CVD in these countries, with rates that tend to be two- to fivefold higher than stroke rates. However, variations exist. Whereas North America, Australia, and central northwestern European HICs experienced significant increases then rapid declines in CVD rates, southern and central European countries experienced a more gradual rise and fall in rates. More specifically, central European countries (i.e., Austria, Belgium, and Germany) declined at slower rates compared to their northern counterparts (i.e., Finland, Sweden, Denmark, and Norway). Countries such as Portugal, Spain, and Japan never reached the high mortality rates that the United States and other countries did, with CHD mortality rates at 200 per 100,000, or less. The countries of Western Europe also exhibit a clear north/south gradient in absolute rates of CVD, with rates highest in northern countries (i.e., Finland, Ireland, and Scotland) and lowest in Mediterranean countries (i.e., France, Spain, and Italy). Japan is unique among the HICs, most likely due to the unique dietary patterns of its population. Although stroke rates increased dramatically, CHD rates did not rise as sharply in Japan. However, Japanese dietary habits are undergoing substantial changes, reflected in an increase in cholesterol levels.

Patterns in low- and middle-income countries (LMICs; gross national income per capita \$11,666) depend, in part, on cultural differences, secular trends, and responses at the country level, with regard to both public health and treatment infrastructure. Although communicable diseases continue to be a major cause of death, CVD has emerged as a significant health concern in LMICs. With 85% of the world's population, LMICs are driving the rates of change in the global burden of CVD (Fig. 238-1). In most LMICs, an urban/rural gradient has emerged for CHD, stroke, and hypertension, with higher rates in urban centers.

However, although CVD rates are rapidly rising globally, vast differences exist among the regions and countries, and even within the



**FIGURE 238-1** Global deaths by cause, 2017. CMNN, communicable, maternal, neonatal, and nutritional disorders; CVD, cardiovascular diseases; INJ, injuries; ONC, other noncommunicable diseases. (Based on data from *Global Burden of Disease Study 2017. Global Burden of Disease Study 2017 [GBD 2017] Results*. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2020.)

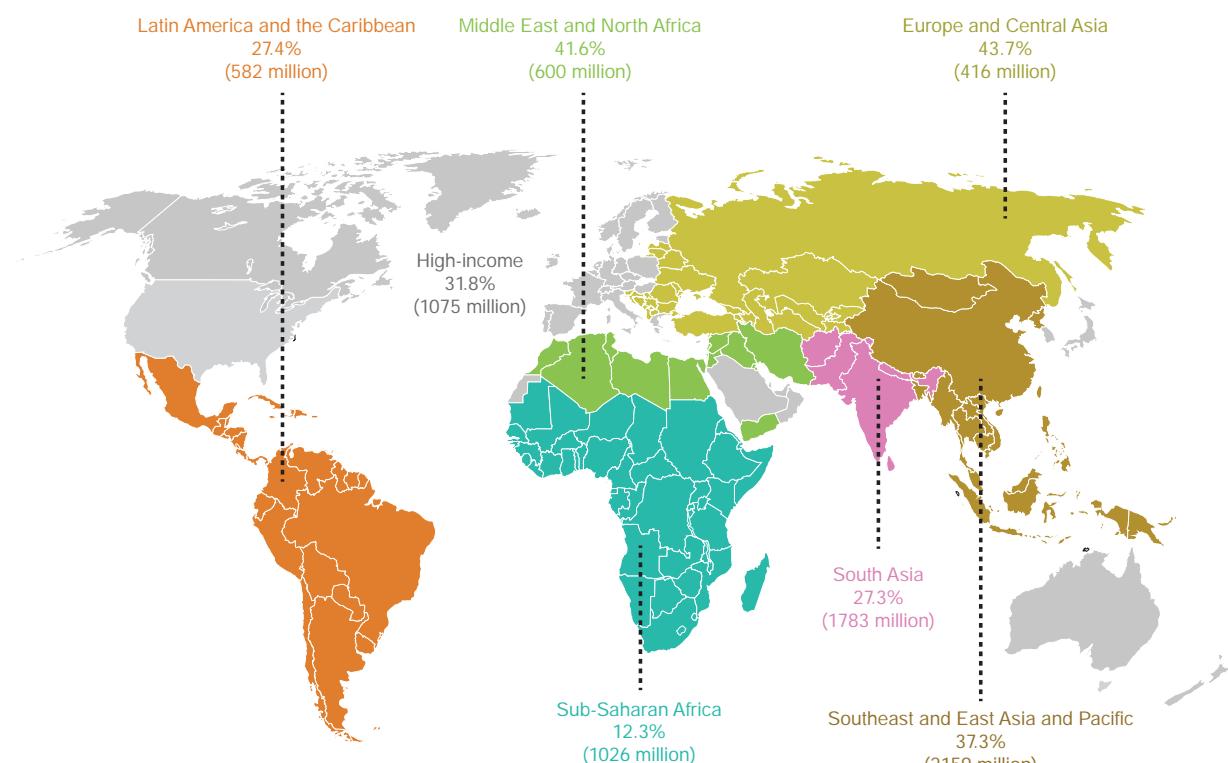
countries themselves (Fig. 238-2). The East Asia and Pacific regions appear to be straddling the second and third phases of the epidemiologic transition. CVD is a major cause of death in China, but like Japan, stroke causes more deaths than CHD in a ratio of about three to one. Vietnam and Cambodia, on the other hand, are just emerging from the pestilence and famine transition. The Middle East and North Africa regions also appear to be entering the third phase of the epidemiologic transition, with increasing life expectancy and CVD death rates just below those of HICs. In general, Latin America appears to be in the third phase of the transition, although there is vast regional heterogeneity with some areas in the second phase of the transition and some in the fourth. The Eastern Europe and Central Asia regions, however, are firmly in the peak of the third phase, with the highest death rates

due to CVD (~66%) in the world. Importantly, deaths due to CHD are not limited to the elderly in this region and have a significant effect on working-age populations. South Asia—and more specifically, India, which accounts for the greatest proportion of the region's population—is experiencing an alarming increase in heart disease. The transition appears to be in the Western style, with CHD as the dominant form of CVD. However, rheumatic heart disease continues to be a major cause of morbidity and mortality. As in South Asia, rheumatic heart disease is also an important cause of CVD morbidity and mortality in sub-Saharan Africa, which largely remains in the first phase of the epidemiologic transition.

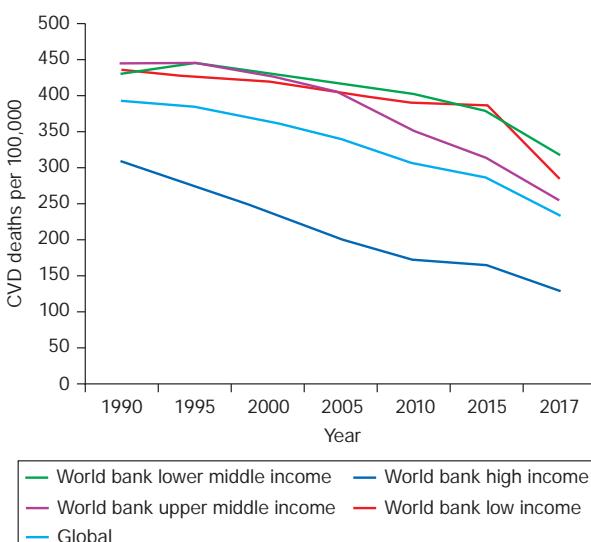
Many factors contribute to this heterogeneity among LMICs. First, the regions are in various stages of the epidemiologic transition. Second, vast differences in lifestyle and behavioral risk factors exist. Third, racial and ethnic differences may lead to altered susceptibilities to various forms of CVD. In addition, it should be noted that for most countries in these regions, accurate country-wide data on cause-specific mortality are not complete.

### GLOBAL TRENDS IN CARDIOVASCULAR DISEASE

Over the past 5 years, there have been changes in the trends of CVD that are reflective of both trends in demographics and management of disease, but also of the way deaths and diseases have been measured and estimated. In 2017, the Global Burden of Disease (GBD) Study updated its estimates with several important changes based on newly available data, refinement in the causes of death, and the introduction of new modeling techniques. The major changes include the addition of an independent estimation of population and fertility, the addition of over 127 country-years of vital registration and verbal autopsy data, revisions of some deaths from "misclassified" to dementia, Parkinson's disease and atrial fibrillation, and the addition of new diseases such as non-rheumatic calcific aortic and degenerative mitral valve disease. CVD accounts for 32% of deaths worldwide, a number expected to increase. In 2017, CHD accounted for 16.0% of all deaths globally and the largest



**FIGURE 238-2** Cardiovascular disease deaths as a percentage of total deaths and total population in seven economic regions of the world defined by the World Bank. (Based on data from *Global Burden of Disease Study 2017. Global Burden of Disease Study 2017 [GBD 2017] Results*. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2020.)



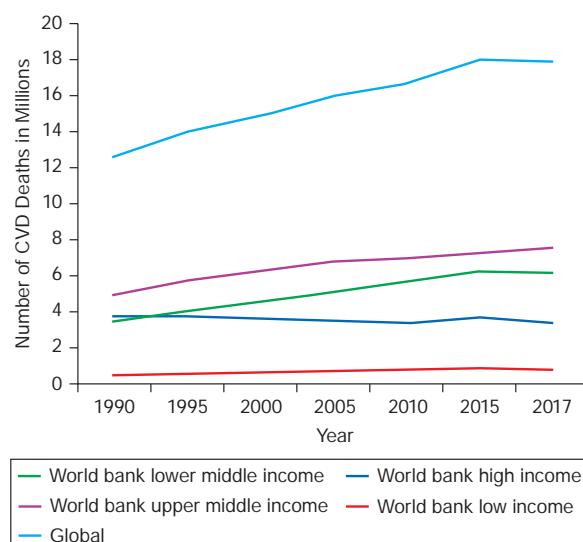
**FIGURE 238-3** Age-standardized cardiovascular diseases (CVD) death rate per 100,000 from 1990 to 2017, by World Bank income. (Based on data from Global Burden of Disease Study 2017. Global Burden of Disease Study 2017 [GBD 2017] Results. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2020.)

portion (10%) of global years of life lost (YLLs) and disability-adjusted life-years (DALYs) (7%). Stroke moved from the third to the second largest cause of death (11.0% of all deaths) and remained the third largest contributor to global YLLs (7%) and DALYs (5%). Together, CHD and stroke accounted for more than a quarter of all deaths worldwide. The burden of stroke is of growing concern among LMICs. The impact of stroke on DALYs and mortality rates is more than three times greater in LMICs as compared to HICs.

With 85% of the world's population, LMICs largely drive global CVD rates and trends. More than 14 million (14.4) CVD deaths occurred in LMICs in 2017, compared to 3.3 million in HICs. Globally, there is evidence of significant delays in age of occurrence and/or improvements in case fatality rates; between 1990 and 2017, the number of CVD deaths increased by 49%, but age-adjusted death rates decreased by 30.4% in the same period. Age-standardized death rates, however, have declined faster in HICs than in middle-income and lower-income regions (Fig. 238-3). Population growth has been greater in LMICs compared to HICs. As a result of slower rates of population growth in HICs, overall CVD deaths remained steady. However, in the LMICs, the population aging and growth outstripped gains in age-adjusted mortality reductions such that overall CVD deaths continued to climb over the past 25 years (Fig. 238-4).

Although HIC population growth will be fueled by immigration from LMICs, the populations of HICs will shrink as a proportion of the world's population. The modest decline in CVD death rates that began in the HICs in the latter third of the twentieth century will continue, but the rate of decline appears to be slowing. However, these countries are expected to see an increase in the prevalence of CVD, as well as the absolute number of deaths as the population ages.

Significant portions of the population living in LMICs have entered the third phase of the epidemiologic transition, and some are entering the fourth stage. Changing demographics play a significant role in future predictions for CVD throughout the world. For example, the population growth rate in Eastern Europe and Central Asia was 1.1% between 2010 and 2017, whereas it was 11% in South Asia. CVD rates will also have an economic impact. Even assuming no increase in CVD risk factors, most countries, but especially India and South Africa, will see a large number of people between 35 and 64 die of CVD over the next 30 years, as well as an increasing level of morbidity among middle-aged people related to heart disease and stroke.



**FIGURE 238-4** Number of cardiovascular diseases (CVD) deaths from 1990 to 2017, by World Bank income. (Based on data from Global Burden of Disease Study 2017. Global Burden of Disease Study 2017 [GBD 2017] Results. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2020.)

## RISK FACTORS

Global variation in CVD rates is related to temporal and regional variations in known risk factors and behaviors. Ecologic analyses of major CVD risk factors and mortality demonstrate high correlations between expected and observed mortality rates for the three main risk factors—smoking, serum cholesterol, and hypertension—and suggest that many regional variations are based on differences in conventional risk factors.

**Behavioral Risk Factors** • **TOBACCO** Over 1.4 billion people use tobacco worldwide. Tobacco use currently causes about 7.1 million deaths annually (12.7% of all deaths), 2.6 million of which are CVD-related. The population of the high-income country group smokes (21.6%) at almost double the rate of the low-income countries (11.2%), whereas the middle-income country group's smoking rate (19.5%) approximates the global average (19.2%). From 2007 to 2017, smoking rates decreased across low-, middle-, and high-income country groups, with relative reductions of 19%, 12%, and 20%, respectively. By 2030, the global average smoking rate is expected to decline from 19% to 16% (women, 4%; men, 28%); however, the number of tobacco users is expected to rise owing to population growth. Secondhand smoke is another well-established cause of CVD, responsible for 575,000 deaths of nonsmokers in 2017. Although smoking bans have both immediate and long-term benefits, implementation varies greatly between countries.

**DIET** Total caloric intake per capita increases as countries develop. With regard to CVD, a key element of dietary change is an increase in intake of saturated animal fats and hydrogenated vegetable fats, which contain atherogenic *trans* fatty acids, along with a decrease in intake of plant-based foods and an increase in simple carbohydrates. Fat contributes <20% of calories in rural China and India, <30% in Japan, and well above 30% in the United States. Caloric contributions from fat appear to be falling in the HICs.

**PHYSICAL INACTIVITY** The increased mechanization that accompanies the economic transition leads to a shift from physically demanding, agriculture-based work to largely sedentary industry- and office-based work. Physical inactivity is responsible for 1.3 million global deaths annually. The global prevalence of physical inactivity has remained steady between 2001 and 2016 (28.5% to 27.5%). In the United States, approximately one-quarter of the adult population does not participate

in any leisure-time physical activity, and only 24.3% of adults reported participating in adequate leisure-time aerobic and muscle-strengthening activity to meet federal guidelines. Physical inactivity is similarly high in other regions of the world and is increasing in countries that are rapidly urbanizing as part of their economic transition. Mortality rates attributable to inactivity are highest in North Africa and the Middle East and in Central and Eastern Europe. In urban China, for example, the proportion of adults who participate in moderate- or high-level activity has decreased significantly, whereas the proportion of those who participate in low-level activity has increased.

### METABOLIC RISK FACTORS

Examination of trends in metabolic risk factors provides insight into changes in the CVD burden globally. Here we describe four metabolic risk factors—lipid levels, hypertension, obesity, and diabetes mellitus—using data from the Global Burden of Disease, Injuries, and Risk Factors Study (GBD 2017). The GBD project identified and compiled mortality and morbidity data from 195 countries from 1980 to 2017.

**Lipid Levels** Worldwide, high cholesterol levels are estimated to play a role in 42% of ischemic heart disease deaths and 9% of stroke deaths, amounting to 4.3 million deaths annually. Although mean population plasma cholesterol levels tend to rise as countries move through the epidemiologic transition, mean serum total cholesterol levels have decreased globally between 1980 and 2008 by 0.08 mmol/L per decade in men and 0.07 mmol/L per decade in women. Large declines occurred in Australasia, North America, and Western Europe (0.19–0.21 mmol/L). Countries in the East Asia and Pacific region experienced increases of >0.08 mmol/L in both men and women. More recent research including Mendelian studies suggests that lipoprotein(a) may act as an individual predictor of CVD risk beyond traditional total or low-density lipoprotein cholesterol through increased cellular lipid accumulation, endothelial dysfunction, and impacts on coagulation. It appears to be elevated in ~20% of the global population, although fewer data are available from LMICs. Nonrandomized data suggest higher rates among those of African descent with twice the levels of Caucasians, with East Asians and South Asians having intermediate levels. There are limited data on clinical agents that target lipoprotein(a), although PCSK9 inhibitors lower it or other specific targets, so this remains an area of intense research.

**Hypertension** Elevated blood pressure is an early indicator of the epidemiologic transition. Observational studies show increased risk of CVD beginning with systolic blood pressures (SBPs) >110–115 mmHg. Between 1990 and 2015, the global prevalence of SBP 110–115 mmHg increased from 73,119 to 81,373 per 100,000, whereas the prevalence of SBP 140 mmHg rose from 17,307 to 20,526 per 100,000. In 2015, of the estimated 3.47 billion adults with SBP 110–115 mmHg, 874 million (25%) had SBP 140 mmHg. While SBP 140 mmHg accounts for only 25% of those with elevated blood pressure, it accounted for 73% (7.8 million) of deaths due to SBP of 110–115 mmHg in 2015. Worldwide, 55% of stroke deaths (3.36 of 6.17 million) and 55% of CHD deaths (4.89 of 8.93 million) are attributable to high blood pressure, accounting for 8.25 million deaths in 2017. From 1990 to 2015, the number of deaths related to SBP 140 mmHg increased in all LMIC groups but fell in HICs. Between 1980 and 2008, the age-standardized prevalence of uncontrolled hypertension decreased even as the number of people with uncontrolled hypertension increased due to population growth and aging. Rising mean population blood pressure also occurs as populations industrialize and move from rural to urban settings. For example, the prevalence of hypertension in urban India is 33.8%, but varies between 14.5 and 31.7% in rural regions. One major concern in LMICs is the high rate of undetected, and therefore untreated, hypertension. This may explain, at least in part, the higher stroke rates in these countries in relation to CHD rates during the early stages of the transition. The high rates of hypertension throughout Asia, especially undiagnosed hypertension, likely contribute to the high prevalence of hemorrhagic stroke in the region. Globally, however, mean SBP has decreased for both sexes (0.8 mmHg per decade for men; 1.0 mmHg per decade for women).

**Obesity** In 2015, an estimated 603.4 million adults and 107.7 million children were obese. Global obesity prevalence was 12.0% among adults (5.0% among children) and is increasing throughout the world, particularly in developing countries where the trajectories are steeper than those experienced by the developed countries. High body mass index (BMI) contributed to 4.0 million deaths worldwide (7.1% deaths from any cause); CVD was the leading cause of these deaths (2.7 million) and also of associated DALYs (66.3 of 120 million) followed by diabetes (0.6 million deaths, 30.4 million DALYs). Women are more affected by obesity than men; from 1975 to 2014, global mean age-standardized BMI increased from 22.1 to 24.4 kg/m<sup>2</sup> in females and from 21.7 to 24.2 kg/m<sup>2</sup> in males, whereas the prevalence of obesity increased from 6.4% to 14.9% in females and 3.2% to 10.8% in males. The proportion of the world's adult women who are either overweight or obese rose from 29.8% to 38.0% between 1980 and 2013, while an increase from 28.8% to 36.9% was observed for men. Country and regional differences are observed. The highest prevalence of male obesity is in the United States, Southern and Central Latin America, Australasia, and Central and Western Europe. For females, the highest prevalence of obesity is in Southern and North Africa, the Middle East, Central and Southern Latin America, and the United States. The lowest prevalence for both males and females was observed in South and Southeast Asia and in East, Central, and West Africa. Generally, the prevalence of obesity for both sexes increased with the increase in sociodemographic index; however, the rise in adult obesity in developed countries has slowed since 2006. In many of the LMICs, obesity appears to coexist with undernutrition and malnutrition. Adolescents are at particular risk.

**Diabetes Mellitus** As a consequence of, or in addition to, increasing BMI and decreasing levels of physical activity, worldwide rates of diabetes—predominantly type 2 diabetes—are on the rise. According to the most recent data from the GBD project, the prevalence of diabetes increased 129.7% for males and 120.9% for females between 1990 and 2017. An estimated 476 million people worldwide have diabetes, and the International Diabetes Foundation predicts this number will reach 693 million by 2045. Nearly 50% of people with diabetes are undiagnosed, and 80% live in LMICs. The Middle East and North Africa have the highest regional age-standardized prevalence (8.7% of the population) and incidence rates (400 per 100,000) of diabetes, whereas East Asia and the Pacific has the lowest (5.8%; 249 per 100,000). Future growth will also largely occur in the Middle East and Africa, along with other LMICs in South Asia and sub-Saharan Africa.

### GENETIC RISK FACTORS

A great deal of effort has recently been invested in understanding how genes affect cardiovascular health in populations. These efforts have focused on germline genetic variants that are related to specific CVDs as well as those that are associated with cardiovascular risk factors. In both cases, every year, the number of associated variants has increased meaningfully to the point that it appears that hundreds or even thousands of variants are associated with these conditions, each explaining a small amount of the population variability in disease and risk factors. Collections of variants have been combined in polygenic risk scores, but these too explain only a small amount of the variability of the disease in the population. Much more data will emerge in the coming years about these associations, the mechanisms that explain these associations, the relationships of variants that are specific to certain tissues such as the heart or the brain, and the interactions between genetic and lifestyle factors in causing disease. Currently, most of the data are among those with European ancestry; however, large-scale efforts are underway to understand the relationships between genes and diseases and their risk factors around the world. The early data suggest non-trivial differences among various world populations. Beyond germline risk, there appears to be increased cardiovascular risk associated with age-related expansion of hematopoietic clones with somatic mutations, including loss-of-function alleles of certain genes. Individuals with these mutations without other hematologic abnormalities are defined as having clonal hematopoiesis of indeterminate potential (CHIP).

Recent studies suggest those with CHIP have up to a twofold increased risk of developing CHD.

## SUMMARY

Although CVD rates are declining in the HICs, they are increasing in many other regions of the world. The consequences of this preventable epidemic will be substantial on many levels, including individual mortality and morbidity, family suffering, and staggering economic costs.

Three complementary strategies can be used to lessen the impact. First, the overall burden of CVD risk factors can be lowered through population-wide public health measures, such as national campaigns against cigarette smoking, unhealthy diets, and physical inactivity. Second, it is important to identify higher risk subgroups of the population who stand to benefit the most from specific, low-cost prevention interventions, including screening for and treatment of hypertension and elevated cholesterol. Simple, low-cost interventions, such as the “polypill”—a regimen of aspirin, a statin, and an antihypertensive agent—also need to be explored. Third, resources should be allocated to acute, as well as secondary, prevention interventions. For countries with limited resources, a critical first step in developing a comprehensive plan is better assessment of cause-specific mortality and morbidity, as well as the prevalence, of the major preventable risk factors.

In the meantime, the HICs must continue to bear the burden of research and development aimed at prevention and treatment, being mindful of the economic limitations of many countries. The concept of the epidemiologic transition provides insight into how to alter the course of the CVD epidemic. The efficient transfer of low-cost preventive and therapeutic strategies could alter the natural course of this epidemic and thereby reduce the excess global burden of preventable CVD.

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physical examination skills over the past few decades at every level, from student to faculty specialist, a development of great concern to both clinicians and medical educators. Classic cardiac findings are recognized by only a minority of internal medicine and family practice residents. Despite popular perceptions, clinical performance does not improve predictably as a function of experience; instead, the acquisition of new examination skills may become more difficult for a busy individual practitioner. Less time is now devoted to mentored cardiovascular examinations during the training of students and residents. One widely recognized outcome of these trends is the progressive overutilization of noninvasive imaging studies to establish the presence and severity of cardiovascular disease even when the examination findings imply a low pretest probability of significant pathology. Proponents of the use of hand-held ultrasound devices to identify and characterize structural cardiac disease have called for its incorporation into educational curricula. Techniques to improve bedside examination skills include repetition, patient-centered teaching conferences, visual display feedback of auscultatory events using Doppler echocardiographic imaging, and simulation-based training.

The evidence base that links the findings from the history and physical examination to the presence, severity, and prognosis of cardiovascular disease has been established most rigorously for coronary artery disease, heart failure, and valvular heart disease. For example, observations regarding heart rate, blood pressure, signs of pulmonary congestion, and the presence of mitral regurgitation (MR) contribute importantly to bedside risk assessment in patients with acute coronary syndromes. Observations from the physical examination in this setting can inform clinical decision-making before the results of cardiac biomarker testing are known. The prognosis of patients with systolic heart failure can be predicted on the basis of the jugular venous pressure (JVP) and the presence or absence of a third heart sound (S<sub>3</sub>). Accurate characterization of cardiac murmurs provides important insight into the natural history of many valvular and congenital heart lesions. Finally, the important role played by the physical examination in enhancing the clinician-patient relationship cannot be overstated.

## THE GENERAL PHYSICAL EXAMINATION

Any examination begins with an assessment of the general appearance of the patient, with notation of age, posture, demeanor, and overall health status. Is the patient in pain or resting quietly, dyspneic or diaphoretic? Does the patient choose to avoid certain body positions to reduce or eliminate pain, as might be the case with suspected acute pericarditis? Are there clues indicating that dyspnea may have a pulmonary cause, such as a barrel chest deformity with an increased anterior-posterior diameter, tachypnea, and pursed-lip breathing? Skin pallor, cyanosis, and jaundice can be appreciated readily and provide additional clues. The appearance of a chronically ill-appearing emaciated patient may suggest the presence of long-standing heart failure or another systemic disorder, such as a malignancy. Various genetic syndromes, often with cardiovascular involvement, can also be recognized easily, such as trisomy 21, Marfan syndrome, and Holt-Oram syndrome. Height and weight should be measured routinely, and both body mass index and body surface area should be calculated. Knowledge of the waist circumference and the waist-to-hip ratio can be used to predict long-term cardiovascular risk. Mental status, level of alertness, and mood should be assessed continuously during the interview and examination.

**Skin** Central cyanosis occurs with significant right-to-left shunting at the level of the heart or lungs, allowing deoxygenated blood to reach the systemic circulation. Peripheral cyanosis or acrocytosis, in contrast, is usually related to reduced extremity blood flow due to small vessel constriction, as seen in patients with severe heart failure, shock, or peripheral vascular disease; it can be aggravated by the use of -adrenergic blockers with unopposed -mediated vasoconstriction. Differential cyanosis refers to isolated cyanosis affecting the lower but not the upper extremities in a patient with a large patent ductus arteriosus (PDA) and secondary pulmonary hypertension with right-to-left shunting at the great vessel level. Telangiectasias on the lips,

## Section 2 Diagnosis of Cardiovascular Disorders

### 239

### Physical Examination of the Cardiovascular System

Patrick T. O’Gara, Joseph Loscalzo



The approach to a patient with known or suspected cardiovascular disease begins with the time-honored traditions of a directed history and a targeted physical examination. The scope of these activities depends on the clinical context at the time of presentation, ranging from an elective ambulatory follow-up visit to a more urgent emergency department encounter. There has been a gradual decline in

**1816** tongue, and mucous membranes, as part of the Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia), resemble spider nevi and can be a source of right-to-left shunting when also present in the lung. Malar telangiectasias also are seen in patients with advanced mitral stenosis (MS) or scleroderma. An unusually tan or bronze discoloration of the skin may suggest hemochromatosis as the cause of the associated systolic heart failure. Jaundice, which may be visible first in the sclerae, has a broad differential diagnosis but, in the appropriate setting, can be consistent with advanced right heart failure and congestive hepatomegaly. Various hereditary lipid disorders sometimes are associated with subcutaneous xanthomas, particularly along the tendon sheaths or over the extensor surfaces of the extremities. Severe hypertriglyceridemia can be associated with eruptive xanthomatosis and lipemia retinalis. Palmar crease xanthomas are specific for type III hyperlipoproteinemia. Pseudoxanthoma elasticum, a disease associated with premature atherosclerosis, is manifested by a leathery, cobblestoned appearance of the skin in the axilla and neck creases and by angiod streaks on funduscopic examination. Extensive lentiginosines have been described in a variety of development delay–cardiovascular syndromes, including Carney's syndrome, which includes multiple atrial myxomas. Cutaneous manifestations of sarcoidosis such as lupus pernio and erythema nodosum may suggest this disease as a cause of an associated dilated cardiomyopathy, especially with heart block, intraventricular conduction delay, or ventricular tachycardia.

**Head and Neck** Dentition and oral hygiene should be assessed in every patient both as a source of potential infection and as an index of general health. A high-arched palate is a feature of Marfan syndrome and other connective tissue disease syndromes. Bifid uvula has been described in patients with Loeys-Dietz syndrome, and orange tonsils are characteristic of Tangier disease. The ocular manifestations of hyperthyroidism have been well described. Many patients with congenital heart disease have associated hypertelorism, low-set ears, or micrognathia. Blue sclerae are a feature of osteogenesis imperfecta. An arcus senilis pattern lacks specificity as an index of coronary heart disease risk. The funduscopic examination is an often-underused method by which to assess the microvasculature, especially among patients with established atherosclerosis, hypertension, or diabetes mellitus. A mydriatic agent may be necessary for optimal visualization. A funduscopic examination should be performed routinely in the assessment of patients with suspected endocarditis and those with a history of acute visual change. Branch retinal artery occlusion or visualization of a Hollenhorst plaque can narrow the differential diagnosis rapidly in the appropriate setting. Relapsing polychondritis may manifest as an inflamed pinna or, in its later stages, as a saddle-nose deformity because of destruction of nasal cartilage; granulomatosis with polyangiitis (Wegener's) can also lead to a saddle-nose deformity.

**Chest** Midline sternotomy, left posterolateral thoracotomy, or infraclavicular scars at the site of pacemaker/defibrillator generator implantation should not be overlooked and may provide the first clue regarding an underlying cardiovascular disorder in patients unable to provide a relevant history. A prominent venous collateral pattern may suggest subclavian or vena caval obstruction. If the head and neck appear dusky and slightly cyanotic and the venous pressure is grossly elevated without visible pulsations, a diagnosis of superior vena cava syndrome should be entertained. Thoracic cage abnormalities have been well described among patients with connective tissue disease syndromes. They include pectus carinatum ("pigeon chest") and pectus excavatum ("funnel chest"). Obstructive lung disease is suggested by a barrel chest deformity, especially with tachypnea, pursed-lip breathing, and use of accessory muscles. The characteristically severe kyphosis and compensatory lumbar, pelvic, and knee flexion of ankylosing spondylitis should prompt careful auscultation for a murmur of aortic regurgitation (AR). Straight back syndrome refers to the loss of the normal kyphosis of the thoracic spine and has been described in patients with mitral valve prolapse (MVP) and its variants. In some patients with cyanotic congenital heart disease, the chest wall appears to be asymmetric, with anterior displacement of the left hemithorax.

The respiratory rate and pattern should be noted during spontaneous breathing, with additional attention to depth, audible wheezing, and stridor. Lung examination can reveal adventitious sounds indicative of pulmonary edema, pneumonia, or pleuritis.

**Abdomen** In some patients with advanced obstructive lung disease, the point of maximal cardiac impulse may be in the epigastrium. The liver is frequently enlarged and tender in patients with chronic heart failure. Systolic pulsations over the liver signify severe tricuspid regurgitation (TR). Splenomegaly may be a feature of infective endocarditis, particularly when symptoms have persisted for weeks or months. Ascites is a nonspecific finding but may be present with advanced chronic right heart failure, constrictive pericarditis, hepatic cirrhosis, or an intraperitoneal malignancy. The finding of an elevated JVP implies a cardiovascular etiology. In nonobese patients, the aorta typically is palpated between the epigastrium and the umbilicus. The sensitivity of palpation for the detection of an abdominal aortic aneurysm (pulsatile and expansile mass) decreases as a function of body size. Because palpation alone is not sufficiently accurate to establish this diagnosis, a screening ultrasound examination is advised when appropriate. The presence of an arterial bruit over the abdomen suggests high-grade atherosclerotic disease, although precise localization is difficult.

**Extremities** The temperature and color of the extremities, the presence of clubbing, arachnodactyly, and pertinent nail findings can be surmised quickly during the examination. Clubbing implies the presence of central right-to-left shunting, although it has also been described in patients with endocarditis. Its appearance can range from cyanosis and softening of the root of the nail bed, to the classic loss of the normal angle between the base of the nail and the skin, to the skeletal and periosteal bony changes of hypertrophic osteoarthropathy, which is seen rarely in patients with advanced lung or liver disease. Patients with the Holt-Oram syndrome have an unopposable, "fingerized" thumb, whereas patients with Marfan syndrome may have arachnodactyly and a positive "wrist" (overlapping of the thumb and fifth finger around the wrist) or "thumb" (protrusion of the thumb beyond the ulnar aspect of the hand when the fingers are clenched over the thumb in a fist) sign. The Janeway lesions of endocarditis are nontender, slightly raised hemorrhages on the palms and soles, whereas Osler's nodes are tender, raised nodules on the pads of the fingers or toes. Splinter hemorrhages are classically identified as linear petechiae in the midposition of the nail bed and should be distinguished from the more common traumatic petechiae, which are seen closer to the distal edge.

Lower extremity or presacral edema in the setting of an elevated JVP defines volume overload and may be a feature of chronic heart failure or constrictive pericarditis. Lower extremity edema in the absence of jugular venous hypertension may be due to profound hypoalbuminemia as seen in nephrotic syndrome or liver failure. Other causes include lymphatic or venous obstruction or, more commonly, venous insufficiency, as would be further suggested by the appearance of varicosities, venous ulcers (typically medial in location), and brownish cutaneous discoloration from hemosiderin deposition (eburnation). Pitting edema can also be seen in patients who use dihydropyridine calcium channel blockers. A Homans sign (posterior calf pain on active dorsiflexion of the foot against resistance) is neither specific nor sensitive for deep venous thrombosis. Muscular atrophy or the absence of hair along an extremity is consistent with severe arterial insufficiency or a primary neuromuscular disorder.

## CARDIOVASCULAR EXAMINATION

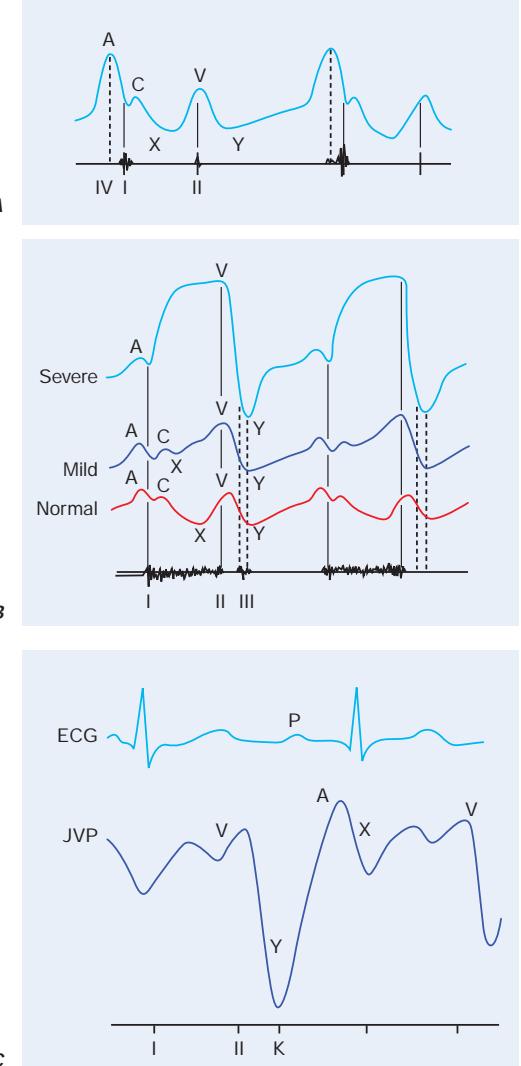
**Jugular Venous Pressure and Waveform** The JVP is the single most important bedside measurement from which to estimate the volume status. The internal jugular vein is preferred because the external jugular vein is valved and not directly in line with the superior vena cava and right atrium. Nevertheless, the external jugular vein has been used to discriminate between high and low central venous pressure (CVP) when tested among medical students, residents, and attending

physicians. Precise estimation of the central venous or right atrial pressure from bedside assessment of the jugular venous waveform has proved difficult. Venous pressure traditionally has been measured as the vertical distance between the top of the jugular venous pulsation and the sternal inflection point (angle of Louis). A distance >4.5 cm at 30° elevation is considered abnormal. However, the actual distance between the mid-right atrium and the angle of Louis varies considerably as a function of both body size and the patient angle at which the assessment is made (30°, 45°, or 60°). The use of the sternal angle as a reference point leads to systematic underestimation of CVP, and this method should be used less for semiquantification than to distinguish a normal from an abnormally elevated CVP. The use of the clavicle may provide an easier reference for standardization. Venous pulsations above this level in the sitting position are clearly abnormal, as the distance between the clavicle and the right atrium is at least 10 cm. The patient should always be placed in the sitting position, with the legs dangling below the bedside, when an elevated pressure is suspected in the semisupine position. It should also be noted that bedside estimates of CVP are made in centimeters of water, but must be converted to millimeters of mercury to provide correlation with accepted hemodynamic norms (1.36 cmH<sub>2</sub>O = 1.0 mmHg).

The venous waveform sometimes can be difficult to distinguish from the carotid pulse, especially during casual inspection. Nevertheless, the venous waveform has several characteristic features, and its individual components can be appreciated in most patients (Fig. 239-1). The arterial pulsation is not easily obliterated with palpation; the venous waveform in patients with sinus rhythm is usually biphasic, while the carotid pulse is monophasic; and the jugular venous pulsation should change with changes in posture or inspiration (unless the venous pressure is quite elevated).

The venous waveform is divided into several distinct peaks. The *a* wave reflects right atrial presystolic contraction and occurs just after the electrocardiographic P wave, preceding the first heart sound (S<sub>1</sub>). A prominent *a* wave is seen in patients with reduced right ventricular compliance; a cannon *a* wave occurs with atrioventricular (AV) dissociation and right atrial contraction against a closed tricuspid valve. In a patient with a wide complex tachycardia, the appreciation of cannon *a* waves in the jugular venous waveform identifies the rhythm as ventricular in origin. The *a* wave is not present with atrial fibrillation. The *x* descent reflects the fall in right atrial pressure after inscription of the *a* wave. The *c* wave, which occurs as the closed tricuspid valve is pushed into the right atrium during early ventricular systole, interrupts this *x* descent and is followed by a further descent. The *v* wave represents atrial filling (atrial diastole) and occurs during ventricular systole. The height of the *v* wave is determined by right atrial compliance as well as the volume of blood returning to the right atrium either antegrade from the cavae or retrograde through an incompetent tricuspid valve. In patients with TR, the *v* wave is accentuated and the subsequent fall in pressure (*y* descent) is rapid. With progressive degrees of TR, the *v* wave merges with the *c* wave, and the right atrial and jugular vein waveforms become "ventricularized." The *y* descent, which follows the peak of the *v* wave, can become prolonged or blunted with obstruction to right ventricular inflow, as may occur with tricuspid stenosis or pericardial tamponade. Normally, the venous pressure should fall by at least 3 mmHg with inspiration. Kussmaul's sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular (LV) systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

Venous hypertension sometimes can be elicited by passive leg elevation or performance of the abdominojugular reflux maneuver. When these signs are positive, a volume-overloaded state with limited compliance of an overly distended or constricted venous system is present. Abdominojugular reflux is produced with firm and consistent pressure over the upper portion of the abdomen, preferably over the right upper quadrant, for >15 s. A positive response is defined by a sustained rise of >3 cm in the JVP during the application of firm abdominal pressure.



**FIGURE 239-1** **A.** Jugular venous pulse wave tracing (top) with heart sounds (bottom) in a patient with reduced right ventricular compliance. The *A* wave represents right atrial presystolic contraction and occurs just after the electrocardiographic P wave and just before the first heart sound (I). In this example, the *A* wave is accentuated and larger than normal due to decreased right ventricular compliance, as also suggested by the right-sided S<sub>1</sub> (IV). The *C* wave may reflect the carotid pulsation in the neck and/or an early systolic increase in right atrial pressure as the right ventricle pushes the closed tricuspid valve into the right atrium. The *x* descent follows the *A* wave just as atrial pressure continues to fall. The *V* wave represents atrial filling during ventricular systole and peaks at the second heart sound (II). The *y* descent corresponds to the fall in right atrial pressure after tricuspid valve opening. **B.** Jugular venous wave forms in mild (middle) and severe (top) tricuspid regurgitation, compared with normal, with phonocardiographic representation of the corresponding heart sounds below. With increasing degrees of tricuspid regurgitation, the waveform becomes "ventricularized." **C.** Electrocardiogram (ECG) (top), jugular venous waveform (JVP) (middle), and heart sounds (bottom) in pericardial constriction. Note the prominent and rapid *y* descent, corresponding in timing to the pericardial knock (K). (Reproduced with permission from J Abrams: *Synopsis of Cardiac Physical Diagnosis*, 2nd ed. Boston, Butterworth Heinemann, 2001.)

The response should be assessed after 10 s of continuous pressure to allow for respiratory artifacts and tensing of the abdominal muscles to subside. Patients must be coached to refrain from breath holding or a Valsalva-like maneuver during the procedure. Performance of the abdominojugular reflux maneuver is useful in predicting a pulmonary artery wedge pressure >15 mmHg in patients with heart failure.

Although the JVP estimates right ventricular filling pressure, it has a predictable relationship with the pulmonary artery wedge pressure.

**1818** In a large study of patients with advanced heart failure, the presence of a right atrial pressure >10 mmHg (as predicted on bedside examination) had a positive value of 88% for the prediction of a pulmonary artery wedge pressure of >22 mmHg. In addition, an elevated JVP has prognostic significance in patients with both symptomatic heart failure and asymptomatic LV systolic dysfunction. The presence of an elevated JVP is associated with a higher risk of subsequent hospitalization for heart failure, death from heart failure, or both.

**Assessment of Blood Pressure** Measurement of blood pressure usually is delegated to a medical assistant but should be repeated by the examining clinician. Accurate measurement depends on body position, arm size, time of measurement, place of measurement, device, device size, technique, and examiner. In general, physician-recorded blood pressures are higher than both nurse-recorded pressures and self-recorded pressures at home. Blood pressure is best measured in the seated position with the arm at the level of the heart and the feet on the floor with the back supported, using an appropriately sized cuff, after 5–10 min of relaxation. When it is measured in the supine position, the arm should be raised to bring it to the level of the mid-right atrium. The length and width of the blood pressure cuff bladder should be 80 and 40% of the arm's circumference, respectively. A common source of error in practice is to use an inappropriately small cuff, resulting in marked overestimation of true blood pressure, or an inappropriately large cuff, resulting in underestimation of true blood pressure. The cuff should be inflated to 30 mmHg above the expected systolic pressure and the pressure released at a rate of 2–3 mmHg/s. Systolic and diastolic pressures are defined by the first and fifth Korotkoff sounds, respectively. Very low (even 0 mmHg) diastolic blood pressures may be recorded in patients with chronic, severe AR or a large arteriovenous fistula because of enhanced diastolic "run-off." In these instances, both the phase IV and phase V Korotkoff sounds should be recorded. Blood pressure is best assessed at the brachial artery level, though it can be measured at the radial, popliteal, or pedal pulse level. In general, systolic pressure increases and diastolic pressure decreases when measured in more distal arteries. Blood pressure should be measured in both arms, and the difference should be <10 mmHg. A blood pressure differential that exceeds this threshold may be associated with atherosclerotic or inflammatory subclavian artery disease, supravalvular aortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures are usually as much as 20 mmHg higher than systolic arm pressures. Greater leg-arm pressure differences are seen in patients with chronic severe AR as well as patients with extensive and calcified lower extremity peripheral arterial disease. The ankle-brachial index (systolic pressure in the dorsalis pedis and/or posterior tibial artery divided by the higher of the two brachial artery pressures) is a powerful predictor of long-term cardiovascular mortality.

The blood pressure measured in an office or hospital setting may not accurately reflect the pressure in other venues. "White coat hypertension" (elevated clinic blood pressure and normal out-of-clinic blood pressure) is defined by at least three separate clinic-based measurements >130/80 mmHg and at least two non-clinic-based measurements <130/80 mmHg in the absence of any evidence of target organ damage. Individuals with white coat hypertension may not benefit from drug therapy, although they may be more likely to develop sustained hypertension over time. Masked hypertension (normal or low clinic blood pressure but elevated out-of-clinic blood pressure) should be suspected when normal or even low blood pressures are recorded in the office in patients with advanced atherosclerotic disease, especially when evidence of target organ damage is present or bruits are audible. Higher systolic blood pressures measured with a 24-h ambulatory blood pressure device are associated with a higher risk of cardiovascular disease and all-cause death independent of blood pressures measured in the outpatient setting.

Orthostatic hypotension is defined by a fall in systolic pressure >20 mmHg or in diastolic pressure >10 mmHg in response to assumption of the upright posture from a supine position within 3 min. There may also be a lack of a compensatory tachycardia, an abnormal response that suggests autonomic insufficiency, as may be seen in patients with

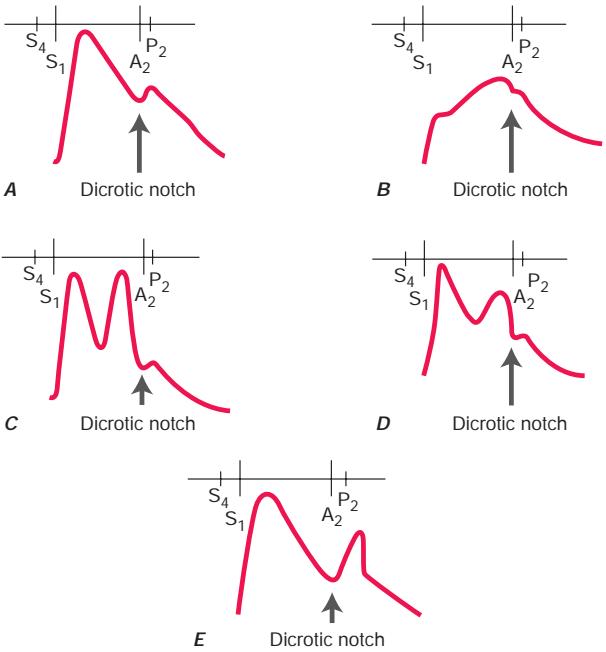
diabetes mellitus or Parkinson's disease. Orthostatic hypotension is a common cause of postural lightheadedness/syncope and should be assessed routinely in patients for whom this diagnosis might pertain. It can be exacerbated by advanced age, dehydration, certain medications, food, deconditioning, and ambient temperature/humidity.

**Arterial Pulse** The carotid artery pulse occurs just after the ascending aortic pulse. The aortic pulse is best appreciated in the epigastrium, just above the level of the umbilicus. Peripheral arterial pulses that should be assessed routinely include the subclavian, brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial. In patients in whom the diagnosis of either temporal arteritis or polymyalgia rheumatica is suspected, the temporal arteries also should be examined. Although one of the two pedal pulses may not be palpable in up to 10% of normal subjects, the pair should be symmetric. The integrity of the arcuate system of the hand is assessed by Allen's test, which is performed routinely before instrumentation of the radial artery. The pulses should be examined for their symmetry, volume, timing, contour, amplitude, and duration. If necessary, simultaneous auscultation of the heart can help identify a delay in the arrival of an arterial pulse. Simultaneous palpation of the radial and femoral pulses may reveal a femoral delay in a patient with upper extremity hypertension and suspected aortic coarctation. The carotid upstrokes should never be examined simultaneously or before listening for a bruit. Light pressure should always be used to avoid precipitation of carotid hypersensitivity syndrome and syncope in a susceptible elderly individual. The arterial pulse usually becomes more rapid and spiking as a function of its distance from the heart, a phenomenon that reflects the muscular status of the more peripheral arteries and the summation of the incident and reflected waves. In general, the character and contour of the arterial pulse depend on the stroke volume, ejection velocity, vascular compliance, and systemic vascular resistance. The pulse examination can be misleading in patients with reduced cardiac output and in those with stiffened arteries from aging, chronic hypertension, or peripheral arterial disease.

The character of the pulse is best appreciated at the carotid level (**Fig. 239-2**). A weak and delayed pulse (*pulsus parvus et tardus*) defines severe aortic stenosis (AS). Some patients with AS may also have a slow, notched, or interrupted upstroke (anacrotic pulse) with a thrill or shudder. With chronic severe AR, by contrast, the carotid upstroke has a sharp rise and rapid fall-off (Corrigan's or water-hammer pulse). Some patients with advanced AR may have a bifid or bisferiens pulse, in which two systolic peaks can be appreciated. A bifid pulse is also described in patients with hypertrophic obstructive cardiomyopathy (HOCM), with inscription of percussion and tidal waves. A bifid pulse is easily appreciated in patients on intraaortic balloon counterpulsation (IABP), in whom the second pulse is diastolic in timing.

*Pulsus paradoxus* refers to a fall in systolic pressure >10 mmHg with inspiration that is seen in patients with pericardial tamponade but also is described in those with massive pulmonary embolism, hemorrhagic shock, severe obstructive lung disease, and tension pneumothorax. Pulsus paradoxus is measured by noting the difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each heartbeat, independent of the respiratory phase. Between these two pressures, the Korotkoff sounds are heard only intermittently and during expiration. The cuff pressure must be decreased slowly to appreciate the finding. It can be difficult to measure pulsus paradoxus in patients with tachycardia, atrial fibrillation, or tachypnea. A pulsus paradoxus may be palpable at the brachial artery or femoral artery level when the pressure difference exceeds 15 mmHg. This inspiratory fall in systolic pressure is an exaggerated consequence of interventricular dependence.

*Pulsus alternans*, in contrast, is defined by beat-to-beat variability of pulse amplitude. It is present only when every other phase I Korotkoff sound is audible as the cuff pressure is lowered slowly, typically in a patient with a regular heart rhythm and independent of the respiratory cycle. Pulsus alternans is seen in patients with severe LV systolic dysfunction and is thought to be due to cyclic changes in intracellular



**FIGURE 239-2** Schematic diagrams of the configurational changes in carotid pulse and their differential diagnoses. Heart sounds are also illustrated. **A.** Normal.  $S_4$ , fourth heart sound;  $S_1$ , first heart sound;  $A_2$ , aortic component of second heart sound;  $P_2$ , pulmonic component of second heart sound. **B.** Aortic stenosis. Anacrotic pulse with slow upstroke to a reduced peak. **C.** Bisferiens pulse with two peaks in systole. This pulse is rarely appreciated in patients with severe aortic regurgitation. **D.** Bisferiens pulse in hypertrophic obstructive cardiomyopathy. There is a rapid upstroke to the first peak (percussion wave) and a slower rise to the second peak (tidal wave). **E.** Dicrotic pulse with peaks in systole and diastole. This waveform may be seen in patients with sepsis or during intraaortic balloon counterpulsation with inflation just after the dicrotic notch. (Reproduced with permission from K Chatterjee, W Parmley [eds]: *Cardiology: An Illustrated Text/Reference*. Philadelphia, Gower Medical Publishers, 1991.)

calcium and action potential duration. When pulsus alternans is associated with electrocardiographic T-wave alternans, the risk for an arrhythmic event appears to be increased.

Ascending aortic aneurysms can rarely be appreciated as a pulsatile mass in the right parasternal area. Appreciation of a prominent abdominal aortic pulse should prompt noninvasive imaging with ultrasound or computed tomography for better characterization. Femoral and/or popliteal artery aneurysms should be sought in patients with abdominal aortic aneurysm disease.

The level of a claudication-producing arterial obstruction can often be identified on physical examination (Fig. 239-3). For example, in a patient with calf claudication, a decrease in pulse amplitude between the common femoral and popliteal arteries will localize the obstruction to the level of the superficial femoral artery, although inflow obstruction above the level of the common femoral artery may coexist. Auscultation for carotid, subclavian, abdominal aortic, and femoral artery bruits should be routine. However, the correlation between the presence of a bruit and the degree of vascular obstruction is poor. A cervical bruit is a weak indicator of the degree of carotid artery stenosis; the absence of a bruit does not exclude the presence of significant luminal obstruction. If a bruit extends into diastole or if a thrill is present, the obstruction is usually severe. Another cause of an arterial bruit is an arteriovenous fistula with enhanced flow.

The likelihood of significant lower extremity peripheral arterial disease increases with typical symptoms of claudication, cool skin, abnormalities on pulse examination, or the presence of a vascular bruit. Abnormal pulse oximetry (a >2% difference between finger and toe oxygen saturation) can be used to detect lower extremity peripheral arterial disease and is comparable in its performance characteristics to the ankle-brachial index.

**Inspection and Palpation of the Heart** The LV apex beat may be visible in the midclavicular line at the fifth intercostal space in thin-chested adults. Visible pulsations anywhere other than this expected location are abnormal. The left anterior chest wall may heave in patients with an enlarged or hyperdynamic left or right ventricle. As noted previously, a visible right upper parasternal pulsation may be suggestive of ascending aortic aneurysm disease. In thin, tall patients and patients with advanced obstructive lung disease and flattened diaphragms, the cardiac impulse may be visible in the epigastrium and should be distinguished from a pulsatile liver edge.

Palpation of the heart begins with the patient in the supine position at 30° and can be enhanced by placing the patient in the left lateral decubitus position. The normal LV impulse is <2 cm in diameter and moves quickly away from the fingers; it is better appreciated at end expiration, with the heart closer to the anterior chest wall. Characteristics such as size, amplitude, and rate of force development should be noted.

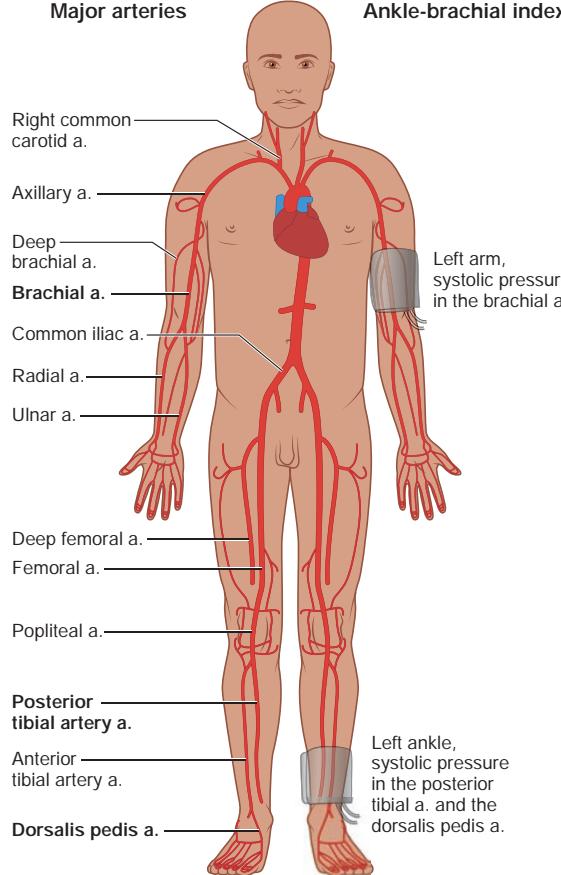
Enlargement of the LV cavity is manifested by a leftward and downward displacement of an enlarged apex beat. A sustained apex beat is a sign of pressure overload, such as that which may be present in patients with AS or chronic hypertension. A palpable presystolic impulse corresponds to the fourth heart sound ( $S_4$ ) and is indicative of reduced LV compliance and the forceful contribution of atrial contraction to ventricular filling. A palpable third sound ( $S_3$ ), which is indicative of a rapid early filling wave in patients with heart failure, may be present even when the gallop itself is not audible. A large LV aneurysm may sometimes be palpable as an ectopic impulse, discrete from the apex beat. HOCM may very rarely cause a triple cadence beat at the apex with contributions from a palpable  $S_4$  and the two components of the bisferiens systolic pulse.

Right ventricular pressure or volume overload may create a sternal lift. Signs of either TR (cv waves in the jugular venous pulse) and/or pulmonary arterial hypertension (a loud single or palpable  $P_2$ ) would be confirmatory. The right ventricle can enlarge to the extent that left-sided events are obscured. A zone of retraction between the right ventricular and LV impulses sometimes can be appreciated in patients with right ventricle pressure or volume overload when they are placed in the left lateral decubitus position. Systolic and diastolic thrills signify turbulent and high-velocity blood flow. Their locations help identify the origin of heart murmurs.

## CARDIAC AUSCULTATION

**Heart Sounds** Ventricular systole is defined by the interval between the first ( $S_1$ ) and second ( $S_2$ ) heart sounds (Fig. 239-4). The first heart sound ( $S_1$ ) includes mitral and tricuspid valve closure. Normal splitting can be appreciated in young patients and those with right bundle branch block, in whom tricuspid valve closure is relatively delayed. The intensity of  $S_1$  is determined by the distance over which the anterior leaflet of the mitral valve must travel to return to its annular plane, leaflet mobility, LV contractility, and the PR interval.  $S_1$  is classically loud in the early phases of rheumatic MS and in patients with hyperkinetic circulatory states or short PR intervals.  $S_1$  becomes softer in the later stages of MS when the leaflets are rigid and calcified, after exposure to -adrenergic receptor blockers, with long PR intervals, and with LV contractile dysfunction. The intensity of heart sounds, however, can be reduced by any process that increases the distance between the stethoscope and the responsible cardiac event, including mechanical ventilation, obstructive lung disease, obesity, pneumothorax, and a pericardial effusion.

Aortic and pulmonic valve closure constitutes the second heart sound ( $S_2$ ). With normal or physiologic splitting, the  $A_2-P_2$  interval increases with inspiration and narrows during expiration. This physiologic interval will widen with right bundle branch block because of the further delay in pulmonic valve closure and in patients with severe MR because of the premature closure of the aortic valve. An unusually narrowly split or even a singular  $S_2$  is a feature of pulmonary arterial hypertension. Fixed splitting of  $S_2$ , in which the  $A_2-P_2$  interval is wide and does not change during the respiratory cycle, occurs in patients with a



**FIGURE 239-3** *A.* Anatomy of the major arteries of the leg. *B.* Measurement of the ankle systolic pressure. The ankle-brachial index (ABI) is calculated by dividing the lower of the two ankle pressures (i.e., the dorsalis pedis or posterior tibia) by the higher of the two arm pressures (i.e., left or right arm). Left and right ABIs should be recorded. (Adapted from NA Khan et al: Does the clinical examination predict lower extremity peripheral arterial disease?. JAMA 295:536, 2006.)

secundum atrial septal defect (ASD). Reversed or paradoxical splitting refers to a pathologic delay in aortic valve closure, such as that which occurs in patients with left bundle branch block, right ventricular pacing, severe AS, HOCM, and acute myocardial ischemia. With reversed or paradoxical splitting, the individual components of  $S_2$  are audible at end expiration, and their interval narrows with inspiration, the opposite of what would be expected under normal physiologic conditions.  $P_2$  is considered loud when its intensity exceeds that of  $A_2$  at the base, when it can be palpated in the area of the proximal main pulmonary artery (second left interspace), or when both components of  $S_2$  can be appreciated at the lower left sternal border or apex. The intensity of  $A_2$  and  $P_2$  decreases with AS and pulmonic stenosis (PS), respectively. In these conditions, a single  $S_2$  may result.

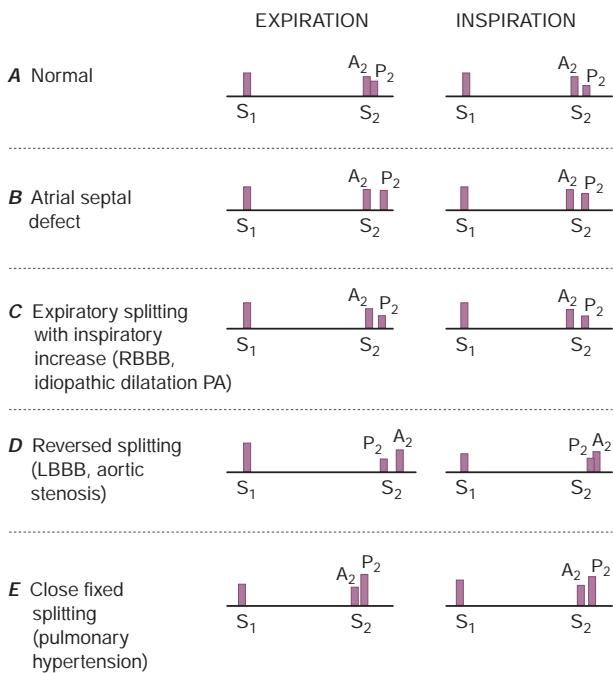
**Systolic Sounds** An ejection sound is a high-pitched early systolic sound that corresponds in timing to the upstroke of the carotid pulse. It usually is associated with congenital bicuspid aortic or pulmonic valve disease; however, ejection sounds are also sometimes audible in patients with isolated aortic or pulmonary root dilation and normal semilunar valves. The ejection sound that accompanies bicuspid aortic valve disease becomes softer and then inaudible as the valve calcifies and becomes more rigid. The ejection sound that accompanies PS moves closer to the first heart sound as the severity of the stenosis increases. In addition, the pulmonic ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. Ejection sounds are often heard more easily at the lower left sternal border than they are at the base. Nonejection sounds (clicks), which occur after the onset of the carotid upstroke, are related to MVP and may be single or multiple. The nonejection click may introduce a murmur.

This click-murmur complex will move away from the first heart sound with maneuvers that increase ventricular preload, such as squatting. On standing, the click and murmur move closer to  $S_1$ .

**Diastolic Sounds** The high-pitched opening snap (OS) of MS occurs after a very short interval after the second heart sound. The  $A_2$ -OS interval is inversely proportional to the height of the left atrial-left ventricular diastolic pressure gradient. The intensity of both  $S_1$  and the OS of MS decreases with progressive calcification and rigidity of the anterior mitral leaflets. The pericardial knock (PK) is also high-pitched and occurs slightly later than the OS, corresponding in timing to the abrupt cessation of ventricular expansion after tricuspid valve opening and to an exaggerated y descent seen in the jugular venous waveform in patients with constrictive pericarditis. A tumor plop is a lower-pitched sound that rarely can be heard in patients with atrial myxoma. It may be appreciated only in certain positions and arises from the diastolic prolapse of the tumor across the mitral valve.

The third heart sound ( $S_3$ ) occurs during the rapid filling phase of ventricular diastole. It can be a normal finding in children, adolescents, and young adults; however, in older patients, it signifies heart failure. A left-sided  $S_3$  is a low-pitched sound best heard over the LV apex. A right-sided  $S_3$  is usually better heard over the lower left sternal border and becomes louder with inspiration. A left-sided  $S_3$  in patients with chronic heart failure is predictive of cardiovascular morbidity and mortality. Interestingly, an  $S_3$  is equally prevalent among heart failure patients with preserved and reduced LV ejection fraction.

The fourth heart sound ( $S_4$ ) occurs during the atrial filling phase of ventricular diastole and indicates LV presystolic expansion. An  $S_4$  is more common among patients who derive significant benefit from the



**FIGURE 239-4** Heart sounds. **A.** Normal. S<sub>1</sub>, first heart sound; S<sub>2</sub>, second heart sound; A<sub>2</sub>, aortic component of the second heart sound; P<sub>2</sub>, pulmonic component of the second heart sound. **B.** Atrial septal defect with fixed splitting of S<sub>2</sub>. **C.** Physiologic but wide splitting of S<sub>2</sub> with right bundle branch block (RBBB). PA, pulmonary artery. **D.** Reversed or paradoxical splitting of S<sub>2</sub> with left bundle branch block (LBBB). **E.** Narrow splitting of S<sub>2</sub> with pulmonary hypertension. (Reprinted by permission from Springer Nature: Springer-Verlag, *Diagnosis of Heart Disease* by NO Fowler, 1991.)

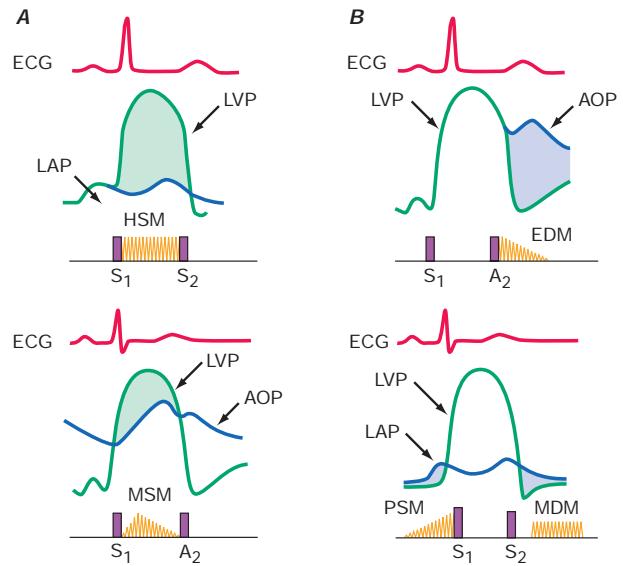
atrial contribution to ventricular filling, such as those with chronic LV hypertrophy or active myocardial ischemia. An S<sub>4</sub> is not present with atrial fibrillation.

**Cardiac Murmurs** Heart murmurs result from audible vibrations that are caused by increased turbulence and are defined by their timing within the cardiac cycle. Not all murmurs are indicative of structural heart disease, and the accurate identification of a benign or functional systolic murmur often can obviate the need for additional testing in healthy subjects. The duration, frequency, configuration, and intensity of a heart murmur are dictated by the magnitude, variability, and duration of the responsible pressure difference between two cardiac chambers, the two ventricles, or the ventricles and their respective great arteries. The intensity of a heart murmur is graded on a scale of 1 to 6; a thrill is present with murmurs of grade 4 or greater intensity. Other attributes of the murmur that aid in its accurate identification include its location, radiation, and response to bedside maneuvers. Although clinicians can detect and correctly identify heart murmurs with only fair reliability, a careful and complete bedside examination usually can identify individuals with valvular heart disease for whom transthoracic echocardiography and clinical follow-up are indicated and exclude subjects for whom no further evaluation is necessary.

Systolic murmurs can be early, mid, late, or holosystolic in timing (Fig. 239-5). Acute severe MR results in a decrescendo early systolic murmur, the characteristics of which are related to the progressive attenuation of the LV to left atrial pressure gradient during systole because of the steep and rapid rise in left atrial pressure in this context. Severe MR associated with posterior leaflet prolapse or flail radiates anteriorly and to the base, where it can be confused with the murmur of AS. MR that is due to anterior leaflet involvement radiates posteriorly and to the axilla. With acute TR in patients with normal pulmonary artery pressures, an early systolic murmur that may increase in intensity with inspiration may be heard at the left lower sternal border, with regurgitant *cv* waves visible in the jugular venous pulse.

A midsystolic murmur begins after S<sub>1</sub> and ends before S<sub>2</sub>; it is typically crescendo-decrescendo in configuration. AS is the most common cause of a midsystolic murmur in an adult. It is often difficult to estimate the severity of the valve lesion on the basis of the physical examination findings, especially in older hypertensive patients with stiffened carotid arteries or patients with low cardiac output in whom the intensity of the systolic heart murmur is misleadingly soft. Examination findings consistent with severe AS would include *parvus et tardus* carotid upstrokes, a late-peaking grade 3 or greater midsystolic murmur, a soft A<sub>2</sub>, a sustained LV apical impulse, and an S<sub>4</sub>. It is sometimes difficult to distinguish aortic sclerosis from more advanced degrees of valve stenosis. The former is defined by focal thickening and calcification of the aortic valve leaflets that is not severe enough to result in obstruction. These valve changes are associated with a Doppler jet velocity across the aortic valve of 2.5 m/s or less. Patients with aortic sclerosis can have grade 2 or 3 midsystolic murmurs identical in their acoustic characteristics to the murmurs heard in patients with more advanced degrees of AS. Other causes of a midsystolic heart murmur include pulmonic valve stenosis (with or without an ejection sound), HOCM, increased pulmonary blood flow in patients with a large ASD and left-to-right shunting, and several states associated with accelerated blood flow in the absence of structural heart disease, such as fever, thyrotoxicosis, pregnancy, anemia, and normal childhood/adolescence.

The murmur of HOCM has features of both obstruction to LV outflow and MR, as would be expected from knowledge of the pathophysiology of this condition. The systolic murmur of HOCM usually can be distinguished from other causes on the basis of its response to bedside maneuvers, including Valsalva, passive leg raising, and standing/squatting. In general, maneuvers that decrease LV preload (or increase LV contractility) will cause the murmur to intensify, whereas maneuvers that increase LV preload or afterload will cause a decrease in the intensity of the murmur. Accordingly, the systolic murmur of HOCM becomes louder during the strain phase of the Valsalva maneuver and after standing quickly from a squatting position. The murmur becomes



**FIGURE 239-5** **A. Top.** Graphic representation of the systolic pressure difference (green shaded area) between left ventricle and left atrium with phonocardiographic recording of a holosystolic murmur (HSM) indicative of mitral regurgitation. ECG, electrocardiogram; LAP, left atrial pressure; LVP, left ventricular pressure; S<sub>1</sub>, first heart sound; S<sub>2</sub>, second heart sound. **B. Top.** Graphic representation of the systolic pressure gradient (green shaded area) between left ventricle and aorta in patient with aortic stenosis. A midsystolic murmur (MSM) with a crescendo-decrescendo configuration is recorded. AOP, aortic pressure. **B. Bottom.** Graphic representation of the diastolic pressure difference between the aorta and left ventricle (blue shaded area) in a patient with aortic regurgitation, resulting in a decrescendo, early diastolic murmur (EDM) beginning with A<sub>2</sub>. **Bottom.** Graphic representation of the diastolic left atrial-left ventricular gradient (blue areas) in a patient with mitral stenosis with a mid-diastolic murmur (MDM) and late presystolic murmurs (PSM).

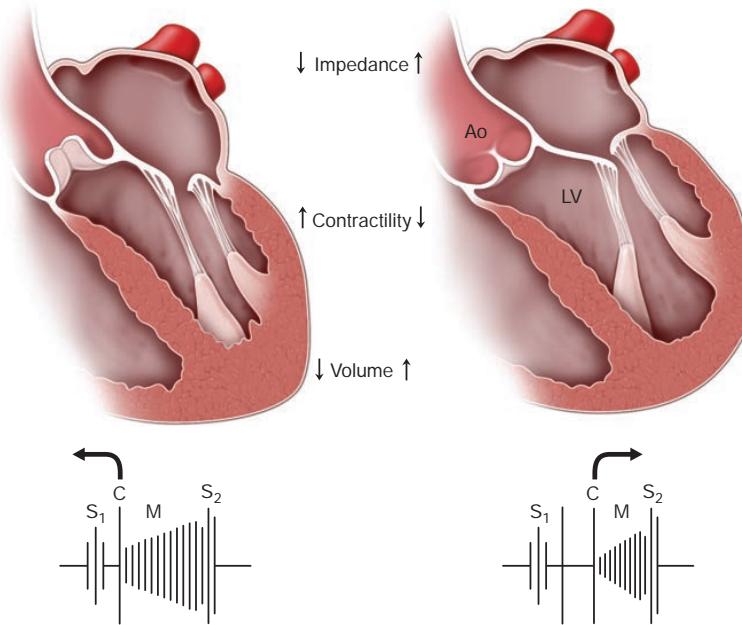
softer with passive leg raising and when squatting. The murmur of AS is typically loudest in the second right interspace with radiation into the carotids, whereas the murmur of HOCM is best heard between the lower left sternal border and the apex. The murmur of PS is best heard in the second left interspace. The midsystolic murmur associated with enhanced pulmonic blood flow in the setting of a large ASD is usually loudest at the mid-left sternal border.

A late systolic murmur, heard best at the apex, indicates MVP. As previously noted, the murmur may or may not be introduced by a nonejection click. Differential radiation of the murmur, as previously described, may help identify the specific leaflet involved by the myxomatous process. The click-murmur complex behaves in a manner directionally similar to that demonstrated by the murmur of HOCM during the Valsalva and stand/squat maneuvers (Fig. 239-6). The murmur of MVP can be identified by the accompanying nonejection click.

Holosystolic murmurs are plateau in configuration and reflect a continuous and wide pressure gradient between the left ventricle and left atrium with chronic MR, the left ventricle and right ventricle with a ventricular septal defect (VSD), and the right ventricle and right atrium with TR. In contrast to acute MR, in chronic MR, the left atrium is enlarged and its compliance is normal or increased to the extent that there is little if any further increase in left atrial pressure from any increase in regurgitant volume. The murmur of MR is best heard over the cardiac apex. The intensity of the murmur increases with maneuvers that increase LV afterload, such as sustained hand grip. The murmur of a VSD (without significant pulmonary hypertension) is holosystolic and loudest at the mid-left sternal border, where a thrill is usually present. The murmur of TR is loudest at the lower left sternal border, increases in intensity with inspiration (Carvallo's sign), and is accompanied by visible *c* waves in the jugular venous wave form and, on occasion, by pulsatile hepatomegaly.

**Diastolic Murmurs** In contrast to some systolic murmurs, diastolic heart murmurs always signify structural heart disease (Fig. 239-5). The murmur associated with acute, severe AR is relatively soft and of short duration because of the rapid rise in LV diastolic pressure and the progressive diminution of the aortic-LV diastolic pressure gradient. In contrast, the murmur of chronic severe AR is classically heard as a decrescendo, blowing diastolic murmur along the left sternal border in patients with primary valve pathology and sometimes along the right sternal border in patients with primary aortic root pathology. With chronic AR, the pulse pressure is wide and the arterial pulses are bounding in character. These signs of significant diastolic run-off are often absent in the acute phase. The murmur of pulmonic regurgitation is also heard along the left sternal border. It is most commonly due to pulmonary hypertension and enlargement of the annulus of the pulmonic valve.  $S_2$  is single and loud and may be palpable. There is a right ventricular/parasternal lift that is indicative of chronic right ventricular pressure overload. A less impressive murmur of PR is present after repair of tetralogy of Fallot or pulmonic valve atresia. In this postoperative setting, the murmur is softer and lower-pitched, and the severity of the accompanying pulmonic regurgitation can be underestimated significantly.

MS is the classic cause of a mid- to late diastolic murmur, which is best heard over the apex in the left lateral decubitus position, is low-pitched or rumbling, and is introduced by an OS in the early stages of the rheumatic disease process. Presystolic accentuation refers to an increase in the intensity of the murmur just before the first heart sound and occurs in patients with sinus rhythm. It is absent in patients with



**FIGURE 239-6** Behavior of the click (C) and murmur (M) of mitral valve prolapse with changes in loading (volume, impedance) and contractility.  $S_1$ , first heart sound;  $S_2$ , second heart sound. With standing (left side of figure), volume and impedance decrease, as a result of which the click and murmur move closer to  $S_1$ . With squatting (right), the click and murmur move away from  $S_1$ , due to the increases in left ventricular volume and impedance (afterload). Ao, aorta; LV, left ventricle. (Adapted from RA O'Rourke, MH Crawford: Curr Prob Cardiol 1:9, 1976.)

atrial fibrillation. The auscultatory findings in patients with rheumatic tricuspid stenosis typically are obscured by left-sided events, although they are similar in nature to those described in patients with MS. "Functional" mitral or tricuspid stenosis refers to the generation of mid-diastolic murmurs that are created by increased and accelerated transvalvular diastolic flow, even in the absence of valvular obstruction, in the setting of severe MR, severe TR, or a large ASD with left-to-right shunting. The Austin Flint murmur of chronic severe AR is a low-pitched mid- to late apical diastolic murmur that sometimes can be confused with MS. The Austin Flint murmur typically decreases in intensity after exposure to vasodilators, whereas the murmur of MS may be accompanied by an OS and also may increase in intensity after vasodilators because of the associated increase in cardiac output. Unusual causes of a mid-diastolic murmur include atrial myxoma, complete heart block, and acute rheumatic mitral valvulitis.

**Continuous Murmur** A continuous murmur is predicated on a pressure gradient that persists between two cardiac chambers or blood vessels across systole and diastole. The murmurs typically begin in systole, envelop the second heart sound ( $S_2$ ), and continue through some portion of diastole. They can often be difficult to distinguish from individual systolic and diastolic murmurs in patients with mixed valvular heart disease. The classic example of a continuous murmur is that associated with a PDA, which usually is heard in the second or third interspace at a slight distance from the sternal border. Other causes of a continuous murmur include a ruptured sinus of Valsalva aneurysm with creation of an aortic-right atrial or right ventricular fistula, a coronary or great vessel arteriovenous fistula, and an arteriovenous fistula constructed to provide dialysis access. There are two types of benign continuous murmurs. The cervical venous hum is heard in children or adolescents in the supraclavicular fossa. It can be obliterated with firm pressure applied to the diaphragm of the stethoscope, especially when the subject turns his or her head toward the examiner. The mammary souffle of pregnancy relates to enhanced arterial blood flow through engorged breasts. The diastolic component of the murmur can be obliterated with firm pressure over the stethoscope.

**TABLE 239-1 Effects of Physiologic Interventions on the Intensity of Heart Murmurs and Sounds****Respiration**

Right-sided murmurs and sounds generally increase with inspiration, except for the PES. Left-sided murmurs and sounds are usually louder during expiration.

**Valsalva Maneuver**

Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HOCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than do left-sided murmurs.

**After VPB or AF**

Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle after a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation do not change or become shorter (MVP).

**Positional Changes**

With **standing**, most murmurs diminish, with two exceptions being the murmur of HOCM, which becomes louder, and that of MVP, which lengthens and often intensifies. With **squatting**, most murmurs become louder, but those of HOCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results.

**Exercise**

Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (hand grip) exercise. Murmurs of MR, VSD, and AR also increase with hand grip exercise. However, the murmur of HOCM often decreases with nearly maximum hand grip exercise. Left-sided S<sub>4</sub> and S<sub>5</sub> sounds are often accentuated by exercise, particularly when due to ischemic heart disease.

**Abbreviations:** AF, atrial fibrillation; AR, aortic regurgitation; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PES, pulmonic ejection sound; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

**Dynamic Auscultation** Diagnostic accuracy can be enhanced by the performance of simple bedside maneuvers to identify heart murmurs and characterize their significance (**Table 239-1**). Except for the pulmonic ejection sound, right-sided events increase in intensity with inspiration and decrease with expiration; left-sided events behave oppositely (100% sensitivity, 88% specificity). As previously noted, the intensity of the murmurs associated with MR, VSD, and AR will increase in response to maneuvers that increase LV afterload, such as hand grip and vasopressors. The intensity of these murmurs will decrease after exposure to vasodilating agents. Squatting is associated with an abrupt increase in LV preload and afterload, whereas rapid standing results in a sudden decrease in preload. In patients with MVP, the click and murmur move away from the first heart sound with squatting because of the delay in onset of leaflet prolapse at higher ventricular volumes. With rapid standing, however, the click and murmur move closer to the first heart sound as prolapse occurs earlier in systole at a smaller chamber dimension. The murmur of HOCM behaves similarly, becoming softer and shorter with squatting (95% sensitivity, 85% specificity) and longer and louder on rapid standing (95% sensitivity, 84% specificity). A change in the intensity of a systolic murmur in the first beat after a premature beat or in the beat after a long cycle length in patients with atrial fibrillation suggests valvular AS rather than MR, particularly in an older patient in whom the murmur of the AS may be well transmitted to the apex (Gallavardin effect). Of note, however, the systolic murmur of HOCM also increases in intensity in the beat after a premature beat. This increase in intensity of any LV outflow murmur in the beat after a premature beat relates to the combined effects of enhanced LV filling (from the longer diastolic period) and postextrasystolic potentiation of LV contractile function. In either instance, forward flow will accelerate, causing an increase in the gradient across the LV outflow tract (dynamic or fixed) and a louder systolic murmur. In contrast, the intensity of the murmur of MR does not change in a postpremature beat, because there is relatively little change in the nearly constant LV to left atrial pressure gradient or

further alteration in mitral valve flow. Bedside exercise can sometimes be performed to increase cardiac output and, secondarily, the intensity of both systolic and diastolic heart murmurs. Most left-sided heart murmurs decrease in intensity and duration during the strain phase of the Valsalva maneuver. The murmurs associated with MVP and HOCM are the two notable exceptions. The Valsalva maneuver also can be used to assess the integrity of the heart and vasculature in the setting of advanced heart failure.

**Prosthetic Heart Valves** The first clue that prosthetic valve dysfunction may contribute to recurrent symptoms is frequently a change in the quality of the heart sounds or the appearance of a new murmur. The heart sounds with a bioprosthetic valve resemble those generated by native valves. A mitral bioprosthesis usually is associated with a grade 1 to 2 midsystolic murmur along the left sternal border (created by turbulence across the valve struts as they project into the LV outflow tract) as well as by a soft mid-diastolic murmur that occurs with normal LV filling. This diastolic murmur often can be heard only in the left lateral decubitus position and after exercise. A high-pitched or holosystolic apical murmur is indicative of pathologic MR due to a paravalvular leak and/or intra-annular bioprosthetic regurgitation from leaflet degeneration, for which diagnostic noninvasive imaging is indicated. Clinical deterioration can occur rapidly after the first expression of mitral bioprosthetic valve failure. A tissue valve in the aortic position is always associated with a grade 1 to 3 midsystolic murmur at the base or just below the suprasternal notch. A diastolic murmur of AR is abnormal in any circumstance. Mechanical valve dysfunction may first be suggested by a decrease in the intensity of either the opening or the closing sound. A high-pitched apical systolic murmur in patients with a mechanical mitral prosthesis and a diastolic decrescendo murmur in patients with a mechanical aortic prosthesis indicate paravalvular regurgitation. Patients with prosthetic valve thrombosis may present clinically with signs of shock, muffled heart sounds, and soft murmurs.

**Pericardial Disease** A pericardial friction rub is nearly 100% specific for the diagnosis of acute pericarditis, although the sensitivity of this finding is not nearly as high, because the rub may come and go over the course of an acute illness or be very difficult to elicit. The rub is heard as a leathery or scratchy three-component or two-component sound, although it may be monophasic. Classically, the three components are ventricular systole, rapid early diastolic filling, and late presystolic filling after atrial contraction in patients in sinus rhythm. It is necessary to listen to the heart in several positions. Additional clues to the presence of acute pericarditis may be present from the history and 12-lead electrocardiogram. The rub typically disappears as the volume of any pericardial effusion increases. Pericardial tamponade can be diagnosed with a sensitivity of 98%, a specificity of 83%, and a positive likelihood ratio of 5.9 (95% confidence interval 2.4–14) by a pulsus paradoxus that exceeds 12 mmHg in a patient with a large pericardial effusion.

The findings on physical examination are integrated with the symptoms previously elicited with a careful history to construct an appropriate differential diagnosis and proceed with indicated imaging and laboratory assessment. The physical examination is an irreplaceable component of the diagnostic algorithm and, in selected patients, can inform prognosis. Educational efforts to improve clinician competence eventually may result in cost saving, particularly if the indications for imaging can be influenced by the examination findings.

**FURTHER READING**

Drazner MH et al: Value of clinician assessment of hemodynamics in advanced heart failure: The ESCAPE trial. *Circ Heart Fail* 1:170, 2008.

Fanaroff AC et al: Does this patient with chest pain have acute coronary syndrome? The Rational Clinical Examination Systematic Review. *JAMA* 314:1955, 2015.

Fang JC, O'Gara PT: The history and physical examination. An evidence-based approach, in *Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine*, 11th ed, Zipes DP et al (eds). Philadelphia, Elsevier/Saunders, 2019, pp 83–101.



An electrocardiogram (ECG or EKG) is a graphical representation of electrical activity generated by the heart. The signals, detected by means of metal electrodes attached to the extremities and chest wall, are amplified and recorded by the *electrocardiograph* device. ECG leads (derivations) are configured to display the instantaneous differences in potential between specific pairs of electrodes. The utility of the ECG derives from its immediate availability as a noninvasive, inexpensive, and highly versatile test. In addition to its use in detecting arrhythmias and myocardial ischemia, it may reveal findings related to life-threatening metabolic disturbances or to increased susceptibility to sudden cardiac arrest (see also Chaps. 306 and 408).

### ELECTROPHYSIOLOGIC BACKGROUND

Depolarization of the heart is the initiating event for cardiac contraction. The electric currents that spread through the heart are produced by three components: cardiac pacemaker cells, specialized conduction tissue, and the heart muscle itself. The ECG records only the depolarization (stimulation) and repolarization (recovery) potentials generated by the “working” atrial and ventricular myocardium (see also Chaps. 244 and 246).

The stimulus initiating the normal heartbeat originates in the *sinoatrial (SA) node* (Fig. 240-1), which possesses spontaneous automaticity. Spread of the depolarization wave through the right and left atria induces contraction of these chambers. Next, the impulse stimulates specialized conduction tissues in the atrioventricular (AV) nodal and His-bundle areas; together, these two regions constitute the AV junction. The bundle of His branches into two main divisions, the right and left bundles, which rapidly transmit depolarization wavefronts in a synchronous way to the right and left ventricular myocardium by way of the Purkinje fibers. The main left bundle fans out into left anterior and left posterior fascicle subdivisions. The depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering coordinated ventricular contraction. Since the cardiac depolarization and repolarization waves have directions and magnitudes, they can be represented by vectors.

### ECG WAVEFORMS AND INTERVALS

The ECG waveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization (Fig. 240-2). The QRS complex represents ventricular depolarization, and the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular

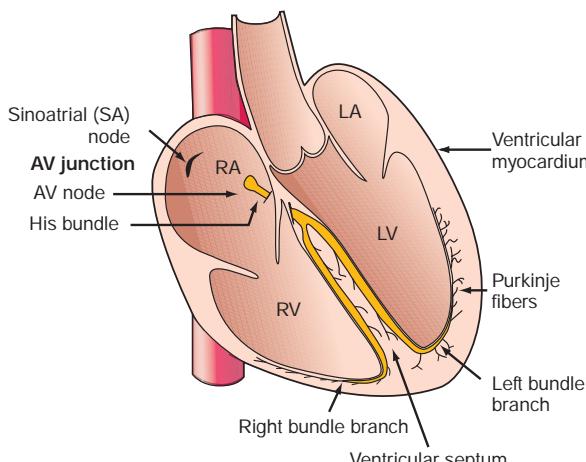


FIGURE 240-1 Schematic of the cardiac conduction system. AV, atrioventricular; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

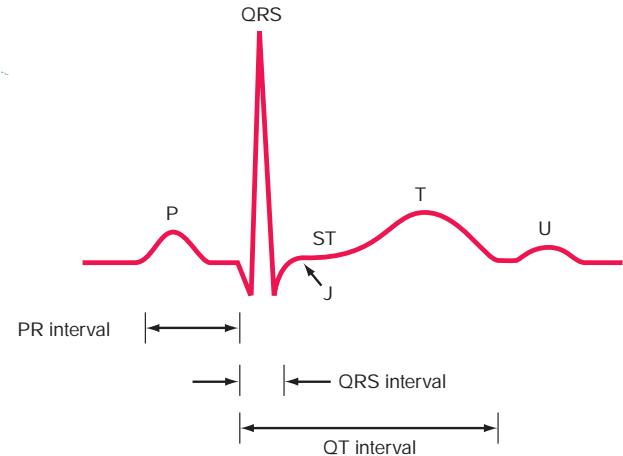
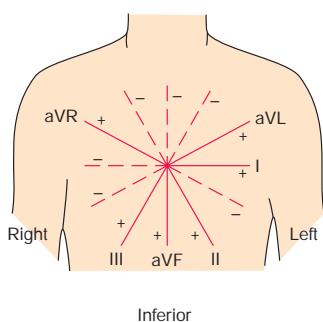
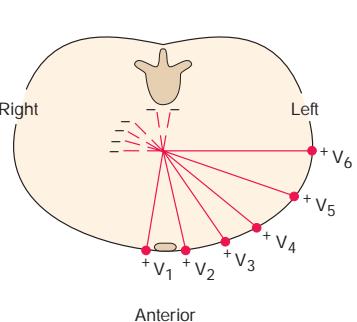


FIGURE 240-2 Basic ECG waveforms and intervals. Not shown is the RR interval, the time between consecutive QRS complexes.

repolarization. The J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization waveforms (ST-T<sub>a</sub>) are usually of too low in amplitude to be detected, but they may become apparent in acute pericarditis, atrial infarction, and AV heart block.

The QRS-T waveforms of the surface ECG correspond in a general way with the different phases of simultaneously obtained ventricular *action potentials*, the intracellular recordings from single myocardial fibers (Chap. 244). The rapid upstroke (phase 0) of the action potential corresponds to the onset of QRS. The plateau (phase 2) corresponds to the isoelectric ST segment, and active repolarization (phase 3) corresponds to the inscription of the T wave. Factors that decrease the slope of phase 0 by impairing the influx of Na<sup>+</sup> (e.g., hyperkalemia and drugs such as flecainide) tend to increase QRS duration. Conditions that prolong phase 2 or 3 (amiodarone, hypocalcemia) increase the QT interval. In contrast, factors (e.g., hypercalcemia, digoxin) associated with shortening of ventricular repolarization duration shorten the QT. The hereditary short QT syndrome and its relationship to sudden cardiac arrest are discussed in Chap. 255.

The ECG is usually recorded on graph paper divided into 1-mm<sup>2</sup> gridlike boxes. When the recording speed is 25 mm/s, the smallest (1 mm) horizontal divisions correspond to 40 ms (0.04 s), with heavier lines at intervals of 200 ms (0.20 s). Vertically, the ECG graph measures the amplitude of a specific wave or deflection (1 mV = 10 mm with standard calibration; the voltage criteria for hypertrophy mentioned below are given in millimeters). There are four major sets of ECG intervals: RR, PR, QRS, and QT/QT<sub>c</sub> (Fig. 240-2). The instantaneous heart rate (beats per minute) can be computed from the interbeat (RR) interval by dividing the number of large (0.20 s) time units between consecutive R waves into 300 or the number of small (40 ms) segments into 1500. The PR interval measures the time (normally 120–200 ms) between atrial and ventricular depolarization, which includes the physiologic delay imposed by stimulation of cells in the AV junction area. The QRS interval (normally 100–110 ms or less) reflects the duration of ventricular depolarization. The QT interval subtends both ventricular depolarization and (primarily) repolarization times and varies inversely with the heart rate. A variety of formulas have been proposed for computing a rate-corrected QT, termed QT<sub>c</sub>, but without formal consensus. The classic “square root” formula (QT = QT/RR, computed in second units) has been criticized for systematic errors at both lower and higher heart rates. One alternative is the Framingham formula (given here for units of milliseconds): QT = QT + 0.154 (1000 – RR). The following upper normal limits (based on longest QT) have been proposed: QT of 460 ms in women and 450 ms in men. Lower limits are less well defined. QT/QT<sub>c</sub> measurements, both visual and electronic, should be assessed in light of inherent limitations in their precise determination from standard ECGs waveforms.

**A****B**

**FIGURE 240-3** The six frontal plane (**A**) and six horizontal plane (**B**) leads provide a three-dimensional representation of cardiac electrical activity.

### ECG LEADS

The 12 conventional ECG leads are divided into two groups: six limb (extremity) leads and six chest (precordial) leads. The limb leads record potentials transmitted onto the *frontal plane* (Fig. 240-3A); the chest leads record potentials transmitted onto the *horizontal plane* (Fig. 240-3B).

The orientation and polarity of the frontal plane leads are represented on a hexaxial diagram (Fig. 240-4). The six chest leads are obtained by exploring electrodes as shown in Fig. 240-5.

Each lead is analogous to a different video camera angle “looking” at the same events—atrial and ventricular depolarization and repolarization—from different spatial orientations. The 12-lead ECG can be supplemented with additional leads in special circumstances. For example, right precordial leads V<sub>1R</sub> to V<sub>6R</sub> are useful in detecting evidence of acute right ventricular ischemia. Bedside monitors and ambulatory ECGs (e.g., Holter monitors, event recorders, patch electrode and other medical wearable devices) usually employ only one or two modified leads. The standard ECG leads are configured such that a positive (upright) deflection is recorded in a lead if a wave of depolarization spreads toward the positive pole of that lead, and a negative deflection is recorded if the wave spreads toward the negative pole. If the *mean* orientation of the depolarization vector is at right angles to a particular

lead axis, a biphasic (equally positive and negative) deflection will be recorded.

## GENESIS OF THE NORMAL ECG

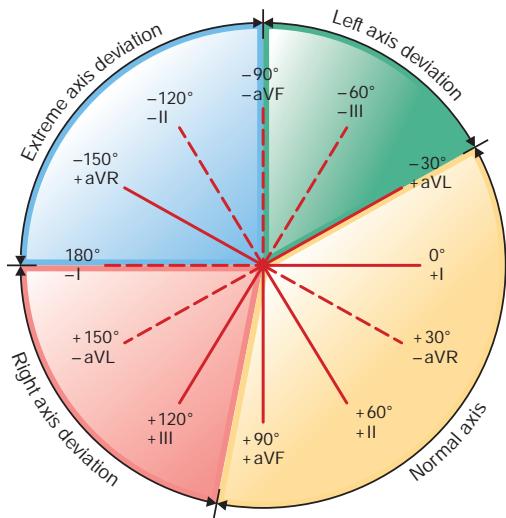
### P WAVE

The normal atrial depolarization vector is oriented downward and toward the subject’s left, reflecting the spread of depolarization from the sinus node to the right and then the left atrial myocardium. Since this vector points toward the positive pole of lead II and toward the negative pole of lead aVR, the sinus-generated P wave will be positive in lead II and negative in aVR. By contrast, activation of the atria from an ectopic pacemaker in the lower part of either atrium or in the AV junction region may produce retrograde P waves (negative in II, positive in aVR). The normal P wave in lead V<sub>1</sub> may be biphasic with a positive component reflecting right atrial depolarization, followed by a small (<1 mm<sup>2</sup>) negative component reflecting left atrial depolarization.

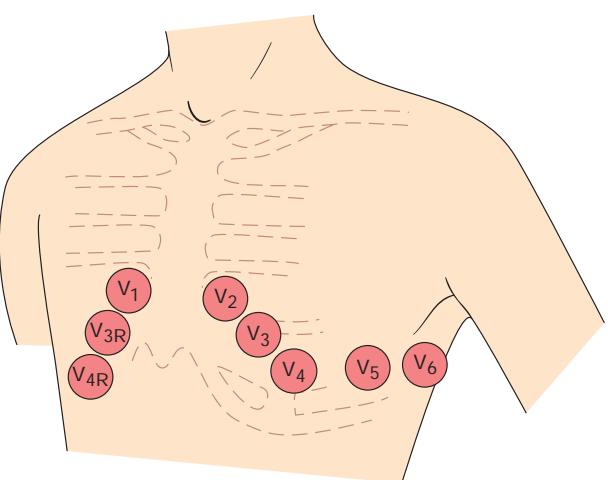
### QRS COMPLEX

Normal ventricular depolarization proceeds as a rapid, continuous spread of activation wave fronts. This complex process can be divided into two major sequential phases, and each phase can be represented by a mean vector (Fig. 240-6). The first phase is depolarization of the interventricular septum from the left to the right and anteriorly (vector 1). The second results from the simultaneous depolarization of the right and left ventricles; it normally is dominated by the more massive left ventricle, so that vector 2 points leftward and posteriorly. Therefore, a right precordial lead (V<sub>1</sub>) will record this biphasic depolarization process with a small positive deflection (septal r wave) followed by a larger negative deflection (S wave). A left precordial lead, for example, V<sub>6</sub>, will record the same sequence with a small negative deflection (septal q wave) followed by a relatively tall positive deflection (R wave). Intermediate leads show a relative increase in R-wave amplitude (normal R-wave progression) and a decrease in S-wave amplitude progressing across the chest from right to left. The lead where the R and S waves are of about equal amplitude is referred to as the *transition zone* (usually V<sub>3</sub> or V<sub>4</sub>) (Fig. 240-7).

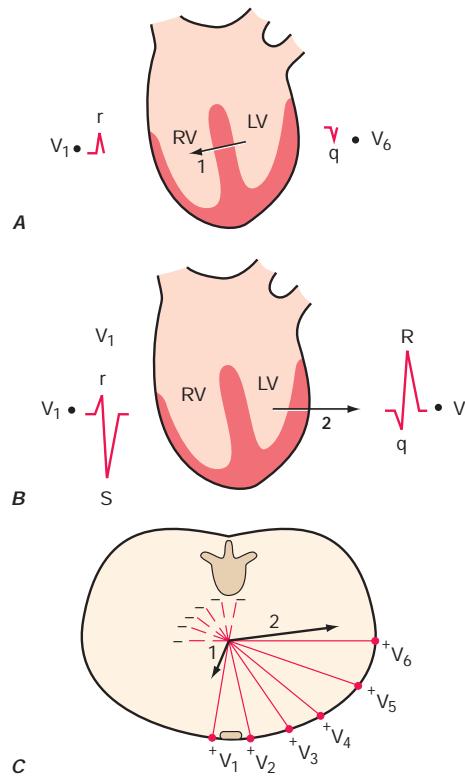
The QRS pattern in the extremity leads may vary considerably from one normal subject to another depending on the *electrical axis* of the QRS, which describes the mean orientation of the QRS vector with reference to the six frontal plane leads. Normally, the QRS axis



**FIGURE 240-4** The frontal plane (limb or extremity) leads are represented on a hexaxial diagram. Each ECG lead has a specific spatial orientation and polarity. The positive pole of each lead axis (solid line) and the negative pole (hatched line) are designated by their angular position relative to the positive pole of lead I (0°). The mean electrical axis of the QRS complex is measured with respect to this display.



**FIGURE 240-5** The horizontal plane (chest or precordial) leads are obtained with electrodes in the locations shown. Additional posterior leads are sometimes placed on the same horizontal plane as V<sub>4</sub> to facilitate detection of acute posterolateral infarction (V<sub>7</sub>, midaxillary line; V<sub>8</sub>, posterior axillary line; and V<sub>9</sub>, posterior scapular line). Right chest leads (V<sub>1R</sub>-V<sub>6R</sub>) may enhance detection of right ventricular involvement in the context of inferior infarction.



**FIGURE 240-6** Ventricular depolarization can be divided into two major phases, each represented by a vector. **A**, The first phase (arrow 1) denotes depolarization of the ventricular septum, beginning on the left side and spreading to the right. This process is represented by a small “septal” r wave in lead V<sub>1</sub> and a small septal q wave in lead V<sub>6</sub>. **B**, Simultaneous depolarization of the left and right ventricles (LV and RV) constitutes the second phase. Vector 2 is oriented to the left and posteriorly, reflecting the electrical predominance of the LV. **C**, Vectors (arrows) representing these two phases are shown in reference to the horizontal plane leads. (Reproduced with permission from AL Goldberger et al: Goldberger's clinical electrocardiography: A simplified approach, 9th ed. Philadelphia, Elsevier/Saunders, 2017.)

ranges from  $-30^\circ$  to  $+100^\circ$  (Fig. 240-4). An axis more negative than  $-30^\circ$  is referred to as *left axis deviation*, and an axis more positive than  $+90^\circ$  to  $+100^\circ$  is referred to as *right axis deviation*. Left axis deviation may occur as a normal variant but is more commonly associated with left ventricular hypertrophy, a block in the anterior fascicle of the left

bundle system (left anterior fascicular block or hemiblock), or inferior myocardial infarction. Right axis deviation also may occur as a normal variant (particularly in children and young adults), as a spurious finding due to reversal of the left and right arm electrodes, or in conditions such as right ventricular overload (acute or chronic), lateral infarction, dextrocardia, left pneumothorax, and left posterior fascicular block.

### T WAVE AND U WAVE

Normally, the mean T-wave vector is oriented roughly concordant with the mean QRS vector (within about  $45^\circ$  in the frontal plane). Since depolarization and repolarization are electrically opposite processes, this normal QRS-T-wave vector concordance indicates that repolarization normally must proceed in the reverse direction from depolarization (i.e., from ventricular epicardium to endocardium). The normal U wave is a small, rounded deflection ( $1\text{ mm}$ ) that follows the T wave and usually has the same polarity as the T wave. An abnormal increase in U-wave amplitude is most commonly due to drugs (e.g., dofetilide, amiodarone, sotalol, quinidine) or to hypokalemia. Very prominent U waves are a marker of increased susceptibility to *torsades de pointes* (Chap. 246).

## MAJOR ECG ABNORMALITIES

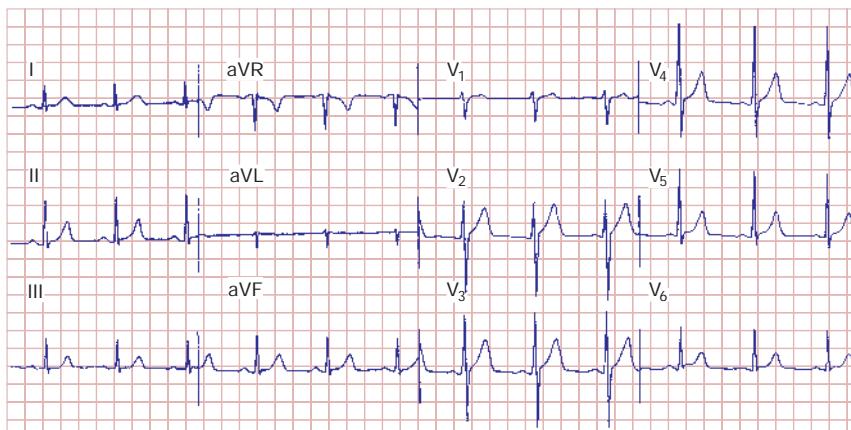
### CARDIAC ENLARGEMENT AND HYPERTROPHY

Right atrial overload (acute or chronic) may lead to an increase in P-wave amplitude ( $2.5\text{ mm}$ ) (Fig. 240-8), previously referred to as “P-pulmonale.” Left atrial overload typically produces a biphasic P wave in V<sub>1</sub>, with a broad negative component or a broad ( $120\text{ ms}$ ), often notched P wave in one or more limb leads (Fig. 240-8). This pattern, historically referred to as “P-mitrale,” may also occur with left atrial conduction delays in the absence of actual atrial enlargement, leading to the more general designation of *left atrial abnormality*.

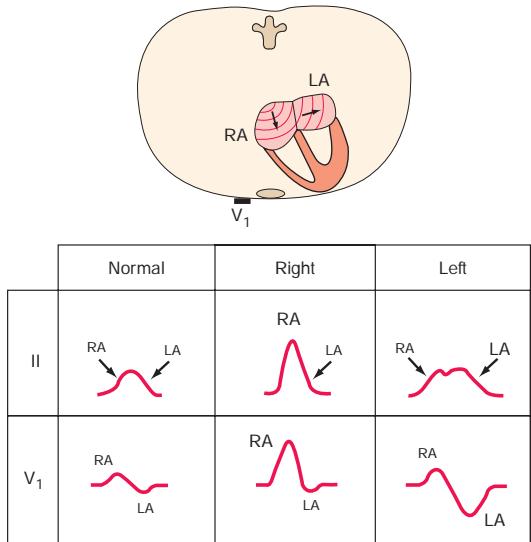
Right ventricular hypertrophy due to a sustained, severe pressure load (e.g., due to tight pulmonic valve stenosis or certain pulmonary artery hypertension syndromes) is characterized by a relatively tall R wave in lead V<sub>1</sub> (R–S wave), usually with right axis deviation (Fig. 240-9); alternatively, there may be a qR pattern in V<sub>1</sub> or V<sub>2</sub>. ST depression and T-wave inversion in the right to mid-precordial leads are also often present. This pattern, formerly called right ventricular “strain,” is attributed to repolarization abnormalities in acutely or chronically overloaded muscle. Prominent S waves may occur in the left lateral precordial leads. Right ventricular hypertrophy due to ostium secundum atrial septal defects, with the accompanying right ventricular volume overload, is commonly associated with an incomplete or complete right bundle branch block pattern with a rightward QRS axis.

*Acute cor pulmonale* due to pulmonary thromboembolism (Chap. 279), for example, may be associated with a normal ECG or a variety of abnormalities. Sinus tachycardia is the most common arrhythmia, although other tachyarrhythmias, such as atrial fibrillation or flutter, may occur. The QRS axis may shift to the right, sometimes in concert with the so-called S<sub>1</sub>Q<sub>3</sub>T<sub>3</sub> pattern (prominence of the S wave in lead I and the Q wave in lead III, with T-wave inversion in lead III). Acute right ventricular dilation also may be associated with slow R-wave progression and ST-T abnormalities in V<sub>1</sub> to V<sub>4</sub> simulating acute anterior infarction. A right ventricular conduction disturbance may appear.

*Chronic cor pulmonale* due to obstructive lung disease (Chap. 296) usually does not produce the classic ECG patterns of right ventricular hypertrophy noted above. Instead of tall right precardial R waves, chronic obstructive lung disease (emphysema) more typically is associated with small R waves in



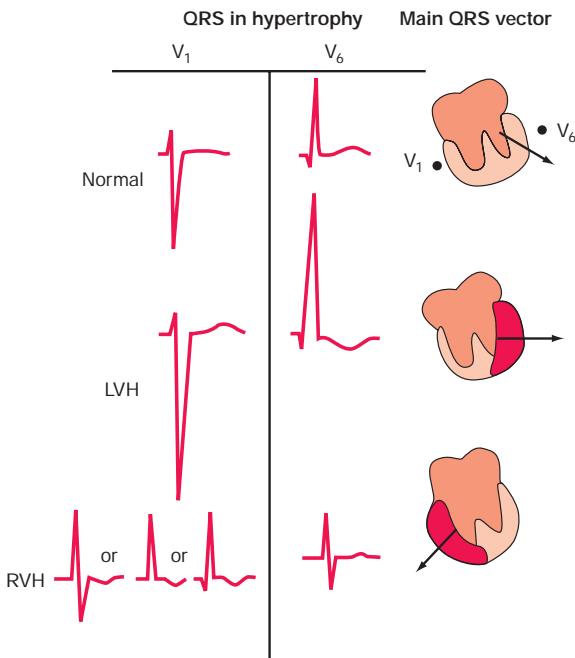
**FIGURE 240-7** Normal electrocardiogram from a healthy male subject. Sinus rhythm is present with a heart rate of 75 beats per minute. PR interval is 160 ms; QRS interval (duration) is 80 ms; QT interval is 360 s; QT<sub>c</sub> (Framingham formula) is 391 ms; the mean QRS axis is about  $+70^\circ$ . The precordial leads show normal R-wave progression with the transition zone (R wave – S wave) in lead V<sub>3</sub>.



**FIGURE 240-8** Right atrial (RA) overload may cause tall, peaked P waves in the limb or precordial leads. Left atrial (LA) abnormality may cause broad, often notched P waves in the limb leads and a biphasic P wave in lead V<sub>1</sub>, with a prominent negative component representing delayed depolarization of the LA. (Reproduced with permission from MK Park, WG Guntheroth: How to Read Pediatric ECGs, 4th ed. St. Louis, Mosby/Elsevier, 2006.)

right to mid-precordial leads (slow R-wave progression) due in part to downward displacement of the diaphragm and the heart. Low-voltage complexes are commonly present, owing to hyperaeration.

Multiple voltage criteria for *left ventricular hypertrophy* (Fig. 240-9) have been proposed on the basis of the presence of tall left precardial R waves and deep right precardial S waves (e.g., SV<sub>5</sub> + [RV<sub>5</sub> or RV<sub>6</sub>] >35 mm). Repolarization abnormalities (ST depression with T-wave inversions, formerly called the left ventricular “strain” pattern) also

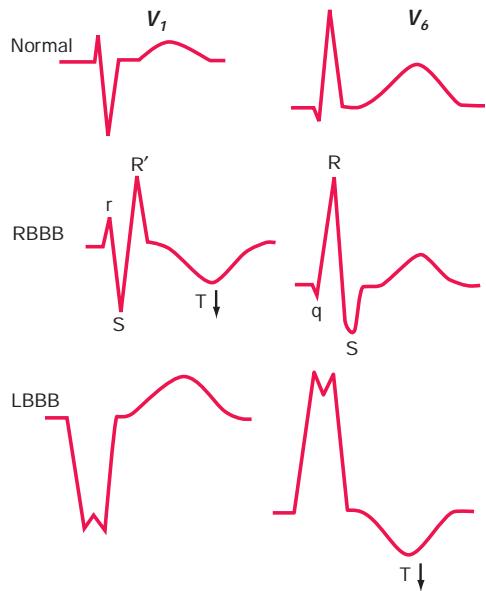


**FIGURE 240-9** Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qr complex in lead V<sub>1</sub>. T-wave inversions may be present in right precordial leads.

may appear in leads with prominent R waves. However, prominent precardial voltages may occur as a normal variant, especially in athletic or young individuals. Left ventricular hypertrophy may increase limb lead voltage with or without increased precardial voltage (e.g., RaVL + SV<sub>3</sub> >20 mm in women and >28 mm in men). The presence of left atrial abnormality increases the likelihood of underlying left ventricular hypertrophy in cases with borderline voltage criteria. Left ventricular hypertrophy often progresses to incomplete or complete left bundle branch block. The sensitivities of conventional voltage criteria for left ventricular hypertrophy are low in middle-age to older adults and may be decreased further in obese persons and smokers, as well as with right bundle branch block. ECG evidence for left ventricular hypertrophy is a major noninvasive marker of increased risk of cardiovascular morbidity and mortality rates, including sudden cardiac death. However, because of false-positive and false-negative diagnoses, the ECG is of limited utility in diagnosing atrial or ventricular enlargement. More definitive anatomic and functional information may be provided at increased cost by echocardiographic and other imaging studies (Chaps. 241 and A9).

### BUNDLE BRANCH BLOCKS AND RELATED PATTERNS

Intrinsic impairment of conduction in either the right or the left bundle system (intraventricular conduction disturbances) leads to prolongation of the QRS interval. With complete bundle branch blocks, the widest QRS interval is 120 ms in duration; with incomplete blocks, the QRS interval is between about 110 and 120 ms. The QRS vector usually is oriented in the direction of the myocardial region where depolarization is delayed (Fig. 240-10). Thus, with right bundle branch block, the terminal QRS vector is oriented to the right and anteriorly (rSR' in V<sub>1</sub> and qRS in V<sub>6</sub> typically). Left bundle branch block alters both early and later phases of ventricular depolarization. The major QRS vector is directed to the left and posteriorly. In addition, the normal early left-to-right pattern of septal activation is disrupted such that septal depolarization proceeds from right to left as well. As a result, left bundle branch block generates wide, predominantly negative (QS) complexes in lead V<sub>1</sub> and entirely positive (R) complexes in V<sub>6</sub>. Waveform patterns identical to those of left bundle branch block, preceded by a sharp (but sometimes low amplitude) spike, are seen in most cases of electronic right ventricular pacing due to the relative delay in left ventricular activation. In contrast, biventricular pacing (cardiac



**FIGURE 240-10** Comparison of typical QRS-T patterns in right bundle branch block (RBBB) and left bundle branch block (LBBB) with the normal pattern in leads V<sub>1</sub> and V<sub>6</sub>. Note the secondary T-wave inversions (arrows) in leads with an rSR' complex with RBBB and in leads with a wide R wave with LBBB.

Bundle branch block may occur in a variety of conditions. In subjects without structural heart disease, right bundle branch block is seen more commonly than left bundle branch block. Right bundle branch block also occurs with heart disease, both congenital (e.g., atrial septal defect) and acquired (e.g., valvular, ischemic). Left bundle branch block is often a marker of one of four underlying conditions associated with increased risk of cardiovascular morbidity and mortality rates: coronary heart disease (frequently with impaired left ventricular function), hypertensive heart disease, aortic valve disease (including after transcatheter aortic valve replacement), and cardiomyopathy. Bundle branch blocks may be chronic or intermittent. A bundle branch block may be rate-related, not uncommonly occurring when the heart rate exceeds some critical value.

Bundle branch blocks and depolarization abnormalities secondary to artificial pacemakers not only affect ventricular depolarization (QRS) but also are characteristically associated with *secondary repolarization* (ST-T) abnormalities. With bundle branch blocks, the T wave is typically opposite in polarity to the last deflection of the QRS (Fig. 240-10). This discordance of the QRS-T-wave vectors is caused by the altered sequence of repolarization that occurs as a consequence of altered depolarization. In contrast, *primary repolarization* abnormalities are independent of QRS changes and are related instead to actual alterations in the electrical properties of the myocardial fibers themselves (e.g., in the resting membrane potential or action potential duration), not just to changes in the sequence of repolarization. Ischemia, electrolyte imbalance, and drugs such as digitalis all cause such primary ST-T-wave changes. Primary and secondary T-wave changes may coexist. For example, T-wave inversions in the right precordial leads with left bundle branch block or in the left precordial leads with right bundle branch block may be important markers of underlying ischemia or other abnormalities. A distinctive abnormality simulating right bundle branch block with ST-segment elevations in the right chest leads is seen with the Brugada pattern (Chap. 255).

Partial blocks in the left bundle system (left anterior or posterior fascicular blocks or hemiblocks) generally do not prolong the QRS duration substantially but instead are associated with shifts in the frontal plane QRS axis (leftward or rightward, respectively). Left anterior fascicular block (QRS axis more negative than  $-45^\circ$ ) is probably the most common cause of marked left axis deviation in adults. In contrast, left posterior fascicular block (QRS axis more rightward than  $+110\text{--}120^\circ$ ) is extremely rare as an isolated finding and requires exclusion of other factors causing right axis deviation mentioned earlier. Intraventricular conduction delays also can be caused by factors extrinsic (toxic) to the conduction system that slow ventricular conduction, particularly hyperkalemia or drugs (e.g., class 1 antiarrhythmic agents, tricyclic antidepressants, phenothiazines). Prolongation of QRS duration does not necessarily indicate a conduction delay but may be due to *preexcitation* of the ventricles via a bypass tract, as in Wolff-Parkinson-White (WPW) patterns (Chap. 249) and related variants.

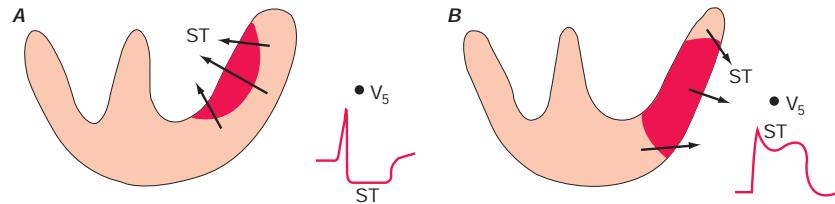
## MYOCARDIAL ISCHEMIA AND INFARCTION

(See also Chap. 275) The ECG is central to the diagnosis of acute and chronic ischemic heart disease. Ischemia exerts complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia lowers the resting membrane potential and shortens the

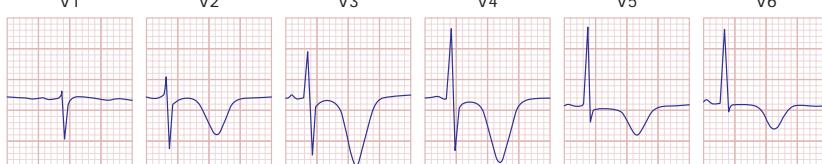
duration of the action potential. Such changes cause a voltage gradient between normal and ischemic zones. As a consequence, current flows between those regions. These currents of injury are represented on the surface ECG by deviation of the ST segment (Fig. 240-11). When the acute ischemia is *transmural*, the ST vector usually is shifted in the direction of the outer (epicardial) layers, producing ST elevations and sometimes, in the earliest stages of ischemia, tall, positive so-called hyperacute T waves over the ischemic zone. With ischemia confined primarily to the *subendocardium*, the ST vector typically shifts toward the subendocardium and ventricular cavity, so that overlying (e.g., anterior precordial) leads show ST-segment depression (with ST elevation in lead aVR). Multiple factors affect the amplitude of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. From a clinical viewpoint, the division of acute myocardial infarction into ST-segment elevation and non-ST elevation types is useful since the consistent efficacy of emergency (minutes to hours) reperfusion therapy is limited to the former group; the evolving indications for acute reperfusion therapy in non-ST elevation myocardial infarction are a focus of intensive investigation (Chap. 274). Takotsubo syndrome may closely simulate the patterns of acute or evolving ST-segment elevation or non-ST-segment elevation myocardial infarction (Chap. 273).

The ECG leads are usually more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example, acute transmural anterior (including apical and lateral) wall ischemia is reflected by ST elevations or increased T-wave positivity in one or more of the precordial leads ( $V_1\text{--}V_4$ ) and leads I and aVL. Inferior wall ischemia produces changes in leads II, III, and aVF. "Posterior" wall ischemia (almost always associated with lateral or inferior involvement) may be indirectly recognized by *reciprocal* ST depressions in leads  $V_1$  to  $V_3$  (thus constituting an ST elevation "equivalent" acute coronary syndrome). Acute right ventricular ischemia usually produces ST elevations in right-sided chest leads (Fig. 240-5). When ischemic ST elevations occur as the earliest sign of acute infarction, they typically are followed within a period ranging from hours to days by evolving T-wave inversions and often by Q waves occurring in the same lead distribution. Reversible transmural ischemia, for example, due to coronary vasospasm (Prinzmetal's angina) may cause transient ST-segment elevations without development of Q waves. Depending on the severity and duration of ischemia, the ST elevations may resolve completely in minutes or be followed by T-wave inversions that persist for hours or even days. Patients with ischemic chest pain who present with deep T-wave inversions in multiple precordial leads (e.g.,  $V_1\text{--}V_4$ , I, and aVL) with or without cardiac enzyme elevations typically have severe obstruction in the left anterior descending coronary artery (Fig. 240-12).

With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial tissue may lead to decreased R-wave amplitude or abnormal Q waves (even in the absence of transmural ischemia) in the anterior or inferior leads (Fig. 240-13). Abnormal Q waves were once considered markers of transmural myocardial infarction, whereas subendocardial infarcts were thought not to produce Q waves. However, correlative studies have indicated that transmural infarcts may occur without Q waves and that subendocardial (nontransmural) infarcts sometimes may be associated with Q waves. Therefore, evolving or chronic infarcts are more appropriately classified as "Q-wave" or "non-Q-wave" (Chap. A7).



**FIGURE 240-11** Acute ischemia causes a current of injury. **A.** With predominant subendocardial ischemia, the resultant ST vector will be directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore will record ST depression. **B.** With ischemia involving the outer ventricular layer (transmural or epicardial injury), the ST vector will be directed outward. Overlying leads will record ST elevation.



**FIGURE 240-12** Severe anterior wall ischemia (with or without infarction) may cause prominent T-wave inversions in the precordial leads and in leads I and aVL. This pattern (sometimes referred to as Wellens T waves) is usually associated with a high-grade stenosis of the left anterior descending coronary artery.

Loss of depolarization forces due to posterior or lateral infarction may cause reciprocal increases in R-wave amplitude in leads V<sub>1</sub> and V<sub>2</sub> without diagnostic Q waves in any of the conventional leads. (Additional leads V<sub>7</sub>–V<sub>9</sub> may show acute changes.) In the weeks and months after infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG after Q-wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder, although not necessarily a frank ventricular aneurysm.

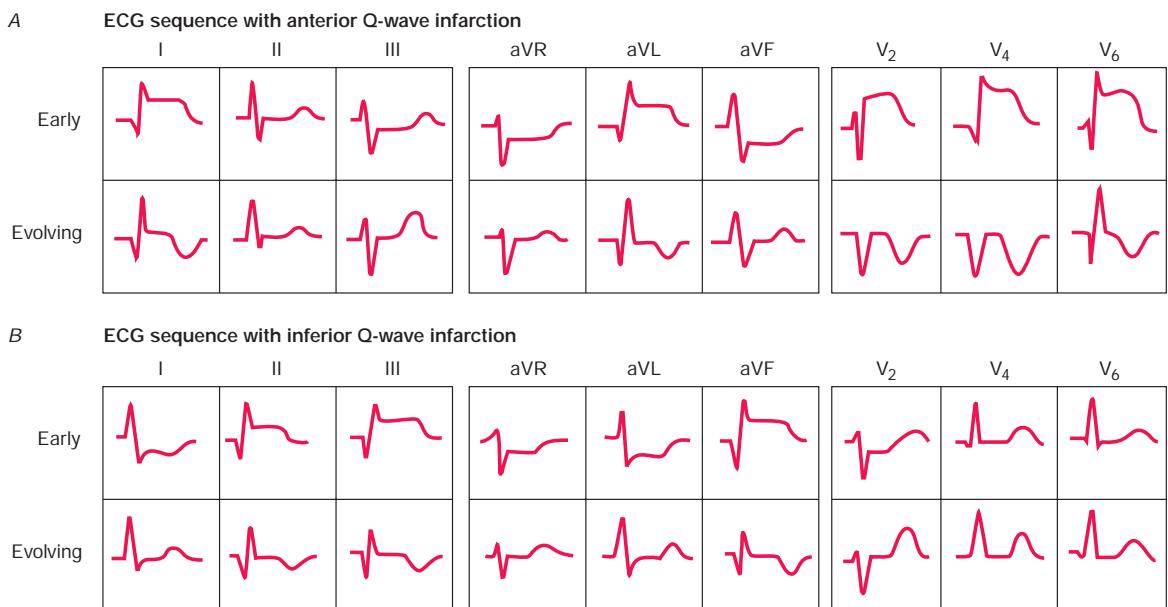
The ECG has important limitations in both sensitivity and specificity in the diagnosis of acute and chronic ischemic heart disease. Although a single normal ECG does not exclude ischemia or even acute infarction, a normal ECG *throughout* the course of an acute infarct is distinctly uncommon. Prolonged chest pain without diagnostic ECG changes therefore should always prompt a careful search for other noncoronary causes of chest pain (Chap. 14). Furthermore, the diagnostic changes of acute or evolving ischemia are often masked by the presence of left bundle branch block, electronic ventricular pacemaker patterns, and Wolff-Parkinson-White preexcitation. However, clinicians may also overdiagnose ischemia or infarction based on the presence of ST-segment elevations or depressions; T-wave inversions; tall, positive T waves; or Q waves *not* related to ischemic heart disease (pseudoinfarct patterns). For example, ST-segment elevations simulating acute ischemia/infarction may occur with acute pericarditis or myocarditis, including COVID-19 infections, as a normal variant (including the typical “early repolarization” pattern), or in a variety of other conditions (Table 240-1). Similarly, tall T waves do not invariably represent hyperacute ischemic changes but may also be caused

by normal variants, hyperkalemia, or cerebrovascular injury, among other causes.

ST-segment elevations and tall, positive T waves are common findings in leads V<sub>1</sub> and V<sub>2</sub> in left bundle branch block or left ventricular hypertrophy in the absence of ischemia. The differential diagnosis of Q waves includes physiologic or positional variants, ventricular hypertrophy, acute or chronic noncoronary myocardial injury, hypertrophic cardiomyopathy, and ventricular conduction disorders. Ventricular hypertrophy, hypokalemia, drugs such as digoxin, and a variety of other factors may cause ST-segment depression mimicking subendocardial ischemia. Prominent T-wave inversion may occur with ventricular hypertrophy, cardiomyopathies, myocarditis, and “stress cardiomyopathies” associated with takotsubo syndrome and cerebrovascular injury (particularly intracranial bleeds), among others causes. Diagnostic confusion may also occur when nonischemic T-wave inversions (“cardiac memory” effect) appear in normally conducted beats in patients with intermittent wide QRS complexes, most commonly due to ventricular pacing or to left bundle branch block.

### METABOLIC FACTORS AND DRUG EFFECTS

A variety of metabolic abnormalities and pharmacologic agents alter the ECG and, in particular, cause changes in repolarization (ST-T) and sometimes QRS prolongation. Certain life-threatening electrolyte disturbances may be diagnosed initially and monitored from the ECG. *Hyperkalemia* produces a sequence of changes (Fig. 240-14), usually beginning with narrowing and peaking (tenting) of the T waves. Further elevation of extracellular K<sup>+</sup> leads to AV conduction disturbances, diminution in P-wave amplitude, and widening of the QRS interval. Severe hyperkalemia eventually causes cardiac arrest with a



**FIGURE 240-13** Sequence of depolarization and repolarization changes with (A) acute anterior and (B) acute inferior wall Q-wave infarctions. With anterior infarcts, ST elevation in leads I and aVL and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterolateral) infarcts may be associated with reciprocal ST depressions in leads V<sub>1</sub> to V<sub>3</sub>. (Reproduced with permission from AL Goldberger et al: Goldberger's clinical electrocardiography: A simplified approach, 9th ed. Philadelphia, Elsevier/Saunders, 2017.)

**TABLE 240-1 Differential Diagnosis of ST-Segment Elevations**

## Myocardial ischemia/infarction

- Noninfarction, transmural ischemia (Prinzmetal's syndrome due to localized coronary spasm)
- Acute myocardial infarction (especially due to epicardial coronary occlusion)
- Takotsubo syndrome ("stress cardiomyopathy")
- Postmyocardial infarction (ventricular aneurysm pattern)
- Acute pericarditis
- Normal variants (including benign "early repolarization" patterns)
- Left ventricular hypertrophy/left bundle branch block<sup>a</sup>
- Other (rarer)
  - Acute pulmonary embolism<sup>a</sup>
  - Brugada patterns (right bundle branch block-like morphology with ST elevations in right precordial leads)
  - Class 1C antiarrhythmic drugs<sup>a</sup>
  - DC cardioversion (transient)
  - Hypercalcemia<sup>a</sup>
  - Hyperkalemia<sup>a</sup>
  - Hypothermia (J [Osborn] waves)
  - Nonischemic myocardial injury
    - Myocarditis syndromes (infectious and non-infectious)
    - Tumor invading left ventricle
    - Trauma to ventricles

<sup>a</sup>Usually localized to V<sub>1</sub>–V<sub>2</sub> or V<sub>3</sub>.

Source: Modified from AL Goldberger et al: *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 9th ed. Philadelphia, Elsevier/Saunders, 2017.

slow sinusoidal type of mechanism ("sine-wave" pattern) followed by asystole. *Hypokalemia* (Fig. 240-15) prolongs ventricular repolarization, often with prominent U waves. Prolongation of the QT interval is also seen with drugs that increase the duration of the ventricular action potential: class 1A antiarrhythmic agents and related drugs (e.g., quinidine, disopyramide, procainamide, tricyclic antidepressants, phenothiazines) and class III agents (e.g., amiodarone [Fig. 240-15], dofetilide, sotalol, ibutilide). Systemic *hypothermia* (Fig. 240-15) also prolongs repolarization, usually with a distinctive convex elevation of the J point (Osborn wave). Marked QT prolongation, sometimes with deep, wide T-wave inversions, may occur with intracranial bleeds, particularly subarachnoid hemorrhage ("CVA T-wave" pattern) (Fig. 240-15). *Hypocalcemia* typically prolongs the QT interval (ST portion), whereas *hypercalcemia* shortens it (Fig. 240-16). Digitalis glycosides

also shorten the QT interval, often with a characteristic "scooping" of the ST-T-wave complex (*digitalis effect*).

**NONSPECIFIC ST-T CHANGES AND LOW QRS VOLTAGE**

Many other factors are associated with ECG changes, particularly alterations in ventricular repolarization. T-wave flattening, minimal T-wave inversions, or slight ST-segment depression ("nonspecific ST-T-wave changes") may occur with a variety of electrolyte and acid-base disturbances, infectious or inflammatory processes, central nervous system disorders, endocrine abnormalities, many drugs, ischemia, hypoxia, and virtually any type of cardiopulmonary abnormality, in addition to physiologic changes (e.g., with posture or with meals). Low QRS voltage is arbitrarily defined as peak-to-trough QRS amplitudes of 5 mm in the six limb leads and/or 10 mm in the chest leads. Multiple factors may be responsible. Among the most serious include pericardial (Fig. 240-17) or pleural effusions, chronic obstructive pulmonary disease, infiltrative cardiomyopathies, and anasarca.

**ELECTRICAL ALTERNANS SYNDROMES**

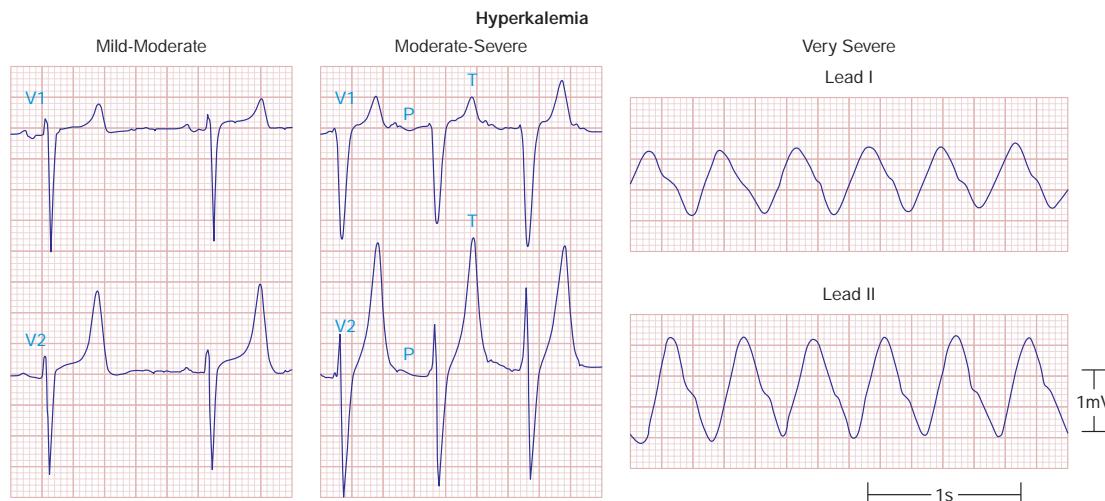
Electrical alternans—a beat-to-beat alternation in one or more components of the ECG signal—is a common type of nonlinear cardiovascular response to a variety of hemodynamic and electrophysiologic perturbations. Total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign of pericardial effusion, usually with cardiac tamponade (Fig. 240-17). In contrast, pure repolarization (ST-T or U wave) alternans is a sign of electrical instability and may precede ventricular tachyarrhythmias.

**CLINICAL INTERPRETATION OF THE ECG**

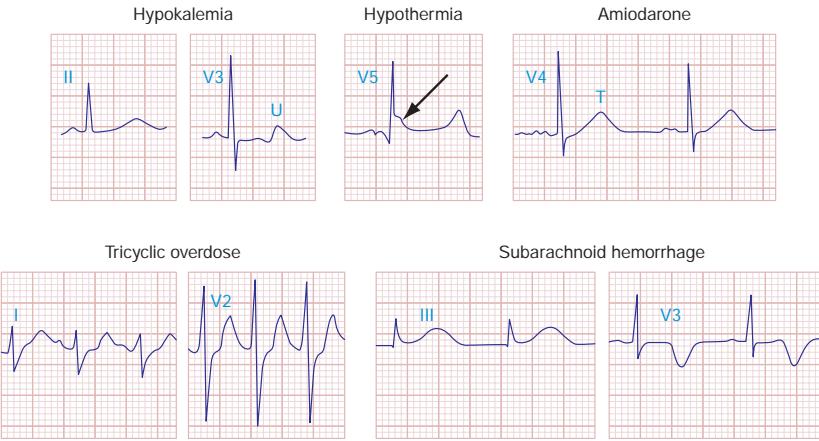
Accurate analysis of ECGs requires thoroughness and care. The patient's age, gender, and clinical status should always be taken into account. Many mistakes in ECG interpretation are errors of omission. Therefore, a systematic approach is essential. The following 14 points should be analyzed carefully in every ECG: (1) standardization (calibration) and technical features (including lead placement and artifacts), (2) rhythm, (3) heart rate, (4) PR interval/AV conduction, (5) QRS interval, (6) QT/QT<sub>c</sub> intervals, (7) mean QRS electrical axis, (8) P waves, (9) QRS voltages, (10) precordial R-wave progression, (11) abnormal Q waves, (12) ST segments, (13) T waves, and (14) U waves. Comparison with any previous ECGs is invaluable.

**COMPUTERIZED ELECTROCARDIOGRAPHY**

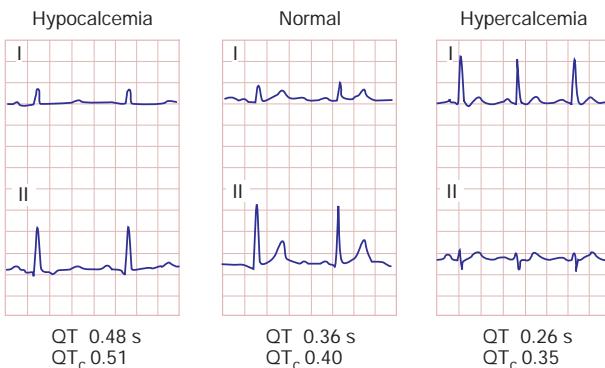
Computerized systems are widely used for immediate retrieval of thousands of ECG records. Fully automated computerized ECG analyses still have major limitations and, therefore, should not be accepted without careful clinician review of both waveforms and intervals.



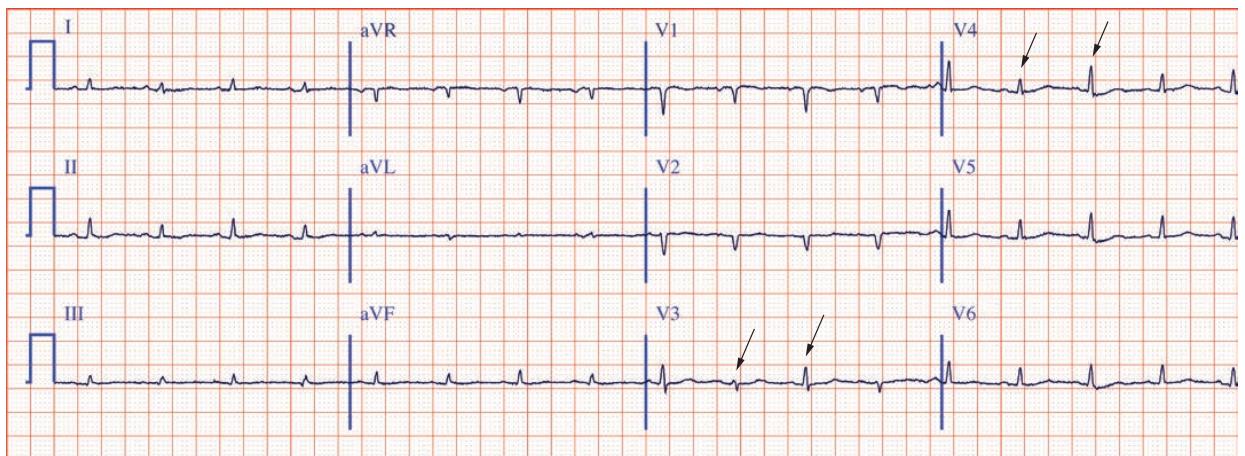
**FIGURE 240-14** The earliest ECG change with hyperkalemia is usually peaking ("tenting") of the T waves. With further increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave pattern leads to asystole unless emergency therapy is given. (Reproduced with permission from AL Goldberger et al: *Goldberger's clinical electrocardiography: A simplified approach*, 9th ed. Philadelphia, Elsevier/Saunders, 2017.)



**FIGURE 240-15** A variety of metabolic derangements, drug effects, and other factors may prolong ventricular repolarization with QT prolongation or prominent U waves. Prominent repolarization prolongation, particularly if due to hypokalemia, inherited “channelopathies,” or certain pharmacologic agents, indicates increased susceptibility to *torsades des pointes* ventricular tachycardia (Chap. 254). Marked systemic hypothermia is associated with a distinctive convex “hump” at the J point (Osborn wave, arrow) due to altered ventricular action potential characteristics. Note QRS and QT prolongation along with sinus tachycardia in the case of tricyclic antidepressant overdose.



**FIGURE 240-16** Prolongation of the Q-T interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and relative or absolute shortening of the QT interval.



**FIGURE 240-17** Classic triad of findings for pericardial effusion with cardiac tamponade: (1) sinus tachycardia; (2) low QRS voltages; and (3) electrical alternans (best seen in leads V<sub>3</sub> and V<sub>4</sub>, in this case; arrows). This triad is highly suggestive of pericardial effusion, usually with tamponade physiology, but is of limited sensitivity. (Adapted from LA Nathanson et al: ECG Wave-Maven. <http://ecg.bidmc.harvard.edu/>.)

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to other types of ultrasound imaging, although the hardware and software are optimized for evaluation of cardiac structure and function. Early echocardiography machines displayed "M-mode" echocardiograms in which a single ultrasound beam was displayed over time on a moving sheet of paper (**Fig. 241-1, left panel**). Modern echocardiographic machinery uses phased array transducers that contain up to 512 elements and emit ultrasound in sequence. The reflected ultrasound is then sensed by the receiving elements. A "scan converter" uses information about the timing and magnitude of the reflected ultrasound to generate an image (**Fig. 241-1, right panel**). This sequence happens repeatedly in "real time" to generate moving images with frame rates that are typically greater than 30 frames per second, but can exceed 100 frames per second. The gray scale of the image features indicates the intensity of the reflected ultrasound; fluid or blood appears black, and highly reflective structures, such as calcifications on cardiac valves or the pericardium, appear white. Tissues such as myocardium appear more gray, and tissues such as muscle display a unique speckle pattern. Although M-mode echocardiography has largely been supplanted by two-dimensional (2D) echocardiography, it is still used because of its high temporal resolution and accuracy for making linear measurements.

The spatial resolution of ultrasound is dependent on the wavelength: the smaller the wavelength and the higher the frequency of the ultrasound beam, the greater are the spatial resolution and ability to discern small structures. Increasing the frequency of ultrasound will increase resolution but at the expense of reduced penetration. Higher frequencies can be used in pediatric imaging or transesophageal echocardiography where the transducer can be much closer to the structures being interrogated, and this is a rationale for using transesophageal echocardiography to obtain higher quality images.

Three-dimensional ultrasound transducers use a waffle-like matrix array transducer and receive a pyramidal data sector. Three-dimensional echocardiography is being increasingly used for assessment of congenital heart disease and valves, although current image quality lags behind 2D ultrasound (**Fig. 241-2**).

In addition to the generation of 2D images that provide information about cardiac structure and function, echocardiography can be used to interrogate blood flow within the heart and blood vessels by using the Doppler principle to ascertain the velocity of blood flow. When ultrasound emitted from a transducer reflects off red blood cells that are moving toward the transducer, the reflected ultrasound will return at a slightly higher frequency than emitted; the opposite is true when flow moves away from the transducer. That frequency difference, termed the *Doppler shift*, is directly related to the velocity of the flow of the red blood cells. The velocity of blood flow between two chambers will be directly related to the pressure gradient between those chambers. A modified form of the Bernoulli equation,

$$p = 4v^2$$

where  $p$  = the pressure gradient and  $v$  = the velocity of blood flow in meters per second, can be used to calculate this pressure gradient in the majority of clinical circumstances. This principle can be used to determine the pressure gradient between chambers and across valves and has become central to the quantitative assessment of valvular heart disease.

There are three types of Doppler ultrasound that are typically used in standard echocardiographic examinations: spectral Doppler, which consists of both pulsed wave Doppler and continuous wave Doppler, and color flow Doppler. Both types of spectral Doppler will display a waveform representing the velocity of blood flow, with time on the horizontal axis and velocity on the vertical axis. Pulsed wave Doppler is used to interrogate relatively low velocity flow and has the ability to determine blood flow velocity at a particular location within the heart. Continuous wave Doppler is used to assess high-velocity flow, but it can only identify the highest velocity in a particular direction and cannot interrogate the velocity at a specific depth location. Both of these techniques can only accurately assess velocities that are in the direction of the ultrasound scan lines, and velocities that are at an angle to the direction of the ultrasound beam will be underestimated. Color flow

## 241

# Noninvasive Cardiac Imaging: Echocardiography, Nuclear Cardiology, and Magnetic Resonance/Computed Tomography Imaging

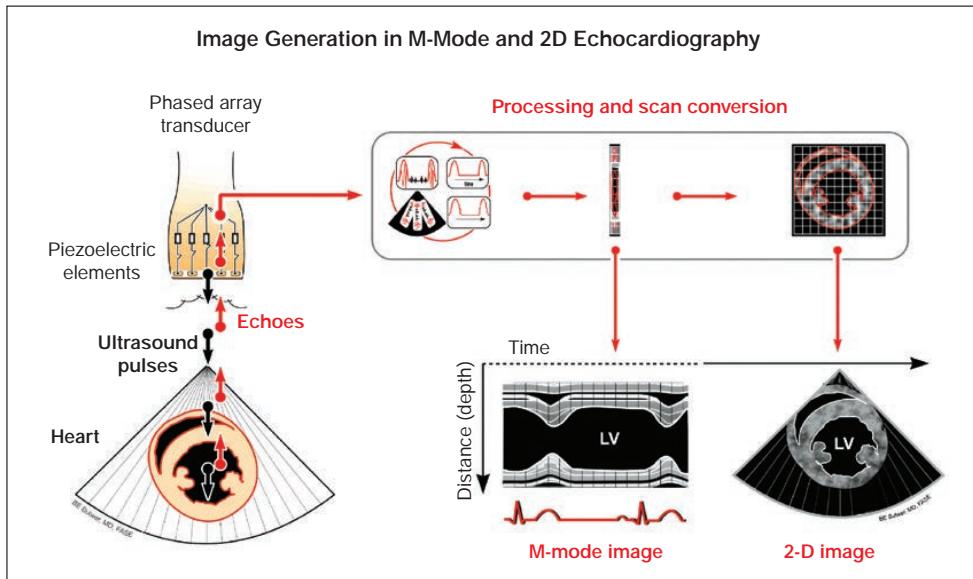
Marcelo F. Di Carli, Raymond Y. Kwong,  
Scott D. Solomon

The ability to image the heart and blood vessels noninvasively has been one of the greatest advances in cardiovascular medicine since the development of the electrocardiogram (ECG). Cardiac imaging complements history taking and physical examination, blood and laboratory testing, and exercise testing in the diagnosis and management of most diseases of the cardiovascular system. Modern cardiovascular imaging consists of echocardiography (cardiac ultrasound), nuclear scintigraphy including positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and computed tomography (CT). These studies, often used in conjunction with exercise or pharmacologic stress testing, can be used independently or in concert depending on the specific diagnostic needs. In this chapter, we review the principles of each of these modalities and the utility and relative benefits of each for the most common cardiovascular diseases.

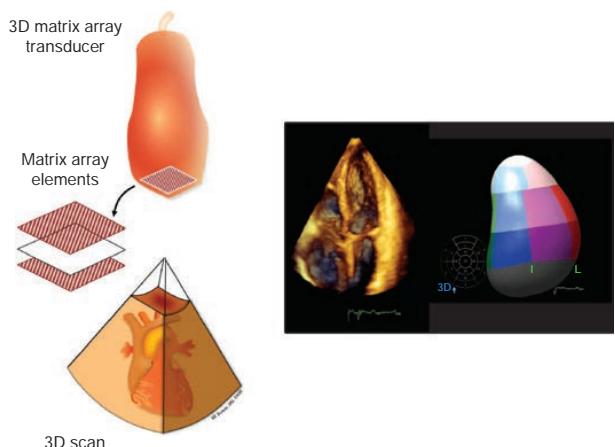
## PRINCIPLES OF MULTIMODALITY CARDIAC IMAGING

### ECHOCARDIOGRAPHY

Echocardiography uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. The basic physical principles of echocardiography are identical



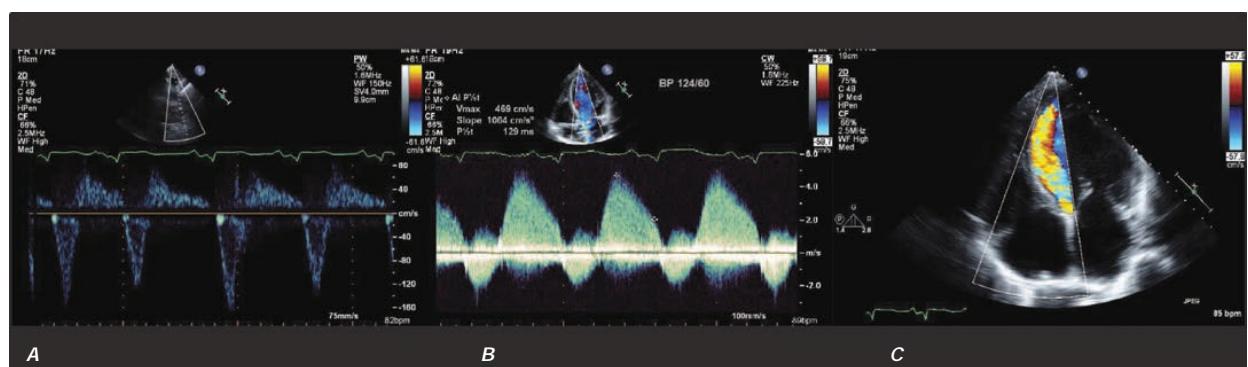
**FIGURE 241-1** Principle of image generation in two-dimensional (2D) echocardiography. An electronically steerable phased-array transducer emits ultrasound from piezoelectric elements, and returning echoes are used to generate a 2D image (right) using a scan converter. Early echocardiography machines used a single ultrasound beam to generate an "M-mode" echocardiogram (see text), although modern equipment generates M-mode echocardiograms digitally from the 2D data. LV, left ventricle.



**FIGURE 241-2** Three-dimensional (3D) probe and 3D image.

Doppler is a form of pulsed wave Doppler in which the velocity of blood flow is color encoded according to a scale and superimposed on a 2D grayscale image in real time, giving the appearance of real-time flow within the heart. The Doppler principle can also be used to assess the velocity of myocardial motion, which is a sensitive way to assess myocardial function (Fig. 241-3). A standard full transthoracic echocardiographic examination consists of a series of 2D views made up of different imaging planes from various scanning locations and spectral and color flow Doppler assessment.

Transesophageal echocardiography is a form of echocardiography in which the transducer is located on the tip of an endoscope that can be inserted into the esophagus. This procedure allows closer, less obstructed views of cardiac structures, without having to penetrate through chest wall, muscle, and ribs. Because less penetration is needed, a higher frequency probe can be used, and image quality and spatial resolution are generally higher than with standard transthoracic imaging, particularly for structures that are more posterior. Transesophageal echocardiography has become the test of choice for assessment of small lesions in the heart such as valvular vegetations, and intracardiac thrombi, including assessment of the left atrial appendage, which is difficult to visualize with standard transthoracic imaging, and for assessment of congenital



**FIGURE 241-3** Three types of Doppler ultrasound. **A** and **B**, Pulsed and continuous wave Doppler waveforms with time on horizontal axis and velocity of blood flow on vertical axis. **C**, Color flow Doppler, where velocities are encoded by colors according to scale on right side of screen and superimposed on a two-dimensional grayscale image.



**FIGURE 241-4** Two examples of hand-held ultrasound equipment: V-Scan (General Electric, *left*) and Sonosite (*right*).

abnormalities. Transesophageal echocardiography requires both topical and systemic anesthesia, generally conscious sedation, and carries additional risks such as potential damage to the esophagus, including the rare possibility of perforation, aspiration, and anesthesia-related complications. Patients generally need to give consent for transesophageal echocardiography and be monitored during and subsequent to the procedure. Transesophageal echocardiography can be carried out in intubated patients and is routinely used for intraoperative monitoring during cardiac surgery.

Stress echocardiography is routinely used to assess cardiac function during exercise and can be used to identify myocardial ischemia or to assess valvular function under exercise conditions. Stress echocardiography is typically performed in conjunction with treadmill or bicycle exercise testing, but it can also be performed using pharmacologic stress, most typically with an intravenous infusion of dobutamine (see section on stress imaging below).

Whereas typical echocardiographic equipment is large, bulky, and expensive, small hand-held or point-of-care ultrasound (POCUS) equipment developed over the past decade now offers diagnostic quality imaging in a package small enough to be carried on rounds (Fig. 241-4). These relatively inexpensive point-of-care devices are slowly gaining full diagnostic capabilities but currently represent an excellent screening tool if used by an experienced operator. As these units become even smaller and less expensive, they are being increasingly used not just by cardiologists but also by emergency medicine physicians, intensivists, anesthesiologists, and internists.

Nevertheless, echocardiography is a nontomographic modality. The image obtained is dependent on the skill of the operator who, holding a transducer, identifies standard views from which measurements can be made. Images that are obtained off-axis can result in incorrect measurements, such as chamber volumes or ejection fraction. As point-of-care echocardiography becomes more commonplace, practitioners will need sufficient training to obtain and interpret images.

Myocardial strain or deformation imaging has emerged as an alternative way to assess cardiac contractile performance. Global and/or regional myocardial strain can be assessed either by Doppler or, more

commonly, by 2D echocardiography. Global longitudinal strain is assessed from the apical view and calculated as the endocardial perimeter length in end diastole minus the endocardial perimeter length in end systole divided by the endocardial perimeter length in end diastole. It is more robust as a measure of contractile function than volumetric-based ejection fraction and has been shown to be predictive of outcome in a variety of cardiac diseases, including heart failure and following myocardial infarction.

## RADIONUCLIDE IMAGING

Radionuclide imaging techniques are commonly used for the evaluation of patients with known or suspected coronary artery disease (CAD), including for initial diagnosis and risk stratification as well as the assessment of myocardial viability. In addition, radionuclide imaging is commonly used in the evaluation of patients with suspected cardiac amyloidosis, myocardial and vascular inflammation, and infective endocarditis. These techniques

use small amounts of radiopharmaceuticals (Table 241-1), which are injected intravenously and trapped in the heart and/or vascular cells. Radioactivity within the heart and vasculature decays by emitting gamma rays. The interaction between these gamma rays and the detectors in specialized scanners (single-photon emission computed tomography [SPECT] and PET) creates a scintillation event or light output, which can be captured by digital recording equipment to form an image of the heart and vasculature. Like CT and MRI, radionuclide images also generate tomographic (three-dimensional) views of the heart and vasculature.

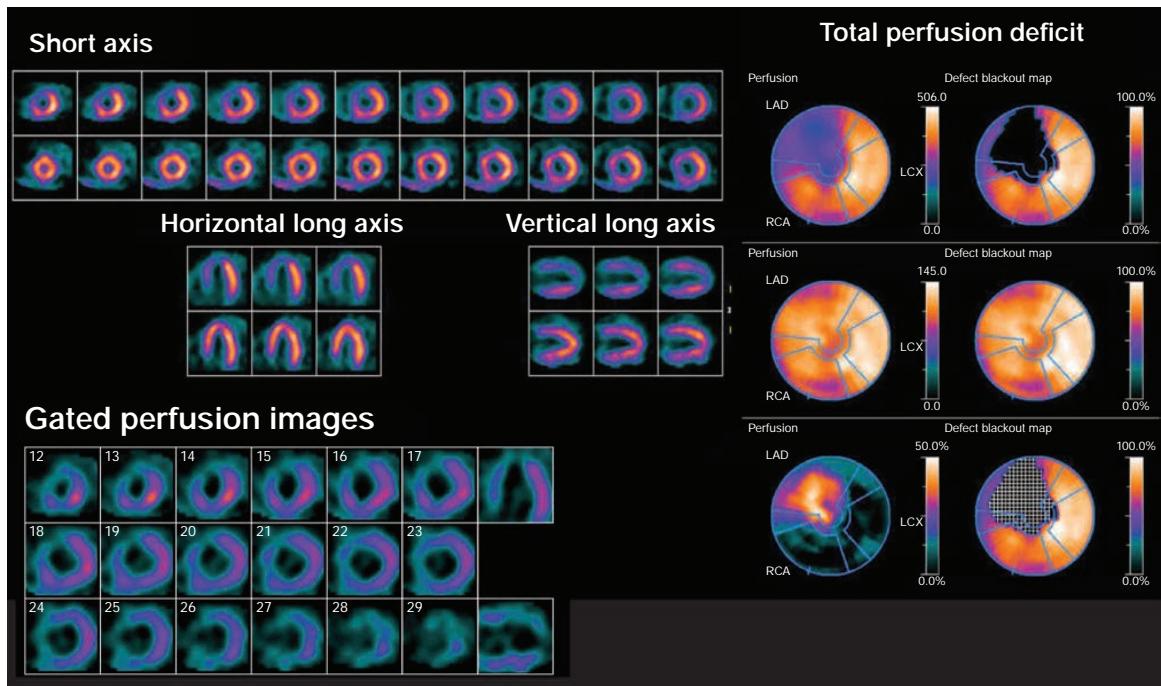
**Radiopharmaceuticals Used in Clinical Imaging** Table 241-1 summarizes the most commonly used radiopharmaceuticals in clinical SPECT and PET imaging.

**Protocols for Stress Myocardial Perfusion Imaging** Both exercise and pharmacologic stress can be used for myocardial perfusion imaging. Exercise stress is generally preferred because it is physiologic and provides additional clinically important information (i.e., clinical and hemodynamic responses, ST-segment changes, exercise duration, and functional status). However, submaximal effort will lower the sensitivity of the test and should be avoided, especially if the test is requested for initial diagnosis of CAD. In patients who are unable to exercise or who exercise submaximally, pharmacologic stress offers an adequate alternative to exercise stress testing. Pharmacologic stress can be accomplished either with coronary vasodilators, such as adenosine, dipyridamole, or regadenoson, or  $\beta_1$ -receptor agonists, such as dobutamine. For patients unable to exercise, vasodilators are the most commonly used stressors in combination with myocardial perfusion imaging. Dobutamine is a potent  $\beta_1$ -receptor agonist that increases myocardial oxygen demand by augmenting contractility, heart rate, and blood pressure similar to exercise. It is generally used as an alternative to vasodilator stress in patients with chronic pulmonary disease, in whom vasodilators may be contraindicated. Dobutamine is also commonly used as a pharmacologic alternative to stress testing in stress echocardiography.

**TABLE 241-1** Radiopharmaceuticals for Clinical Nuclear Cardiology

RADIOPHARMACEUTICAL	IMAGING TECHNIQUE	PHYSICAL HALF-LIFE	APPLICATION
$^{99m}\text{Tc}$ -sestamibi	SPECT	6 h	Myocardial perfusion imaging
$^{99m}\text{Tc}$ -tetrofosmin	SPECT	6 h	Myocardial perfusion imaging
$^{201}\text{TI}$	SPECT	72 h	Myocardial perfusion imaging
$^{123}\text{I}$ -metaiodobenzylguanidine (MIBG)	SPECT	13 h	Cardiac sympathetic innervation
$^{82}\text{Ru}$	PET	76 s	Myocardial perfusion imaging
$^{13}\text{N}$ -ammonia	PET	10 min	Myocardial perfusion imaging
$^{18}\text{F}$ -fluorodeoxyglucose	PET	110 min	Myocardial viability and inflammation imaging

Abbreviations: PET, positron emission tomography; SPECT, single-photon emission computed tomography.



**FIGURE 241-5** Tomographic stress (top of each pair) and rest myocardial perfusion images with technetium-99m sestamibi single-photon emission computed tomography imaging demonstrating a large perfusion defect throughout the anterior and anteroseptal walls. The right panel demonstrates the quantitative extent of the perfusion abnormality at stress (top bull's-eye), at rest (middle bull's-eye), and the extent of defect reversibility (lower bull's-eye). The lower left panel demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction.

### Myocardial Perfusion and Viability Imaging Protocols

Imaging protocols are tailored to the individual patient based on the clinical question, patient's risk, ability to exercise, body mass index, and other factors.

For SPECT imaging, technetium-99m ( $^{99m}\text{Tc}$ )-labeled tracers are the most commonly used imaging agents because they are associated with the best image quality and the lowest radiation dose to the patient (Fig. 241-5). Selection of the protocol (stress-only, single-day, or 2-day) depends on the patient and clinical question. After intravenous injection, myocardial uptake of  $^{99m}\text{Tc}$ -labeled tracers is rapid (1–2 min). After uptake, these tracers become trapped intracellularly in mitochondria and show minimal change over time. This is why  $^{99m}\text{Tc}$  tracers can be helpful in patients with chest pain of unclear etiology occurring at rest, because patients can be injected while having chest pain and imaged some time later after symptoms subside. Indeed, a normal myocardial perfusion study following a rest injection in a patient with active chest pain effectively excludes myocardial ischemia as the cause of chest pain (high negative predictive value). While used commonly in the past for perfusion imaging, thallium-201 protocols are now rarely used because they are associated with a higher radiation dose to the patient.

PET myocardial perfusion imaging is an alternative to SPECT and is associated with improved diagnostic accuracy and lower radiation dose to patients (Table 241-1). The ultra-short half-life of some PET radiopharmaceuticals in clinical use (e.g., rubidium-82) is the primary reason why imaging is generally combined with pharmacologic stress, as opposed to exercise. However, exercise is possible for relatively longer-lived radiotracers (e.g.,  $^{13}\text{N}$ -ammonia). PET imaging protocols are typically faster than SPECT but more expensive. In comparison to SPECT, PET has improved spatial and contrast resolution and provides absolute measures of myocardial perfusion (in mL/min per gram of tissue), thereby providing the patients' regional and global coronary flow reserve. The latter helps improve diagnostic accuracy and risk stratification, especially in obese patients, women, and higher risk individuals (e.g., diabetes mellitus) (Fig. 241-6). Contemporary PET and SPECT

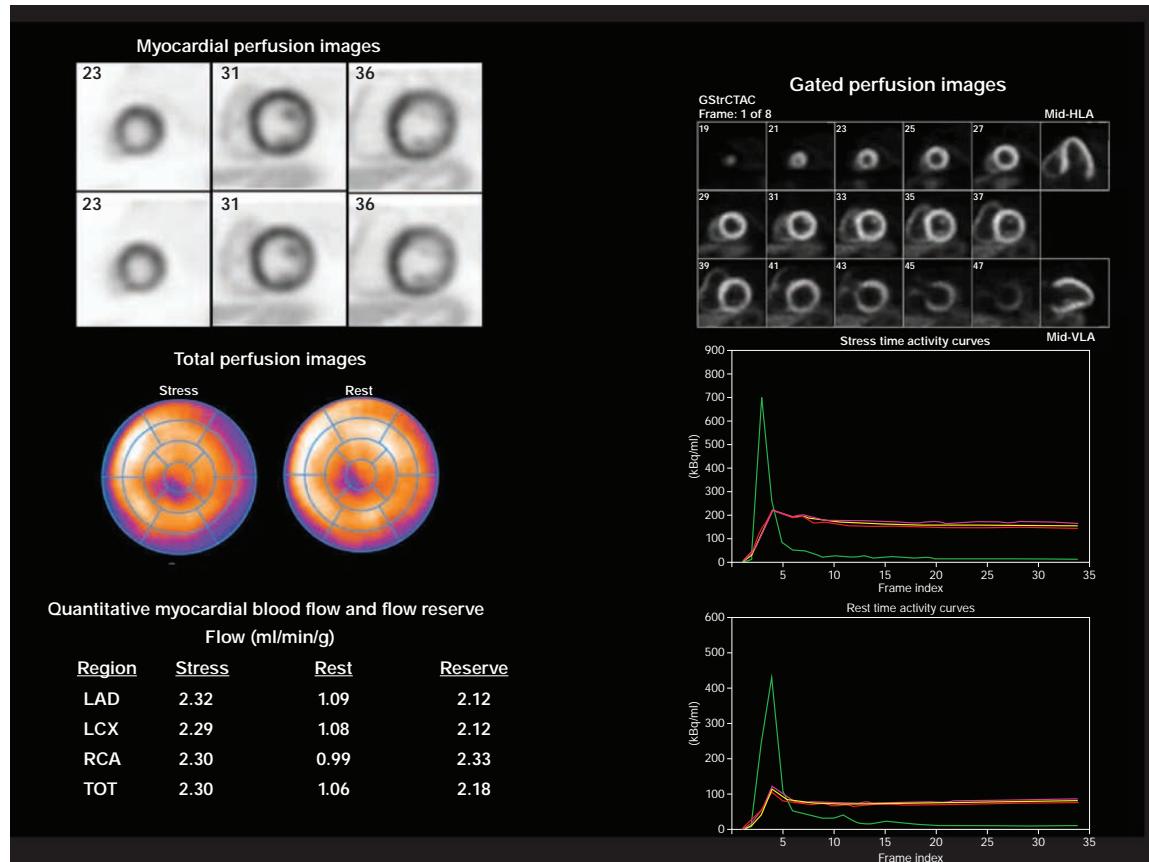
scanners are combined with a CT scanner (so-called *hybrid PET/CT* and *SPECT/CT*). CT is used primarily to guide patient positioning in the field of view and for correcting inhomogeneities in radiotracer distribution due to attenuation by soft tissues (so-called *attenuation correction*). However, it can also be used to obtain diagnostic data including coronary artery calcium (CAC) score and/or CT coronary angiography (discussed below).

For the evaluation of myocardial viability in patients with ischemic cardiomyopathy, myocardial perfusion imaging (with SPECT or PET) is usually combined with metabolic imaging (i.e., fluorodeoxyglucose [FDG] PET). In hospital settings lacking access to PET scanning, thallium-201 SPECT imaging is an excellent alternative. FDG PET is also used in the evaluation of myocardial and vascular inflammation and in patients with suspected infective endocarditis.

Bone scintigraphy with SPECT is currently used for the evaluation of patients with suspected cardiac amyloidosis. As discussed below under applications in new-onset heart failure, bone-seeking  $^{99m}\text{Tc}$  radiotracers (Table 241-1) are currently used to diagnose transthyretin cardiac amyloidosis with high accuracy.

### CARDIAC COMPUTED TOMOGRAPHY

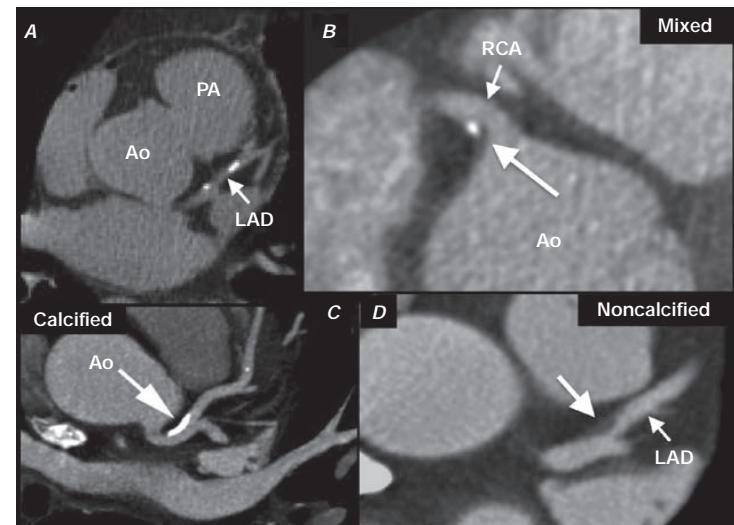
CT acquires images by passing a thin x-ray beam through the body at many angles to generate cross-sectional images. The x-ray transmission measurements are collected by a detector array and digitized into pixels that form an image. The grayscale information in individual pixels is determined by the attenuation of the x-ray beam along its path by tissues of different densities, referenced to the value for water in units known as Hounsfield units. In the resulting CT images, bone appears bright white, air is black, and blood and muscle show varying shades of gray. However, due to the limited contrast between cardiac chambers and vascular structures, iodinated contrast agents are necessary for most cardiovascular indications. Cardiac CT produces tomographic images of the heart and surrounding structures. With modern CT scanners, a three-dimensional dataset of the heart can be acquired in 5–15 s with submillimeter spatial resolution.



**FIGURE 241-6** Multidimensional cardiac imaging protocol with positron emission tomography. The left upper panel demonstrates stress and rest short-axis images of the left and right ventricles demonstrating normal regional myocardial perfusion. The middle panel demonstrates the quantitative bull's-eye display to evaluate the extent and severity of perfusion defects. The lower right panel illustrates the time-activity curves for quantification of myocardial blood flow. The right upper panel demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TOT, total left ventricle.

**CT Calcium Scoring** CT calcium scoring is the simplest application of cardiac CT and does not require administration of iodinated contrast. The presence of coronary artery calcification has been associated with increased burden of atherosclerosis and cardiovascular mortality. Coronary calcium is then quantified (e.g., Agatston score) and categorized as minimal (0–10), mild (10–100), moderate (100–400), or severe (>400) (Fig. 241-7). CAC scores are then normalized by age and gender and reported as percentile scores. Population-based studies in asymptomatic cohorts have reported high cardiac prognostic value of CT calcium score. With appropriate techniques, the radiation dose associated with CAC scanning is very low (~1–2 mSv).

**CT Coronary Angiography** Coronary CT angiography (CTA) is a clinically important alternative to stress testing in selected patients with suspected CAD. Imaging of the coronary arteries by CT is challenging because of their small luminal size and because of cardiac and respiratory motion. Respiratory motion can be reduced by breath-holding, and cardiac motion is best reduced by slowing the patient's heart rate, ideally to under 60 beats/min, using intravenous or oral beta blockade or other rate-lowering drugs. When performing a coronary CTA, image quality is further enhanced using sublingual nitroglycerin to enlarge the coronary lumen just prior to contrast injection. Imaging the whole-heart volume is



**FIGURE 241-7** Examples of non-contrast- and contrast-enhanced coronary imaging with computed tomography (CT). **A**, Calcified coronary plaques in the distal left main and proximal left anterior descending coronary artery (LAD) in a noncontrast cardiac CT scan. Calcium deposits are dense and present as bright white structures on CT, even without contrast enhancement. **B**, **C**, and **D**, Different types of atherosclerotic plaques on contrast-enhanced CT scans. Importantly, noncalcified plaques are evident only on contrast-enhanced CT scans. AO, aorta; PA, pulmonary artery; RCA, right coronary artery.

synchronized to the administration of weight-based and appropriately timed intravenous iodinated contrast. Image acquisition is linked to the timing of the cardiac cycle through ECG triggering. The resulting images are then postprocessed using a three-dimensional workstation, which facilitates interpretation of the coronary anatomy and estimation of the severity of atherosclerosis (Fig. 241-7). A modified version of the enhanced protocol outlined for coronary CTA is used for the evaluation of patients with structural heart disease, especially for preprocedural planning of those undergoing transcatheter valve replacement.

### CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging is based on imaging of protons in hydrogen, which is an advantage, given the abundance of water in the human body. When the body is placed inside an MRI scanner, protons in different tissues, such as in simple fluid or complex macromolecules such as fat or protein, interact with the magnetic field at their unique frequencies. A set of orthogonal gradient coils in the scanner is designed to locate protons spatially so that radiofrequency (RF) pulses of energy can be delivered to select imaging planes of interest. Once the RF pulses stop, the energy absorbed will be released, collected by the phased-array receiver coils placed on the patient's body surface, digitally recorded in a data matrix known as the *K*-space, and then reconstructed into a magnetic resonance image. The large arrays of software methods of delivering RF pulses are known as *pulse sequences*, which aim at extraction of different types of cardiac structural or physiologic information. In CMR, T1-weighted pulse sequences are most common, and they assess cardiac structure and function, blood flow, and myocardial perfusion with pharmacologic stress. T2-weighted and T2\*-weighted pulse sequences, on the other hand, evaluate myocardial edema and myocardial iron infiltration, respectively. In recent years, T1 and T2 mapping have become routinely used in experienced centers in quantifying myocardial tissue characteristics, with T1 mapping most commonly used to scale the spectrum of myocardial inflammation or fibrosis and T2 mapping for myocardial edema. Using a combination of these methods (above), a CMR can accurately assess cardiac structure and function, myocardial infarction, ischemia, and infiltration. Currently, the most common indications for CMR include assessing etiology of cardiomyopathy, detection of myocardial ischemia from other chest pain syndromes, and defining myocardial substrates of arrhythmias. Vector ECG-gating and repetitive patient breath-holding are used by convention to suppress cardiac and respiratory motions, respectively. However, with technical advent, rapid data collection algorithm and diaphragmatic position gating have eliminated the need for ECG-gating and breath-holding in challenging situations. A list of common pulse sequences used in CMR is shown in Table 241-2.

### ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION

Echocardiography, CMR, and cardiac CT are all capable of assessing cardiac structure and function, although echocardiography is generally considered the primary imaging method for these assessments. Radioisotope imaging can also be used to assess left ventricular regional and global systolic function. Echocardiography is most often used to assess the size of all four chambers and thickness of ventricular walls, which are affected by both cardiac and systemic diseases.

The structure of the left ventricle is generally assessed by determining its volume and mass. Left ventricular volumes can be easily estimated from 2D echocardiography by using methods incorporating geometric assumptions. The accuracy of these echocardiographic methods is reduced when foreshortening of the imaging plane leads to underestimation of volumes. Moreover, these methods require accurate delineation of the endocardial border. In this regard, high-resolution tomographic techniques such as CMR or cardiac CT are more accurate for volumetric assessment. Three-dimensional (3D) echocardiography does not require any geometric assumptions about the left ventricle for quantification of volumes and ejection fraction. However, 3D echocardiographic imaging requires substantial expertise and currently is not widely used in practice.

**TABLE 241-2 Clinical Cardiac Magnetic Resonance Pulse Sequences and Their Application**

PULSE SEQUENCE	KEY IMAGING INTERESTS
<b>Cardiac Morphology</b>	
Still frame imaging (black or bright blood)	Cardiac structures
<b>Cardiac Function</b>	
Cine imaging	Left ventricular volume and function
Cine myocardial tagging	Left ventricular deformation (strain)
<b>Blood Flow Imaging</b>	
Velocity-encoded phase contrast	Cardiac and great vessel flow
<b>Stress Testing</b>	
Myocardial perfusion imaging	Regional myocardial blood flow
Cine imaging	Regional wall motion
<b>Myocardial Tissue Characterization</b>	
Late gadolinium enhancement	Myocardial infarction and infiltrative disease
T2-weighted imaging	Myocardial edema
Iron content imaging	Myocardial iron infiltration
<b>Magnetic Resonance Angiography</b>	
Aorta, peripheral and coronary arteries	Luminal stenosis and vessel wall remodeling

Left ventricular dilatation is common to a number of cardiac diseases. For example, regional dysfunction secondary to myocardial infarction can ultimately lead to progressive ventricular dilatation or remodeling. Although dilatation often begins in the region affected by the infarction, subsequent compensatory dilatation can occur in remote myocardial regions as well. The presence of regional wall motion abnormalities associated with ventricular thinning (reflecting scar) in a coronary distribution is strongly suggestive of an ischemic etiology. Regional wall motion can be accurately assessed by echocardiography, CMR, and cardiac CT. Direct assessment of infarcted myocardium is possible with both CMR (evident as areas of late gadolinium enhancement [LGE]) and radionuclide imaging (as assessed by regional perfusion or metabolic defects at rest). CMR can be particularly useful in determining etiology of cardiomegaly and ventricular dysfunction, with LGE in coronary distributions being nearly pathognomonic for infarction (Video 241-1).

More global ventricular dilatation is seen in cardiomyopathy and dilatation due to valvular heart disease. Idiopathic, nonischemic cardiomyopathies will typically result in global ventricular dilatation and dysfunction, with thinning of the walls. Patients with substantial ventricular dysynchrony due to conduction abnormalities will have a typical pattern of contraction (e.g., delay of contraction of the lateral wall with left bundle branch block). As discussed later in this chapter, regurgitant lesions of either the mitral or aortic valves can lead to substantial ventricular dilatation, and assessment of ventricular size is integral in the evaluation and timing of surgical correction. Because changes in ventricular size are used clinically to determine which patients should undergo valve surgery, accurate assessment of changes in ventricular size is essential. Although serial echocardiography can provide these data, serial assessment by CMR may be more accurate when appreciation of subtle changes over time is important.

Left ventricular wall thickness and mass are also important measures of cardiac and systemic disease. The left ventricle will hypertrophy under any condition in which its afterload is increased, including conditions that obstruct outflow, such as aortic stenosis, hypertrophic cardiomyopathy, and subaortic membranes; in postcardiac aortic obstruction seen in coarctation; or in systemic conditions characterized by increased afterload, such as hypertension. The pattern of ventricular hypertrophy can change depending on the etiology. Aortic stenosis and hypertension are typically characterized by concentric hypertrophy, in which the ventricular walls thicken "concentrically"

and cavity size is usually small. In volume overload conditions such as mitral or aortic regurgitation, there may be minimal increase in ventricular wall thickness, but substantial ventricular dilatation leads to marked increases in left ventricular mass.

Ventricular wall thickness can be measured and ventricular mass can be calculated by either echocardiography or CMR. Although radionuclide imaging and cardiac CT can also provide measures of left ventricular mass, they are not generally used for this purpose. Although measurement of wall thickness with echocardiography is relatively straightforward and accurate, determining left ventricular mass by echocardiography requires using one of several formulas that takes into account both wall thickness and ventricular cavity dimensions. Assessment of left ventricular mass by CMR has the advantage of not requiring geometric assumptions and is thus more accurate than echocardiography.

### ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC FUNCTION

Assessment of ejection fraction, or the percentage of blood ejected with each beat, has been the primary method to assess systolic function and is generally calculated by subtracting end-systolic volume from end-diastolic volume and dividing by end-diastolic volume. All cardiac imaging modalities can provide direct measurements of left ventricular ejection fraction (LVEF). As discussed above, tomographic techniques (e.g., CMR, CT, and radionuclide imaging) are generally more accurate and reproducible than echocardiography because there are no geometric assumptions and these techniques are not dependent on operator skill. An LVEF of 55% or greater is generally considered normal, and an LVEF of 50–55% is considered in the low-normal range, although these can vary widely; normal ejection fraction tends to be higher in women than in men.

Newer methods to assess systolic function, such as myocardial strain or deformation imaging using speckle-tracking methods on echocardiography, or myocardial tagging or feature tracking on CMR, can provide a more sensitive approach to detection of systolic dysfunction, in part, because these measures are geometry independent. Additional assessments based on these novel methods include assessment of myocardial twist and torsion. Regional strain patterns can differ in various diseases. For example, in cardiac amyloidosis, it is common to see a reduction in myocardial strain at the base of the heart with relative sparing of the apex. Strain imaging is being used more commonly in conditions such as valvular heart disease and early detection of cardiotoxicity following chemotherapy and/or radiation therapy. In addition to estimation or calculation of ejection fraction, stroke volume can be assessed by any of the imaging methods, by subtracting the end-systolic volume from the end-diastolic volume, or by quantifying forward flows using echocardiographic Doppler methods or phase-contrast CMR imaging. They offer measures of systolic function other than LVEF.

### ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Echocardiography remains the primary method for clinical assessment of diastolic function, in part, because echocardiography has the highest temporal resolution of all the imaging techniques. Recent advances in Doppler tissue imaging allow for accurate assessment of the velocity of myocardial wall motion by assessing the excursion of the mitral annulus in diastole. Mitral annular relaxation velocity, or E', is inversely related to the time constant of relaxation, tau, and has been shown to have prognostic significance in patients with heart failure. Dividing the standard mitral inflow maximal velocity, E, by the mitral annular relaxation velocity yields E/E', which has been shown to correlate with left ventricular filling pressures. The utility of standard E and A wave ratios for assessment of diastolic function has been questioned. Mitral deceleration time can be a useful measure if very short (<150 ms), suggesting restrictive physiology and severe diastolic dysfunction. Left atrial volume is considered an integrator of diastolic function, and minimal volume may be more reflective of left ventricular filling pressures than maximal volume. Several grading methods for diastolic function have been proposed that take into account a number

of diastolic parameters, including Doppler tissue-based relaxation velocities, pulmonary venous Doppler, and left atrial size (**Fig. 241-8**). Diastolic function worsens with aging, and most diastolic parameters need to be adjusted for age.

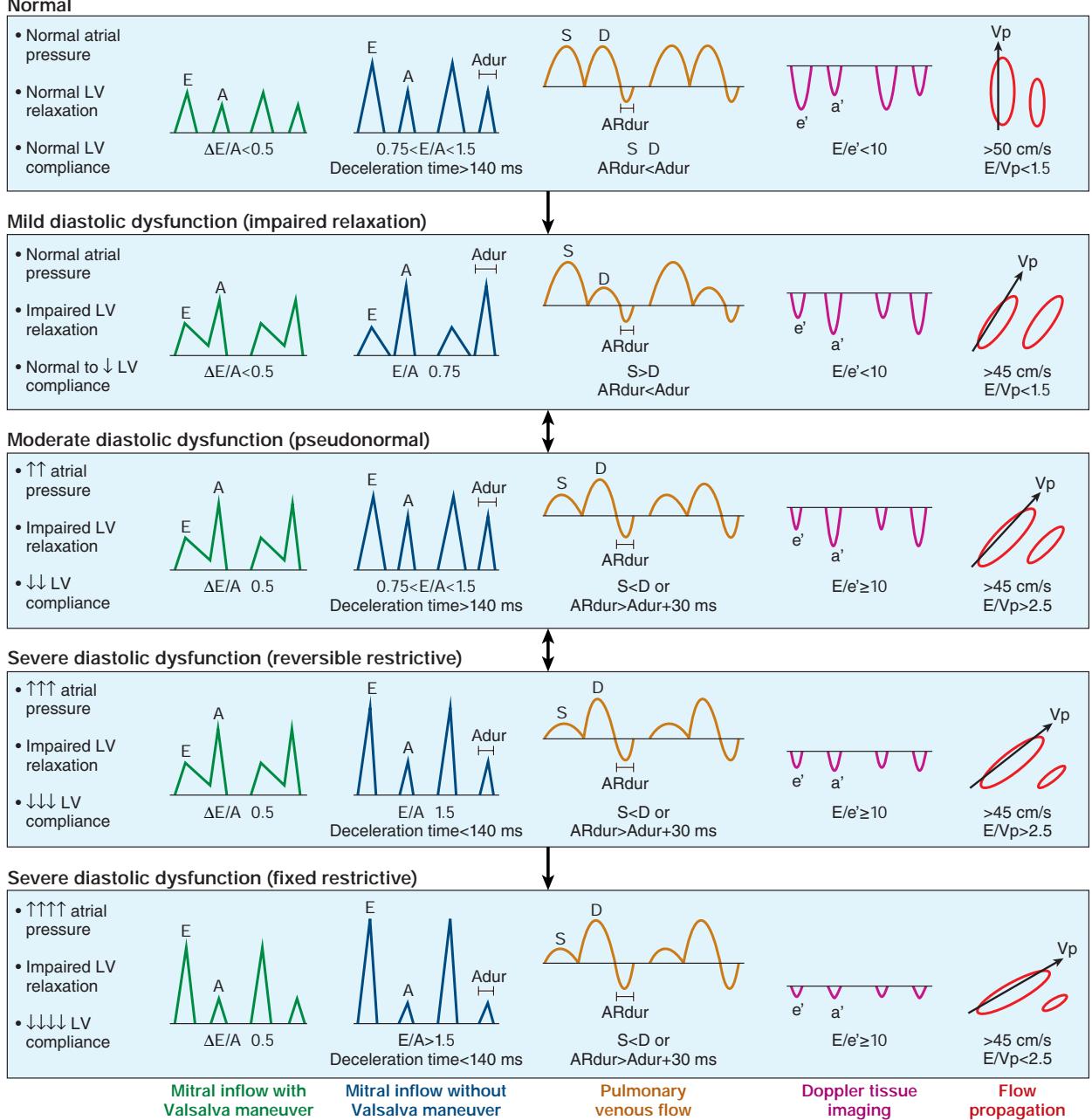
### ASSESSMENT OF RIGHT VENTRICULAR FUNCTION

Right ventricular size and function have been shown to be prognostically important in a variety of conditions and can be assessed by echocardiography, CMR, CT, or radionuclide imaging methods. CMR is considered the most accurate noninvasive technique to evaluate the structure and ejection fraction of the right ventricle (**Video 241-2**). Assessment of the right ventricle by echocardiography has generally been qualitative, owing in part to the unusual geometry of the right ventricle. However, several quantitative methods are available for assessment of right ventricular function, including fractional area change (FAC = [diastolic area – systolic area]/diastolic area), which has been shown to correlate with outcomes in heart failure and after myocardial infarction. Excursion of the tricuspid annulus (tricuspid annular plane systolic excursion [TAPSE]) is another method to assess right ventricular function, although it is mostly used in research settings.

Abnormalities of right ventricular size and function are generally secondary to either diseases that affect the right ventricle intrinsically or disease in which the right ventricle responds to abnormalities elsewhere in the heart or pulmonary vasculature. Intrinsic diseases that affect the right ventricle include congenital abnormalities, including hypoplastic right ventricle and arrhythmogenic right ventricular dysplasia, and acquired conditions, such as right ventricular infarction and infiltrative diseases. Right ventricular dilatation can occur due to both chronic and acute processes. Long-standing pulmonary hypertension or pulmonary outflow tract obstruction leads to right ventricular hypertrophy and ultimately dilatation. An acute process that can cause profound right ventricular dilatation and dysfunction is acute pulmonary embolism. In the setting of acute occlusion of a pulmonary artery or branch, an acute rise in pulmonary vascular resistance causes a previously normal right ventricle to dilate and fail due to the increased afterload. In acute pulmonary embolism, right ventricular dilatation and dysfunction are signs of substantial hemodynamic compromise and are associated with a marked increased risk of death. In addition to right ventricular dilatation, acute pulmonary embolism is often associated with a specific pattern of regional right ventricular dysfunction, commonly referred to as the McConnell sign, characterized by preservation of right ventricular wall motion in the basal and apical regions and dyskinesis in the region of the mid right ventricular free wall. This abnormality is highly specific for acute pulmonary embolism and is likely secondary to acute increases in right ventricular load.

Any disease that causes increased pulmonary vascular resistance can lead to right ventricular dilatation and dysfunction. For example, long-standing chronic obstructive pulmonary disease increases pulmonary vascular resistance and results in cor pulmonale. Acute pneumonia can cause findings that are similar to acute pulmonary embolism, and right ventricular dysfunction has been a hallmark of severe COVID-19 disease due to either macro- or microthrombosis in the pulmonary vasculature. In patients with right ventricular dilatation without obvious pulmonary disease, intracardiac shunts should be considered. The increased flow through the pulmonary vasculature as a result of an atrial septal or ventricular septal defect can, over time, result in elevation in pulmonary vascular resistance with subsequent dilatation and hypertrophy of the right ventricle. Right ventricular dilatation and dysfunction can be seen in left-sided heart disease, and patients who develop RV dilatation and dysfunction due to predominantly left-sided disease have worse outcomes.

In addition to assessment of left and right ventricular structure and function, assessment of the other cardiac chambers also provides important clues to intracardiac and systemic diseases. Enlargement of the left atrium is common in patients with hypertension and is also suggestive of increased left ventricular filling pressures; indeed, left atrial size is often termed the “hemoglobin A<sub>1c</sub>” of diastolic function because left atrial enlargement reflects long-standing increase in



**FIGURE 241-8** Stages of diastolic function based on various parameters, including mitral inflow (with and without Valsalva maneuver), Doppler tissue imaging, pulmonary venous flow, and flow propagation. (Adapted from MM Redfield et al: Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 289:194, 2003.)

left-sided filling pressures. Right atrial dilatation and dilatation of the inferior vena cava are common in conditions in which central venous pressure is elevated.

## PATIENT SAFETY CONSIDERATIONS

### RADIATION EXPOSURE

Both cardiac CT and radionuclide imaging expose patients to ionizing radiation. Several recent publications have raised concern regarding the potential harmful effects of ionizing radiation associated with cardiac imaging. The *effective dose* is a measure used to estimate the biologic effects of radiation and is expressed in millisieverts (mSv). However, measuring the radiation effective dose associated with diagnostic imaging is complex and imprecise and often results in varying estimates, even

among experts. The effective dose from a typical myocardial perfusion SPECT scan ranges between ~4 and 11 mSv, depending on the protocol and type of scanner used. The effective dose from a typical myocardial perfusion PET scan is lower, ~2.0–4 mSv. Radiation exposure associated with cardiac CT is variable and, as with radionuclide imaging, also depends on the imaging protocol and scanner used. Although historic radiation doses with cardiac CT have been quite high, the introduction of newer technologies (e.g., x-ray tube modulation, prospective ECG gating) has resulted in a significant dose reduction. The current average radiation dose for a coronary CTA ranges from 3 to 15 mSv and, in selected cases, can be as low as 1 mSv. Imaging laboratories follow the ALARA (as low as reasonably achievable) principle when balancing the clinical need and imaging approach. By comparison, the average dose for invasive coronary angiography is ~7 mSv, whereas exposure

**1840** to radiation from natural sources in the United States amounts to ~3 mSv annually.

The risk of a fatal malignancy from medical imaging-related radiation is difficult to estimate precisely but is likely small and difficult to discern from the background risk of natural malignancies. The small but potential radiation risks from imaging mandate an assessment of the risk-versus-benefit ratio in the individual patient. In this context, one must not fail to take into account the risks of missing important diagnostic information by not performing a test (which could potentially influence near-term management and outcomes) for a theoretical concern of a small long-term risk of malignancy. Before ordering any test, especially one associated with ionizing radiation, we must ensure the appropriateness of the study and that the potential benefits outweigh the risks. The likelihood that the study being considered will affect clinical management of the patient should be addressed before testing is performed. It is also important that "routine" follow-up scans in asymptomatic individuals be avoided.

### CONTRAST AGENTS

Contrast agents are commonly used in cardiac CT, CMR, and echocardiography. Although their use significantly enhances the diagnostic information of each of these tests, there are also potential risks from the administration of contrast agents that should be considered.

The risk of adverse reactions from iodinated contrast agents used in cardiac CT is well established. The precise pathogenesis of contrast reactions following intravascular administration of iodinated contrast media is not known. The overall incidence of contrast reactions is 0.4–3% with nonionic formulations and higher for ionic formulations. Most contrast adverse reactions are mild and self-limiting. The risk of contrast-induced nephropathy (CIN) in patients with relatively normal renal function (estimated glomerular filtration rate [eGFR] >60 mL/min) is low. In most patients, CIN is self-limited, and renal function usually returns to baseline within 7–10 days, without progressing to chronic renal failure. However, this risk increases in patients with GFR <60 mL/min, especially older diabetic subjects. In such patients, appropriate screening and pre- and postscan hydration are necessary.

The use of gadolinium-based contrast agents (GBCAs) enhances the versatility of CMR imaging. There are many commercially available GBCAs in the United States, but their use in cardiac imaging is off-label. Mild reactions from GBCAs, such as skin pruritis or erythema, occur in ~1% of patients, but severe or anaphylactic reactions are very rare at ~1 in 100,000 patients. All GBCAs are chelated to make the compounds nontoxic and facilitate renal excretion. Older generation (group I) linear-structured GBCAs have been associated with a rare but serious condition known as nephrogenic systemic fibrosis (NSF), which is an interstitial inflammatory reaction manifested as fibrosis of tissues or internal organs and even death. Risk factors to developing NSF include high-dose use in presence of severe renal dysfunction (eGFR <30 mL/min per 1.73 m<sup>2</sup>), need for hemodialysis, an eGFR <15 mL/min per 1.73 m<sup>2</sup>, acute renal deterioration, and concurrent proinflammatory/systemic illnesses. Newer-generation (group II) macrocyclic-structured GBCAs have a substantially improved safety profile, including in patients with chronic kidney dysfunction and, indeed, have become the agents of choice in most MRI centers. The

American College of Radiology considers the use of group II agents as safe, including in patients with renal dysfunction or dialysis. With widespread use of group II GBCAs, routine pretest screening, and weight-based dosing, a near-zero incidence of NSF has been reported in the past decade.

Contrast agents can also be used in echocardiography. Injected agitated saline is used routinely to assess cardiac shunts, because these "bubbles" are too large to traverse the pulmonary circulation. After saline injection, the presence of bubbles in the left side of the heart is indicative of shunt, although the location can sometimes be difficult to determine. The current U.S. Food and Drug Administration (FDA)-approved use of echocardiographic contrast agents is for opacification of left-sided chambers and to improve delineation of left ventricular endocardial border in patients with suboptimal echocardiograms. These agents are either albumin- or lipid-based microspheres filled with inert gases, typically perfluorocarbons. They are considered extremely safe, although they have, in extremely rare instances, been associated with allergic reactions and neurologic events.

### SAFETY CONSIDERATIONS OF CMR IN PATIENTS WITH PACEMAKERS AND DEFIBRILLATORS

There are now multiple FDA-approved MRI-conditional internal cardiac defibrillators and pacemakers that are safe for patients who need an MRI study. For non-FDA-approved cardiac devices (legacy devices), collective evidence has indicated that MRI studies can be safely performed at 1.5 T under normal operational settings, in the absence of fractured, epicardial, or abandoned leads, and when an experienced staff is available to interrogate the cardiac device before and after the MRI study. The Centers for Medicare and Medicaid Services have approved and expanded coverage of MRI studies in patients with an implanted legacy device.

## PATIENT-CENTERED APPLICATIONS OF CARDIAC IMAGING

### CORONARY ARTERY DISEASE

The basis for the diagnostic application of imaging tests in patients with known or suspected CAD should be viewed considering the pretest probability of disease as well as the specific characteristics of imaging tests (i.e., sensitivity and specificity). In symptomatic patients, the prevalence or pretest probability of CAD differs based on the type of symptom (typical angina, atypical angina, noncardiac chest pain), as well as on age, gender, and coronary risk factors. In an individual patient, the results of the initial test inform the posttest likelihood of CAD. In patients undergoing sequential testing (e.g., ECG treadmill testing followed by stress imaging), the posttest probability of disease after the first test becomes the pretest likelihood of disease for the second test. Regardless of the sequence, the expectation is that a test will provide sufficient information to confirm or exclude the diagnosis of CAD and that such information will allow accurate risk stratification to be able to guide management decisions.

**Table 241-3** summarizes the relative diagnostic accuracies of cardiac imaging modalities for the diagnosis of CAD.

**TABLE 241-3 Comparative Diagnostic Accuracy of Cardiac Imaging Approaches to Coronary Artery Disease**

IMAGING MODALITY	PUBLISHED DATA	SENSITIVITY	SPECIFICITY
Exercise echocardiography	15 studies (n = 1849 patients)	84%	82%
Dobutamine echocardiography	28 studies (n = 2246 patients)	80%	84%
SPECT MPI	113 studies (n = 11,212 patients)	88%	76%
Myocardial perfusion PET	9 studies (n = 650 patients)	93%	81%
CMR perfusion	37 studies (n = 2841 patients)	91%	81%
CMR wall motion	14 studies (n = 754 patients)	83%	86%
Coronary CTA	18 studies (n = 1286 patients)	99%	89%

*Note:* In these studies, the diagnosis of coronary artery disease was based on the presence of a >50% or >70% stenosis on invasive coronary angiography.

*Abbreviations:* CMR, cardiac magnetic resonance; CTA, computed tomography angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

It is important to highlight that most studies included in meta-analyses of the diagnostic accuracy of cardiac imaging modalities for the diagnosis of CAD were retrospective, small, single-center studies, comprising predominantly male patients with a high prevalence of CAD (>50–60%). Multicenter studies assessing the performance of individual modalities or comparing different modalities have consistently resulted in more modest diagnostic accuracies, tracking more closely with how these tests perform in clinical practice.

**Stress Echocardiography** The hallmark of myocardial ischemia during stress echocardiography is the development of new regional wall motion abnormalities and reduced systolic wall thickening (Video 241-3). Stress echocardiography can be performed in conjunction with exercise or dobutamine stress. Stress echocardiography is best at identifying inducible wall motion abnormalities in previously normally contracting segments. In a patient with wall motion abnormalities at rest, the specificity of stress echocardiography is reduced, and worsening regional function of a previously abnormal segment might reflect worsening contractile function in the setting of increased wall stress rather than new evidence of inducible ischemia.

The advantages of stress echocardiography over other stress imaging techniques include its relatively good diagnostic accuracy, widespread availability, no use of ionizing radiation, and relatively low cost. Limitations of stress echocardiography include (1) the technical challenges associated with image acquisition at peak exercise because of exertional hyperpnea and cardiac excursion, (2) the fact that rapid recovery of wall motion abnormalities can be seen with mild ischemia (especially with one-vessel disease, which limits sensitivity), (3) difficulty detecting residual ischemia within an infarcted territory because of resting wall motion abnormality, (4) high operator dependence for acquisition of echocardiographic data and analysis of images, and (5) the fact that good-quality complete images viewing all myocardial segments occur in only 85% of patients. Newer techniques, including second harmonic imaging and the use of intravenous contrast agents, improve image quality, but their effect on diagnostic accuracy has not been well documented.

As with nuclear perfusion imaging, stress echocardiography is often used for risk stratification in patients with suspected or known CAD. A negative stress echocardiogram is associated with an excellent prognosis, allowing identification of patients at low risk. Conversely, the risk of adverse events increases with the extent and severity of wall motion abnormalities on stress echocardiography.

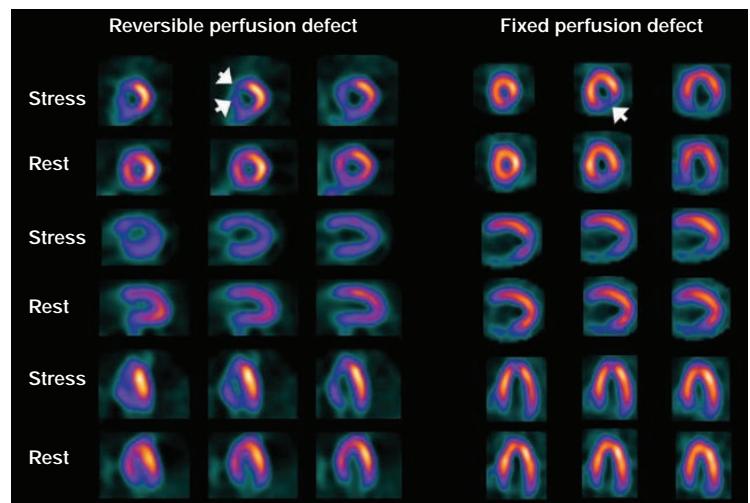
**Stress Radionuclide Imaging SPECT** Myocardial perfusion imaging is the most common form of stress imaging tests for CAD evaluation. The presence of a reversible myocardial perfusion defect is indicative of ischemia (Fig. 241-9, left panel), whereas a fixed perfusion defect generally reflects prior myocardial infarction (Fig. 241-9, right panel). As discussed above, PET has advantages compared to SPECT, but it is not widely available and is more expensive and, thus, considered an emerging technology in clinical practice.

Nuclear perfusion imaging is another robust approach to diagnose obstructive CAD, quantify the magnitude of inducible myocardial ischemia, assess the extent of tissue viability, and guide therapeutic management (i.e., selection of patients for revascularization). One of the most valuable clinical applications of radionuclide perfusion imaging is for risk stratification. It is well established that patients with a normal SPECT or PET study exhibit a low rate of major adverse cardiac events of <1% annually. Importantly, the risks of death and myocardial infarction increase linearly with increasing magnitude of perfusion abnormalities, reflecting the extent and severity of CAD.

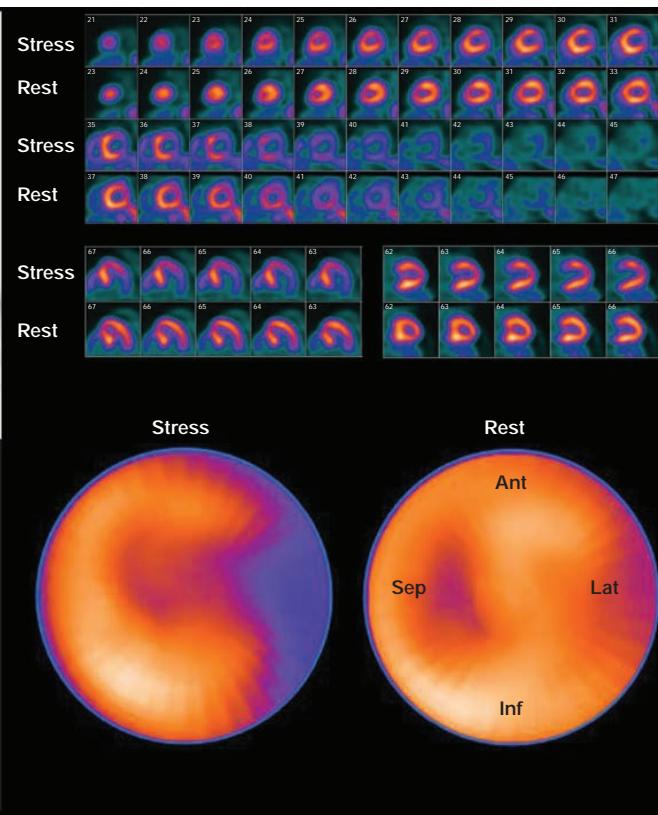
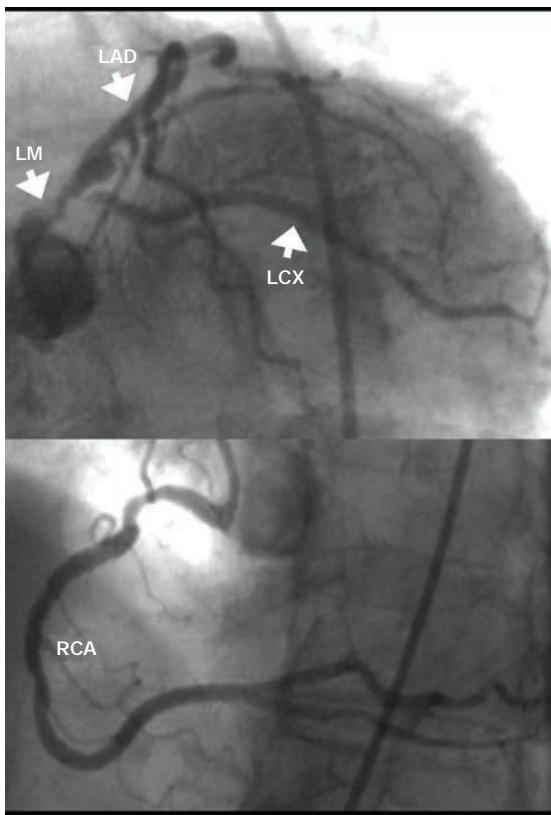
Despite the widespread use and clinical acceptance of radionuclide imaging in CAD evaluation, a recognized limitation of this approach is that it often uncovers only coronary territories supplied by the most severe stenoses. Consequently, it is relatively insensitive to accurately delineate the extent of obstructive angiographic CAD, especially in the setting of multivessel disease. The use of quantitative myocardial blood flow and coronary flow reserve with PET can help mitigate this limitation. In patients with so-called “balanced” ischemia or diffuse CAD, measurements of coronary flow reserve uncover areas of myocardium at risk that would generally be missed by performing only relative assessments of myocardial perfusion (Fig. 241-10). Conversely, a normal coronary flow reserve is associated with a very high negative predictive value for excluding high-risk angiographic CAD. These measurements of coronary flow reserve also contribute to risk stratification across the spectrum of ischemic changes, including patients with visually normal myocardial perfusion.

**HYBRID CT AND NUCLEAR PERFUSION IMAGING** Because many of the newer generation nuclear medicine scanners integrate CT and a gamma camera in the same acquisition gantry, it is now possible to acquire and quantify myocardial scar and ischemia and CAC scoring from a single dual-modality study (SPECT/CT or PET/CT) (Fig. 241-11). The rationale for this integrated approach is predicated on the fact that the perfusion imaging approach is designed to uncover only obstructive atherosclerosis. Conversely, CAC scoring provides a quantitative measure of the anatomic extent of atherosclerosis. This provides an opportunity to improve the conventional models for risk assessment using nuclear imaging alone, especially in patients without known CAD.

**Cardiac CT** Voluminous plaques are more prone to calcification, and stenotic lesions frequently contain large amounts of calcium. Indeed, there is evidence that high CAC scores are generally predictive of a higher likelihood of obstructive CAD, and the available data support the concept of a threshold phenomenon governing this relationship (i.e., Agatston score >400). However, given the fact that CAC scores are not specific markers of obstructive CAD, one should be cautious in using this information as the basis for referral of patients to coronary angiography, especially in symptomatic patients with low-risk stress tests. Conversely, CAC scores <400, especially in symptomatic patients with intermediate-high likelihood of CAD, as in those with typical angina, may be less effective in excluding CAD, especially in young symptomatic men and women who may have primarily noncalcified atherosclerosis (Fig. 241-12).



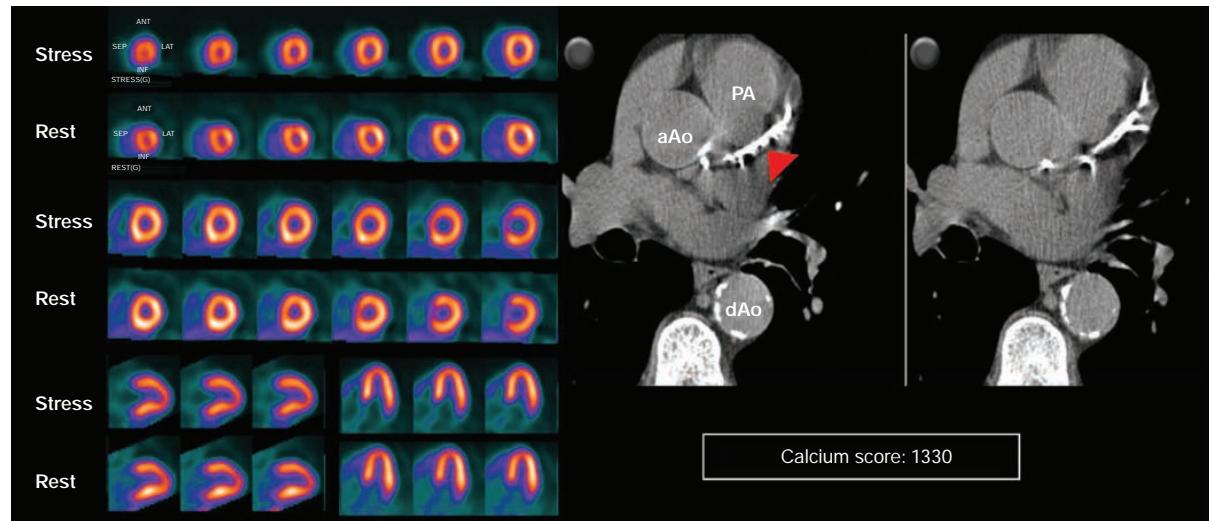
**FIGURE 241-9** Selected technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography images of two different patients demonstrating a reversible perfusion defect involving the anterior and septal left ventricular wall, reflecting ischemia in the left anterior descending coronary territory (arrows in left panel) and a fixed perfusion defect involving the inferior and inferolateral walls consistent with myocardial scar in the right coronary territory (arrow in right panel).



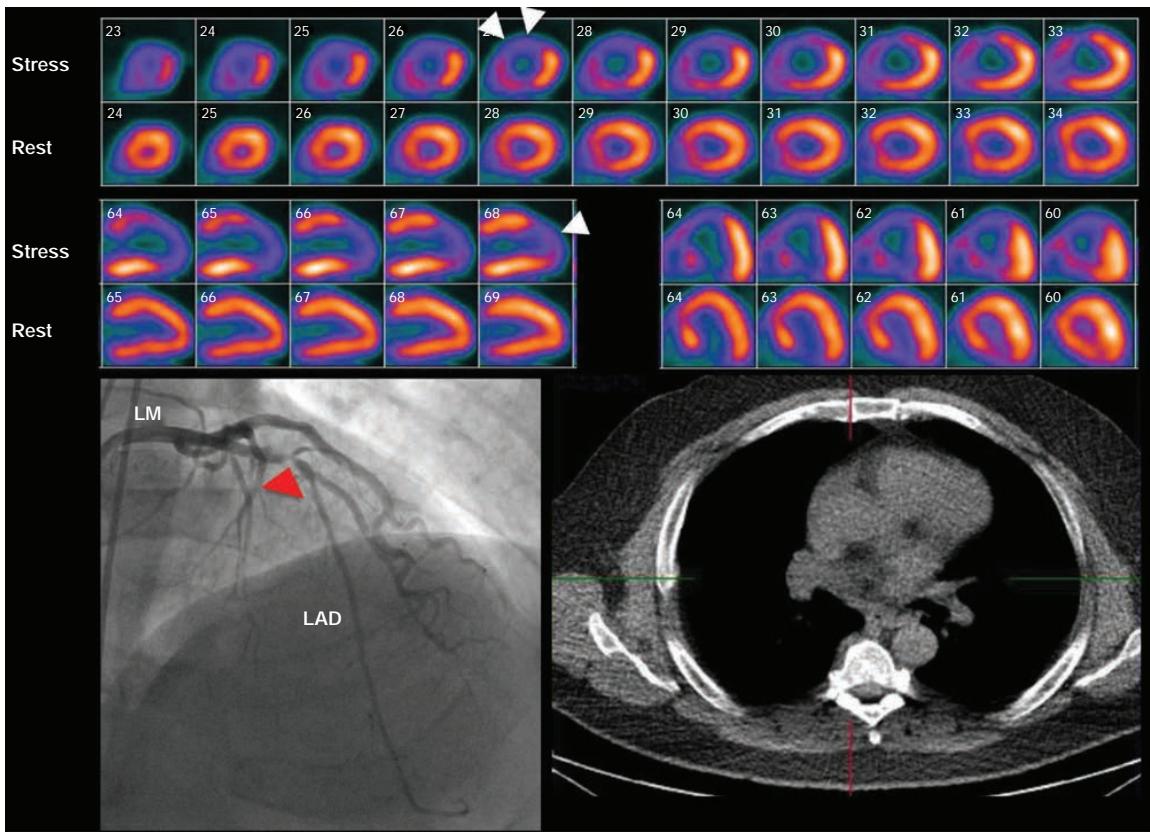
**FIGURE 241-10** Coronary angiographic (*left panel*) and rubidium-82 myocardial perfusion positron emission tomography (*right panel*) in an 85-year-old female with diabetes presenting with chest pain. The coronary angiogram demonstrates significant stenoses of the left main and circumflex coronary arteries. However, the perfusion images demonstrate only a reversible lateral wall defect. Quantification of stress and rest myocardial blood flow demonstrated a significant, global reduction on coronary flow reserve (estimated at 1.2, normal value >2.0), reflecting extensive myocardium risk that was underestimated by the semiquantitative estimates of myocardial perfusion. LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; RCA, right coronary artery.

As discussed above, the improved temporal and spatial resolution of modern multidetector CT scanners offers a unique noninvasive approach to delineate the extent and severity of coronary atherosclerosis with coronary CTA. The extremely high sensitivity of this approach offers a very effective means for excluding the presence of

CAD (high negative predictive value) (Table 241-3). In the setting of high coronary calcium scores (e.g., >400), however, specificity is reduced because the blooming artifact of calcium does not allow one to evaluate the vessel lumen accurately. Given the high negative predictive value of CTA, a normal scan result effectively excludes



**FIGURE 241-11** Stress and rest rubidium-82 myocardial perfusion positron emission tomography (PET) images (*left*) and noncontrast gated computed tomography (CT) images (*right*) delineating the extent and severity of coronary artery calcifications obtained with integrated PET/CT imaging. The images demonstrate extensive atherosclerosis (Agatston coronary calcium score = 1330) without flow-limiting disease based on the normal perfusion study. aAo, ascending aorta; dAo, descending aorta; PA, pulmonary artery.



**FIGURE 241-12** Stress and rest rubidium-82 myocardial perfusion positron emission tomography images (top), noncontrast gated computed tomography images (lower right), and selected coronary angiographic images obtained on a 59-year-old male patient with atypical angina. Despite the absence of significant coronary calcifications (Agatston calcium score = 0), the perfusion images demonstrated a dense and reversible perfusion defect involving the anterior and anteroseptal walls (arrows), reflecting significant obstructive disease in the left anterior descending coronary artery (LAD), confirmed on angiography. LM, left main artery.

obstructive CAD and abolishes the need for further investigation. As discussed below, this may be quite useful in patients with low-intermediate clinical risk presenting to the emergency department (ED) for chest pain. However, the limited capability of this technique to determine which coronary plaques are flow limiting can make abnormal scan results more difficult to interpret, especially in terms of the possible need of revascularization. There are emerging data suggesting that by adding a stress myocardial perfusion CT evaluation (similar to stress perfusion CMR) (Fig. 241-13, top panel) or an estimated fractional flow reserve (so-called FFR<sub>CT</sub>) (Fig. 241-13, lower panel), one can define the hemodynamic significance of anatomic stenosis. FFR<sub>CT</sub> is beginning to enter routine clinical practice. However, CT myocardial perfusion remains an emerging technology.

As with invasive coronary angiography, assessments of the extent of CAD by CTA can also provide useful prognostic information. A low 1-year cardiac event rate has been reported for patients without coronary atherosclerosis on CTA. For patients with obstructive CAD, the risk of adverse cardiac events increases proportionally with the extent of angiographically obstructive CAD. There is new evidence that even the presence of nonobstructive atherosclerosis increases the risk of adverse cardiac events.

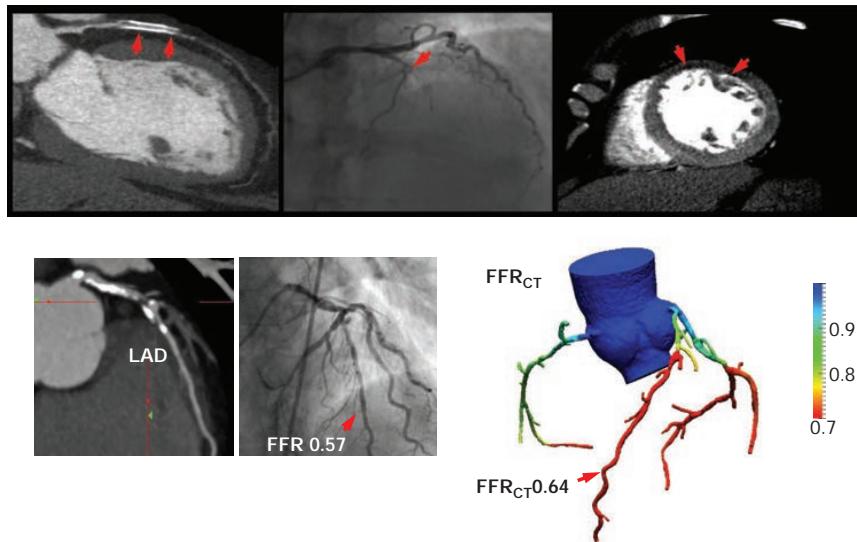
Although CTA can be helpful in assessing patency of bypass grafts, the assessment of stents is somewhat more challenging because the limited spatial resolution of CT and stent diameter (<3 mm being associated with the highest number of partial lumen visualization and nondiagnostic scans) both contribute to limited clinical results.

**CMR Imaging** CMR evaluates for ischemia from CAD by assessing regional myocardial perfusion or regional wall motion at rest and during pharmacologic stress with an intravenous infusion of

vasodilator agent or dobutamine. Myocardial perfusion is evaluated by injecting a GBCA bolus followed by imaging data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Relative perfusion deficits are recognized as regions of low signal intensity (black) within the myocardium (Video 241-4). Several minutes after GBCA injection, LGE imaging allows detection of bright areas of myocardial scar (white), which permits comparison of regions of hypoperfusion and infarction to quantify myocardial ischemia (Fig. 241-14).

With better delineation of the endocardial borders, dobutamine CMR has better diagnostic accuracy than dobutamine echocardiography for detection of CAD, especially in patients with poor acoustic window (Table 241-3). High-dose dobutamine carries the risk of serious ventricular arrhythmias (~1%), but most cases can be prevented with proper monitoring of vital signs and regional cine function. The advantages of stress perfusion CMR over SPECT include its higher spatial resolution, which allows detection of subendocardial ischemia or infarction that may be missed by SPECT. As with other imaging modalities, stress CMR studies also provide robust risk stratification. In a recent randomized controlled trial, a stress CMR-guided strategy was shown to improve the guidance toward the use of invasive investigation and coronary revascularization.

**Selecting a Testing Strategy in Patients without Known CAD** As discussed above, there are many options for the evaluation of a patient with suspected CAD presenting with chest pain symptoms. The critical questions to be answered by a testing strategy include the following: (1) Does the chest pain reflect obstructive CAD? (2) What are the short- and long-term risks? (3) Does the patient need to be considered for revascularization? With improved guideline-directed



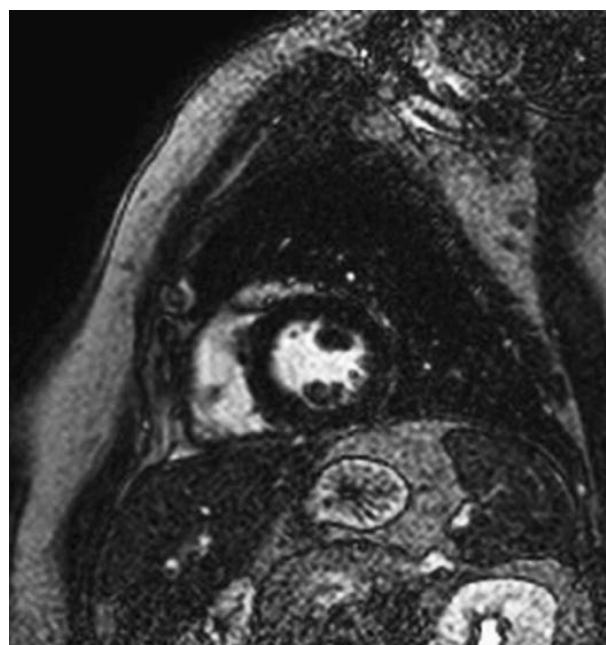
**FIGURE 241-13** Examples of novel approaches to the assessment of flow-limiting coronary artery disease (CAD) with cardiac computed tomography (CT). In the top panel, representative views of coronary CT angiogram (CTA; left), coronary angiogram (middle), and stress myocardial perfusion CT (right) images in a patient with CAD and prior stenting of the left anterior descending coronary artery (LAD) are presented. On the CTA, the stent (arrows) is totally occluded as evidenced by the loss of contrast enhancement distal to the stent. The coronary angiogram demonstrates a concordant total occlusion of the LAD. On the perfusion CT images, there is a black rim (arrows) involving the anterior and anterolateral walls, indicating the lack of contrast opacification during stress consistent with myocardial ischemia. (Images courtesy of CORE 320 investigators.) The lower panel illustrates an example of fractional flow reserve (FFR) estimates with coronary CTA (left) compared to the reference standard of invasive FFR. The FFR reflects the pressure differential between a coronary segment distal to a stenosis and the aorta. In normal coronary arteries, there is no gradient, and FFR is 1. An FFR <0.80 is consistent with a hemodynamically significant stenosis. (Images courtesy of Dr. James Min, Cornell University, New York.)

medical therapy (GDMT), large-scale clinical trials have indicated the benefits of GDMTs in which the majority of the patients with stable CAD are at low risk of serious cardiac events on the basis of GDMT alone, with coronary revascularization best reserved for patients with severe symptoms despite adequate medical therapy. Imaging, however, will continue to play a significant role in diagnosing the etiology of chest pain and risk assessment of individual patients.

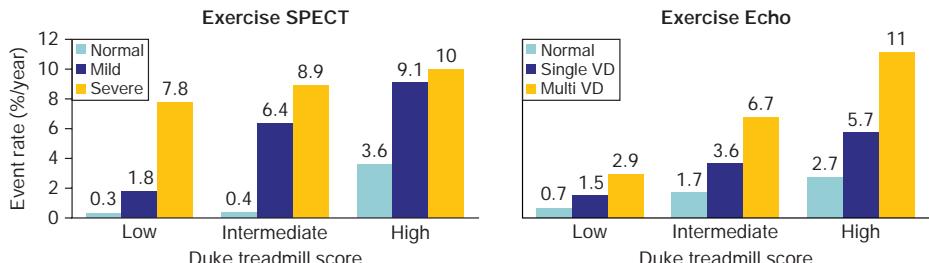
For symptomatic patients without a prior history of CAD and a normal or nearly normal resting ECG who are able to exercise, the American College of Cardiology/American Heart Association guidelines recommend standard exercise treadmill testing (ETT) as the initial testing strategy. The guidelines further suggest that patients who are categorized as low risk by ETT (e.g., those achieving >10 metabolic equivalents [METS] without chest pain or ECG changes) be treated initially with medical therapy, and those with high-risk ETT findings (i.e., typical angina with >2 mm ST-segment depression in multiple leads, ST elevation during exercise, drop in blood pressure, or sustained ventricular arrhythmias) be referred for coronary angiography.

The use of exercise testing in women presents difficulties that are not seen in men, reflecting the differences in the lower prevalence of obstructive CAD in women and the different accuracy of exercise testing in men and women. Compared with men, the lower pretest probability of disease in women means that more test results are false positive. In some of these patients, a positive ETT may reflect true myocardial ischemia caused by microvascular coronary artery dysfunction (so-called *microvascular disease*). In addition, the inability of many women to exercise to maximum aerobic capacity, the greater prevalence of mitral valve prolapse and microvascular disease, and possibly other reasons may contribute to the differences with men as well. The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that stress imaging may be preferred over standard stress testing. However, recent data from the WOMEN study suggest that in symptomatic, low-risk women who can exercise, standard ETT is a very effective initial diagnostic strategy as compared to stress radionuclide imaging. Indeed, the 2-year outcomes were similar in both diagnostic strategies, and the ETT-first approach resulted in 48% lower costs compared to exercise radionuclide imaging.

Patients who cannot undergo an ETT or those at intermediate-high risk after ETT (e.g., low exercise capacity, chest pain, and/or ST-segment depression without high-risk features) will often require additional testing, either stress imaging or coronary CTA, to more accurately characterize clinical risk. Most common stress imaging strategies in intermediate-risk patients include stress echocardiography and radionuclide imaging. However, CMR and PET in experienced centers have both been shown to have higher test accuracy than SPECT, and CMR has been shown to be more cost-effective than SPECT. In patients



**FIGURE 241-14** The image shows the late gadolinium enhancement image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.



**FIGURE 241-15** Incremental risk stratification of stress imaging over Duke treadmill score in patients with suspected coronary artery disease. Stress imaging is most valuable in the intermediate-risk group. SPECT, single-photon emission computed tomography; VD, vessel disease. (Reproduced with permission from R Hachamovitch et al: Exercise myocardial perfusion SPECT in patients without known coronary artery disease. *Circulation* 93:905, 1996; <https://www.ahajournals.org/doi/full/10.1161/01.CIR.93.5.905>.)

with intermediate clinical risk, stress imaging with either SPECT or echocardiography has been shown to accurately reclassify patients who are initially classified as intermediate risk by ETT as low or high risk (Fig. 241-15). Following this staged strategy of applying the low-cost ETT first and reserving more expensive imaging to refine risk stratification to patients initially classified as intermediate risk by ETT is more cost-effective than applying stress or anatomic imaging as the initial test routinely.

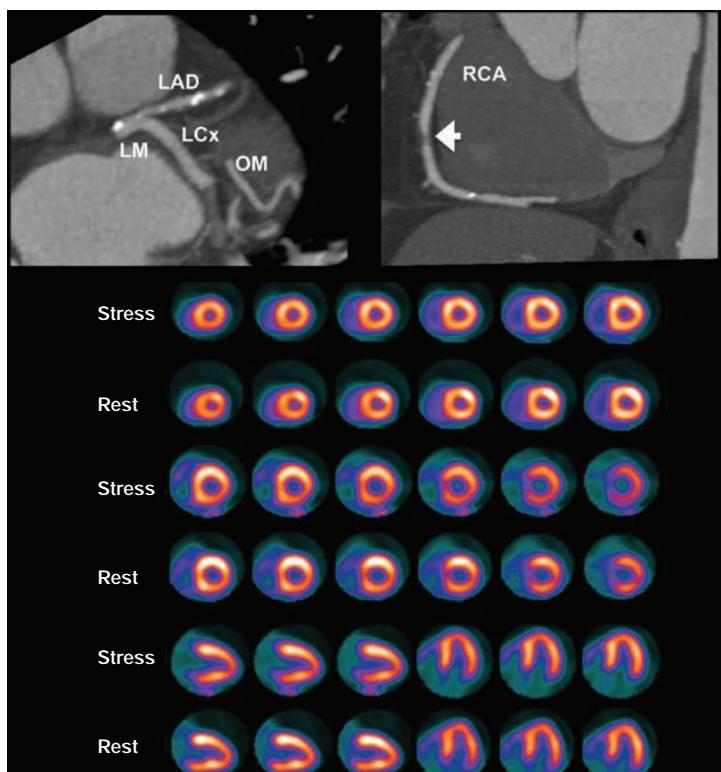
An imaging strategy is the recommended first step for patients who are unable to exercise to an adequate workload and/or those with abnormal resting ECGs (e.g., left ventricular hypertrophy with strain, left bundle branch block). Importantly, the most recent documents regarding appropriate use of imaging also considered that an imaging strategy may be an appropriate first step in patients with intermediate-high likelihood of CAD (e.g., diabetics, renal impairment) due to increased

overall sensitivity for diagnosis of CAD and improved risk stratification. In considering an imaging strategy, the evidence supporting the role of ischemia assessment versus anatomy must be considered. From the discussion above, for patients with atypical chest pain and a low pretest risk of CAD, a normal coronary CTA is helpful because it effectively excludes the presence of obstructive CAD and the need for further testing, defines a low clinical risk, and makes management decisions regarding referral to coronary angiography straightforward. However, in patients with an intermediate or higher pretest risk, coronary CTA is less effective in excluding obstructive CAD owing to its limited accuracy to define stenosis severity and predict ischemia; however, abnormal CTA results are more problematic to interpret and to use as the basis for defining the potential need of invasive coronary angiography and revascularization. In such patients, a follow-up stress test is usually required to determine the possible need of revascularization (Fig. 241-16).

The justification of stress imaging in testing strategies has hinged on the identification of which patients may benefit from a revascularization strategy by means of non-invasive estimates of jeopardized myocardium rather than angiography-derived anatomic stenoses. However, recent evidence from the ISCHEMIA trial suggests that optimal medical therapy provides comparable prognostic benefit to coronary revascularization in patients with moderate myocardial ischemia. Coronary revascularization is reserved for patients with very extensive evidence of ischemia by stress imaging and/or inadequate symptom control by optimal medical therapy. While the available data suggest similar diagnostic accuracy for SPECT and echocardiography but higher for PET and CMR, the choice of strategy depends on availability and local expertise.

**Selecting a Testing Strategy in Patients with Known CAD** Use and selection of testing strategies in symptomatic patients with established CAD (i.e., prior angiography, prior myocardial infarction, prior revascularization) differ from those in patients without prior CAD. Although standard ETT may help distinguish cardiac from noncardiac chest pain, exercise ECG has several limitations following myocardial infarction and revascularization (especially coronary artery bypass grafting). These patients frequently have rest ECG abnormalities. In addition, there is a clinical need to document both the magnitude and localization of ischemia to be able to direct therapy, especially the potential need for targeted revascularization. Consequently, imaging tests are preferred for evaluating patients with known CAD.

There are also important differences in the effectiveness of imaging tests in these patients. As discussed above, coronary CTA is limited in patients with prior revascularization. While CTA provides excellent visualization of the bypass grafts, the native circulation tends to get heavily calcified and is generally not a good target for imaging with CTA. Likewise, blooming artifacts from metallic stents also limit the application of coronary



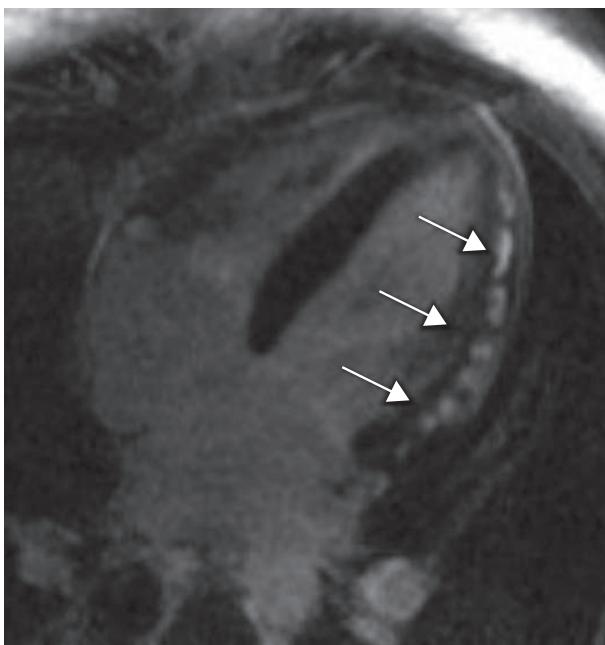
**FIGURE 241-16** Selected views from coronary computed tomography angiographic (CTA) images (top panel) and stress and rest rubidium-82 myocardial perfusion positron emission tomography images (lower panel) obtained on a 64-year-old male patient with atypical angina. The CTA images demonstrate dense focal calcifications in the left main (LM) and left anterior descending (LAD) coronary arteries and a significant noncalcified plaque in the mid right coronary artery (RCA; arrow). The myocardial perfusion images demonstrated no evidence of flow-limiting stenosis. LCx, left circumflex artery; OM, obtuse marginal branch.

**1846** CTA in patients with prior percutaneous coronary intervention. If an anatomic strategy is indicated, direct referral to invasive angiography is preferred.

Stress imaging approaches are especially useful and preferred in symptomatic patients with established CAD. As in patients without prior CAD, normal imaging studies in symptomatic patients with established CAD also identify a low-risk cohort. In those with abnormal stress imaging studies, the degree of abnormality relates to posttest risk. In addition, stress imaging approaches can localize and quantify the magnitude of ischemia, thereby assisting in planning targeted revascularization procedures. As in patients without prior CAD, the choice of stress imaging strategy depends on availability and local expertise.

**Testing Strategy Considerations in Patients Presenting with Chest Pain to the ED** Although acute chest pain is a frequent reason for patient visits to the ED, only a small minority of those presentations represent an acute coronary syndrome (ACS). Strategies used in the evaluation of these patients include novel cardiac biomarkers (e.g., serum troponins), conventional stress testing (ETT), and noninvasive cardiac imaging. It is generally accepted that the primary goal of this evaluation is exclusion of ACS and other serious conditions rather than detection of CAD.

The routine evaluation of acute chest pain in most centers in the United States includes admission to a chest pain unit to rule out ACS with the use of serial ECGs and cardiac biomarkers. In selected patients, stress testing with or without imaging may be used for further risk stratification. Stress echocardiography and radionuclide imaging are among the most frequently used imaging approaches in these patients. Multiparametric CMR imaging has also been used successfully in patients with acute chest pain ([Video 241-5](#)). Due to its ability to probe multiple aspects of myocardial physiology, cardiac anatomy, and tissue characterization with LGE imaging, CMR is useful in diagnosing conditions that mimic ACS (e.g., acute myocarditis, takotsubo cardiomyopathy, pericarditis) ([Fig. 241-17](#)).



**FIGURE 241-17** A four-chamber long-axis late gadolinium enhancement (LGE) image of a patient with acute myocarditis. Note that the LGE primarily involved the epicardial aspect of the myocardium (arrows), sparing the endocardium, which is a feature that distinguishes myocarditis from myocardial infarction, which affects the endocardium. Also note the multiple foci of LGE in this case affecting the lateral wall of the left ventricle. Viral myocarditis often presents with this pattern.

As discussed above, coronary CTA is a rapid and accurate imaging technique to exclude the presence of CAD and is well suited for the evaluation of patients with acute chest pain ([Fig. 241-18](#)). Four randomized clinical trials have demonstrated the feasibility, safety, and accuracy of coronary CTA in the ED as compared to usual care (which typically includes stress imaging). Patients in these trials had a very low clinical risk. Overall, there were no deaths and very few myocardial infarctions without differences between the groups. Likewise, there were no differences in postdischarge ED visits or rehospitalizations. These studies showed decreased length of stay with coronary CTA, and most but not all reported cost savings. An observation from a recent meta-analysis was that, compared to usual care, more patients assigned to coronary CTA underwent cardiac catheterization (6.3% vs 8.4%, respectively) and revascularization (2.6% vs 4.6%, respectively). The relative increased frequency in the referral to cardiac catheterization and revascularization after coronary CTA compared to stress imaging testing strategies has also been observed in patients with stable chest pain syndromes.

Taken together, the available data clearly suggest that not all patients presenting with acute chest pain require specialized imaging testing. Patients with very low clinical risk and negative biomarkers (especially high-sensitivity troponin assays) can be safely triaged. The use of imaging tests in patients with low-intermediate risk should be carefully considered, especially given the trade-offs discussed above.

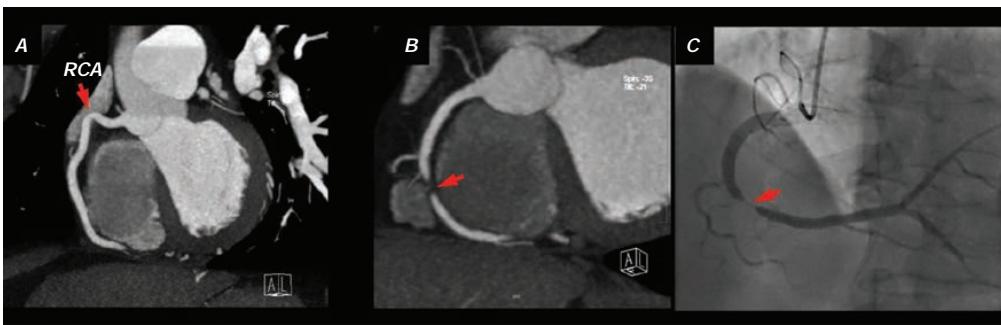
## VALVULAR HEART DISEASE

Abnormalities of any of the four valvular structures in the heart can lead to significant cardiac dysfunction, heart failure, or even death. Echocardiography, CMR, and cardiac CT can be used for the evaluation of valvular heart disease, although echocardiography is generally considered the first imaging test for the assessment of valvular heart disease. In addition, echocardiography is the most cost-effective screening method for valvular heart disease. In some cases, CMR can complement echocardiography when echocardiographic acoustic window is inadequate, to quantify blood flow data more precisely, or to provide complimentary assessment of adjacent vascular structures relevant to the valvular condition.

Echocardiography can be used to assess both regurgitant and stenotic lesions of any of the cardiac valves. Typical indications for echocardiography to assess valvular heart disease include cardiac murmurs identified on physical examination, symptoms of breathlessness that may represent valvular heart disease, syncope or presyncope, and preoperative exams in patients undergoing bypass surgery. A standard echocardiographic examination should include qualitative and quantitative assessment of all valves regardless of indication and should serve as an adequate screening test for significant valvular disease.

**Assessment of Aortic Stenosis** Aortic stenosis, one of the most common forms of valvular heart disease, most often occurs because of gradual progression of valvular calcification in both normal and congenitally abnormal valves. Assessment of aortic stenosis is most commonly performed with echocardiography, although techniques for quantitative assessment of aortic stenosis with CMR have been developed and increasingly used over the past decade. Echocardiographic assessment generally begins with visual inspection of the valve. This allows for assessment of valvular morphology, whether it is tricuspid, bicuspid, or some variant; degree of leaflet calcification; and leaflet excursion.

The normal aortic valve consists of three leaflets or cusps: the right coronary, the left coronary, and the noncoronary cusps. Abnormalities of cusp development are some of the most common congenital heart anomalies, the most common of which is bicuspid aortic valve, with two opening leaflets rather than three ([Fig. 241-19](#)). The aortic valve can be visualized on echocardiography, although sometimes it can be difficult to distinguish true bicuspid aortic valve from variants, including the presence of a vestigial commissure (raphe). Bicuspid aortic valve, one of the most common congenital anomalies, predisposes to both aortic stenosis and aortic insufficiency.



**FIGURE 241-18** Representative coronary computed tomography angiographic (CTA) images of two patients presenting to the emergency department with chest pain and negative biomarkers. The patient in **A** had angiographically normal coronary arteries; the panel shows a representative view of the right coronary artery (RCA). **B** and **C** show a corresponding significant stenosis in the mid portion of the RCA on both the CTA (**B**) and invasive angiographic view (**C**). (Images used with permission from Dr. Quynh Truong, Massachusetts General Hospital, Boston, MA.)

The degree of aortic stenosis is assessed by estimating both the pressure gradient across the valve and the valve area. Patients with moderate aortic stenosis or higher generally have peak instantaneous velocities of 3.0 m/s and higher, and often higher than 4.0 m/s, corresponding to pressure gradients of 36 and 64 mmHg, respectively. Because pressure gradients across the aortic valve can be underestimated in patients with severe left ventricular dysfunction, estimation of valve area by the continuity principle is the most accurate technique for assessing the severity of the stenosis. However, evaluation of the patient with so-called low-flow or low-gradient aortic stenosis can be challenging and sometimes requires provocative testing such as dobutamine echocardiography. In these cases, it is important to distinguish whether the valve is indeed capable of opening further or simply behaving like a stenotic valve because of the low-pressure gradient.

Aortic valve areas  $<1.0 \text{ cm}^2$  are generally considered severe, and valve areas  $<0.6 \text{ cm}^2$  are considered critical. Because patients with good left ventricular function can often tolerate severe aortic stenosis for a considerable period of time, valve areas or gradients alone should not be used to determine whether an individual patient should undergo aortic valve surgery as this remains a clinical decision.

Some patients with apparent aortic stenosis have subvalvular or even supravalvular obstruction. Hypertrophic cardiomyopathy represents the classic form of subvalvular aortic stenosis, but this is usually easily distinguished from aortic stenosis on echocardiography as the valve leaflets can be seen opening during systole. Subaortic membranes can behave very similarly to leaflet aortic stenosis, and the membranes themselves can be very thin and difficult to visualize, although the presence of a murmur, a gradient across the valve with aortic leaflets that appear to open normally, is highly suggestive of a membrane. Supravalvular aortic stenosis, although exceedingly rare, also occurs.

The emergence of transcatheter aortic valve intervention as a therapeutic option for patients with severe aortic stenosis who are not optimal candidates for surgical replacement has resulted in a very important clinical role for multimodality imaging. Imaging plays a critical role in preprocedural planning, intraprocedural implantation optimization, and follow-up of these patients. CT plays an important role in defining the eligibility of the proposed access site (CTA of the aorta

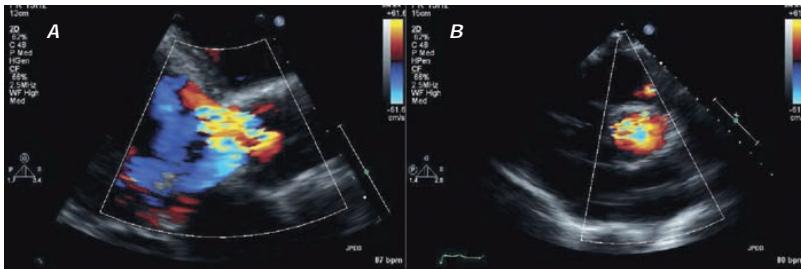
and iliac arteries) and in defining the anatomic relationships between the aortic valve and aortic root, left ventricle, and coronary ostia. Cardiac CT and transesophageal echocardiography are also used to define the device size. Transesophageal echocardiography is used during the device implantation to ensure the best prosthesis–patient match, to assess prosthesis position and function after deployment, and to identify immediate complications (e.g., aortic insufficiency, paravalvular leak resulting from patient–prosthesis mismatch). Echocardiography is the imaging modality of choice for long-term surveillance.

**Assessment of Aortic Regurgitation** Assessment of aortic regurgitation requires qualitative assessment of the aortic valve structure. Aortic regurgitation is common with congenital abnormalities of the aortic valve, the most common of which is bicuspid aortic valve. Aortic regurgitation often coexists with aortic stenosis, and it is not uncommon for patients to have both severe aortic stenosis and regurgitation. Congenital abnormalities of the aortic leaflets, such as bicuspid aortic valve, are common causes of aortic insufficiency. Dilatation of the aortic root, as occurs in patients with hypertension and other disorders in which aortic dilatation can occur, can also lead to aortic regurgitation even when the valve leaflets are intrinsically normal due to malcoaptation of the leaflets. Aortic root dilatation is common in patients with aortic regurgitation, both as a cause or coexisting lesion, and the aortic root and ascending aorta should be measured and followed in these patients (Fig. 241-20).

Because aortic regurgitation can result in dilatation of the left ventricle over time with ultimate reduction in ventricular function, caring for the patient with aortic regurgitation requires serial assessment of ventricular size and function. Patients whose ventricles dilate beyond an end-systolic diameter of 5.5 cm or whose LVEF declines below normal are at significantly higher risk of death or heart failure, and these measures are often used to decide the need for valve surgery. Quantitation of regurgitation itself can be performed using a number of methods. Semiquantitative visual assessment of aortic regurgitant jet width and depth by color flow Doppler remains the most used. The jet diameter as a ratio of the left ventricular outflow tract diameter proximal to the valve represents one of the most reliable indices of severity



**FIGURE 241-19** Normal aortic valve in the parasternal long-axis view (**A**) and short-axis view (**B**), and bicuspid aortic valve showing typical 10 o'clock to 4 o'clock leaflet orientation (**C**).



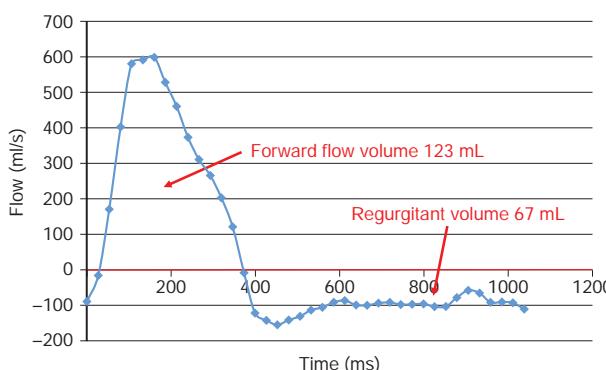
**FIGURE 241-20** Aortic regurgitation visualized by color flow Doppler in the parasternal long-axis view (**A**) and the parasternal short-axis view (**B**).

and correlates well with angiographic assessment. Similarly, the vena contracta, which represents the smallest diameter of the regurgitant flow at the level of the valve, can be used to assess the severity of aortic regurgitation. Other Doppler-based methods include assessing the pressure half-time, or rate of decline of the pressure gradient between the aorta and left ventricle, a measure of acuity of aortic regurgitation, and assessing aortic flow reversal in the descending aorta. The regurgitant volume can be calculated by comparing the flow across the aortic and pulmonic valves, assuming the pulmonic valve is competent. Central or perivalvular aortic regurgitation is common in patients following TAVR and is generally assessed immediately after the procedure and on follow-up echocardiography.

CMR offers several advantages over echocardiography in the assessment of aortic regurgitation. CMR is more accurate than echocardiography for assessing small changes in cardiac size or function longitudinally in patients with aortic insufficiency. In addition, CMR can accurately quantify aortic regurgitant volume secondary to aortic insufficiency better than echocardiography. CMR can also capture aortic size in 3D that may be helpful in determining the etiology of the aortic regurgitation or in monitoring progression of the condition (**Fig. 241-21** and **Video 241-6**).

**Assessment of Mitral Regurgitation** The normal mitral valve consists of an anterior and posterior leaflet in a saddle shape configuration (**Fig. 241-22**). The leaflets are attached to the papillary muscles via chordae tendineae that insert on the ventricular side of the leaflets. Mitral regurgitation can occur due to abnormalities of the leaflets, the chordal structures, or the ventricle, or any combination of these (**Fig. 241-23**).

Mitral valve prolapse, in which one leaflet moves behind the plane of the other leaflet, can be due to myxomatous degeneration of the valves and leaflet redundancy, disruption of chordal structures secondary to degenerative disease, or papillary muscle rupture or dysfunction following myocardial infarction. Regurgitant jets can be visualized using color flow Doppler. The velocity of regurgitant jets is driven by the pressure gradient between the two chambers. This velocity



**FIGURE 241-21** The resultant flow curve generated from phase contrast imaging demonstrates a forward flow of 123 mL and a regurgitant volume of 67 mL, yielding a regurgitant fraction of 54% indicating severe aortic regurgitation.

tends to be quite high for left-sided regurgitant lesions, including mitral regurgitation and aortic regurgitation, resulting in turbulent jets on color flow Doppler (**Fig. 241-23**). Visual estimation of color flow Doppler is generally sufficient for qualitative assessment of regurgitant severity but can dramatically under- or overestimate regurgitation severity, particularly when regurgitant jets are quite eccentric. For this reason, quantitative assessment is generally recommended, especially when making clinical decisions about surgical intervention. The proximal isovelocity surface area (PISA) method is generally used for quantitative

assessment of severity of mitral regurgitation. This method relies on estimation of the velocity of flow acceleration at a specific distance proximal to the valve with the assumption that the flow accelerates in concentric hemispheres.

As with aortic insufficiency, assessment of ventricular structure and function is also integral in the evaluation of mitral regurgitation. Although some patients have mitral regurgitation due to intrinsic abnormalities of the valve itself, in others, the valve can be relatively normal but the mitral regurgitation can be secondary to dilatation and remodeling of the left ventricle. So-called functional mitral regurgitation is generally secondary to apical displacement of the papillary muscles in a dilated ventricle, resulting in the leaflets of the mitral valve being pulled toward the apex of the heart, resulting in poor coaptation during systole and resultant relatively central mitral regurgitation. This type of mitral regurgitation can generally be distinguished from intrinsic mitral valve disease, and the surgical or procedural treatment of these conditions can be different. Knowledge of the etiology of mitral regurgitation can be important for a surgeon planning mitral valve surgery. Moreover, new procedural approaches to mitral valve disease may be different depending on the etiology.

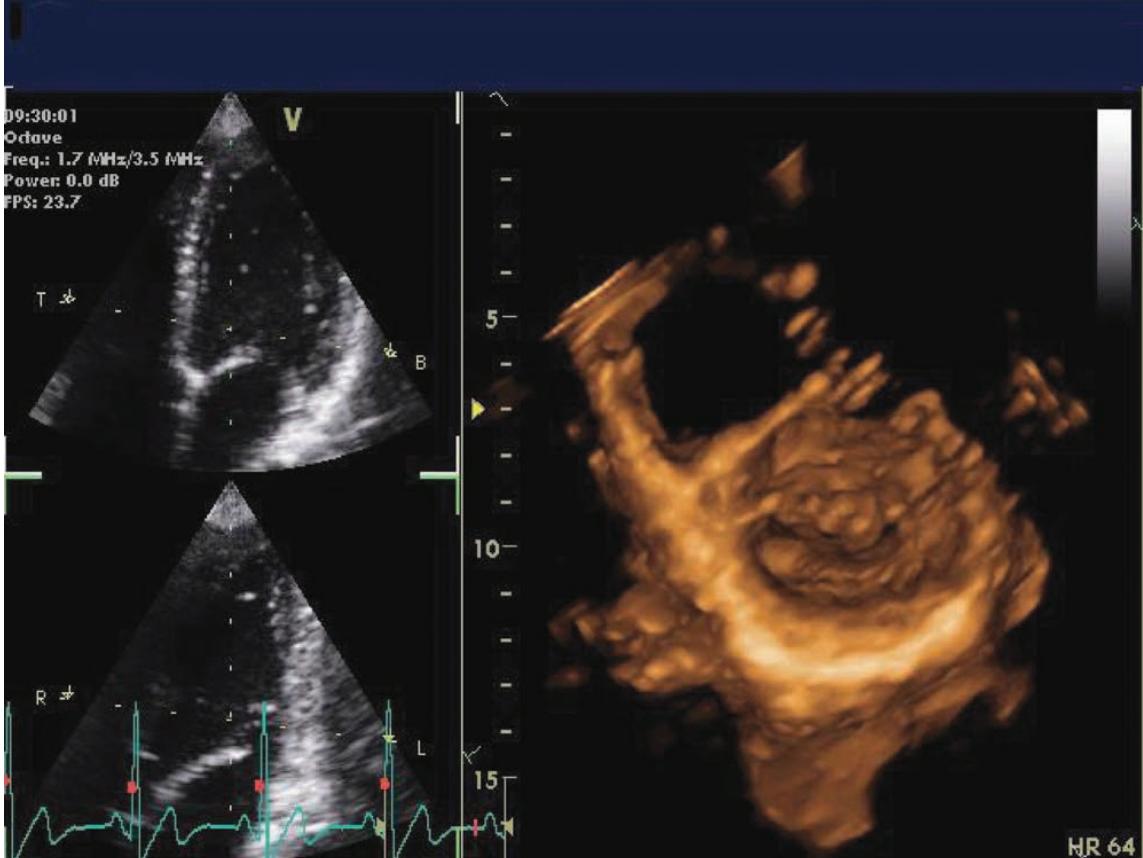
Ventricular dilatation is an important predictor of outcome in patients with mitral regurgitation of any cause. It is important to realize that in a patient with significant mitral regurgitation, a large portion of the blood being ejected from the left ventricle with every beat is regurgitant, thus artificially increasing the ejection fraction. Thus, an ejection fraction of 55% in a patient with severe mitral regurgitation may actually represent substantial reduction in myocardial systolic function.

CMR can be helpful in evaluating mitral regurgitation in a subset of patients when echocardiographic assessment is inadequate. CMR can directly quantify regurgitant volume of the mitral regurgitant jet or indirectly quantify regurgitant volume by measuring the difference of left ventricular stroke volume and aortic forward flow.

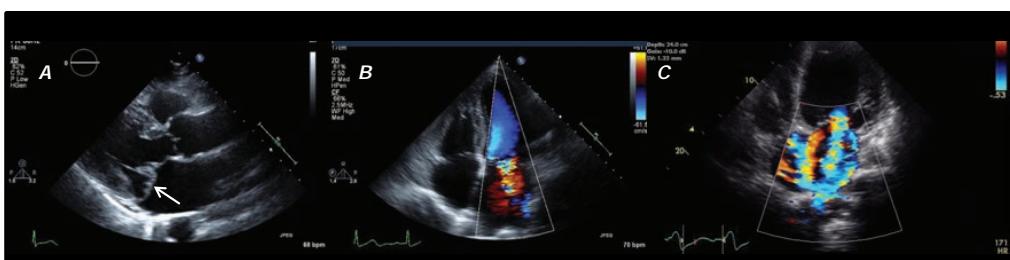
**Assessment of Mitral Stenosis** Rheumatic mitral disease remains the most common cause of mitral stenosis, although mitral stenosis can also result from severe calcification of the mitral leaflets. Rheumatic mitral stenosis has a distinct appearance characterized by tethering at the leaflet tips and relative pliability of the leaflets themselves, resulting in a hockey stick-type deformation particularly of the anterior leaflet (**Fig. 241-24**). Narrowing of the mitral orifice impedes flow from the left atrium to the left ventricle, resulting in increased pressures in the left atrium, which are then transmitted backward into the pulmonary vasculature and the right side of the heart. When mitral stenosis is suspected, echocardiography can be useful for determining etiology (specifically whether it is rheumatic or not), estimating the valve areas and gradients across the valve, assessing the left atrium, and assessing right ventricular size and function. Assessment of left atrial size and right ventricular size and function is particularly useful in helping determine the severity of the mitral stenosis.

## MYOCARDIAL INFARCTION AND HEART FAILURE

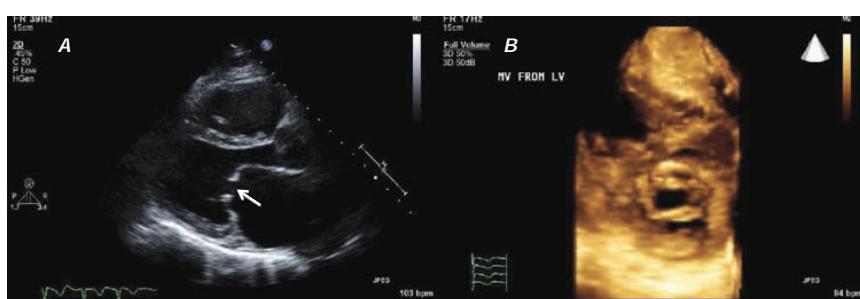
**Role of Imaging after Myocardial Infarction** Imaging can be useful in the immediate and long-term follow-up of patients with myocardial infarction. As discussed earlier in the chapter, LGE



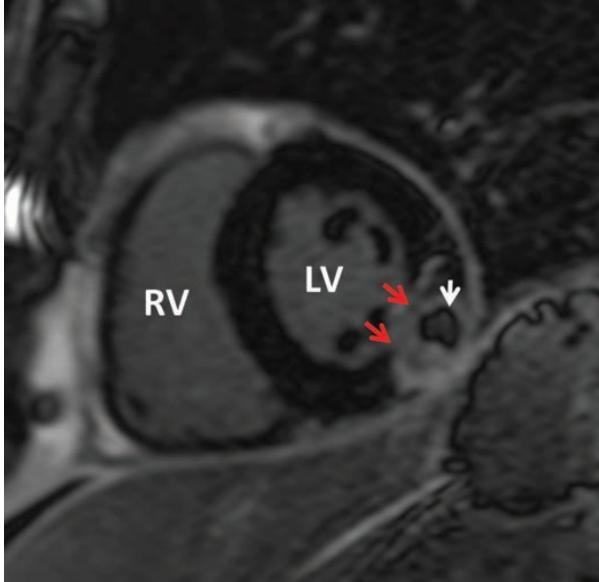
**FIGURE 241-22** Normal mitral valve in two-dimensional views (*left*) and with three-dimensional imaging (*right*).



**FIGURE 241-23** **A.** Mitral valve prolapse with posterior leaflet visualized prolapsing behind the plane of the anterior leaflet (arrow). **B.** Color flow Doppler showing mitral regurgitation in a patient with mitral valve prolapse. **C.** Severe functional mitral regurgitation in a patient with a dilated left ventricle.



**FIGURE 241-24** **A.** Rheumatic mitral stenosis showing pliable leaflets tethered at the tips (arrow). Note the characteristically enlarged left atrium. **B.** Mitral stenosis visualized from a three-dimensional echocardiogram.



**FIGURE 241-25** Example of a patient who presented with inferior ST-segment elevation myocardial infarction (MI) after several days of intermittent chest pain. The MRI confirmed an inferior MI by the location of late gadolinium enhancement (LGE; red arrows). In addition, there is a central area of microvascular obstruction (dark region surrounded by the bright LGE, white arrow). LV, left ventricle; RV, right ventricle.

imaging by CMR is the best technique for imaging for presence or the extent of infarcted myocardium. In a recent multicenter study, LGE imaging identified infarct location accurately and detected acute and chronic infarcts at a sensitivity of 99 and 94%, respectively. In addition, regions of microvascular obstruction (no-reflow) can be seen as dense hypoenhanced areas within the core of a bright region of infarction (Fig. 241-25). Both the presence of LGE and microvascular obstruction are markers of increased clinical risk.

While echocardiography is often used to assess myocardial function immediately after myocardial infarction, myocardial stunning is common in the early post-myocardial infarction period, especially in patients who undergo reperfusion therapy. In these patients, either partial or complete recovery of ventricular function is common within several days, so that early estimation of ejection fraction may be misleading. In patients with uncomplicated myocardial infarction, imaging can generally be deferred for several days so that a more accurate assessment of cardiac function, including regional wall motion, can be assessed (Fig. 241-26).



**FIGURE 241-26** Acute left anterior descending artery distribution myocardial infarction at end systole showing akinetic region (arrows).

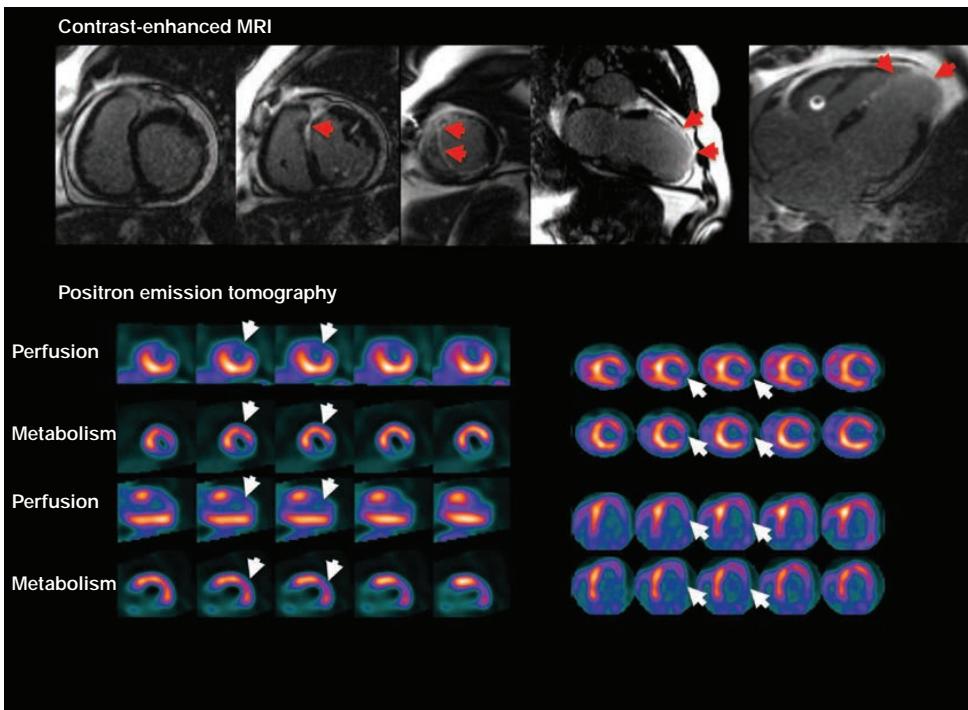
Echocardiography is the best method for assessment of patients with suspected mechanical complications after myocardial infarction. These include mitral regurgitation secondary to either papillary muscle dysfunction or rupture of papillary muscle head, ventricular septal defect, or even cardiac rupture. A new severe systolic murmur should raise suspicions for either severe mitral regurgitation or ventricular septal defect. While cardiac rupture is often catastrophic, contained ruptures, also known as *pseudoaneurysms*, can occur, and early diagnosis and surgical treatment are the best way to maximize survival. The presence of thrombus within the pericardial space following myocardial infarction should immediately raise suspicion of myocardial rupture and represents a surgical emergency.

Some patients demonstrate progressive left ventricular dilatation and dysfunction, known as *cardiac remodeling*, after myocardial infarction. Assessment of cardiac function and regional wall motion is useful in the follow-up period, generally between 1 and 6 months following infarction. The persistence of left ventricular systolic dysfunction following infarction is used to determine the type of therapy (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are typically used in patients with systolic dysfunction following myocardial infarction).

In patients with acute or subacute myocardial infarction, investigation of residual ischemia and/or viability is occasionally an important clinical question, especially among those with recurrent symptoms after myocardial infarction (Fig. 241-27). All cardiac imaging techniques can provide information regarding myocardial viability and ischemia. The available data suggest that radionuclide imaging, especially PET, is highly sensitive, with higher negative predictive value than dobutamine echocardiography. In contrast, dobutamine echocardiography tends to be associated with higher specificity and positive predictive accuracy than the radionuclide imaging methods. The experience with CMR suggests that it offers similar predictive accuracies as those seen with dobutamine echocardiography.

**Role of Imaging in New-Onset Heart Failure** Echocardiography is usually a first-line test in patients presenting with new-onset heart failure. As discussed above, this test provides a direct assessment of ventricular function and can help distinguish patients with reduced from those with preserved ejection fraction. In addition, it provides additional structural information including an assessment of valves, myocardium, and pericardium.

Although coronary angiography is commonly performed in patients with reduced ejection fraction, the determination of heart failure etiology in an individual patient may be difficult even if angiographically obstructive CAD is present. Indeed, patients with heart failure and no angiographic CAD may have typical angina or regional wall motion abnormalities on noninvasive imaging, whereas patients with angiographically obstructive CAD may have no symptoms of angina or history of myocardial infarction. Thus, the appropriate classification for any given patient is not always clear, and it often requires the complementary information of coronary angiography and noninvasive imaging. As discussed above, stress radionuclide imaging and echocardiography can be helpful in delineating the extent and severity of inducible myocardial ischemia and viability. Multiparametric CMR can be quite helpful in the differential diagnosis of heart failure etiologies. Apart from quantifying left and right ventricular volumes and function, CMR can provide information about myocardial ischemia and scar. The pattern of LGE helps differentiate infarction (typically starting in the subendocardium and involving a coronary territory) from other forms of infiltrative or inflammatory cardiomyopathies (typically involving the mid- or subepicardial layers without following a coronary distribution) (Fig. 241-28). In addition, it can assess the presence of myocardial edema using T1 or T2 tissue mapping methods to provide information about the chronicity of ACSs or noncoronary inflammatory conditions (e.g., myocarditis). Other methods such as T2<sup>\*</sup> mapping of myocardial iron deposition assess the extent of iron infiltration that can lead to cardiac toxicity. Infiltrative cardiomyopathy such as amyloidosis typically has a restrictive cardiomyopathy pattern characterized by biventricular increased wall thickness and bilateral



**FIGURE 241-27** Examples of myocardial viability patterns obtained with cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) in three different patients with coronary artery disease. The top panel demonstrates extensive late gadolinium enhancement (bright white areas) involving the anterior, anteroseptal, and apical left ventricular walls (arrows), consistent with myocardial scar and nonviable myocardium. The lower left panel demonstrates rubidium-82 myocardial perfusion and <sup>18</sup>F-fluorodeoxyglucose (FDG) images showing a large and severe perfusion defect in the anterior, anterolateral, and apical walls, indicating preserved glucose metabolism (so-called *perfusion-metabolic mismatch*) consistent with viable myocardium. The right lower panel shows similar PET images demonstrating concordant reduction in perfusion and metabolism (so-called *perfusion-metabolic match*) in the lateral wall, consistent with nonviable myocardium.

atrial enlargement, as assessed by both echocardiography and CMR. CMR of patients with cardiac amyloidosis often also demonstrates a characteristic pattern of diffuse endocardial infiltration of the left ventricle and the atria (Fig. 241-28). On strain echocardiography, patients with cardiac amyloidosis show a reduction in systolic function, which typically spares the apical left ventricular segments. Bone scintigraphy complements the use of echocardiography and CMR in cardiac amyloidosis by allowing accurate noninvasive distinction of transthyretin (ATTR) from light chain (AL) cardiac amyloidosis: ATTR typically shows intense <sup>99m</sup>Tc tracer uptake compared to patients with AL amyloidosis (Fig. 241-29). Hypertrophic cardiomyopathy has variable degree of increased ventricular thickness and often is seen to have outflow obstruction and intense LGE in regions with marked hypertrophy (Fig. 241-30). CMR also can quantify myocardial iron content in patients at risk of iron-overload cardiomyopathy (Video 241-7).

PET metabolic imaging has a complementary role in the evaluation of inflammatory cardiomyopathies, especially sarcoidosis where the presence of focal and/or diffuse glucose uptake can help identify areas of active inflammation. In addition, for patients undergoing immunosuppressive therapy, PET is frequently used to monitor therapeutic response (Fig. 241-31). In patients with ischemic cardiomyopathy, radionuclide imaging in general and PET in particular are frequently used to quantify the presence and extent of myocardial ischemia and viability to assist with clinical decision making related to myocardial revascularization (Fig. 241-26).

### ASSESSING CARDIAC FUNCTION IN PATIENTS UNDERGOING CANCER TREATMENT

Therapies used to treat cancer can adversely affect the cardiovascular system. As the efficacy of cancer treatment and survival improve, many patients are presenting with late adverse consequences from chemotherapy and/or radiation therapy on cardiovascular function. Thus, the morbidity and mortality from late cardiovascular complications

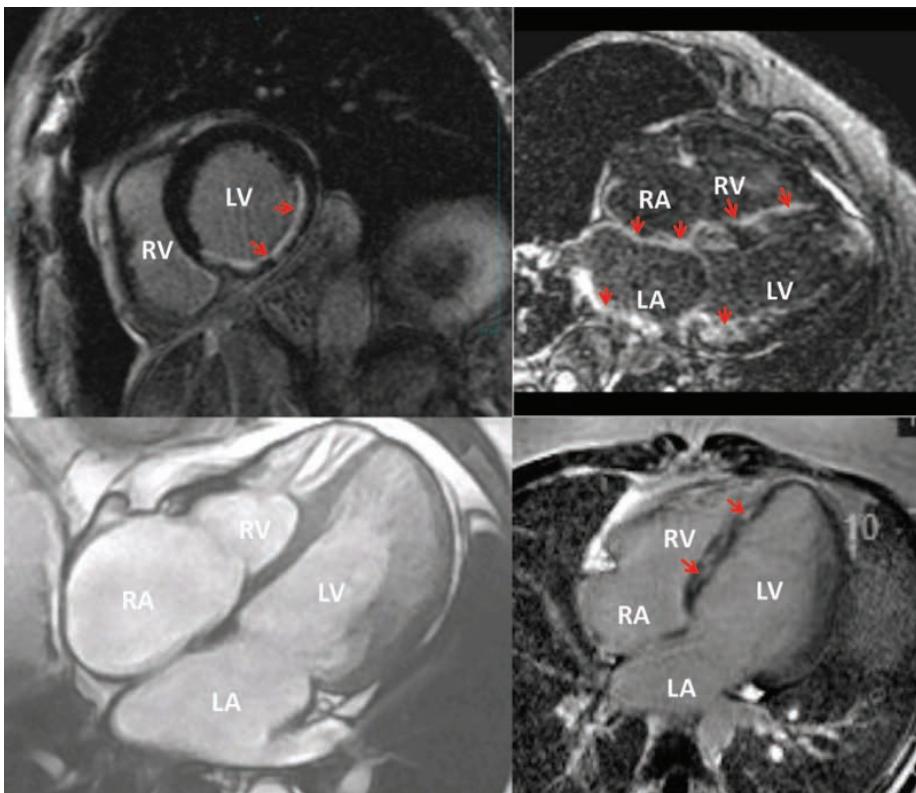
threaten to offset the early gains in cancer survival, especially among children and young adults. Early recognition and treatment of cardiomyocyte injury are critical for successful application of preventative therapies but difficult because the adverse effects on cardiac function are a relatively late manifestation after exposure to anticancer therapy.

The accepted standard for clinical diagnosis of cardiotoxicity is defined as a >5% reduction in LVEF to <55% with symptoms of heart failure, or a >10% drop in LVEF to <55% in patients who are asymptomatic. Thus, noninvasive imaging plays a major role in diagnosing and monitoring for cardiac toxicity in patients undergoing cancer treatment. Radionuclide angiography has been the technique of choice for quite some time. However, echocardiography now plays a major role in this application.

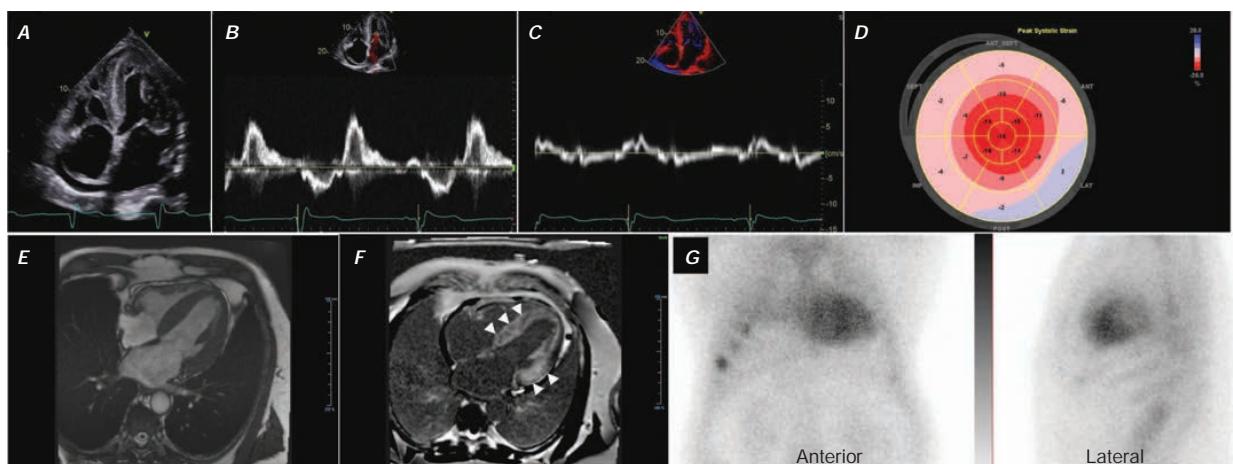
Recently, more novel imaging approaches have been advocated, including deformation imaging with echocardiography and fibrosis imaging with CMR. These techniques have shown promising results in experimental animal models and in humans. In addition, there are also proof-of-concept studies in animal models using molecular imaging approaches targeting the mechanisms of cardiac toxicity (e.g., apoptosis and oxidant stress), which can presumably provide the earliest signs of the off-target effects of these therapies. However, these techniques are currently considered experimental.

### PERICARDIAL DISEASE

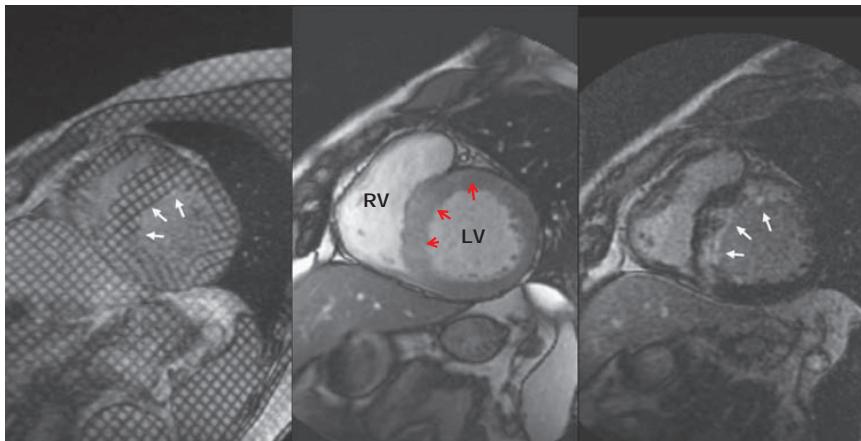
The fibroelastic pericardial sac surrounding the heart consists of a visceral, or epicardial, layer and a parietal layer, with a generally small amount of pericardial fluid in between layers. The pericardium is generally quite pliable and moves easily with the heart during contraction and relaxation. Abnormalities of the pericardium can affect cardiac function primarily by impairing the heart's ability to fill. Inflammation of the pericardium can lead to an accumulation of fluid between the two layers, or *pericardial effusion*, which can be visualized by echocardiography, CMR, or CT. Other reasons for accumulation



**FIGURE 241-28** Differentiation of various cardiomyopathies by cardiac magnetic resonance (CMR). The *left upper panel* shows the short-axis late gadolinium enhancement (LGE) imaging of a patient who suffered an acute myocardial infarction. Note LGE of the endocardial myocardium in the inferior wall extending from the septum to the lateral wall associated with myocardial thinning (arrows). The *right upper panel* shows the long-axis LGE imaging of a patient who has cardiac amyloidosis. Note the diffuse LGE throughout left ventricular myocardium, the left atrium, and the interatrial septum (arrows). In addition, the blood pool is characteristically dark in signal indicating sequestration of gadolinium contrast out of the blood pool after injection due to a high burden of amyloidosis in other organs. The *left lower panel* shows a cine diastolic long-axis image of a patient with a nonischemic dilated cardiomyopathy. Note that there is extensive sponge-like noncompacted myocardium of the left ventricle (LV) as well as dilation of all four cardiac chambers. This patient has a nonischemic dilated cardiomyopathy secondary to LV noncompaction. The *right lower panel* shows a 22-year-old female patient with a recent episode of acute chest pain and troponin elevation. Note the multiple mid-wall foci of LGE, which suggests acute myocarditis (arrows). LA, left atrium; RA, right atrium; RV, right ventricle.



**FIGURE 241-29** Multimodality cardiac imaging in a 71-year-old man with history of atrial fibrillation, heart failure with preserved ejection fraction, numbness in his fingers, a history of bilateral carpal tunnel surgery, and remote history of back surgery with L3 and S1 fusion. *A*, Two-dimensional echocardiogram demonstrating moderate increase in left ventricular thickness with a visually estimated left ventricular ejection fraction of 45–50% and small pericardial effusion. *B* and *C*, Mitral inflow and tissue Doppler demonstrating abnormal diastolic function ( $E/e'$  was >20, consistent with elevated left ventricular filling pressure). *D*, Bull's-eye strain map demonstrating abnormal global longitudinal strain at the basal segments (pink and blue colors) with characteristic apical sparing (red color). *E*, Cardiac MRI study showing normal left ventricular cavity size, mildly increased left ventricular mass, and mildly enlarged right and left atria. *F*, The MRI shows a large amount of diffuse late gadolinium enhancement of all myocardial left ventricular segments, but it is more prominent in a circumferential subendocardial pattern (arrowheads). *G*, The  $^{99m}\text{Tc}$  pyrophosphate images demonstrate increased myocardial uptake of the radiotracer (uptake in the heart is greater than ribs, grade 3). (Images courtesy of Dr. Sarah Cuddy, Brigham and Women's Hospital.)

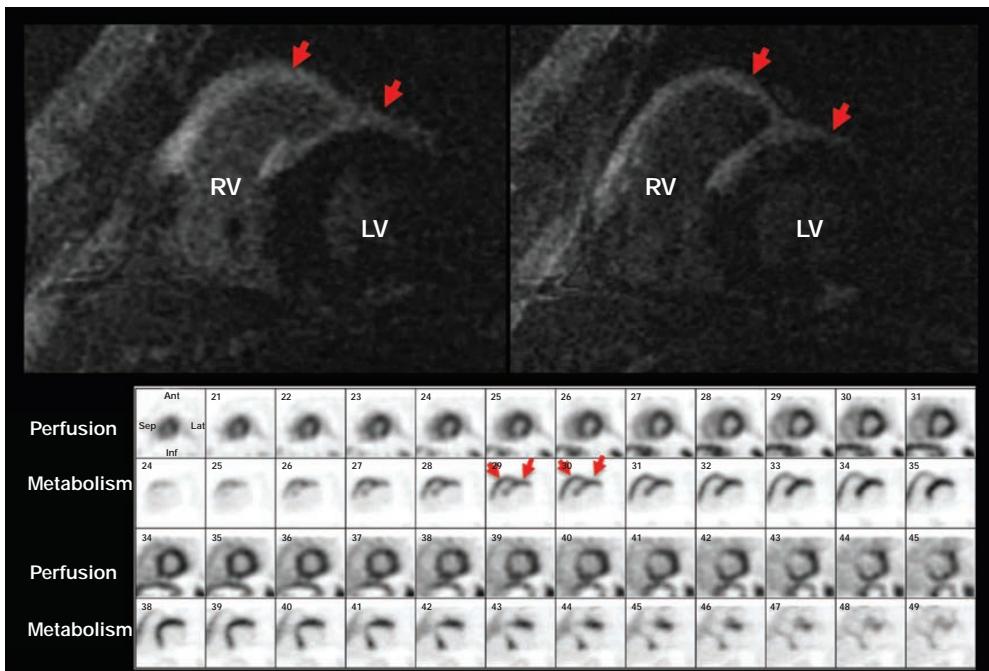


**FIGURE 241-30** This figure demonstrates three pulse sequence techniques by cardiac magnetic resonance that are often used to assess patients with hypertrophic cardiomyopathy, all displayed in the mid short-axis scan plane. The center panel demonstrates that the left ventricle (LV) was markedly thickened in its wall thickness especially in the LV septum (red arrows). This finding was matched by marked regions of late gadolinium enhancement (LGE), which was consistent with fibrosis in these segments (right panel, white arrows). The left panel was cine myocardial tagging in the same slice plane. Myocardial tagging is used to assess the normal intramyocardial strain by assessing distortion of the myocardial grids during systole. In this case, despite normal-appearing systolic radial wall thickening, the myocardial strain as assessed by the distortion of grids was markedly reduced (left panel, white arrows). This finding is consistent with substantial myofibril disarray in the anterior and anteroseptal segments in this patient. RV, right ventricle.

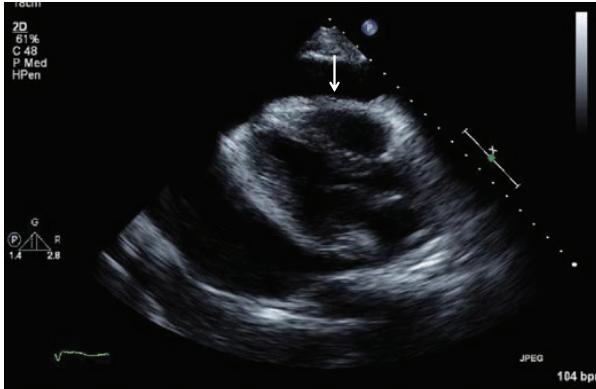
of pericardial fluid include infection, malignancy, and bleeding into the pericardium. The latter can be the result of catastrophic processes such as trauma, cardiac rupture, perforation in the setting of a cardiac procedure, cardiac surgery, or dissection of the aorta with extension in the pericardium.

Echocardiography remains the initial test of choice for assessing pericardial disease, especially effusions (Fig. 241-32). Moreover, echocardiography can be useful in evaluating for pericardial constrictive physiology, in which a thick noncompliant pericardium impairs cardiac filling. The location, size, and physiologic consequences of accumulated pericardial effusion can generally easily be determined

by echocardiography. Pericardial tamponade occurs when enough pericardial fluid accumulates so that the intrapericardial pressure exceeds filling pressures of the heart, generally the right ventricle. The balance between intrapericardial pressure and ventricular pressure is more important than the extent of fluid accumulation. Conditions in which pericardial effusions accumulate over a long period of time, as can be the case in the setting of malignant effusions, can lead to large pericardial fluid accumulations without the classic hemodynamic findings associated with pericardial tamponade. In contrast, rapid accumulations of pericardial fluid, such as those that occur due to cardiac rupture or perforation, can lead to tamponade physiology without



**FIGURE 241-31** Representative cardiac magnetic resonance (CMR; top panel) and positron emission tomography (PET; lower panel) images from a 45-year-old male presenting with complete heart block. The CMR images demonstrate extensive late gadolinium enhancement in the subepicardial left ventricular (LV) anterior and anteroseptal walls and also in the right ventricular (RV) free wall (arrows). The PET images demonstrate extensive fluorodeoxyglucose uptake in the same areas, most consistent with active inflammation due to sarcoidosis.



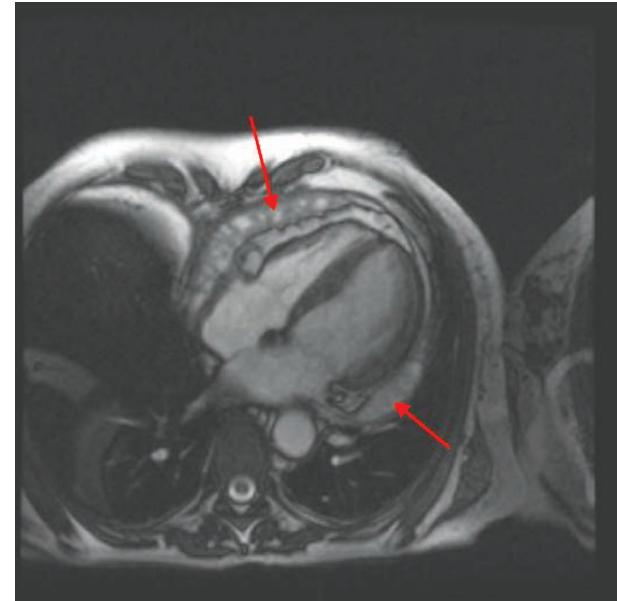
**FIGURE 241-32** Pericardial effusion with tamponade physiology. The right ventricle (arrow) is small and collapsing in end diastole due to increased pericardial pressure.

very large effusions. In patients with suspected pericardial effusion or tamponade, echocardiography can usually be performed rapidly, at the bedside, and even by operators with limited skill. The distance from the parietal to the visceral pericardial layer can be measured, and when this exceeds ~1 cm, an effusion is considered significant. Echocardiographic features suggestive of tamponade include diastolic collapse of the right ventricular free wall, suggestive of pericardial pressures that exceed right ventricular filling pressures, and Doppler evidence of respiratory flow variation, which is the Doppler equivalent of pulsus paradoxus. Despite the benefits of echocardiography in suspected pericardial tamponade, the diagnosis of tamponade remains a clinical diagnosis, and other important features, such as patient's blood pressure in the presence of pulsus paradoxus, need to be taken into account when considering therapeutic options.

Chronic inflammation of the pericardium leads to thickening and calcification of the parietal pericardium, resulting in pericardial constriction in which diastolic filling can be severely impaired. In these cases, filling of the ventricles comes to an abrupt halt when the volume of ventricular filling is impaired by the constricting pericardium. Assessment of pericardial thickness in these patients is important, but it is just as important to note that approximately one in five patients with severe pericardial constriction have no significant pericardial thickening by imaging or at surgery. Thus, a lack of thickened pericardium does not rule out pericardial constriction, and patients' signs and symptomatology and physiologic evidence of constriction should be assessed independently. Pericardial constriction typically demonstrates marked respiratory changes in diastolic flow on Doppler echocardiography, in contrast to restrictive cardiomyopathy, but substantial overlap exists. CT and CMR offer tomographic, whole-heart assessment of pericardial thickening and other anatomy abnormalities in pericardial constriction, such as enlarged atria, vena cavas, and pleural and pericardial effusions (Figs. 241-33 and 241-34 and Videos 241-8 and 241-9). CMR offers the additional information of pericardial fibrosis and inflammation by LGE imaging and evidence of constrictive physiology (e.g., regional relaxation concordance due to myocardial adhesions, abnormal septal bounce with Valsalva maneuver) (Fig. 241-34).

### CARDIAC THROMBUS AND MASS

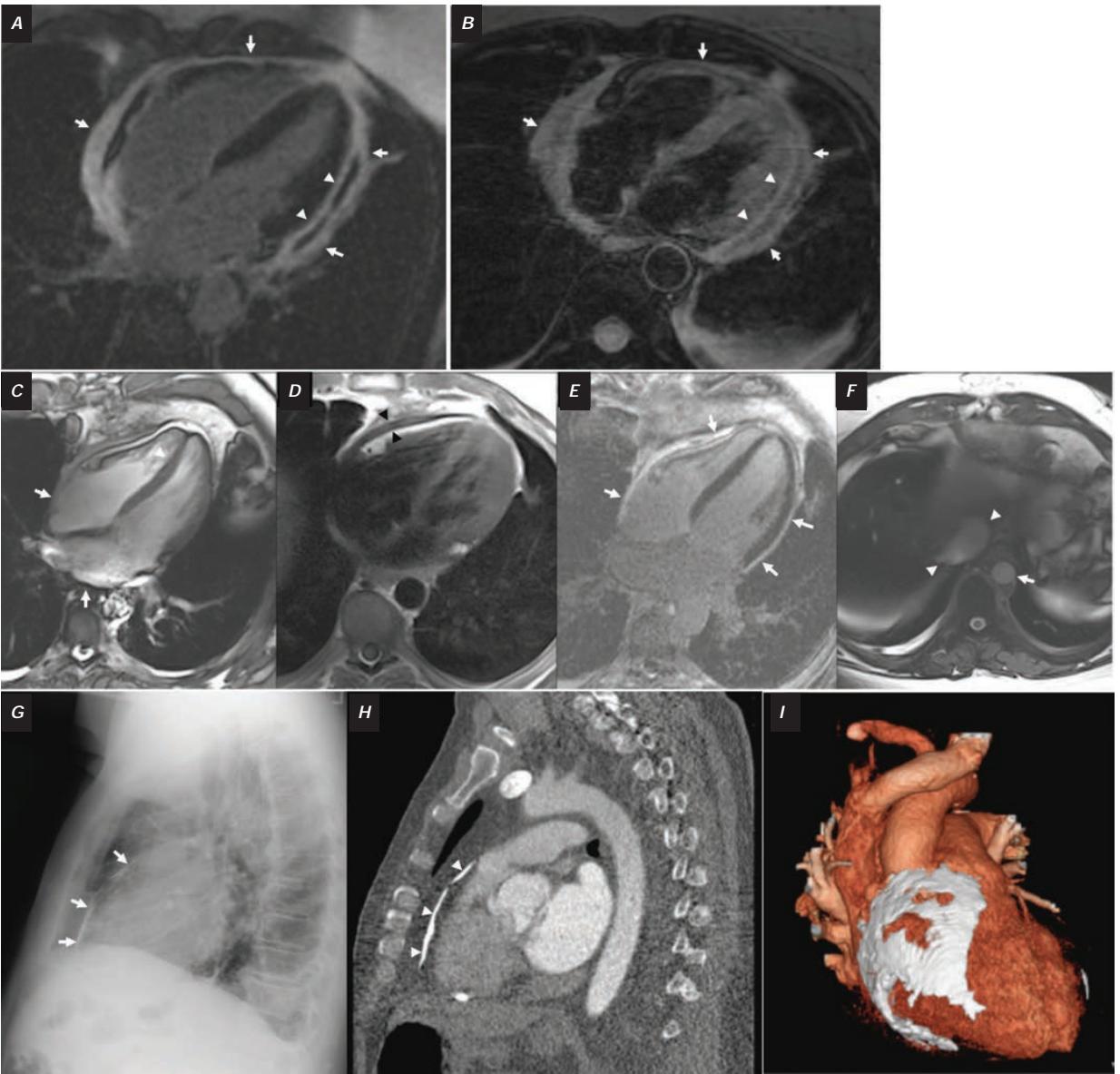
Echocardiography is usually the modality that first detects a cardiac mass with differential diagnoses including thrombus, tumor, or vegetation. Given their unrestricted tomographic views and multiplanar three-dimensional imaging, CMR and CT can complement echocardiography by further characterizing the physical features of the cardiac mass. Compared to CT, CMR has the advantage of higher tissue contrast differentiation, more robust cine imaging, and the use of multi-faceted techniques within the same imaging session to determine the physiologic characteristics of the mass. Gadolinium contrast enhancement patterns of increased capillary perfusion can detect vascularity within a mass, which differentiates a tumor from a thrombus. Structures that are known to mimic a cardiac mass include (1) anatomic



**FIGURE 241-33** A female patient developed pericardial constriction and right heart failure, secondary to radiation therapy for breast cancer. Note the multiple pericardial adhesions (red arrows).

variants, such as the Eustachian valve, Chiari network, crista sagittalis or terminalis, and the right ventricular moderator band, and (2) "pseudotumors," such as interatrial septal aneurysm, coronary or aortic aneurysm, lipomatous hypertrophy of interatrial septum, hiatal hernia, or a catheter/pacemaker lead. Coexisting abnormalities that raise the likelihood of a cardiac thrombus (Fig. 241-35) include regional wall motion abnormality from an infarction or ventricular aneurysm, atrial fibrillation leading to slow flow in the left atrial appendage, or presence of venous catheters or recent endovascular injury. CMR has the advantage of being able to assess regional wall motion and infarction or ventricular aneurysm in matching scan planes, adjacent to the cardiac thrombus, using cine and LGE imaging, respectively. For ventricular thrombus, gadolinium-enhanced LGE imaging can detect thrombus at a higher sensitivity than echocardiography by depicting high-contrast difference between the dark thrombus and its adjacent structures and by imaging in three dimensions. In addition, mural thrombus does not enhance on first-pass perfusion and often has a characteristic "etched" appearance (black border surrounding a bright center) on LGE imaging, thus providing higher diagnostic specificity than anatomic information alone (Fig. 241-36). Comparing the signal intensities of a mass before and after contrast injection may confirm the lack of tissue vascularity (i.e., thrombus) by the lack of signal enhancement after contrast administration. Like intracardiac thrombus, regions of microvascular obstruction also appear dark, but microvascular obstruction is confined within the myocardium and surrounded by infarction and thus can be differentiated from intracardiac thrombus. Cardiac CT imaging is ideally suited for small thrombus in the left atrial appendage, especially in cases where transesophageal echocardiography is suboptimal or not feasible.

The majority of cardiac malignancy is metastatic, which is about twentyfold more common than primary cardiac malignancies. Metastasis to the heart can be the result of direct invasion (e.g., lung and breast), lymphatic spread (e.g., lymphomas and melanomas), or hematogenous spread (e.g., renal cell carcinoma). Primary benign cardiac tumors are seen mostly in children and young adults and include atrial myxoma, rhabdomyoma, fibroma, and endocardial fibroelastoma (Fig. 241-37). Atrial myxomas are often seen as a round or multilobed mass in the left atrium (75%), right atrium (20%), or ventricles or mixed chambers (5%). They typically have inhomogeneous brightness in the center on cine steady-state free precession imaging due to their gelatinous



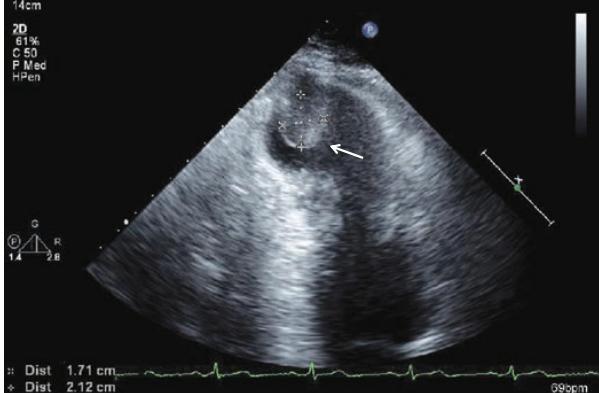
**FIGURE 241-34** Representative cardiac magnetic resonance (CMR) and CT features of pericardial disease. **A.** Four-chamber late gadolinium enhanced image showing severe, diffuse enhancement of both the visceral (arrowheads) and parietal (arrows) layers of the pericardium. The black signal between the two layers represents effusion. **B.** Axial T2-weighted image showing severe thickening and increased signal of both the visceral (arrowheads) and parietal (arrows) layers of the pericardium. **C.** Four-chamber steady-state free precession (bright-blood) image in early diastole showing the apical interventricular septum bowed to the left (white arrowhead) due to the increased right-sided ventricular volume at the expense of the left ventricular volume. Dilated atria (white arrows) are also a feature of constriction. **D.** Axial T1-weighted double inversion recovery (black-blood) image showing increased thickness of the pericardium  $>4$  mm (black arrowhead). **E.** Four-chamber late gadolinium enhanced image showing diffuse enhancement of the thickened pericardium (white arrows). **F.** Axial steady-state free precession (bright-blood) image showing dilated inferior vena cava (IVC) (white arrowheads), which is greater than twice the size of the normal aorta (white arrow). Under normal conditions, the IVC should be similar in size to the aorta. **G.** Lateral chest radiograph showing calcification of the pericardium anteriorly (arrows). **H.** Corresponding sagittal view from computed tomography angiography (CTA) showing the calcified pericardium (arrowheads). **I.** Three-dimensional rendered segmented image from the CTA showing the extent of the pericardial calcification. (Images courtesy of Dr. Michael Steigner, Brigham and Women's Hospital.)

contents and may have a pedunculated attachment to the fossa ovalis. Primary malignant cardiac tumors are rare and may include angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma.

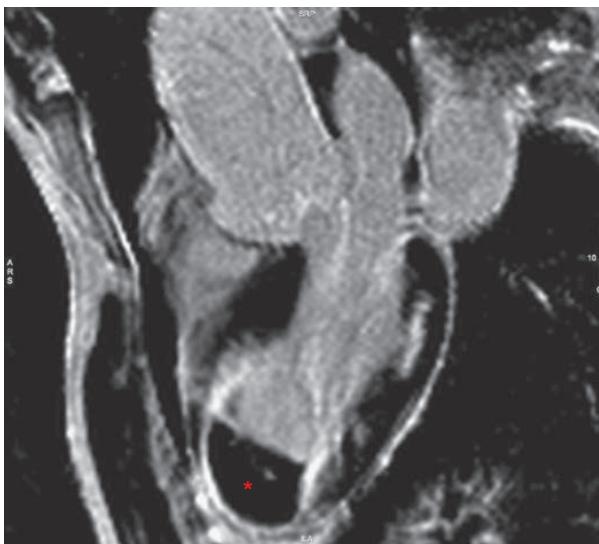
#### ROLE OF IMAGING IN INFECTIOUS AND INFLAMMATORY DISEASE

Patients with suspected endocarditis often undergo echocardiography for the purpose of identifying vegetations or intramyocardial abscesses. Vegetations are generally highly mobile structures that most typically are attached to valves or present in areas of the heart with turbulent

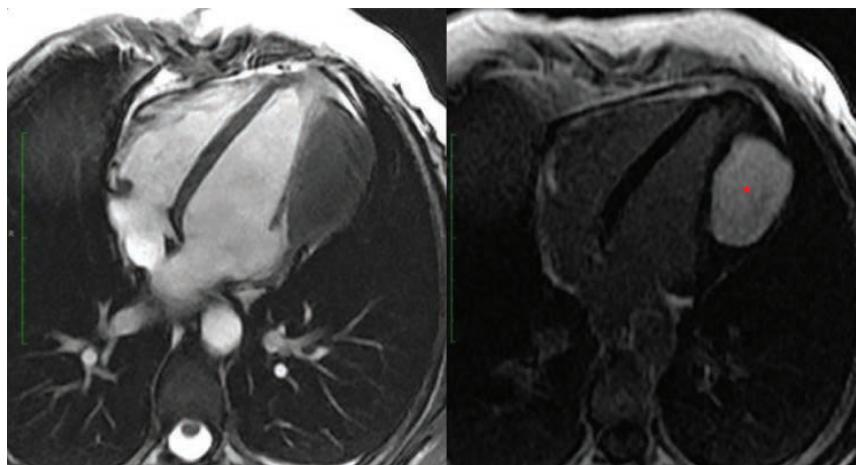
flow. The absence of a vegetation on echocardiography does not rule out endocarditis, because small vegetations below the resolution of the imaging techniques can be present. Echocardiography remains the best technique for assessment of vegetations because its high temporal resolution allows visualization of the typical oscillating motion, although large vegetations can be visualized with other techniques (Fig. 241-38). The size and location of a vegetation do not necessarily provide any specific information about the type of infection. Abscesses, particularly around the aortic and mitral annuli, are particularly concerning in patients with endocarditis and should be suspected in patients



**FIGURE 241-35** Cardiac thrombus (arrow) in an apical aneurysmal region following acute myocardial infarction.



**FIGURE 241-36** Late gadolinium image of a massive anterior infarction complicated by a dyskinetic left ventricular aneurysm and intracavitary thrombus (red asterisk).



**FIGURE 241-37** A case of a cardiac fibroma. A patient presented with shortness of breath and was found to have a large myocardial mass on echocardiography. Cine cardiac magnetic resonance imaging confirmed the large myocardial mass involving the anterolateral wall. Shortly after gadolinium contrast was injected, the myocardial mass demonstrated intense accumulation of contrast on late gadolinium enhancement imaging (right panel, asterisk). This is a case of cardiac fibroma. The patient also has gingival hyperplasia and bifid thoracic ribs, a part of the rare Gorlin's syndrome.

with prolongation of cardiac intervals in the setting of endocarditis. Visualization of both vegetations and possible abscesses is best done with transesophageal echocardiography, particularly in patients with prosthetic valves. Indeed, transesophageal echocardiography is the first test of choice in a patient with a mechanical mitral or aortic valve and suspected endocarditis (Fig. 241-38). Vegetations should be measured because their size has prognostic importance and can be used to decide whether a patient should be taken to surgery.

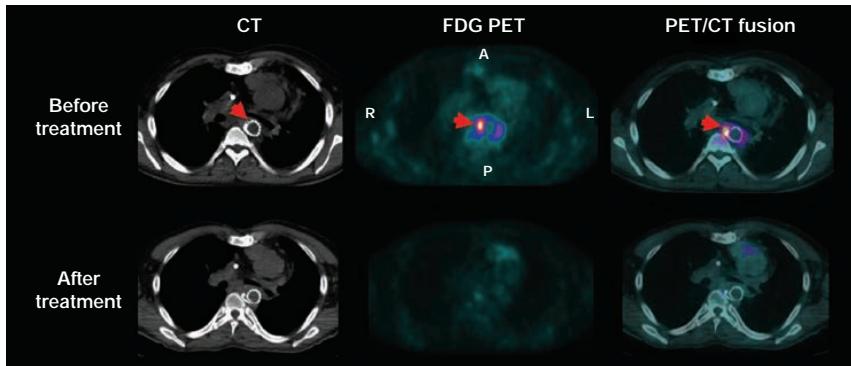
PET metabolic imaging is emerging as a potentially useful imaging technique to identify the source of infection in patients with prosthetic valves, vascular grafts, and implantable pacemakers/defibrillators, especially in patients in whom echocardiography and/or blood cultures are negative. There is an emerging literature documenting the potential value of macrophage-targeted metabolic imaging with <sup>18</sup>F-FDG and PET (Fig. 241-39). Likewise, FDG PET is also useful to identify vascular inflammation and monitor the response to immunosuppressive therapy (Fig. 241-40).

### EVALUATION OF COMMON CONGENITAL ABNORMALITIES IN THE ADULT

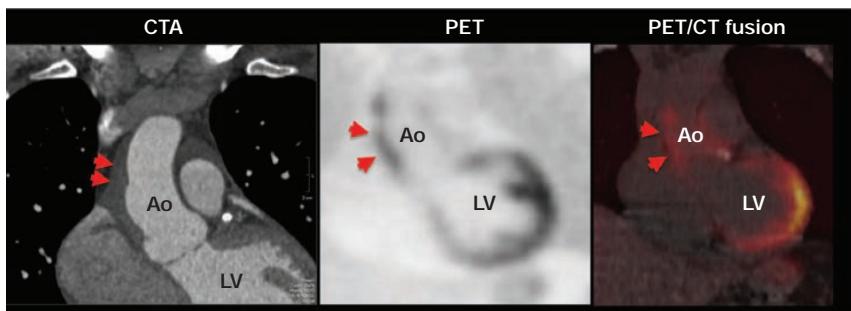
While a discussion of complex congenital heart disease is beyond the scope of this chapter, several common congenital abnormalities are present in adults, and cardiac imaging is essential to diagnosing and managing these conditions. Abnormalities of the interatrial septum probably represent the most common adult congenital cardiac abnormalities. Patent foramen ovale (PFO) can be identified in almost 25% of patients. In patients with PFO, a one-way flap in the region of the fossa ovalis is normally kept closed by the left atrial pressure, which is generally higher than right atrial pressure for much of the cardiac cycle. However, right-to-left flow through a PFO can occur any time the right atrial pressure exceeds the left atrial pressure, including with maneuvers or conditions in which intrathoracic pressure is increased. The presence of a PFO can increase the likelihood of the paradoxical embolus, and thus the presence of a PFO should be determined in patients with stroke or systemic embolus of unknown etiology. Because the one-way flap of the PFO will be closed during much of the cardiac cycle, color flow Doppler will usually not reveal a PFO. Instead, agitated saline (bubble study) is the best way to assess for PFO or atrial septal defect. Saline is agitated and injected peripherally and then enters the right atrium. If no shunt is present, only the right side of the heart will be pacified because the air bubbles will be too small to traverse the lungs. Because PFO is a one-way flap, maneuvers should be used to temporarily increase right atrial pressure. Either a Valsalva maneuver or sniff maneuver can be effective.



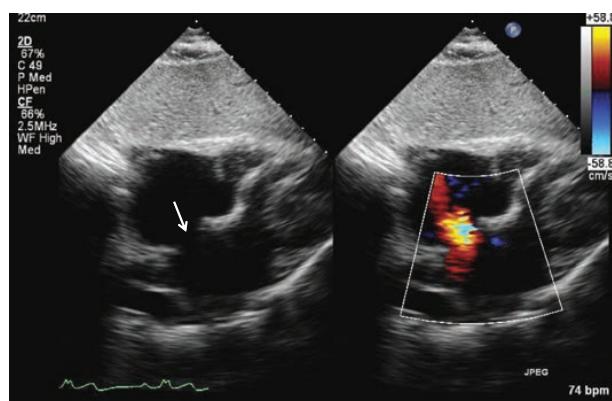
**FIGURE 241-38** Vegetation on native mitral valve (*left panel, arrow*). Left atrium (LA) and left ventricle (LV) are indicated. *Middle panel* shows a vegetation on a mechanical prosthesis (St. Jude) indicated by an arrow; *right panel* shows vegetation on prosthesis after excision.



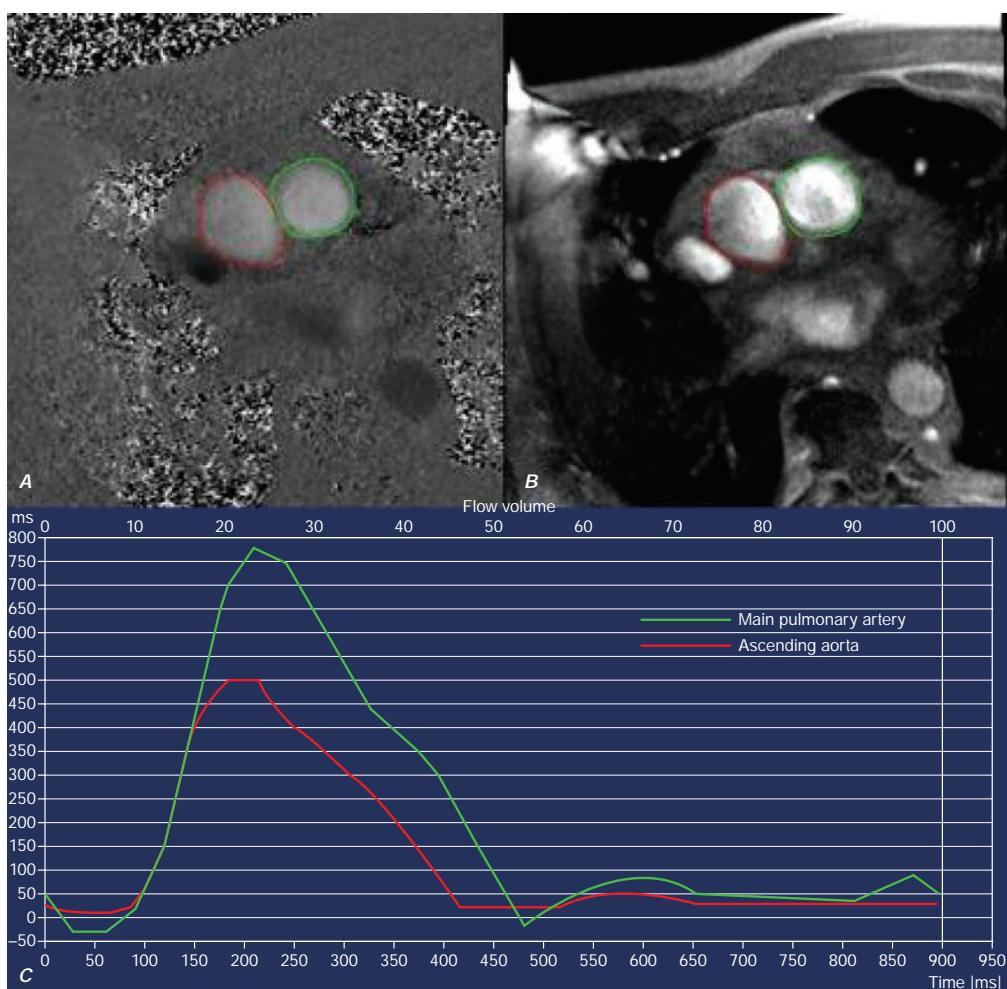
**FIGURE 241-39** Representative cross-sectional computed tomography (CT; *left*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle*), and fused CT and PET (*right*) images before and after antibiotic treatment in a patient with fever and suspected infection of the stent placed in the descending portion of the aortic arch (*arrow*) for treatment of aortic coarctation. The FDG images before treatment demonstrate intense glucose uptake within the stent, consistent with inflammation/infection. The lower panel demonstrates significant attenuation of the FDG signal after treatment. (*Images used with permission from Dr. Sharmila Dorbala, Brigham and Women's Hospital.*)



**FIGURE 241-40** Representative coronal computed tomography (CT) angiographic (CTA; *left panel*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle panel*), and fused CT and PET (*right panel*) images in a patient with suspected aortitis. The CTA images demonstrate thickening of the ascending aorta (Ao), which correlates with intense, focal FDG uptake consistent with active inflammation. LV, left ventricle.



**FIGURE 241-41** Large secundum-type atrial septal defect (*arrow*) noted in the subcostal view with color flow Doppler showing flow through the defect (*right*).



**FIGURE 241-42** **A** and **B** are phase contrast images that display blood flow (phase images on **A**) and anatomy (structural images on **B**) of the aorta (red) and pulmonary artery (green). **C** demonstrates the flow curves of the aorta (red) and the pulmonary artery (green). Note that the total flow (area under the curve) was substantially higher in the pulmonary artery than the aorta, indicative of a marked elevated pulmonary-to-systemic shunt ratio, as a result of the partial anomalous pulmonary venous return that drained into the superior vena cava.

Atrial septal defects occur most commonly in the region of the fossa ovalis, referred to as secundum-type defects (Fig. 241-41). Additional atrial septal defects include defects of the sinus venosus and atrium primum. Color flow Doppler echocardiography is usually sufficient for diagnosis of a secundum-type atrial septal defect, but agitated saline is generally needed for the diagnosis of other types of atrial septal defects.

Ventricular septal defects can generally be visualized by color flow Doppler as turbulent high-velocity jets from the left to the right ventricle. In cases where the jet origin is unclear, continuous wave Doppler can estimate the velocities. These would be expected to be extremely high to reflect the pressure gradient between the left and right ventricles. Defects can occur in both the muscular and membranous portions of the ventricular septum.

In patients with either atrial or ventricular septal defects, estimation of the severity of the left-to-right shunt is essential and can be an important determinant in management decisions. Shunts are generally assessed by echocardiography by assessing the relationship between pulmonary flow and aortic flow, the Qp/Qs ratio. Shunts and cardiac anatomy of most congenital heart diseases can also be accurately evaluated by CMR (Fig. 241-42).

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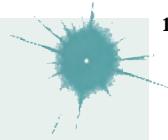
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**VIDEO 241-1** Cine steady-state free precession (SSFP) imaging (*left*) in short axis in a patient who had a large anterior myocardial infarction. Only one cut of a stack of short axis is shown. This method allows quantification of left ventricular (LV) and right ventricular (RV) volumes in diastole and systole and calculation of the LV ejection fraction, stroke volumes, and cardiac output (a product of LV stroke volume and heart rate). Note that in this case there is anterior and anteroseptal akinesia (lack of systolic wall thickening, as shown by the left cine movie, *red arrows*) matching by a near-transmural myocardial infarction as seen by the matching late gadolinium enhancement (LGE) image (*right picture, white arrows*).

## 242

## Diagnostic Cardiac Catheterization and Coronary Angiography

Jane A. Leopold, David P. Faxon



**VIDEO 241-2** This is cine cardiac magnetic resonance (CMR) imaging of a patient in the long-axis four-chamber view. Note that the basal aspect of the right ventricular (RV) free wall is thickened, aneurysmal, and akinetic (red arrows). The global RV systolic function is mildly reduced, and the RV is dilated. CMR can image the RV using tomographic views and can quantify the RV volumes and ejection fraction volumetrically. This is a patient who presented with syncopal spells and inducible ventricular tachycardia on subsequent workup. He was diagnosed to have arrhythmogenic right ventricular dysplasia.

**VIDEO 241-3** Exercise echocardiogram showing rest images on left and poststress images on right, with parasternal long-axis, upper panel, and apical four-chamber, lower panel, end-systolic frames. Following exercise, the distal septal/apical region becomes akinetic. A = upper left (UL); B = upper right (UR); C = lower left (LL); D = lower right (LR).

**VIDEO 241-4** The video shows cardiac magnetic resonance (CMR) myocardial perfusion imaging during vasodilating stress, in three parallel short-axis views. A bolus of gadolinium contrast was injected intravenously while rapid imaging acquisition occurred. The contrast enhances the right ventricle first, then travels through the pulmonary circulation, enters the left ventricle (LV), and then perfuses the LV myocardium. Myocardial perfusion defects with this technique show as black subendocardial rims, reflecting lack of contrast accumulation due to ischemia and/or scar. In this case, the anterior wall has a severe perfusion defect (red arrow). Figure 241-14 shows the late gadolinium enhancement (LGE) image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

**VIDEO 241-5** A 60-year-old female presented with intermittent chest pain of 3 days in duration but was pain-free at the time of assessment in the emergency department. Admission electrocardiogram (ECG) demonstrated T-wave inversion in the anterior precordial lead, but cardiac enzymes were normal. A resting cardiac magnetic resonance (CMR) study reviewed a large area of anteroseptal hypokinesis (left picture, region of hypokinesis shown by the red arrows), matching with a large resting perfusion defect (middle picture, perfusion defect shown by the blue arrows). Late gadolinium enhancement (LGE) imaging (right picture), however, did not show any enhancement to indicate any infarction in the anteroseptal wall, suggesting that the hypocontractile and hypoperfused anteroseptal wall was viable. Urgent coronary angiography demonstrated an acute thrombus in the mid left anterior descending coronary artery, which required coronary stenting. This case represents an example of acute coronary syndrome with hibernating but viable myocardium in the anteroseptal wall. The anteroseptal wall recovered contractile function when reassessed 6 months later.

**VIDEO 241-6** A patient with severe aortic regurgitation quantified by cardiac magnetic resonance (CMR). Notice the dark flow jet during diastole across the aortic valve. For quantitation of the aortic regurgitation severity, a cross-sectional cut was made just below the aortic valve, perpendicular to the aortic regurgitation jet, using phase contrast flow imaging. Apart from aortic regurgitation fraction and volume, CMR also can volumetrically quantify ventricular sizes and dimensions of the aorta, which are useful in monitoring patients with aortic valve diseases.

**VIDEO 241-7** These are T2 images of the heart (left panel) and the liver (right panel) of a patient who has hemochromatosis. Note that iron and the liver are markedly darkened in these movies, indicating high load of iron in the heart muscle and liver. The rate of signal reduction (decay) in the myocardium and liver can be calculated as T2\* value expressed in milliseconds. In this case, the T2\* was at 10 ms. T2\* <20 ms in patients with cardiomyopathy has been shown to indicate iron toxicity as the etiology of the cardiomyopathy, and it carries prognostic value for such patients at risk of cardiac iron toxicity.

**VIDEO 241-8** This video shows the heart in long and short axis. Note the large atria, thickened pericardium, and extensive pericardial adhesions. Given the extensive pericardial adhesions, there is little shearing motion of the ventricles against the parietal pericardium.

**VIDEO 241-9** This video shows the heart in long axis with a four-chamber view. The steady-state free precession (bright-blood) cine shows the early diastolic filling bounce of the apical interventricular septum due to constrictive physiology.

Diagnostic cardiac catheterization and coronary angiography are considered the gold standard in the assessment of the anatomy and physiology of the heart and its associated vasculature. In 1929, Forssmann demonstrated the feasibility of cardiac catheterization in humans when he passed a urological catheter from a vein in his arm to his right atrium and documented the catheter's position in the heart by x-ray. In the 1940s, Cournand and Richards applied this technique to patients with cardiovascular disease to evaluate cardiac function. These three physicians were awarded the Nobel Prize in 1956. In 1958, Sones inadvertently performed the first selective coronary angiography when a catheter in the left ventricle slipped back across the aortic valve, engaged the right coronary artery, and power-injected 40 mL of contrast down the vessel. The resulting angiogram provided superb anatomic detail of the artery, and the patient suffered no adverse effects. Sones went on to develop selective coronary catheters, which were modified further by Judkins, who developed preformed catheters and allowed coronary artery angiography to gain widespread use as a diagnostic tool. In the United States, cardiac catheterization is the second most common operative procedure, with more than 1.0 million procedures performed annually.

### CARDIAC CATHETERIZATION

#### INDICATIONS, RISKS, AND PREPROCEDURE MANAGEMENT

Cardiac catheterization and coronary angiography are indicated to evaluate the extent and severity of cardiac disease in symptomatic patients and to determine if medical, surgical, or catheter-based interventions are warranted (Table 242-1). They are also used to exclude severe disease in symptomatic patients with equivocal findings on non-invasive studies and in patients with chest-pain syndromes of unclear etiology for whom a definitive diagnosis is necessary for management. Cardiac catheterization is not mandatory prior to cardiac surgery in some younger patients who have uncomplicated congenital or valvular heart disease that is well defined by noninvasive imaging and who do not have symptoms or risk factors that suggest concomitant coronary artery disease.

The risks associated with elective cardiac catheterization are relatively low, with a reported risk of <0.1% for myocardial infarction, 0.01% for stroke, and 0.05% for death. For elective and emergent procedures, the in-hospital mortality is 1.4%. These risks increase substantially if the catheterization is performed emergently, during acute myocardial infarction, or in hemodynamically unstable patients. Additional risks of the procedure include tachy- or bradyarrhythmias that require countershock or pharmacologic therapy, acute renal failure leading to transient or permanent dialysis, vascular complications that necessitate surgical repair or percutaneous intervention, and significant access-site bleeding. Of these risks, vascular access-site bleeding is the most common complication, occurring in 1.5–2.0% of patients, with major bleeding events associated with a worse short- and long-term outcome.

In patients who understand and accept the risks associated with cardiac catheterization, there are no absolute contraindications when the procedure is performed in anticipation of a life-saving intervention. Relative contraindications do, however, exist; these include decompensated congestive heart failure; acute renal failure; severe chronic renal insufficiency, unless dialysis is planned; bacteremia; acute stroke; active gastrointestinal bleeding; excessive anticoagulation or recent lytic administration; severe, uncorrected electrolyte abnormalities; a

**TABLE 242-1 Indications for Cardiac Catheterization and Coronary Angiography****CORONARY ARTERY DISEASE****Asymptomatic or Symptomatic**

High risk for adverse outcome based on noninvasive testing

Sudden cardiac death

Sustained (&gt;30 s) monomorphic ventricular tachycardia

Nonsustained (&lt;30 s) polymorphic ventricular tachycardia

**Symptomatic**

Canadian Cardiology Society Class II, III, or IV stable angina on medical therapy

Acute coronary syndrome (unstable angina and non-ST-segment elevation myocardial infarction)

Chest-pain syndrome of unclear etiology and equivocal findings on noninvasive tests

**ST-Segment Elevation Acute Myocardial Infarction**

Reperfusion with primary percutaneous coronary intervention

Persistent or recurrent ischemia

Pulmonary edema and/or reduced ejection fraction

Cardiogenic shock or hemodynamic instability

Risk stratification or positive stress test after acute myocardial infarction

Mechanical complications—mitral regurgitation, ventricular septal defect

**Valvular Heart Disease**

Suspected severe valve disease in symptomatic patients—dyspnea, angina, heart failure, syncope

Infective endocarditis with need for cardiac surgery

Asymptomatic patients with aortic regurgitation and cardiac enlargement or ↓ ejection fraction

Prior to cardiac surgery or transcatheter aortic valve replacement or other percutaneous valvular interventions in patients with suspected coronary artery disease

**Congestive Heart Failure**

New-onset angina or suspected undiagnosed coronary artery disease

New-onset cardiomyopathy of uncertain cause or suspected to be due to coronary artery disease

**Congenital Heart Disease**

Prior to surgical correction or percutaneous interventions, when symptoms or noninvasive testing suggests coronary disease

Suspicion for congenital coronary anomalies

**Pericardial Disease**

Symptomatic patients with suspected cardiac tamponade or constrictive pericarditis

**Cardiac Transplantation**

Preoperative and postsurgical evaluation

**Other Conditions**

Hypertrophic cardiomyopathy with angina

Diseases of the aorta when knowledge of coronary artery involvement is necessary for management

history of an anaphylactic/anaphylactoid reaction to iodinated contrast agents without premedication; and a history of allergy/anaphylaxis/bronchospasm to aspirin in patients for whom progression to a percutaneous coronary intervention is likely and aspirin desensitization has not been performed.

Contrast allergy and contrast-induced acute kidney injury merit further consideration, because these adverse events may occur in otherwise healthy individuals and prophylactic measures exist to reduce risk. Allergic reactions to contrast agents occur in <5% of cases, with severe anaphylactoid (clinically indistinguishable from anaphylaxis, but not mediated by an IgE mechanism) reactions occurring in 0.1–0.2% of patients. Mild reactions manifest as nausea, vomiting, and urticaria, while severe anaphylactoid reactions lead to hypotensive

shock, pulmonary edema, and cardiorespiratory arrest. Patients with a history of significant contrast allergy should be premedicated for at least 24 hours prior to planned coronary angiography with corticosteroids and antihistamines ( $H_1$ -blockers) and studies performed with nonionic, low-osmolar contrast agents that have a lower reported rate of allergic reactions.

Contrast-induced acute kidney injury, defined as an increase in creatinine >0.5 mg/dL or 25% above baseline that occurs 48–72 h after contrast administration, occurs in ~2–7% of patients with rates of 20–30% reported in high-risk patients, including those with diabetes mellitus, congestive heart failure, chronic kidney disease, anemia, older age, or who present with an ST-segment elevation myocardial infarction. Dialysis is required in 0.3–0.7% of patients and is associated with a fivefold increase in in-hospital mortality. For all patients, adequate intravascular volume expansion with intravenous 0.9% saline (1.0–1.5 mL/kg per hour) for 3–12 h before and continued 6–24 h after the procedure limits the risk of contrast-induced acute kidney injury by >50%. Pretreatment with *N*-acetylcysteine (Mucomyst) has not reduced the risk of contrast-induced acute kidney injury consistently and, therefore, is no longer recommended routinely. Diabetic patients treated with metformin should stop the drug 24 h prior to the procedure and not restart until 48 h after contrast administration to limit the associated risk of lactic acidosis. Other strategies to decrease risk include the administration of sodium bicarbonate (3 mL/kg per hour) 1 h before and 6 h after the procedure (similar outcome to saline infusion); use of low- or iso-osmolar contrast agents; and limiting the volume of contrast to <50 mL per procedure.

Cardiac catheterization is performed after the patient has fasted for 6 h and has received intravenous conscious sedation to remain awake but sedated during the procedure. All patients with suspected coronary artery disease are pretreated with 325 mg aspirin. In patients in whom the procedure is likely to progress to a percutaneous coronary intervention, an additional antiplatelet agent should be started: clopidogrel (600-mg loading dose and 75 mg daily), prasugrel (60-mg loading dose and 10 mg daily), or ticagrelor (180-mg loading dose and 90 mg twice daily). Prasugrel should not be selected for individuals with prior stroke or transient ischemic attack and is not recommended for patients 75 years of age or older. Warfarin is held starting 2–3 days prior to the catheterization to allow the international normalized ratio (INR) to fall to <1.7 and limit access-site bleeding complications. The direct oral anticoagulants (DOACs) should be stopped 24–48 h prior to the test. Cardiac catheterization is a sterile procedure, so antibiotic prophylaxis is not required.

**TECHNIQUE**

Cardiac catheterization and coronary angiography provide a detailed hemodynamic and anatomic assessment of the heart and coronary arteries. The selection of procedures is dependent on the patient's symptoms and clinical condition, with some direction provided by noninvasive studies.

**Vascular Access** Cardiac catheterization procedures are performed using a percutaneous technique to enter the femoral or radial artery and femoral, brachial, or internal jugular vein as the access sites for left and right heart catheterization, respectively. A flexible sheath is inserted into the vessel over a guidewire, allowing diagnostic catheters to be introduced into the vessel and advanced toward the heart using fluoroscopic guidance. The radial artery (or rarely the brachial artery) access site is advantageous in patients with peripheral arterial disease that involves the abdominal aorta, iliac, or femoral vessels; severe iliac artery tortuosity; morbid obesity; or preference for early postprocedure ambulation. Use of radial artery access is the preferred access route due to a lower rate of access-site bleeding complications and improved patient comfort. A normal modified Allen's test or Barbeau test confirming dual blood supply to the hand from the radial and ulnar arteries is recommended prior to access at this site. The internal jugular or antecubital veins serve as the preferred access sites to the right heart when the patient has an inferior vena cava filter in place or requires prolonged hemodynamic monitoring.

**Right Heart Catheterization** This procedure measures pressures in the right heart and pulmonary artery. Right heart catheterization is no longer a routine part of diagnostic cardiac catheterization, but it is reasonable in patients with unexplained dyspnea, pulmonary hypertension, valvular heart disease, pericardial disease, right and/or left ventricular dysfunction, congenital heart disease, and suspected intracardiac shunts. Right heart catheterization most commonly uses a balloon-tipped flotation catheter that is advanced sequentially to the right atrium, right ventricle, pulmonary artery, and pulmonary wedge position (as a surrogate for left atrial pressure) using fluoroscopic guidance; in each cardiac chamber, pressure is measured and blood samples are obtained for oxygen saturation analysis to screen for intracardiac shunts and calculate a cardiac output.

**Left Heart Catheterization** This procedure measures pressures in the left heart as a determinant of left ventricular performance. With the aid of fluoroscopy, a catheter is guided to the ascending aorta and across the aortic valve into the left ventricle to provide a direct measure of left ventricular pressure. In patients with a tilting-disc prosthetic aortic valve, crossing the valve with a catheter is contraindicated, and the left heart may be accessed via a transseptal technique from the right atrium using a needle-tipped catheter to puncture the atrial septum at the fossa ovalis. Once the catheter crosses from the right to the left atrium, it can be advanced across the mitral valve to the left ventricle. This technique is also used for mitral valvuloplasty. Heparin is given for prolonged procedures to limit the risk of stroke from embolism of clots that may form on the catheter. For patients with heparin-induced thrombocytopenia, the direct thrombin inhibitors bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of the procedure) or argatroban (350 µg/kg bolus, 15 µg/kg per min for the duration of the procedure) may be used.

## HEMODYNAMICS

A comprehensive hemodynamic assessment involves obtaining pressure measurements in the right and left heart and peripheral arterial system and determining the cardiac output (**Table 242-2**). The shape

and magnitude of the pressure waveforms provide important diagnostic information; an example of normal pressure tracings is shown in **Fig. 242-1**. In the absence of valvular heart disease, the atria and ventricles are “one chamber” during diastole when the tricuspid and mitral valves are open, whereas in systole, when the pulmonary and aortic valves are open, the ventricles and their respective outflow tracts are considered “one chamber.” These concepts form the basis by which hemodynamic measurements are used to assess valvular stenosis. When aortic stenosis is present, there is a systolic pressure gradient between the left ventricle and the aorta; when mitral stenosis is present, there is a diastolic pressure gradient between the pulmonary capillary wedge (left atrial) pressure and the left ventricle (**Fig. 242-2**). Hemodynamic measurements also discriminate between aortic stenosis and hypertrophic obstructive cardiomyopathy where the asymmetrically hypertrophied septum creates a dynamic intraventricular pressure gradient during ventricular systole. The magnitude of this obstruction is measured using an end-hole catheter positioned at the left ventricular apex that is pulled back while recording pressure; once the catheter has passed the septal obstruction and is positioned in the apex of the left ventricle, a gradient can be measured between the left ventricular apex and the aorta. Hypertrophic obstructive cardiomyopathy is confirmed by the Brockenbrough-Braunwald sign: following a premature ventricular contraction, there is an increase in the left ventricular–aorta pressure gradient with a simultaneous decrease in the aortic pulse pressure. The finding of a decrease in pulse pressure is absent in aortic stenosis.

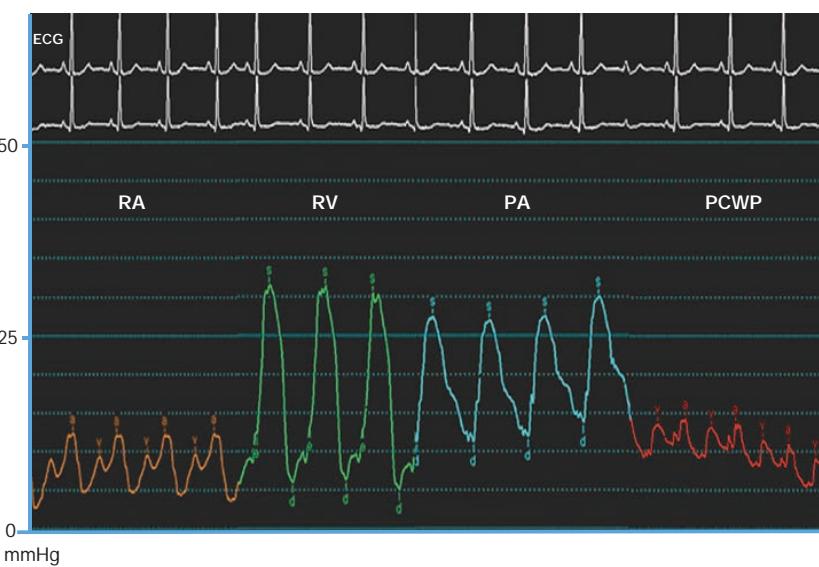
Regurgitant valvular lesions increase volume (and pressure) in the “receiving” cardiac chamber. In severe mitral and tricuspid regurgitation, the increase in blood flow to the atria takes place during ventricular systole, leading to an increase in the *v* wave (often two times greater than the mean pressure). The size of the *v* wave is a measure of the compliance of the left atrium but is not a reliable measure of the severity of the mitral regurgitation. Severe aortic regurgitation leads to a decrease in aortic diastolic pressure with a concomitant rise in left ventricular end-diastolic pressure, resulting in equalization of pressures between the two chambers at end diastole.

Hemodynamic measurements are also used to differentiate between cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy (**Table 242-3**). In cardiac tamponade, right atrial pressure is increased with a decreased or absent “*y*” descent, indicative of impaired right atrial emptying in diastole, and there is diastolic equalization of pressures in all cardiac chambers. In constrictive pericarditis, right atrial pressure is elevated with a prominent “*y*” descent, indicating rapid filling of the right ventricle during early diastole. A diastolic dip and plateau, or “square root sign,” in the ventricular waveforms due to an abrupt halt in ventricular filling during diastole, elevated right ventricular and pulmonary artery pressures, and discordant pressure changes in the right and left ventricles with inspiration (right ventricular systolic pressure increases while left ventricular systolic pressure decreases) are observed. In the absence of constriction, the two ventricular pressures are concordant. The latter hemodynamic phenomenon is the most specific for constriction. Restrictive cardiomyopathy may be distinguished from constrictive pericarditis by a marked increase in right ventricular and pulmonary artery systolic pressures (usually >60 mmHg), a separation of the left and right ventricular diastolic pressures by >5 mmHg (at baseline or with acute volume loading), and concordant changes in left and right ventricular diastolic filling pressures with inspiration (both increase).

**Cardiac Output** Cardiac output is measured by the Fick method or the thermodilution technique. Typically, the Fick method and thermodilution technique are both performed during cardiac catheterization, although the Fick method is considered more reliable in the presence of tricuspid regurgitation and in low-output states. The Fick method uses oxygen as the indicator substance and is based on the principle that the amount of a substance taken up or released by an organ (oxygen consumption) is equal to the product of its blood flow (cardiac output) and the difference in the concentration of the substance in the arterial

**TABLE 242-2 Normal Values for Hemodynamic Measurements**

Pressures (mmHg)	
Right atrium	
Mean	0–5
a wave	1–7
v wave	1–7
Right ventricle	
Peak systolic/end diastolic	17–32/1–7
Pulmonary artery	
Peak systolic/end diastolic	17–32/1–7
Mean	9–19
Pulmonary capillary wedge (mean)	4–12
Left atrium	
Mean	4–12
a wave	4–15
v wave	4–15
Left ventricle	
Peak systolic/end diastolic	90–130/5–12
Aorta	
Peak systolic/end diastolic	90–130/60–85
Mean	70–100
Resistances (dyn·s/cm <sup>5</sup> )	
Systemic vascular resistance	900–1400
Pulmonary vascular resistance	40–120
Oxygen Consumption Index ([L·min]/m <sup>2</sup> )	
Arteriovenous oxygen difference (vol %)	3.5–4.8
Cardiac index ([L·min]/m <sup>2</sup> )	2.8–4.2



**FIGURE 242-1** Normal hemodynamic waveforms recorded during right heart catheterization. Atrial pressure tracings have a characteristic "a" wave that reflects atrial contraction and a "v" wave that reflects pressure changes in the atrium during ventricular systole. Ventricular pressure tracings have a low-pressure diastolic filling period and a sharp rise in pressure that occurs during ventricular systole. d, diastole; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle; s, systole.

and venous circulation (arterial-venous oxygen difference). Thus, the formula for calculating the Fick cardiac output is:

$$\text{Cardiac output (L/min)} = (\text{oxygen consumption [mL/min]}) / (\text{arterial-venous oxygen difference [mL/L]})$$

Oxygen consumption is estimated as 125 mL oxygen/minute × body surface area, and the arterial-venous oxygen difference is determined by first calculating the oxygen-carrying capacity of blood (hemoglobin [g/100 mL] × 1.36 [mL oxygen/g hemoglobin] × 10) and multiplying this product by the fractional oxygen saturation. The indicator dilution method measures the concentration of a substance that is injected proximally, adequately mixes with blood, and is then sampled distally. In contemporary practice, thermodilution cardiac outputs are measured using temperature as the indicator. Measurements are made with a thermistor-tipped catheter that detects temperature deviations in the pulmonary artery after the injection of 10 mL of room-temperature normal saline into the right atrium.

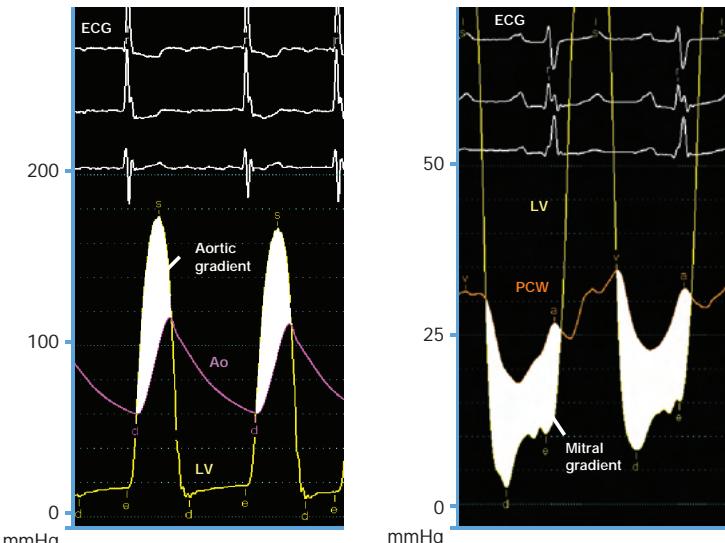
**Vascular Resistance** Resistance across the systemic and pulmonary circulations is calculated by extrapolating from Ohm's law of electrical resistance and is equal to the mean pressure gradient divided by the mean flow (cardiac output). Therefore, systemic vascular resistance is  $(\text{mean aortic pressure} - \text{mean right atrial pressure}) / \text{cardiac output}$  multiplied by 80 to convert the resistance from Wood units to  $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ . Similarly, the pulmonary vascular resistance is  $(\text{mean pulmonary artery} - \text{mean pulmonary capillary wedge pressure}) / \text{cardiac output} \times 80$ . Pulmonary vascular resistance is lowered by oxygen, nitroprusside, calcium channel blockers, prostacyclin infusions, and inhaled nitric oxide; these therapies may be administered during catheterization to determine if increased pulmonary vascular resistance is fixed or reversible.

**Valve Area** Hemodynamic data may also be used to calculate the valve area using the Gorlin formula that equates the area to the flow across the valve divided by the pressure gradient between the cardiac chambers surrounding the valve. The formula for the assessment of

valve area is:  $\text{Area} = (\text{cardiac output [cm}^3/\text{min]}/[\text{systolic ejection period or diastolic filling period}][\text{heart rate}]) / 44.3 \times \text{square root of the pressure gradient}$ , where C = 1 for aortic valve and 0.85 for the mitral valve. A valve area of  $<1.0 \text{ cm}^2$  and a mean gradient of  $>40 \text{ mmHg}$  indicate severe aortic stenosis, while a valve area of  $<1.5 \text{ cm}^2$  and a mean gradient  $>5-10 \text{ mmHg}$  are consistent with moderate-to-severe mitral stenosis; in symptomatic patients with a mitral valve area  $>1.5 \text{ cm}^2$ , a mean gradient  $>15 \text{ mmHg}$ , pulmonary artery pressure  $>60 \text{ mmHg}$ , or a pulmonary artery wedge pressure  $>25 \text{ mmHg}$  after exercise is also considered significant and may warrant intervention. The modified Hakki formula has also been used to estimate aortic valve area. This formula calculates the valve area as the cardiac output (L/min) divided by the square root of the pressure gradient. Aortic valve area calculations based on the Gorlin formula are flow-dependent, and therefore, for patients with low cardiac outputs, it is imperative to determine if a decreased valve area actually reflects a fixed stenosis or is overestimated by a low cardiac output and stroke volume that is

insufficient to open the valve leaflets fully. In these instances, cautious hemodynamic manipulation using dobutamine to increase the cardiac output and recalculation of the aortic valve area may be necessary.

**Intracardiac Shunts** In patients with congenital heart disease or unexplained hypoxemia, detection, localization, and quantification of the intracardiac shunt should be evaluated. A shunt should be suspected when there is unexplained arterial desaturation or increased oxygen saturation of venous blood. A "step up" or increase in oxygen content indicates the presence of a left-to-right shunt while a "step down" indicates a right-to-left shunt. The shunt is localized by detecting a difference in oxygen saturation levels of 5–7% between adjacent



**FIGURE 242-2** Severe aortic and mitral stenosis. Simultaneous recording of left ventricular (LV) and aortic (Ao) pressure tracings demonstrates a 62-mmHg mean systolic gradient (shaded area) that corresponds to an aortic valve area of  $0.6 \text{ cm}^2$  (left). Simultaneous recording of LV and pulmonary capillary wedge (PCW) pressure tracings reveals a 14-mmHg mean diastolic gradient (shaded area) that is consistent with critical mitral stenosis (mitral valve area =  $0.5 \text{ cm}^2$ ). d, diastole; e, end diastole; s, systole.

**TABLE 242-3 Hemodynamic Findings in Tamponade, Constrictive Pericarditis, and Restrictive Cardiomyopathy**

	CARDIAC TAMPONADE	CONSTRICITIVE PERICARDITIS	EFFUSIVE-CONSTRICITIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY
Pericardial pressure	↑	↑	↑	Normal
Right atrium pressure	↑	↑	↑ (Fails to decrease by 50% or to <10 mmHg after pericardiocentesis)	↑
Right atrium pressure waveform	Prominent "x" descent Diminished or absent "y" descent	Prominent "x" descent Prominent "y" descent	Prominent "x" descent "y" descent less prominent than expected	Prominent "y" descent
Right ventricle systolic pressure	<50 mmHg	<50 mmHg	<50 mmHg	>60 mmHg
Right ventricle end-diastolic pressure		>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	<1/3 right ventricular systolic pressure Less than left ventricular end-diastolic pressure by 5 mmHg
Right ventricle pressure waveform		Dip and plateau or "square root" sign	Dip and plateau or "square root" sign	Dip and plateau or "square root" sign
Right ventricle-left ventricle systolic pressure relationship with inspiration	Discordant	Discordant	Discordant	Concordant

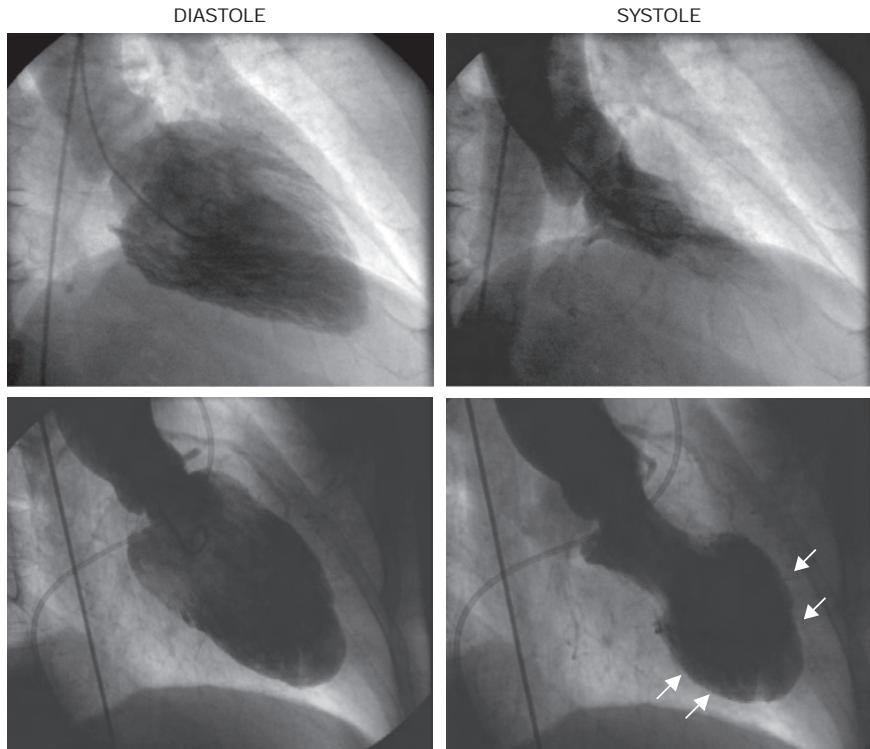
cardiac chambers. The severity of the shunt is determined by the ratio of pulmonary blood flow ( $Q_p$ ) to the systemic blood flow ( $Q_s$ ), or  $Q_p/Q_s = ([\text{systemic arterial oxygen content} - \text{mixed venous oxygen content}] / [\text{pulmonary vein oxygen content} - \text{pulmonary artery oxygen content}])$ . For an atrial septal defect, a shunt ratio of 1.5 is considered significant and factored with other clinical variables to determine the need for intervention. When a congenital ventricular septal defect is present, a shunt ratio of 2.0 with evidence of left ventricular volume overload is a strong indication for surgical correction.

### VENTRICULOGRAPHY AND AORTOGRAPHY

Ventriculography to assess left ventricular function may be performed during cardiac catheterization. A pigtail catheter is advanced retrograde across the aortic valve into the left ventricle, and 30–45 mL of contrast is power-injected to visualize the left ventricular chamber during the cardiac cycle. The ventriculogram is usually performed in the right anterior oblique projection to examine wall motion and mitral valve function. Normal wall motion is observed as symmetric contraction of all segments; hypokinetic segments have decreased contraction, akinetic segments do not contract, and dyskinetic segments appear to bulge paradoxically during systole (Fig. 242-3). Ventriculography may also reveal a left ventricular aneurysm, pseudoaneurysm, or diverticulum and can be used to assess mitral valve prolapse and the severity of mitral regurgitation. The degree of mitral regurgitation is estimated by comparing the density of contrast opacification of the left atrium with that of the left ventricle. Minimal contrast reflux into the left atrium is considered 1+ mitral regurgitation, while contrast density in the left atrium that is greater than that in the left ventricle with reflux of contrast into the pulmonary veins within

three beats defines 4+ mitral regurgitation. When it takes more than 3 beats but fully fills the atrium, it is 3+. Both 3+ and 4+ are considered severe regurgitation. Ventriculography performed in the left anterior oblique projection can be used to identify a ventricular septal defect. Calculation of the ventricular volumes in systole and diastole allows calculation of stroke volume and cardiac output.

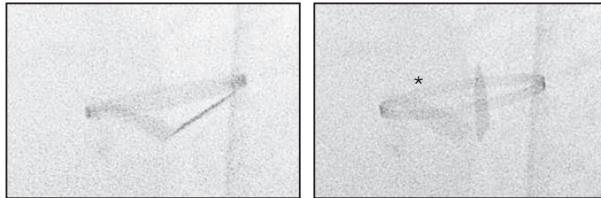
Aortography in the cardiac catheterization laboratory visualizes abnormalities of the ascending aorta, including aneurysmal dilation and involvement of the great vessels, as well as dissection with compression of the true lumen by an intimal flap that separates the true



**FIGURE 242-3** Left ventriculogram at end diastole (left) and end systole (right). In patients with normal left ventricular function, the ventriculogram reveals symmetric contraction of all walls (top). Patients with coronary artery disease may have wall motion abnormalities on ventriculography as seen in this 60-year-old male following a large anterior myocardial infarction. In systole, the anterior, apical, and inferior walls are akinetic (white arrows) (bottom).

## DIASTOLE

## SYSTOLE



**FIGURE 242-4** Cinefluoroscopic detection of mechanical valve leaflet dysfunction. Images of a bileaflet mechanical valve in the aortic position taken during diastole (left) and systole (right) show that one leaflet opens normally during systole while the other leaflet (below asterisk) remains immobile and fixed consistent with valve leaflet thrombosis.

and false lumina. Aortography can also be used to identify patent saphenous vein grafts that elude selective cannulation, identify shunts that involve the aorta such as a patent ductus arteriosus, evaluate the takeoff or proximal anatomy of the great vessels, and provide a qualitative assessment of aortic regurgitation using a 1+–4+ scale similar to that used for mitral regurgitation.

### CINEFLUOROSCOPY OF PROSTHETIC MECHANICAL VALVES

Prosthetic valve leaflet dysfunction may occur as a result of thrombus or obstruction of leaflet excursion by pannus (Fig. 242-4). The incidence of prosthetic valve thrombosis in left-sided valves is 0.1–6.0% per patient-year with differences in rates attributable to valve type, position, anticoagulation status, and left ventricular function. Prosthetic valve dysfunction should be suspected in patients with subtherapeutic anticoagulation with a low mean INR, a prothrombotic state, recent-onset heart failure, cardiogenic shock, cardiac arrest, thromboembolic event, or, in asymptomatic patients, an increasing gradient across the valve. Cinefluoroscopy visualizes the motion of mechanical valve leaflets, is noninvasive, is available in most centers, and can be performed rapidly with minimal radiation exposure. Prosthetic mechanical valves should be imaged *en face* and at a 90° angle over several cardiac cycles to document opening and closing of the valve leaflets as well as motion of the base ring. Each type of prosthetic valve has leaflet opening and closing angles that are reported by the manufacturer and can be used to determine if movement or closure of the valve leaflets is restricted, suggestive of mechanical obstruction.

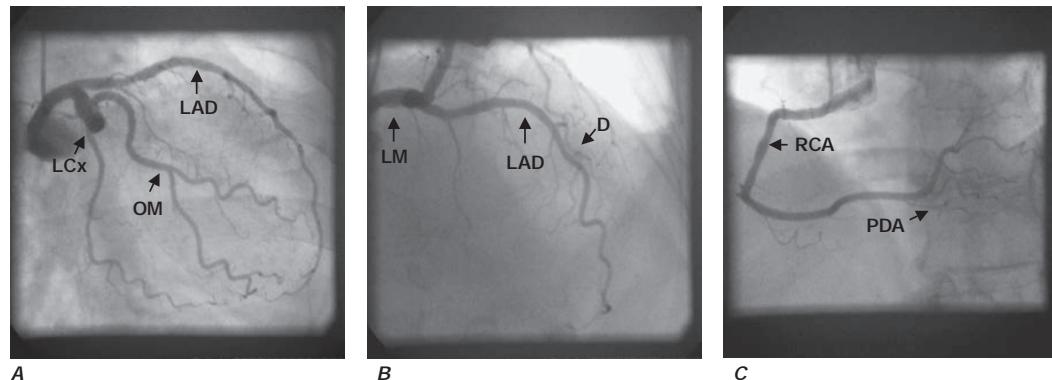
### CORONARY ANGIOGRAPHY

Selective coronary angiography is almost always performed during cardiac catheterization and is used to define the coronary anatomy and determine the extent of epicardial coronary artery and coronary artery bypass graft disease. Specially shaped coronary catheters are used to

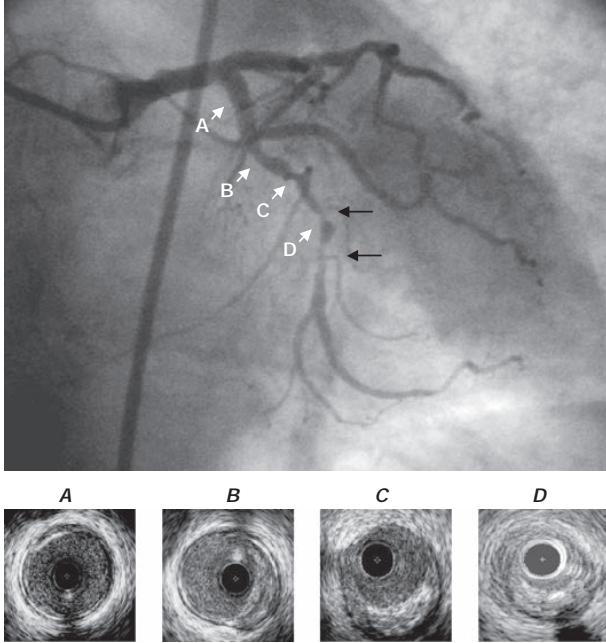
engage the left and right coronary ostia. Hand injection of radiopaque contrast agents creates a coronary “luminogram” that is recorded as radiographic images (cine angiography). Because the coronary arteries are three-dimensional objects that are in motion with the cardiac cycle, angiograms of the vessels using several different orthogonal projections are taken to best visualize the vessels without overlap or foreshortening.

The normal coronary anatomy is highly variable between individuals, but, in general, there are two coronary ostia and three major coronary vessels—the left anterior descending, the left circumflex, and the right coronary arteries with the left anterior descending and left circumflex arteries arising from the left main coronary artery (Fig. 242-5). When the right coronary artery is the origin of the atrioventricular nodal branch, the posterior descending artery, and the posterior lateral vessels, the circulation is defined as right dominant; this is found in ~85% of individuals. When these branches arise from the left circumflex artery, as occurs in ~5% of individuals, the circulation is defined as left dominant. The remaining ~10% of patients have a codominant circulation with the posterior descending vessel arising from both the right coronary and the posterior lateral vessels from left coronary circulation. In some patients, a ramus intermedius branch arises directly from the left main coronary artery that trifurcates into the left anterior descending, ramus, and circumflex arteries; this finding is a normal variant. Coronary artery anomalies occur in 1–2% of patients, with separate ostia for the left anterior descending and left circumflex arteries being the most common (0.41%).

Coronary angiography visualizes coronary artery stenoses as luminal narrowings on the cine angiogram. The degree of narrowing is referred to as the percent stenosis and is determined visually by comparing the most severely diseased segment with a proximal or distal “normal segment”; a stenosis >50% is considered significant (Fig. 242-6). Online quantitative coronary angiography can provide a more accurate assessment of the percent stenosis and lessen the tendency to overestimate lesion severity visually. The presence of a myocardial bridge, which most commonly involves the left anterior descending artery, may be mistaken for a significant stenosis; this occurs when a portion of the vessel dips below the epicardial surface into the myocardium and is subject to compressive forces during ventricular systole. The key to differentiating a myocardial bridge from a fixed stenosis is that the “stenosed” part of the vessel returns to normal during diastole. Coronary calcification is also seen during angiography prior to the injection of contrast agents. Collateral blood vessels may be seen traversing from one vessel to the distal vasculature of a severely stenosed or totally occluded vessel. Thrombolysis in myocardial infarction (TIMI) flow grade, a measure of the relative duration of time that it takes for contrast to opacify the coronary artery fully, may provide an additional clue to the degree of lesion severity, and the presence of TIMI grade 1 (minimal filling) or 2 (delayed filling) suggests that a severe coronary artery stenosis is present.



**FIGURE 242-5** Normal coronary artery anatomy. **A.** Coronary angiogram showing the left circumflex (LCx) artery and its obtuse marginal (OM) branches. The left anterior descending (LAD) artery is also seen but may be foreshortened in this view. **B.** The LAD and its diagonal (D) branches are best seen in cranial views. In this angiogram, the left main (LM) coronary artery is also seen. **C.** The right coronary artery (RCA) gives off the posterior descending artery (PDA), so this is a right dominant circulation.



**FIGURE 242-6 Coronary stenoses on cine angiogram and intravascular ultrasound.** Significant stenoses in the coronary artery are seen as narrowings (black arrows) of the vessel. Intravascular ultrasound shows a normal segment of artery (**A**), areas with eccentric plaque (**B, C**), and near total obliteration of the lumen at the site of the significant stenosis (**D**). Note that the intravascular ultrasound catheter is present in the images as a black circle.

### INTRAVASCULAR ULTRASOUND, OPTICAL COHERENCE TOMOGRAPHY, FRACTIONAL FLOW RESERVE, AND CORONARY FLOW RESERVE

During coronary angiography, intermediate stenoses (40–70%), indeterminate findings, or anatomic findings that are incongruous with the patient's symptoms may require further interrogation. In these cases, intravascular ultrasound (IVUS) provides a more accurate anatomic assessment of the coronary artery and the degree of coronary atherosclerosis (Fig. 242-6). IVUS is performed using a small flexible catheter with a 40-mHz transducer at its tip that is advanced into the coronary artery over a guidewire. Data from IVUS studies may be used to image atherosclerotic plaque precisely, determine luminal cross-sectional area, and measure vessel size; it is also used during or following percutaneous coronary intervention to assess the stenosis and determine the adequacy of stent placement. Optical coherence tomography (OCT) is a catheter-based imaging technique that uses near-infrared light to generate images with better spatial resolution than IVUS (12–18 microns vs 150–200 microns); however, the depth of field is smaller. The advantage of OCT imaging over IVUS lies in its ability to image characteristics of the

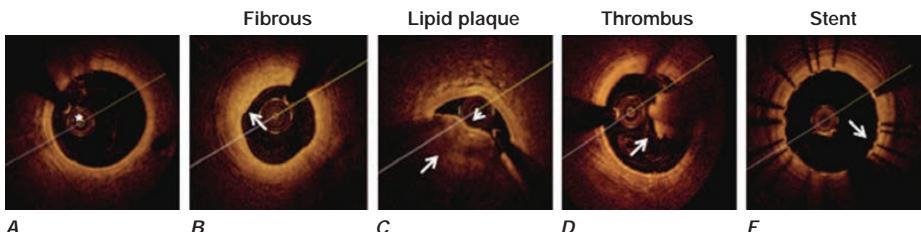
atherosclerotic plaque (lipid, fibrous cap) with high definition and to assess coronary stent placement, apposition, and patency (Fig. 242-7).

Measurement of the fractional flow reserve provides a functional assessment of the stenosis and is more accurate in predicting long-term clinical outcome than imaging techniques. The fractional flow reserve is the ratio of the pressure in the coronary artery distal to the stenosis divided by the pressure in the artery proximal to the stenosis at maximal vasodilation. Fractional flow reserve is measured using a coronary pressure-sensor guidewire at rest and at maximal hyperemia following the infusion of adenosine (Fig. 242-8). A fractional flow reserve of <0.80 indicates a hemodynamically significant stenosis that would benefit from intervention. The instantaneous wave-free ratio, which measures the gradient across the stenosis during the latter part of diastole, does not require the use of adenosine and may be preferred for some patients with asthma or documented allergy to adenosine. An instantaneous wave-free ratio of <0.89 is considered positive for ischemia. Resting gradients have also been shown to predict a significant stenosis. Using both pressure and velocity, an index of myocardial resistance can also be calculated. Studies have shown this to be an important predictor of outcome as well.

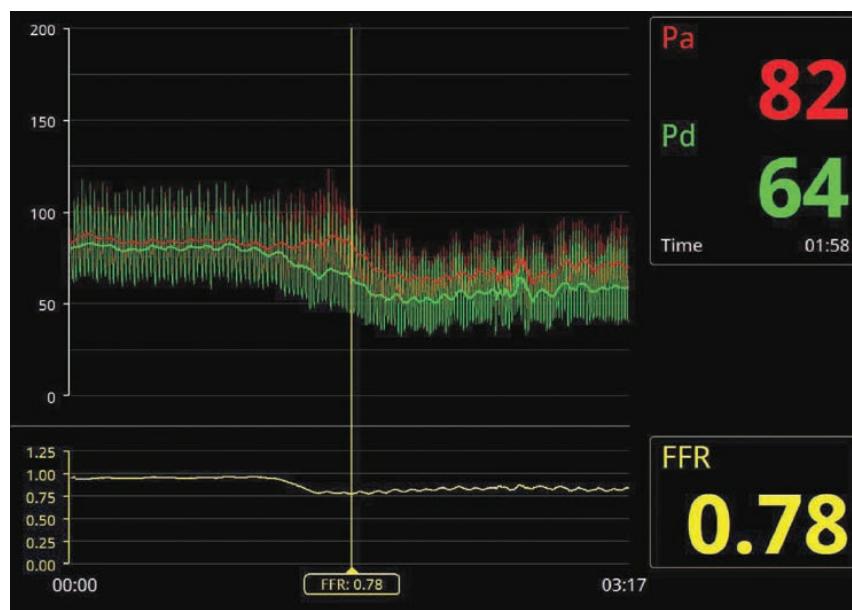
Microvascular dysfunction can be evaluated by assessing coronary flow reserve, the ratio between coronary blood flow at maximal hyperemia and rest. Coronary flow reserve is measured using a Doppler wire- or pressure wire-based thermodilution technique in patients with unexplained chest pain or ischemia and no obstructive coronary artery disease. A coronary flow reserve <2.0 is considered abnormal.

### POSTPROCEDURE CARE

Once the procedure is completed, vascular access sheaths are removed. If the femoral approach is used, direct manual compression or vascular closure devices that immediately close the arteriotomy site with a staple/clip, collagen plug, or sutures are used to achieve hemostasis. These devices decrease the length of supine bed rest (from 6 h to 2–4 h) and improve patient satisfaction but have not been shown definitively to be superior to manual compression with respect to access-site complications. With radial-artery access, the sheath is removed and a plastic wristband with an air pillow is used to keep pressure on the access site while maintaining flow through the radial artery. Bed rest is needed for only 2 h. When cardiac catheterization is performed as an elective outpatient procedure, the patient completes postprocedure bed rest in a monitored setting and is discharged home with instructions to liberalize fluids because contrast agents promote an osmotic diuresis, to avoid strenuous activity, and to observe the vascular access site for signs of complications. Overnight hospitalization may be required for high-risk patients with significant comorbidities, patients with complications occurring during the catheterization, or patients who have undergone a complicated percutaneous coronary intervention. Hypotension early after the procedure may be due to inadequate fluid replacement or retroperitoneal bleeding from the access site. Patients who received >2 Gy of radiation during the procedure should be examined for signs of erythema. For patients who received higher doses (>5 Gy), clinical follow-up within 1 month to assess for skin injury is recommended.



**FIGURE 242-7 Optical coherence tomography imaging.** **A.** The optical coherence tomography (OCT) catheter (\*) in the lumen of a coronary artery with limited neointima formation. The intima is seen with high definition, but unlike intravascular ultrasound imaging, the vessel media and adventitia are not well visualized. **B.** A fibrous plaque (arrow) is characterized by a bright signal. **C.** A large, eccentric, lipid-rich plaque obscures part of the vessel lumen. Because lipid in the plaque absorbs light, the lipid-rich plaque appears as a dark area with irregular borders (arrow). The plaque is covered by a thin fibrous cap (arrowhead) typical of a vulnerable plaque. **D.** A thrombus (arrow) adherent to a ruptured plaque that is protruding into the vessel lumen. **E.** A coronary stent is well opposed to the vessel wall. The stent struts appear as short bright lines with dropout behind the struts (arrow).



**FIGURE 242-8.** Fractional flow reserve. The fractional flow reserve is measured using a coronary pressure-sensor guidewire that measures the ratio of the pressure in the coronary artery distal to the stenosis (Pd, green) divided by the pressure in the artery proximal to the stenosis (Pa, red) at maximal hyperemia following the injection of adenosine. A fractional flow reserve of <0.80 indicates that revascularization would be beneficial.

### FURTHER READING

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electrophysiology also ushered in the development of antiarrhythmic drugs utilized by cardiac electrophysiologists.

The modern era of clinical cardiac electrophysiology began with the first recordings of human intracardiac electrograms in the 1960s. Initially, invasive electrophysiology studies were limited as diagnostic tools. This included serial electrophysiologic testing to evaluate arrhythmia mechanisms and evaluate arrhythmia suppression by antiarrhythmic drugs, and programmed stimulation of the heart for risk stratification of sudden cardiac death. In the 1960s and 1970s, cardiac surgery was the only available invasive treatment for cardiac arrhythmias. The subsequent development of radiofrequency catheter ablation in the 1980s ushered in the era of interventional cardiac electrophysiology. In addition, with the development of implanted cardiac rhythm management devices including pacemakers and defibrillators, clinical cardiac electrophysiology became a distinct medical subspecialty.

### CELLULAR ELECTROPHYSIOLOGY

The cardiac action potential (AP) drives the electrophysiologic behavior of all cardiac myocytes. The AP is characterized morphologically by five distinct phases, termed phases 0–4, as shown in Fig. 243-1. Moreover, as ventricular electrophysiologic activity accounts for the QRS and T complexes of the surface ECG, each AP phase in ventricular tissues corresponds to distinct phases in the surface ECG: Phase 0, the rapid upstroke, corresponds to the QRS deflection; phases 1–2 account for the ST segment; phase 3 accounts for the T wave; while phase 4 corresponds to the segment between the end of the T wave and the subsequent QRS deflection. In addition, the P wave corresponds to atrial depolarization, while the PR interval corresponds to the time between initiation of atrial depolarization to the initiation of ventricular depolarization, comprised (typically) for the most part by the conduction time through the AV node.

AP morphologies are the result of the precise and carefully timed sequences of opening, closing, and inactivation of an array of membrane ion channels in response to cellular membrane potential changes, ligands that bind to the ion channel complex, or membrane stretch in a time-dependent fashion. The open ion channel allows flux of specific charged ions through a central pore, resulting in electrical (ionic) currents that drive the AP. The activity of different subsets of ion channels drives the different phases of the AP. Specific ionic currents that flux through an open channel are driven by the electrochemical gradient

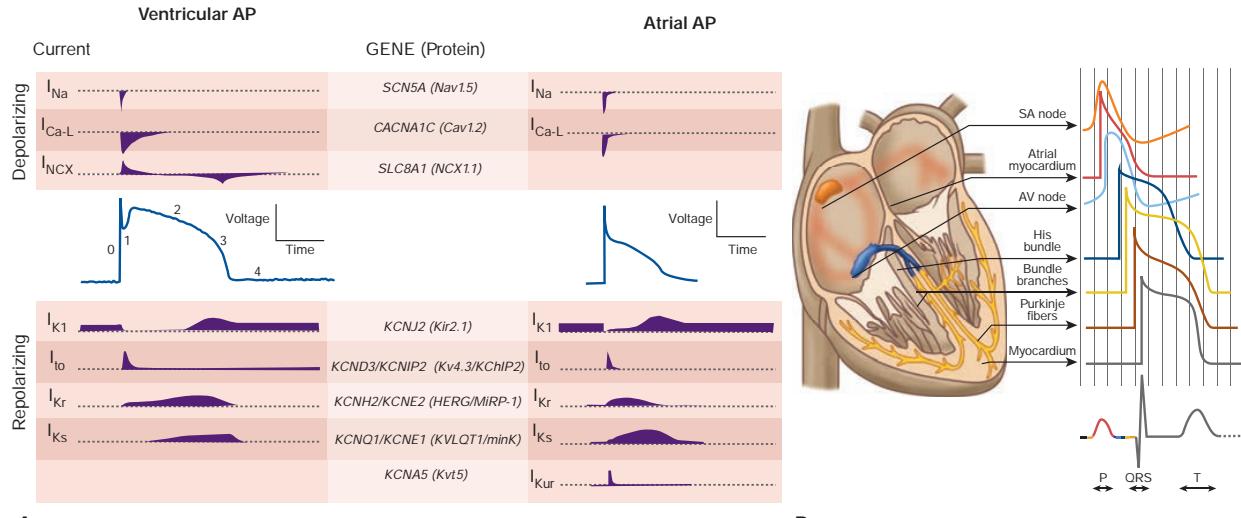
## Section 3 Disorders of Rhythm

### 243 Principles of Clinical Cardiac Electrophysiology

William H. Sauer, Bruce A. Koplan, Paul C. Zei

#### HISTORICAL PERSPECTIVE

Clinical cardiac electrophysiology is the subspecialty of cardiology that focuses on the study and management of heart rhythm disorders. The development of the modern surface electrocardiogram (ECG) by Willem Einthoven more than 100 years ago enabled understanding of the relationship between cardiac electrical potentials, mechanical cardiac function, and pathophysiology of cardiac arrhythmias. In the mid-twentieth century, the recording of cellular membrane currents enabled the understanding that the surface ECG represents the sum of cellular cardiac electrical activity. An understanding of cellular



**FIGURE 243-1** **A.** Cellular atrial and ventricular action potentials. Phases 0–4 are the rapid upstroke, early repolarization, plateau, late repolarization, and diastole, respectively. The ionic currents and their respective genes are shown above and below the action potentials. The currents that underlie the action potentials vary in atrial and ventricular myocytes. Potassium current ( $I_{K1}$ ) is the principal current during phase 4 and determines the resting membrane potential of the myocyte. Sodium current generates the upstroke of the action potential (phase 0); activation of  $I_{Na}$  with inactivation of the Na current inscribes early repolarization (phase 1). The plateau (phase 2) is generated by a balance of repolarizing potassium currents and depolarizing calcium current. Inactivation of the calcium current with persistent activation of potassium currents (predominantly  $I_{Kr}$  and  $I_{Ks}$ ) causes phase 3 repolarization. Currents that result in membrane depolarization are grouped at the top of the figure above the action potentials, while repolarizing currents are shown below the action potentials. **B.** A surface ECG representation of sinus rhythm is shown with respective intracardiac action potentials that are active during each phase of the ECG. Each cardiac conduction region's action potential is shown in the upper portion of the panel, with colors reflected in the ECG segment shown in the lower portion of the panel. Note that during the P wave, atrial depolarization is active. During the PR interval, the AV nodal, His, bundle branches, and Purkinje fibers are active (in sequence), although these action potentials are not discernible on the surface ECG. During the QRS interval, ventricular action potentials are active, with the QRS morphology most reflective of the sequence of ventricular tissue action potential activation. The ST segment is predominantly determined by the plateau phase 2 of the ventricular action potential. The T wave is determined largely by ventricular repolarization (phase 3), while the isoelectric segment is the result of the electrically neutral phase 4 of the ventricular action potential.

of that particular ion across the membrane, which in turn is driven by ion pumps or transporters/exchangers, which in turn are catalyzed by ATP (Fig. 243-2).

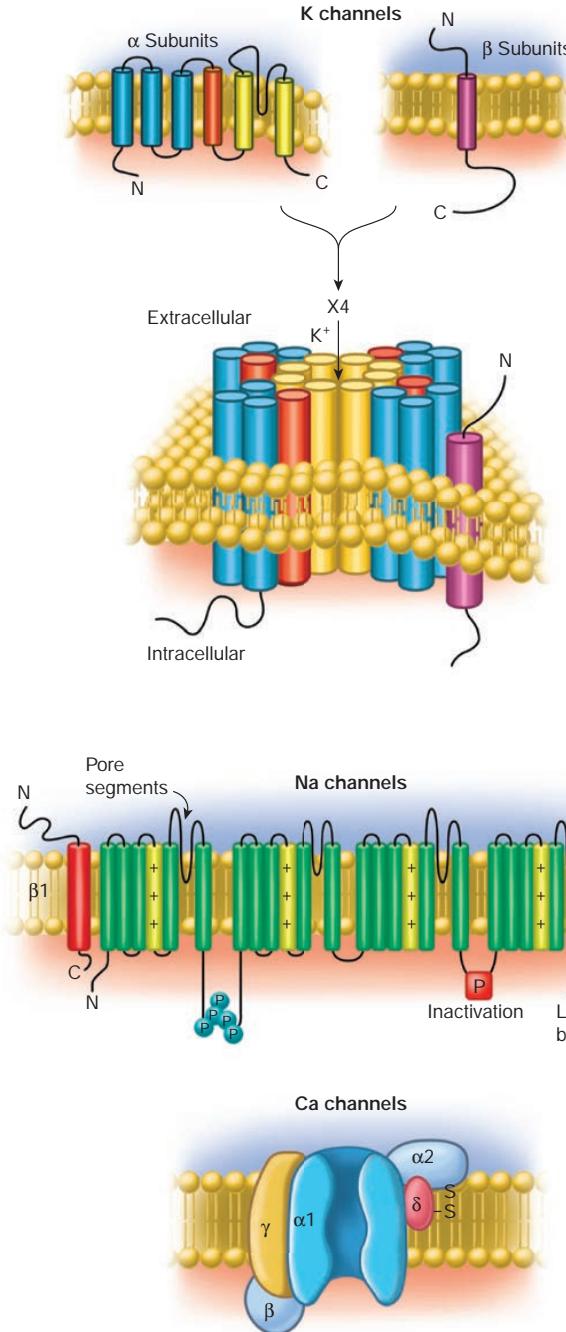
Ion channels are complex, multi-subunit transmembrane glycoproteins that contain a central pore that is selective for particular ionic species (selectivity); a “gating” apparatus that regulates the opening, closing, and inactivation apparatus; and often one or more regulatory subunits. Most channels gate in response to changes in membrane potential, a specific ligand, or mechanical deformation. The molecular underpinnings of these specific functional properties of channels have become well understood through decades of basic electrophysiologic study using the tools of voltage clamp and patch clamp techniques, and more recently, molecular, genetic, and structural/crystallographic techniques.

The structural makeup of most ion channels contains several common motifs. All channels form a central conducting pore, with ionic selectivity determined by specific amino acids that line the central pore. The central pore of most channels is formed by the P domain, a series of hydrophilic amino acid residues, with one of several structural variants: four separate homologous alpha subunits, each with homologous P domains (voltage-gated K channels); a single alpha subunit with four internally homologous P domains (voltage-gated Na or Ca channels); or two internally homologous P domains from two separate subunits (most ligand-gated K channels). A series of one or more transmembrane segments surrounds the central pore. In voltage-gated channels, the fourth of six segments, the S4 segment, contains a series of charged amino acid residues that functions as a voltage sensor, responding to changes in membrane potential by facilitating protein conformational changes that result in channel opening or closing (gating). In ligand-activated channels, the binding of a ligand (transmitters, molecules, or other ions) results in channel opening or closing, while deformations in membrane shape determine gating in stretch-activated channels. In addition, in many ion channels, a complex of auxiliary proteins is associated with the primary alpha subunit; most auxiliary

subunits appear to facilitate regulation of ion channel expression and activity. A distinct type of transmembrane protein complex is the gap junction complex. A large multimeric complex of connexin subunits forms a large, nonselective pore that spans and thereby connects adjacent myocytes. This allows free flux of ions between adjacent myocytes, facilitating impulse propagation across myocardial tissues.

Due to the physiologic gradient of their respective ions across the cell membrane, Na and Ca channels account for most inward, or depolarizing, currents in cardiac myocytes, and these channels respond to membrane depolarization with rapid opening, relatively rapid closing, and inactivation. Na and Ca currents therefore drive phase 0 depolarization of the AP. Potassium channels, on the other hand, account for most of the repolarizing currents seen in cardiac myocytes. Relatively slow K channel opening, as well as Na and Ca channel closing and inactivation, drives the plateau of phases 1–2 as well as the repolarizing phase 3 of the AP. Mutations in K channel subtypes are causative of many inherited channelopathies. Mutations that either inherently delay the closing or inactivation of K channels result in prolongation of the QT interval, leading to many forms of inherited long QT syndrome.

The morphologic and functional properties of APs vary across different regions of the heart. These variations are the result of variations in the active ionic currents during each phase of the AP, which in turn reflects regional variation in ion channel expression. In atrial and ventricular myocytes, Na currents dominate the rapid upstroke (phase 1) of the AP, while in nodal tissues, Ca currents, which activate more slowly, dominate phase 1. Hence, for instance, drugs that bind and block the cardiac Na channel demonstrate efficacy in treating tachyarrhythmias arising from the atria and ventricles, whereas Ca channel blocking agents demonstrate efficacy at nodal tissues. During the pre-depolarizing phase 4 of the AP, ionic currents remain relatively quiescent in atrial and ventricular myocytes as they await local depolarization that triggers the next AP. In contrast, in sinus nodal tissues, which possess the property of automaticity, or intrinsic rhythmic



**FIGURE 243-2** Topology and subunit composition of the voltage-dependent ion channels. Potassium channels are formed by the tetramerization of  $\alpha$  or pore-forming subunits and one or more  $\beta$  subunits; only single  $\beta$  subunits are shown for clarity. Sodium and calcium channels are composed of  $\alpha$  subunits with four homologous domains and one or more ancillary subunits. In all channel types, the loop of protein between the fifth and sixth membrane-spanning repeat in each subunit or domain forms the ion-selective pore. In the case of the sodium channel, the channel is a target for phosphorylation, the linker between the third and fourth homologous domain is critical to inactivation, and the sixth membrane-spanning repeat in the fourth domain is important in local anaesthetic antiarrhythmic drug binding. The Ca channel is a multi-subunit protein complex with the  $\alpha_1$  subunit containing the pore and major drug-binding domain.

depolarization, there is gradual depolarization observed during phase 4, until a threshold is reached that initiates the next AP. In these nodal tissues, this depolarizing phase 4 current is generated by a semiselective  $\text{Na}/\text{Ca}$  channel, termed the “funny current” or  $I_f$ , which is the target for the medication ivabradine.

## NORMAL CARDIAC IMPULSE PROPAGATION

The normal cardiac impulse initiates and travels through specialized conduction fibers, often referred to as the cardiac conduction system. Each impulse is initiated in the sinoatrial (SA) node, located at the lateral junction between the superior vena cava (SVC) and right atrium (RA). SA nodal tissues exhibit automaticity, such that a reliable, rhythmic impulse emanates from the SA node. The SA node (along with the AV node) is richly innervated by autonomic fibers, allowing precise and dynamic control of heart rate and overall function by the central nervous system. The normal impulse then travels across the RA then the LA across preferential conduction pathways, initiating atrial systole. Once the impulse reaches the AV node, conduction occurs in a relatively slow time frame through the AV nodal tissues. This conduction time not only serves to provide physiologic AV synchrony, but it also is reflected in the surface ECG as the PR interval, or time between the atrial inscription and the subsequent ventricular, or QRS, complex. In normal hearts, the AV node serves as the only electrical connection between atria and ventricles. Both the SA and AV nodes respond exquisitely to autonomic input; for instance, with exercise and increased adrenergic tone, the PR interval physiologically shortens. After the AV node, the impulse travels through a network of specialized conduction fibers: the bundle of His divides into a right and left bundle branch, which transmit conduction to the right and left ventricles, respectively. The left bundle then divides further into left anterior and left posterior fascicles. The fascicles then further divide into Purkinje fibers. The conduction velocity of electrical impulses is much higher in Purkinje fibers (2–3 m/s) than in myocardial cells (0.3–0.4 m/s). Different connexins in gap junctions of Purkinje networks are partially responsible for more rapid conduction. This network of conductive Purkinje fibers is located endocardially and serves to rapidly transmit depolarization throughout the ventricles, such that myocardial depolarization, and hence mechanical contraction, occur rapidly and in a coordinated, synchronized fashion, optimizing mechanical contraction of the ventricles. Repolarization of the ventricular myocardium, on the other hand, occurs relatively slowly and progresses from the epicardial surface back toward the endocardium. Hence, the T wave inscription in most ECG leads is concordant with the QRS complex.

## MECHANISMS OF CARDIAC ARRHYTHMIAS

Cardiac arrhythmias are the manifestation of abnormalities in the initiation and/or propagation of the cardiac electrical impulse. Bradyarrhythmias result most commonly from abnormalities in the specialized conduction tissues. Abnormal function of the SA node may result in pathologic sinus bradycardia; AV node disease may result in conduction block; pathology in the His-Purkinje system may result in conduction block as well. Tachyarrhythmias may arise from not only nearly every location within the conduction tissues, but also within atrial or ventricular tissues. Tachyarrhythmias are typically classified by mechanism: enhanced automaticity refers to abnormal spontaneous depolarization, which can occur along the conduction system, the atria, or ventricles; triggered arrhythmias result from abnormal afterdepolarizations that occur in either phase 2/3 (early afterdepolarizations) or phase 4 (delayed afterdepolarizations) of the AP; reentry results from circus movement of an electrical impulse (see Table 243-1 and Fig. 243-3).

**Table 243-1 Overview of the Mechanisms of Cardiac Tachyarrhythmias**

TACHYARRHYTHMIA CATEGORY	MECHANISM	PROTOTYPICAL ARRHYTHMIAS
Abnormal Automaticity	Enhanced (acceleration of phase 4 repolarization)	Idiopathic VT; AT
	Suppressed (absent or decelerated phase 4 repolarization)	Sinus node dysfunction
Triggered Activity	EADs	TdP in long QT syndrome, PVCs
	DADs	Reperfusion PVCs/VT, AT and VT with digitalis toxicity
Reentry	1) Anatomical or functional confinement of a circuit (i.e., scar, accessory pathway); 2) unidirectional block after a premature impulse; 3) wave of excitation that travels in a single direction returning to its point of origin	AVNRT, AVRT, atrial flutter, scar-related VT

### ENHANCED AUTOMATICITY

Automaticity, defined as spontaneous depolarizations occurring during phase 4 of the AP, is a normal property of several myocardial tissues, including the SA node, AV node, and the His-Purkinje system. The automaticity of the SA node triggers the normal cardiac impulse. When the automaticity of a more proximal conduction system tissue is unreliable or slow, the automaticity of a more distal aspect of the conduction system may result in an “escape rhythm” that may maintain cardiac output. Automaticity in these tissues results from phase 4 depolarization of cellular membranes driven by several ionic currents. In the SA node, the nonselective Na/Ca If current drives this depolarization,

while in other tissues K currents, Ca currents, or even the Na/Ca and ATP-driven Na/K exchangers contribute.

The rate of depolarization during phase 4 drives the frequency APs, and hence automaticity rate of these tissues. In nodal tissues, this rate of depolarization is highly regulated by the autonomic system. Parasympathetic input results in local acetylcholine (ACh) release, which then binds the IK<sub>ACh</sub> potassium channel complex (specifically via a G protein mediated mechanism). The opening of IK<sub>ACh</sub> channels, resulting in K efflux, hyperpolarizes these cells, resulting in slowing of phase 4 depolarization, thereby slowing the automaticity rate. Sympathetic input, via catecholamines, activates both alpha- and beta-adrenergic receptors. Beta-1 adrenergic stimulation results in activation of L-type Ca channels, Ca influx, and as a result, enhanced depolarization rates during phase 4, and increased automaticity rates. The normal range of SA automaticity rates is between 30–220 beats/min, corresponding to the normal range of rates during sinus rhythm. The sinus rate at any instant is therefore a dynamic balance between sympathetic and parasympathetic input, with the latter dominating in the restful state. The intrinsic heart rate (IHR) is defined as the “native” automaticity rate of the SA node, absent any autonomic input.

Abnormally enhanced automaticity may occur at any site that exhibits automaticity, including the SA node, AV node, or His-Purkinje system, resulting in pathologic tachycardia. In addition, in pathologic states, other stereotyped regions in the heart may exhibit enhanced automaticity, including the pulmonary veins, coronary sinus superior vena cava, and ventricular outflow tracts. Injury to myocardium, whether through ischemia or other mechanisms, may alter its cellular membrane properties, resulting in automaticity in these tissues. For instance, the border zones of infarcted ventricular myocardium, or rapidly reperfused ischemic myocardium, often exhibit automatic arrhythmias including PVCs or automatic idioventricular rhythms (AVIR). Abnormal automaticity in the pulmonary veins is believed to underpin the triggers that drive paroxysmal atrial fibrillation, while automaticity elsewhere in the atria drives atrial tachycardias.

### AFTERDEPOLARIZATIONS AND TRIGGERED ARRHYTHMIAS

Afterdepolarizations and triggered arrhythmias refer to abnormal depolarizations that occur in the late phases of the AP (afterdepolarizations) that can initiate sustained arrhythmias. Early afterdepolarizations (EADs) occur typically during phases 2–3 of the AP and may be facilitated by intracellular Ca loading. When the QT interval prolongs, typically in a heterogeneous fashion across the ventricles, EADs may trigger wavefronts of abnormal depolarizations, resulting in torsades de pointes (TdP), a nonsustained or sustained ventricular arrhythmia that may result in cardiac arrest. Medications that prolong QT interval, as well as other QT prolonging factors including hypokalemia, hypomagnesemia, and bradycardia, predispose the ventricles to EADs leading to TdP. Electrical remodeling in cardiomyopathies may also predispose to QT prolongation and risk of EADs and TdP.

Delayed afterdepolarizations (DADs) are abnormal depolarizations occurring in phase 4 of the AP. The mechanism underlying DADs is increased intracellular Ca, which then enhances repetitive depolarizations during the late phases of the AP. As a result, repetitive depolarizations ensue, including the well-described phenomenon of bidirectional ventricular tachycardia. Digitalis glycoside toxicity, ischemia, and catecholamines are the most commonly described causes for DADs.

### REENTRY

Reentry refers to the circus movement of a wavefront of electrical activation. Reentry can occur around a fixed anatomic barrier, referred to as anatomic reentry, or around a functionally blocked or refractory barrier or anchor, termed functional reentry. Initiation and maintenance of a reentrant arrhythmia requires (1) unidirectional block, where the electrical wavefront can only propagate in one direction, and (2) slow conduction, a zone within the reentrant circuit where conduction is relatively slow, allowing the remainder of the circuit to repolarize and recover from refractoriness (the inability to re-excite).

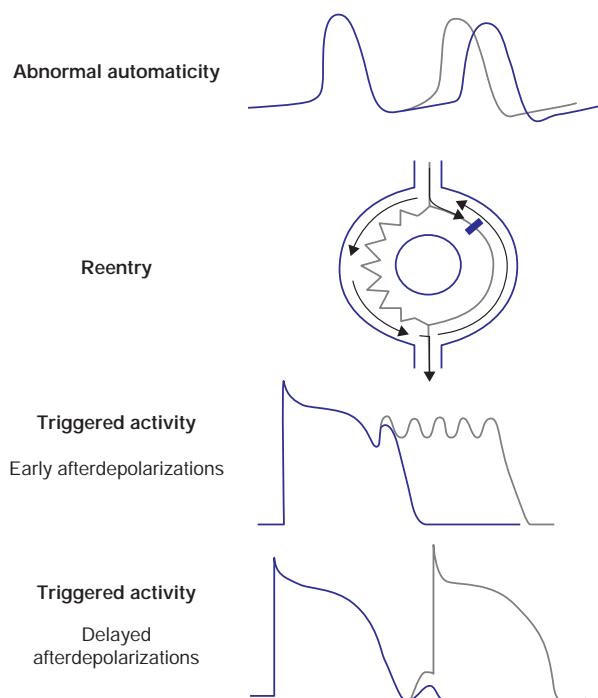


FIGURE 243-3 Schematic action potentials with early afterpolarizations (EADs) and delayed afterdepolarizations (DADs).

The more common form of reentry is anatomic, which requires a defined electrical/anatomic circuit with a pathway around a fixed barrier. A wavefront of depolarization encounters a barrier to conduction that allows propagation in only one direction (unidirectional block), forcing activation preferentially along one limb or pathway. Due to slow conduction, the depolarization wavefront travels through the remaining circuit and continually encounters tissues that have recovered from refractoriness and are hence excitable. This results in perpetual circus movement. Moreover, if the total length of the circuit exceeds a distance determined by the product of the conduction velocity ( $\theta$ ) of the tissue and the refractory period (duration) of that tissue ( $tr$ ), referred to as the wavelength of tachycardia ( $\lambda = \theta \times tr$ ), an excitable gap, where tissue is recovered from refractory and able to depolarize, is created, allowing reentry. Reentry is the mechanism for several clinically important and common cardiac arrhythmias, including atrial flutter, AV nodal reentry, AV reciprocating tachycardia utilizing an accessory pathway, and scar-based reentrant VT.

When reentry occurs in the absence of a fixed anatomic barrier, it is termed *functional reentry*. A nidus of partially refractory tissue anchors the depolarization wavefront, resulting in a circular or rotational reentrant wavefront. In this case, the reentrant circuit or activity tends to be less stable than that from anatomic reentry, resulting in variations in depolarization rate and propensity to easily terminate and/or reinitiate. There is evidence that functional reentry is the underlying mechanism for perpetuation and maintenance of both atrial fibrillation (AF) and ventricular fibrillation (VF). In both of these apparently chaotic and disorganized arrhythmias, multiple wavefronts resulting from multiple functional reentrant circuits appear to drive arrhythmia in many, if not most, instances. Underlying pathology of the myocardium resulting in heterogeneous electrophysiologic properties, altered activation, and repolarization properties predispose myocardial tissues to initiation and propagation of functional reentry-based arrhythmias.

In addition to intrinsic alterations in cellular membrane electrophysiologic properties that underpin most arrhythmias, extrinsic factors may precipitate other architectural and tissue changes that contribute proarrhythmia. Ischemia and infarct may create regions of heterogeneous fibrosis, resulting in islands of scar surrounded by injured tissue. This creates the anatomic substrate that can sustain anatomic reentry, which underlies scar-based VT, as well as many macro-reentrant atrial arrhythmias. Peri-infarct border zones often contain injured myocardium as well, and the resultant alterations in cellular membrane properties may promote enhanced automaticity or triggered arrhythmias. Chronic ischemia also results in downregulation of connexin proteins and gap junctions, resulting in slowed impulse propagation, which is one of the factors required for reentrant arrhythmias. Alterations in ion channel function, either through inherited mutations or through drug effect, can promote arrhythmias. QT prolongation can occur when the closing of potassium channels that should hyperpolarize cells is delayed or slowed, or when the closing or inactivation of Na channels is impaired.

## UNDERPINNINGS OF THE TREATMENT OF ARRHYTHMIAS

Pharmacologic therapies for arrhythmias are directed toward the specific underlying mechanism. For enhanced automaticity-based arrhythmia, medications that target phase 4 depolarization, including Ca channel blockers, beta-adrenergic blockers (via indirect action on adrenergic input), or ivabradine may be used. For triggered activity-based arrhythmia, correcting the precipitating factor is most effective. This includes, among other therapies, removal of digitalis glycosides from the body, removal of QT-prolonging medications, or even increasing heart rate, thereby shortening QT interval. For reentrant arrhythmia, medications that increase the refractory period, in particular K channel blocking agents, will hence increase the wavelength of conduction beyond the circuit length of tachycardia, resulting in inability to sustain reentry. Medications that slow conduction velocity, if only partially effective, may have the paradoxical effect of shortening the wavelength of tachycardia compared to the anatomic circuit length, resulting in a larger excitable gap. This explains much of the

proarrhythmic effect of many antiarrhythmic medications. Therefore, for these agents, which typically include Na channel blockers, sufficient dosing is required to slow conduction velocity to the point of extinguishing meaningful arrhythmia circuit conduction.

A major aspect of clinical cardiac electrophysiology that has evolved over several decades is the ability to mechanically disrupt arrhythmic substrates through catheter-based (or rarely surgical) ablation. For automaticity-based arrhythmias, precise localization and elimination through ablation of the site of focal automaticity is effective in eliminating arrhythmia. For anatomic reentrant circuits, identifying a critical zone of slow conduction that both sustains reentry and is amenable to focused ablation and damaging that zone through ablation is effective for most reentrant arrhythmias. In contrast, given the lack of a fixed anatomic circuit, and perhaps also due to the presence of multiple, often migratory, circuits, it appears that mechanical disruption, typically through catheter-based ablation, of identified sites of functional reentry appears to be ineffective in eliminating arrhythmia.

## CARE OF THE ARRHYTHMIA PATIENT

### EVALUATION AND DIAGNOSIS

The evaluation of a patient with suspected arrhythmia begins with a directed history and physical examination, which must include an ECG. The history and examination should focus on determining the nature of symptoms attributable to the arrhythmia itself and clues to potential underlying cardiac, medical, or metabolic conditions that may predispose to specific arrhythmias, and hence direct further studies and evaluations, ultimately directing appropriate therapy, prognosis, and counseling. Family history may also provide clues toward possible inherited arrhythmia syndromes. Symptoms attributable to arrhythmia can vary from vague sensation of fatigue, chest pain, dyspnea, or lightheadedness to more specific sensation of rapid, slow, or irregular heart rate. Premature contractions, whether atrial or ventricular, may be sensed as extra beats, or if these extrasystoles result in diminished stroke volume for that particular beat, a sensation of a missed beat. Second, the hemodynamic sequelae of impaired cardiac output may result in symptoms, from presyncope to frank syncope, dyspnea, chest discomfort, or generalized weakness. Importantly, as the cadence and duration of arrhythmia episodes are highly variable, the temporal manifestations of arrhythmia symptoms may vary significantly. Sporadic episodes of arrhythmia will result in intermittent symptoms, including syncope if hemodynamic compromise is significant; protracted episodes of arrhythmia may cause persistent symptoms. In patients with underlying compromise in cardiac function, most typically in patients with structural heart disease, arrhythmia leading to diminished cardiac output may trigger or exacerbate symptoms associated with the underlying condition such as angina, congestive heart failure, or hypoxia-associated symptoms.

Inciting factors or associations may also provide clues to the diagnosis. Arrhythmias associated with activities that increase adrenergic tone, such as exercise, stimulant intake, or emotional stress, may suggest not only tachyarrhythmias but also automaticity-triggered arrhythmias. However, keep in mind that exceptions will occur. Medication use may be highly suggestive of an etiology: use of Ca channel blockers or beta blockers may suggest bradycardia exacerbated by these medications. Medications known to potentially prolong QT interval may suggest a malignant ventricular arrhythmia, specifically TdP. Eliciting a thorough family history, not only for known arrhythmia diagnoses, but of unexplained sudden death, may point toward a heritable syndrome. Demographic factors may point toward or away from certain diagnoses. For instance, AF rarely occurs in children and young adults, save rare familial forms, or AF associated with structural heart disease; a strong male predominance, as well as a higher prevalence in certain ethnic populations such as Southeast Asians, is seen in Brugada syndrome; inappropriate sinus tachycardia is nearly exclusively a condition affecting young women; degenerative conduction system disease leading to symptomatic bradycardia is most commonly a condition seen in older patients.

Arrhythmias may run the gamut from benign to malignant, life-threatening etiologies. Therefore, an important aspect of the evaluation of suspected arrhythmia is to discern patient prognosis, which then informs treatment. Arrhythmias that result in more significant hemodynamic compromise, and therefore more profound symptoms, tend to correlate with more malignant disease. In turn, the higher the suspicion for a malignant arrhythmia, the more aggressive the evaluation will likely be. Loss of consciousness, which may be the result of cardiac arrhythmia but also other etiologies that may be more benign, presents a particularly challenging yet common diagnostic dilemma. Therefore, careful thought into the appropriate evaluation for a patient with syncope is critical. In general, the presence of underlying structural abnormality of ventricular myocardium favors more malignant arrhythmias, both due to the increased risk of lethal ventricular arrhythmias, as well as potential inability to hemodynamically tolerate any particular arrhythmia.

The ECG is the cornerstone and most important diagnostic test that should be performed on every patient with suspected arrhythmia. A 12-lead resting ECG may offer clues to the diagnosis. Most simply, if active arrhythmia is captured on the ECG, a definitive diagnosis can be made. In addition, evidence suggesting underlying cardiac disease, such as prior myocardial infarction, LVH and possible hypertrophic cardiomyopathy, atrial disease, or baseline conduction system disease may suggest a diagnosis. A subset of conditions that predispose to arrhythmia, both inherited or acquired, may be discerned as well, including ventricular preexcitation, prolonged or shortened QT interval, or ECG findings suggestive of specific inherited conditions such as Brugada syndrome or right ventricular cardiomyopathy.

However, the ECG typically records only 6 s of cardiac electrical activity, and therefore more intermittent and transient arrhythmias, particularly those not typically associated with abnormalities on the resting ECG, may not be seen. Many arrhythmias, including forms of both SVT and VT, can only be diagnosed definitively if an ECG is performed during active arrhythmia and/or symptoms from arrhythmia, or alternatively provoked in the electrophysiology laboratory. Therefore, various forms of ambulatory monitoring may be performed to attempt to capture ECG activity during active arrhythmia. A growing variety of monitoring options are available; the most appropriate option should be primarily guided by the cadence of suspected arrhythmia episodes. For instance, if daily symptoms occur, a 24- or 48-hour continuous Holter monitor is appropriate. On the other hand, a patient-activated event recorder is inappropriate in a patient with syncope, as the arrhythmic event will likely have passed once the patient reawakens.

Attempts at provoking arrhythmia may be warranted in the appropriate circumstances. An ECG-monitored treadmill test may elicit exercise-induced arrhythmias, or if LQT is suspected, QT interval that fails to shorten appropriately with increased heart rate may be helpful. Pharmacologic provocation may be indicated for certain suspected diagnoses, such as Brugada syndrome. Judicious and appropriate use of carotid sinus massage or other means to enhance vagal tone may be helpful to diagnose carotid hypersensitivity or overall vagally mediated syncope.

Tilt table testing (TTT) involves having a patient strapped to a tiltable table. While monitoring HR and BP, the patient is quickly moved from a supine to upright position. In patients with suspected autonomic dysfunction-mediated syncope or presyncope, this provocation may elicit a paradoxical vagal response, resulting in bradycardia and/or sinus pauses as well as hypotension, and perhaps frank syncope. However, given significant lack of both sensitivity and specificity, the current role of TTT is unclear, and TTT has widely fallen out of favor.

Invasive electrophysiologic testing is the nearest to a gold-standard diagnostic modality for many arrhythmias. Catheter-based recordings of intracardiac electrograms, with or without provocative pacing or pharmacologic maneuvers, may elicit the clinical arrhythmia. This will in turn help to define the mechanism of arrhythmia. However, one must keep in mind that for certain arrhythmia mechanisms, such as automaticity-driven tachycardia, EP study may fail to elicit

arrhythmia due to the often transient and multifactorial nature of initiation of these arrhythmias. The nature of arrhythmia elicited will in turn aid in determination of the patient's prognosis. In a typical EP study, catheters are placed within the heart, typically via femoral venous access. Baseline conduction properties are measured. Provocative maneuvers including electrical pacing maneuvers, programmed stimulation, and pharmacologic provocation are performed. In the modern era, the vast majority of invasive EP studies are performed in conjunction with planned catheter ablation, although programmed ventricular stimulation for risk stratification of sudden death may still be utilized occasionally. EP study during catheter ablation is performed both to confirm diagnosis and localize appropriate ablation target(s) but also to evaluate the efficacy of ablation performed during the procedure.

Depending on the suspected arrhythmia diagnosis, further testing may be indicated. If structural heart disease is suspected, echocardiography is most often the best next test, as it can assess for underlying structural disease, evaluate LV function, and assess atrial dimensions and mitral valve function if AF is suspected, both of which are fair prognostic indicators. In patients in whom underlying coronary artery disease is suspected, an evaluation for coronary ischemia is indicated. Further evaluation for underlying structural heart disease will be directed based on the differential diagnosis. Cardiac CT provides broad diagnostic utility, depending on the scanning protocol, including evaluation for ischemia, ventricular scar, anatomic evidence of CAD, congenital anomalies, and left atrial anatomy. Cardiac MRI provides significant resolution of soft-tissue characteristics and may be used to assess for ischemia, infarct, myopathy, or infiltrative disease. Cardiac PET can also discern underlying ischemia, as well as metabolic/inflammatory/infiltrative conditions.

## TREATMENT

### Cardiac Arrhythmias

#### ANTIARRHYTHMIC DRUG THERAPY

The effects of pharmacologic agents on cardiac electrophysiologic properties are often complex and, in many instances, remain incompletely understood. The complexity is the result of complex pharmacodynamics and pharmacokinetics, in particular significant cross-reactivity of certain drugs across different targets as well as variable effects on drug targets across drugs within the same category. There are regional differences in drug effect within the myocardium, and interpatient variations in drug metabolism play important roles. This has in part led to many instances of harm that have come from the adverse effects of many agents used over the years. In fact, many antiarrhythmic agents currently in use carry significant risks of side effects, some of which may be significant and even lethal. Therefore, judicious use of antiarrhythmic medications by those with appropriate knowledge base and experience is warranted. The practical result of the narrow therapeutic index of this class of medications has rendered their use more and more as ancillary options (**Table 243-2**).

The traditional nomenclature of antiarrhythmic drugs (AADs) is known as the Vaughan Williams classification schema. In this schema, there are four classes (I–IV; Table 243-2). Class I AADs primarily target the Na channel, Class II agents target the beta-adrenergic receptor, Class III agents target potassium channels, and Class IV agents target Ca channels. Class I agents are further subdivided into three subclasses based on the kinetics of drug to Na channel interactions. Class IA agents, including procainamide and quinidine, possess intermediate binding kinetics and potency. Class IB agents, including lidocaine and mexiletine, possess rapid binding kinetics and relatively low potency. Class IC agents (flecainide, propafenone) possess slow kinetics and high potency. Class II agents consist entirely of beta adrenergic blocking agents. Class III agents (sotalol, dofetilide, ibutilide) specifically target the HERG potassium channel and risk prolongation of the QT interval through effects on the K channel (HERG) that in large

**Table 243-2** Antiarrhythmic Drug Actions

DRUG	CLASS ACTIONS				OTHER ACTIONS/COMMON SIDE EFFECTS
	I	II	III	IV	
Quinidine	++		++		Anticholinergic
Flecainide	+++		+		Can promote reentrant arrhythmias (AFL, VT)
Propafenone	++	+			Mild beta-blocker effect
Amiodarone	++	++	+++	+	Multiorgan toxicity with long-term use
Sotalol		++	+++		Prominent beta-blocker effect
Dofetilide			+++		Prolongation of QT at slower heart rates
Dronedarone	+	+	+	+	Mild effect
Ibutilide			+++		Used only for acute cardioversion
Ranolazine	++		++		Late sodium channel blockade
Lidocaine	++				Used for reperfusion arrhythmias

part determine phases 2/3 of the AP, and hence ventricular repolarization. Class IV agents are cardioselective Ca channel blockers including verapamil and diltiazem. This classification has significant limitations, however. Many AADs interact with multiple ion channels, and as a result many exhibit behavior consistent with multiple classes. Amiodarone, in particular, exhibits properties of all AAD classes.

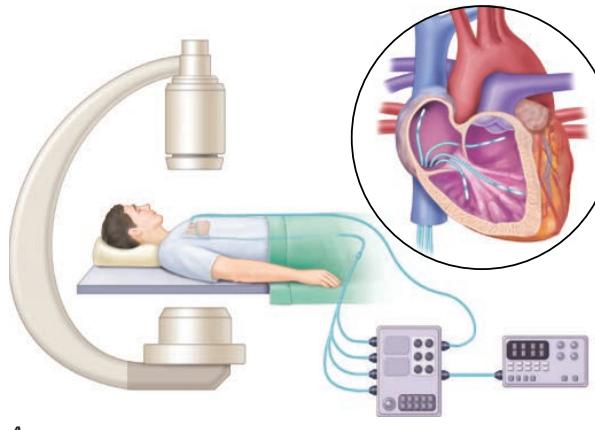
### CATHETER ABLATION

The rationale that underlies catheter ablation for cardiac arrhythmia is that an anatomic substrate can be identified and localized, and mechanical disruption of that substrate will eliminate the cardiac arrhythmia. For automaticity-driven arrhythmias, a focal source of automaticity is identified, localized, and ablated. For anatomic reentrant arrhythmias, a critical zone of slow conduction that sustains arrhythmia and can be reasonably targeted is ablated. Moreover, the ablation target must be in a location deemed at acceptable risk of not damaging critical structures such as the native conduction system, coronary arteries, or epicardial structures including the esophagus and phrenic nerve. Advances in electroanatomical mapping, a technology that uses alterations in electrical impedance and a magnetic field as measured by an intracardiac mapping catheter, have allowed for real-time reconstruction of cardiac chambers and identification of arrhythmogenic tissue to be targeted for ablation while safely avoiding nontargeted critical structures. Intracardiac

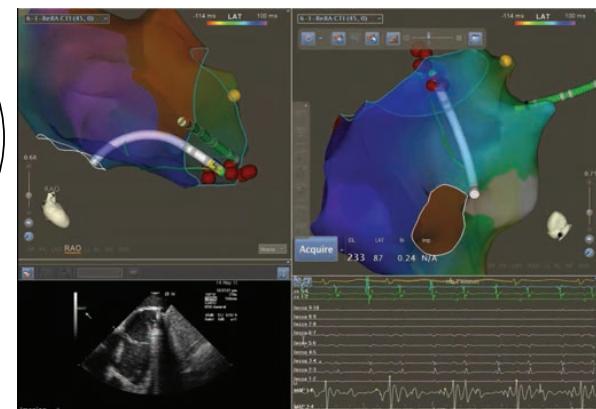
echocardiography has also been used to enhance the safety of invasive electrophysiologic procedures with real-time visualization of cardiac structures (**Fig. 243-4**).

In the 1950s–1960s, as the underlying anatomic substrates for arrhythmias became better understood, open surgical disruption of arrhythmia circuits was the only available interventional and curative therapy for many arrhythmias. Surgical ligation of accessory pathways or resection of ischemic VT substrates was performed at specialized surgical centers. The first attempts at clinical catheter ablation utilized direct current (DC) energy. This resulted in a jarring pulse of electrical energy that would indeed ablate cardiac tissue, but with a difficult-to-control scope, often leading to significant complications. Radiofrequency (RF) energy was adapted to catheter-based cardiac ablation in the 1980s. Radiofrequency alternating electrical current (300–550 kHz) delivered through a catheter tip results in local tissue heating and permanent injury. This type of ablation is similar to the technology used in electrosurgical techniques using a Bovie electrocautery device. For more than 35 years, RF delivery via catheters has been iteratively optimized such that it has become the most common and mainstay energy source for catheter ablation. Catheter ablation is indicated for a wide variety of clinical arrhythmias, including SVT, accessory pathways, atrial flutter, atrial fibrillation, PVCs, and VT. Alternative ablative energy sources have been explored over the years, including light spectrum (laser), microwave, ultrasound, and more recently pulsed field electroporation, which injures targeted myocardium through high energy, ultra-short pulses of electrical current that disrupts the lipid cell membrane, resulting in permanent cell death. Recently, the well-established ablative technique of stereotactic (focused and directed) external beam ionizing radiation has been applied to the heart to treat various arrhythmias, including VT and AF. This particular treatment modality holds promise given its ability to target regions of the heart that may be inaccessible to catheters, as well as the completely noninvasive, and thereby theoretically lower risk, nature of the procedure.

The most widely applied non-RF ablative energy source today is cryotherapy, where an ablative catheter tip is cooled to a temperature range (typically below  $-40^{\circ}\text{C}$ ) that results in permanent tissue death. Cryotherapy is most widely applied to ablation of paroxysmal atrial fibrillation, via an expandable balloon introduced sequentially into each pulmonary vein and cooled to produce a circumferential ablative lesion at the ostium/antrum of each pulmonary vein (see **Fig. 243-4B**).



A



B

**FIGURE 243-4** Catheter ablation of cardiac arrhythmias. **A**, A schematic of the catheter system and generator in a patient undergoing radiofrequency catheter ablation (RFCA); the circuit involves the catheter in the heart and a dispersive patch placed on the body surface (usually the back). The inset shows a diagram of the heart with a series of intracardiac catheters placed via the IVC, typically through femoral venous access. Catheters are located at the high right atrium, His bundle location, RV apex, and through a transseptal puncture within the left atrium. **B**, Images from an electroanatomic mapping system are shown during mapping and ablation of typical cavo-tricuspid isthmus-dependent atrial flutter. This system allows three-dimensional real-time localization and annotation of catheter position and cardiac anatomy to guide mapping and ablation. In this instance, two projections of the map are shown at the top of the RA, an RAO, and LAO caudal view. Annotations of ablation lesion delivery are shown as red dots. In the left lower aspect of this panel, a simultaneous image from intracardiac echocardiography (ICE) is shown of the RA, with the ablation catheter in view in all three images. In the lower aspect of this panel, surface ECG and intracardiac electrograms acquired in real-time are shown.

## IMPLANTED ELECTRICAL DEVICE THERAPY

Implanted cardiac rhythm management devices are commonly utilized to manage arrhythmia. The first definitive pacemaker was implanted in 1958 and this technology has evolved to be the mainstay in the management of bradyarrhythmias. Sinus node dysfunction or AV conduction disease, particularly with symptoms, are the primary indications for most implanted pacemakers. Pacemakers are typically implanted percutaneously, with conductive/sensing wires, or leads, inserted through the upper extremity venous system into the right atrial and/or ventricular myocardium, with the lead tip secured to the myocardium mechanically. The leads are connected to a pulse generator that is placed typically in the prepectoral space, which contains electronic circuitry and a battery, allowing sensing and/or delivery of pacing stimuli to maintain adequate heart rate. More recently, a completely leadless pacemaker inserted through a large femoral venous sheath directly into the RV endocardium has become available. Although these devices possess more limited pacing options, they likely reduce the risks associated with transvenous lead systems, including infection or lead fracture requiring extraction.

Implanted cardioverter-defibrillators (ICDs) are placed in a similar fashion to pacemakers. However, ICDs have the ability to sense abnormal ventricular arrhythmias and deliver either antitachycardia pacing or defibrillation to prevent sudden death. In patients who experience a potentially lethal VA, ICD therapy may be lifesaving. Indications for ICD therapy are considered for either primary prevention of sudden cardiac death (SCD) due to arrhythmia in an at-risk patient, or as secondary prevention in a patient who has survived an SCD event. More recently, a completely subcutaneous ICD system has become available, avoiding intravenous leads that increase risk for systemic infection, and potentially the procedure to extract a potentially fibrosed lead in cases of lead malfunction or endovascular infection.

### Acknowledgment

David Spragg and Gordon Tomaselli contributed to this chapter in the 20th edition and some material from that chapter has been retained here.

### FURTHER READING

- Callans DJ: *Josephson's Clinical Cardiac Electrophysiology: Techniques and Interpretations*, 6th ed. Philadelphia, Wolters Kluwer, 2020.
- Ellenbogen K et al (eds): *Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy*, 5th ed. Philadelphia, Elsevier, 2016.
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# 244

## The Bradyarrhythmias: Disorders of the Sinoatrial Node

William H. Sauer, Bruce A. Koplan

The sinoatrial (SA) node serves as the natural pacemaker of the heart and has variable rates in response to parasympathetic and sympathetic stimulation. If the sinus node is dysfunctional or suppressed a subsidiary pacemaker in the atrioventricular node or specialized conduction system will take over leading to a slower junctional or ventricular rhythm. Symptoms of sinus node dysfunction can vary but typically present as fatigue, exercise intolerance, or dyspnea. The diagnostic evaluation includes an investigation into reversible causes of sinus bradycardia, confirmation of sinus node dysfunction with outpatient

telemetry monitoring or exercise testing, and possibly cardiac imaging if structural heart disease is suspected. Once irreversible sinus node dysfunction is confirmed, permanent pacemaker implantation is the only reliable therapy for symptomatic bradycardia.

### STRUCTURE AND PHYSIOLOGY OF THE SA NODE

The SA node region is rather complex in structure. Clusters of myocytes with pacemaker activity are surrounded by fibroblasts, endothelial cells, and transitional cells. These clusters of small fusiform cells in the sulcus terminalis on the epicardial surface of the heart at the right atrial–superior vena caval junction envelop the SA nodal artery. The SA node is structurally heterogeneous, but the central prototypic nodal cells have fewer distinct myofibrils than does the surrounding atrial myocardium, no intercalated disks visible on light microscopy, a poorly developed sarcoplasmic reticulum, and no T tubules. Cells in the peripheral regions of the SA node are transitional in both structure and function. The SA nodal artery arises from the right coronary artery in 55–60% and the left circumflex artery in 40–45% of persons. This feature along with a protective extracellular matrix of connective tissue insulates the SA node from the hyperpolarizing influence of the larger atrium. In addition, the alignment of this complex matrix is associated with nearly unidirectional electrical propagation to the atrium (Fig. 244-1).

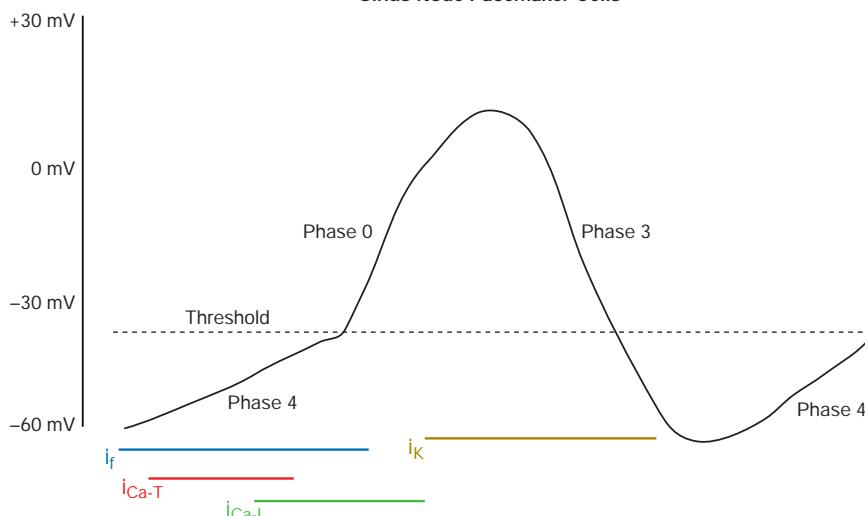
Pacemaker cells spontaneously depolarize in a continuous manner setting the natural rate of depolarization and myocardial contraction. Action potential depolarization in the SA node is normally at a resting rate of 60–100 beats/min. The autonomic nervous system exhibits control over the sinus node, with a preponderance of parasympathetic innervation at baseline. Removal of parasympathetic tone or an increase in sympathetic innervation leads to an increase in rate of depolarization. In denervated hearts, the rate of electrical depolarization (intrinsic heart rate) is approximately 100 beats/min, reflecting the rate of automaticity of the sinus node uninhibited by parasympathetic tone. The complement of ionic currents present in nodal cells results in a less negative resting membrane potential compared with atrial or ventricular myocytes. Electrical diastole in nodal cells is characterized by slow diastolic depolarization (phase 4), which generates an action potential as the membrane voltage reaches threshold. The action potential upstrokes (phase 0) are slow compared with atrial or ventricular myocytes, being mediated by calcium rather than sodium current.

Cells with properties of SA nodal tissue are electrically connected to the remainder of the myocardium by cells with an electrophysiologic phenotype between that of nodal cells and that of atrial or ventricular myocytes. Cells in the SA node exhibit the most rapid phase 4 depolarization and thus are the dominant pacemakers in a normal heart.

Myocytes within the SA node complex include specialized cells surrounded by fibrous tissue. Unlike atrial and ventricular cells, sinus node pacemaker cells have no true resting potential, but instead depolarize automatically and repetitively after the end of an action potential, and the depolarizing current in the SA node myocytes results primarily from slow calcium currents instead of fast sodium channels, which are absent in SA node cells. Spontaneous phase 4 depolarization results from a combination of slow inward depolarizing sodium currents ( $I_{Na}$ , "funny currents"), along with T-type and L-type calcium channels. The upstroke of depolarization in SA node myocytes is slower and lower in amplitude than in ventricular myocytes.

In patients <85 years of age, the resting heart rate is strongly influenced by parasympathetic tone at baseline. Absence or elimination of autonomic influence on the SA node leads to an intrinsic heart rate that is normally 100–110 beats/min. The myocytes within the SA node that initiate pacing change with different rates. A superior shift occurs at higher heart rates and an inferior shift at lower heart rates, which may lead to a slightly different P wave inscribed on ECGs recorded during different rates of sinus rhythm.

In addition, a progressive decline in maximum heart rate occurs with age, although the resting heart rate normally remains unchanged. Intrinsic heart rate declines 5–6 beats/min for each decade of age. However, the constancy of resting heart rate is associated with a gradual decrease in parasympathetic tone and a transition to predominant sympathetic tone by the ninth decade.



**FIGURE 244-1** Cellular ion currents involved in depolarization and automaticity of SA nodal pacemaker cells. Phase 4 spontaneous depolarization results from  $i_f$  (funny current, along with T- and L-type calcium channels. Phase 0 is the depolarization phase of the action potential. This is followed by phase 3 repolarization, which results from the outward directed hyperpolarizing  $K^+$  currents.  $i_f$ , funny current;  $i_{Ca-T}$ , T-type calcium current;  $i_{Ca-L}$ , L-type calcium current;  $i_K$ , potassium current.

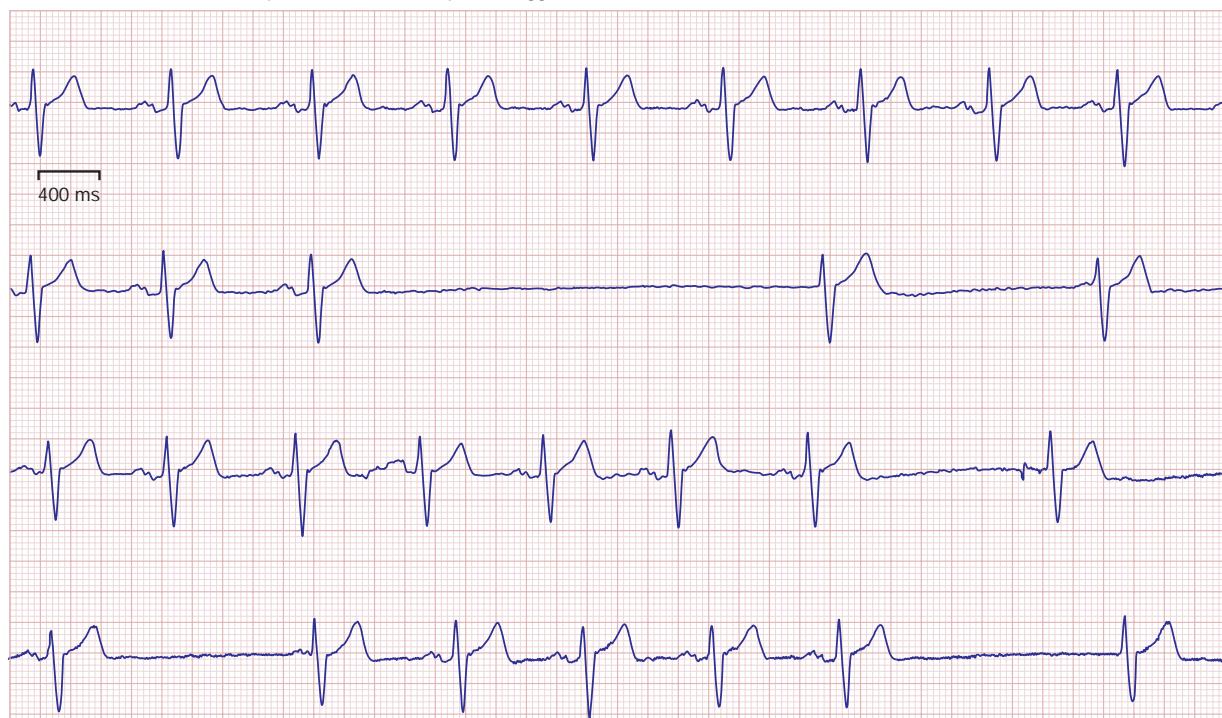
### DIAGNOSIS OF SA NODAL DISEASE

Intrinsic sinus node disease is sometimes referred to as sick sinus syndrome or sinus node dysfunction (SND) and can manifest as fatigue, exercise intolerance, or syncope resulting from either reduced heart rate or pauses. Electrocardiographic recording plays a central role in the diagnosis and management of SA node dysfunction. The correlation between symptoms and slow heart rate or pauses is essential in

determining whether bradycardia may be considered pathologic and necessitating intervention. Baseline ECG can detect baseline sinus bradycardia but may not indicate symptom correlation in certain settings. To address the limitations of the resting ECG, longer-term recording employing mobile telemetry devices such as Holter monitors or mobile cardiac telemetry can also be helpful in correlating symptoms with rate abnormalities ([Fig. 244-2](#)).

4

Sinus (55 bpm), pause (3.4 seconds)  
08/18/20 12:22:10pm Associated with patient triggered event



**FIGURE 244-2** Sinoatrial exit block. A pause in the heart rhythm is seen that results from a sinus pause. On the second line of the tracing there is a pause that results from the absence of a sinus beat (absent P wave) and no subsequent QRS. This is followed by a junctional escape beat and eventually recovery of the presence of sinus rhythm P waves.

In addition, commercially available wearable devices, such as watches with electrocardiographic recording capabilities, can also have excellent fidelity electrograms that may also be utilized. Contemporary event monitors may be automatically triggered to record the ECG when certain programmed heart rate criteria are met and implantable monitors permit very long-term recording (years) in particularly challenging patients. Treadmill testing can be utilized to assess for maximum heart rate. It is worth noting, however, that standard Bruce protocol treadmill testing may be helpful in detecting abnormalities in maximum heart rate, but more insidious chronotropic incompetence that manifests as abnormalities of rate increase during submaximal exercise may be more evident with treadmill protocols that have more gradual effort increases.

Once there is evidence of sinus node dysfunction, it is important to rule out reversible causes of resting sinus bradycardia or chronotropic incompetence. **Table 244-1** lists the potentially reversible causes of sinus node disease and includes hypothyroidism and rate-slowning medications. Many patients with sleep apnea will have high vagal tone during sleep and especially during apneic events. Sinus bradycardia and sinus pauses frequently are seen if a patient is being monitored during this period. Sleep apnea, a common reversible cause, should be suspected if marked sinus bradycardia and prolonged sinus pauses are observed in a telemetry monitoring period during sleep.

**TABLE 244-1 Reversible Causes of Sinus Node Dysfunction**  
Medical Conditions Associated with Sinus Bradycardia

- Hypothyroidism
- Sleep apnea
- Hypoxia
- Hypothermia
- Increased intracranial pressure
- Lyme disease
- Myocarditis
- COVID-19
- Vagal reflex (cough, pain, etc.)

#### Medications Associated with Sinus Node Dysfunction

##### Antihypertensive Medications

- Beta-adrenergic receptor blockers
- Clonidine
- Methyldopa
- Nondihydropyridine calcium channel blockers

##### Antiarrhythmic Medications

- Amiodarone
- Dronedarone
- Flecainide
- Procainamide
- Propafenone
- Quinidine
- Sotalol
- Ivabradine

##### Psychiatric Medications

- Donepezil
- Lithium
- Opioid analgesics
- Phenothiazine antiemetics and antipsychotics
- Phenytoin
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants

##### Other

- Anesthetic drugs (propofol)
- Cannabis
- Digoxin
- Muscle relaxants

If structural heart disease is suspected, transthoracic echocardiography should be used to detect potential cardiac abnormalities associated with sinus node dysfunction (**Fig. 244-3**). Advanced cardiac imaging is indicated for evaluation of possible myocardial diseases such as amyloidosis, infiltrative cardiomyopathy, or myocarditis. Invasive electrophysiology testing solely to assess sinus node function is rarely utilized beyond the noninvasive techniques mentioned. In patients who are also undergoing electrophysiology studies (EPS) for other indications, evaluation of sinus node function as part of the EPS may be considered. In symptomatic patients with suspected SND, EPS may rarely be considered when the diagnosis remains uncertain and after initial noninvasive evaluation is inconclusive. Investigation of the sinus node during EPS can consist of determination of sinus node recovery time (SNRT) and sinoatrial conduction time (SACT). In addition, the intrinsic heart rate [ $118.1 - (0.57 \times \text{age})$ ] can be assessed via pharmacologic blockade of autonomic tone with intravenous propranolol and atropine. EPS is not widely used, however, as there is no evidence that abnormal SNRT or SACT alone can be used as an indication for permanent pacing (PPM). There is no indication for EPS in asymptomatic patients with sinus bradycardia.

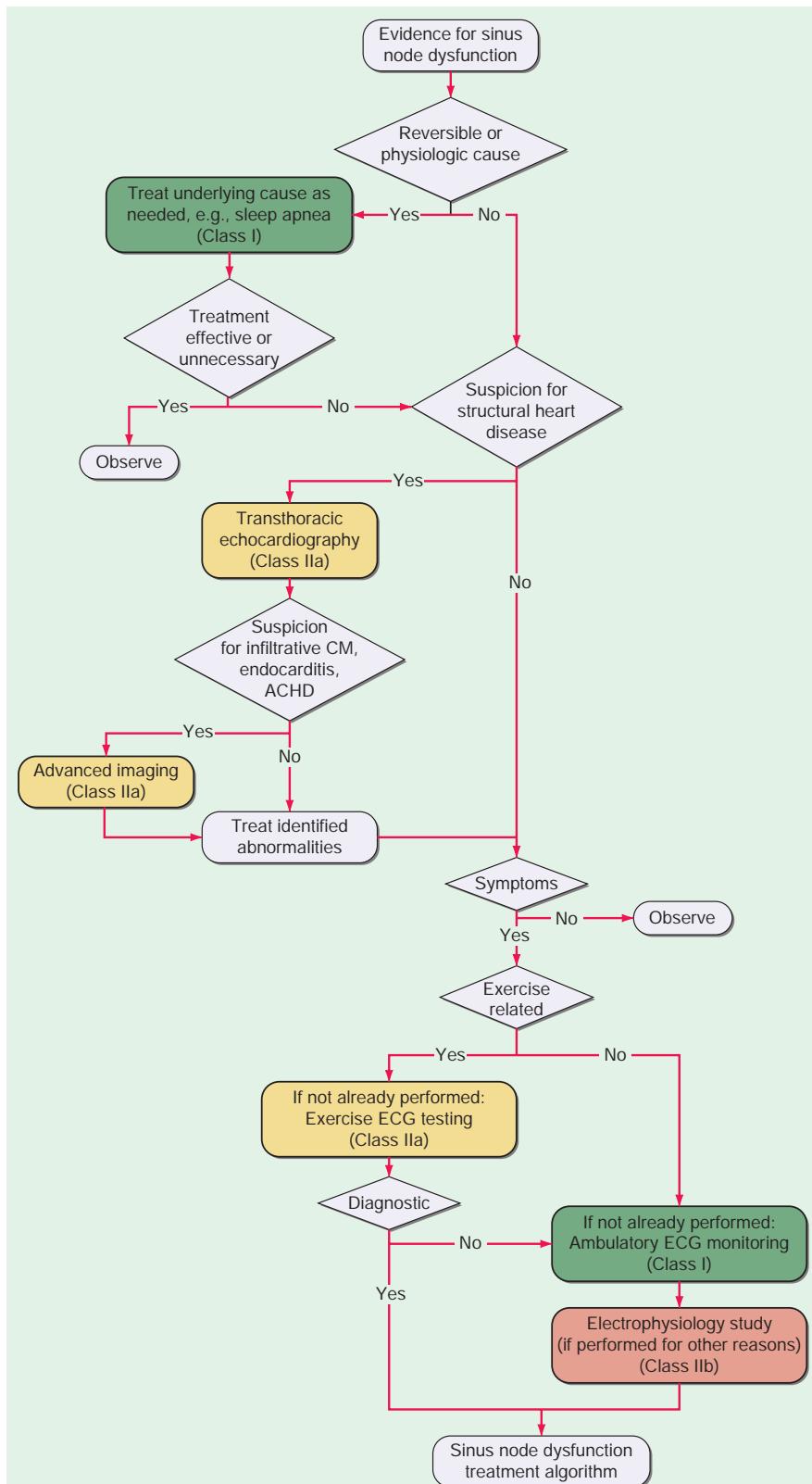
#### SA NODAL DYSFUNCTION SUBTYPES

SND can be categorized into problems with impulse formation and problems with impulse conduction. The term *sick sinus syndrome* may be used interchangeably with SND and refers to a group of related conditions comprising problems of both impulse formation and impulse conduction.

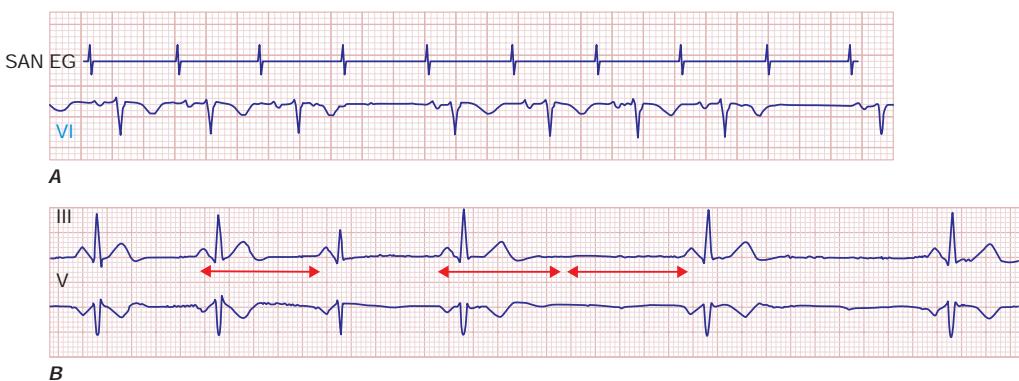
**Sinus Node Exit Block (See Fig. 244-4)** “Sinus arrest” results from failure of impulse formation within the sinus node. Sinoatrial exit block results from failure of sinus node activity to propagate to the atrium. Sinoatrial exit block can have similar pattern characteristics of types of AV node block. It can manifest as complete SA block. Type I SA block involves fixed delay out of the sinus node. Type II SA block can occur with either progressive delay and then intermittent failure to propagate to the atrium (Mobitz I type) or fixed delay with intermittent failure to conduct (Mobitz II). The mass of the sinus node is not large enough to have an appearance on the ECG. Instead, the P waves that result from atrial depolarization can provide information that reflects the health of the sinus node. Type II second-degree SA block can be inferred on the ECG if the sinus rate abruptly transitions to a sinus rate that is half the previous rate (every other sinus depolarization is blocked from exiting to the atrium). Sinoatrial Wenckebach can be inferred from the ECG in the setting of progressive shortening of the P-P interval leading up to a sinus pause. This is due to progressive prolongation of sinoatrial conduction, but to a lesser extent with each successive prolongation. This is similar to the typical progressive shortening of the R-R interval that is observed with AV nodal Wenckebach. Other types of SA block require invasive EPS to decipher. The exercise of determining the type of SA block with invasive electrophysiology testing is typically not necessary because it does not alter management.

**Tachy-Brady Syndrome** Tachycardia-bradycardia (tachy-brady) syndrome is a subset of sick sinus syndrome/sinus node disease that consists of high heart rates (most commonly atrial fibrillation) with alternating symptomatic bradycardia or offset pauses (**Fig. 244-5**). Commonly, medications that are needed for rate control of tachycardia exacerbate bradycardia episodes, and thus the presence of tachy-brady syndrome is often a reason to consider pacemaker implantation.

**Chronotropic Incompetence** Chronotropic incompetence (CI) is broadly defined as the inability of the heart to increase its rate to meet activity or demand. Compared to an increase stroke volume, the increase in heart rate is a stronger contributor to the increase in oxygen uptake ( $\text{VO}_2$ ) during aerobic exercise. Therefore, CI can be associated with severe exercise intolerance and increased cardiovascular events and overall mortality. CI can take many forms including failure to achieve a maximum heart rate [ $208 - (0.7 \times \text{age})$ ], heart rate instability with exercise, or failure to achieve submaximal heart rate. Due to this



**FIGURE 244-3 Evaluation of bradycardia and conduction disease.** In patients with sinus node dysfunction, reversible causes should be identified and eliminated when possible. If no reversible cause can be identified, structural heart disease should be considered and evaluated for, if appropriate. If no symptoms are present, an observation strategy is appropriate. In patients who are symptomatic, further evaluation with ambulatory monitoring or exercise testing to identify symptom-rhythm correlation should be considered. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Heart Rhythm* 16:e128, 2019.)



**FIGURE 244-4** **A.** Mobitz type I SA nodal exit block. A theoretical SA node electrogram (SAN EG) is shown. Note that there is grouped beating producing a regularly irregular heart rhythm. The SA node EG rate is constant with progressive delay in exit from the node and activation of the atria, inscribing the P wave. This produces subtly decreasing P-P intervals before the pause, and the pause is less than twice the cycle length of the last sinus interval. **B.** Mobitz type II SA nodal exit block. This panel shows sinus rhythm in the first four beats followed by a sinus pause with the absence of a P wave. The interval comprising the absent P wave is exactly twice as long as the preceding P-P interval consistent with type II sinoatrial exit block. SA, sinoatrial.

latter category, standard exercise testing can, at times, fail to recognize a patient with CI as some patients can achieve an appropriate maximum heart rate but may exhibit heart rate instability. Ambulatory heart rate monitoring along with a diary can be helpful to correlate symptoms with abnormally slow heart rates. Because CI can be insidious and multiple definitions exist, it can be easily overlooked.

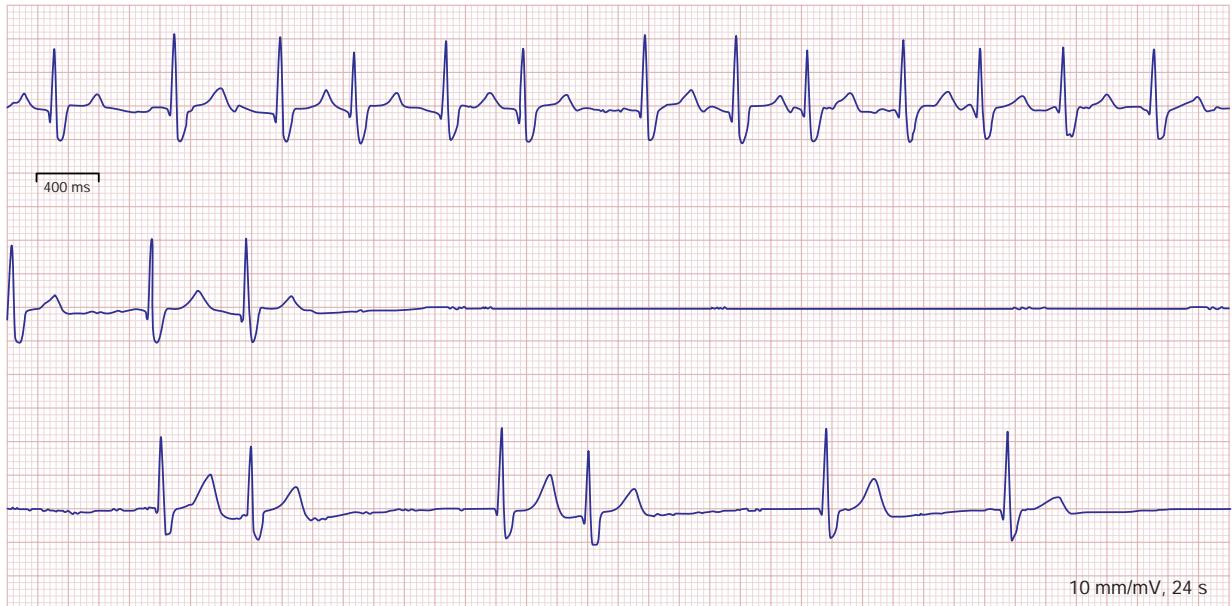
**Sinus Node Fibrosis** Clinical SND is most common in older adults. This is due to normally occurring age-associated increase in fibrotic tissue in the SA node, which can exacerbate any degree of SND. A loss of pacemaker cells in the sinus node is also seen with age. It is worth noting, however, that while increased fibrosis in the SA node and decreased numbers of pacemaker myocytes are part of a normal process of aging, SND is pathologic and there are many elderly patients with extensive fibrosis and normal heart rate.

**SA Nodal Ischemia and Infarction** Sinus bradycardia is common in patients with acute inferior or posterior MI and can be

exacerbated by increased vagal tone (Bezold-Jarisch reflex) or with the use of drugs such as morphine and beta blockers. Ischemia of the SA nodal artery probably occurs in acute coronary syndromes more typically with involvement with the right coronary artery, and even with infarction, the effect on SA node function most often is transient. However, there are rare cases where sinoatrial infarction can affect sinus node function. One potential complication of atrial fibrillation ablation is the inadvertent injury to the SA nodal artery that may be coursing over a targeted ablation region in the right and left atrium. SND and arrest have been described following ablation of atrial fibrillation and flutter.

**Carotid Sinus Hypersensitivity and Neurally Mediated Bradycardia** Sinus bradycardia is a prominent feature of carotid sinus hypersensitivity and neurally mediated bradycardia associated with the cardioinhibitory variant of vasovagal syncope. Carotid hypersensitivity with recurrent syncope or presyncope associated with a

Termination of Atrial Fibrillation (90–105 bpm), Pause (7.4 seconds)  
09/04/20 06:22:16pm



**FIGURE 244-5** Offset pause and tachy-brady syndrome. An offset pause after termination of atrial fibrillation is seen and is consistent with tachy-brady syndrome.

predominant cardioinhibitory component responds to pacemaker implantation. The vasodepressor effect of the enhanced vagal tone is unaffected by the pacing support, but the lack of bradycardia often prevents injury with this subtype of vasovagal syncope. Several randomized trials have investigated the efficacy of permanent pacing in patients with drug-refractory vasovagal syncope, with mixed results. Although initial trials suggested that patients undergoing pacemaker implantation have fewer recurrences and a longer time to recurrence of symptoms, at least one follow-up study did not confirm these results.

## TREATMENT

### SA Nodal Disease

#### TEMPORARY PACING FOR TRANSIENT SUPPORT

In symptomatic patients presenting with sinus node disease, removing any possible reversible cause remains the initial strategy. Acute myocardial infarction, electrolyte abnormalities, medications, and hypothyroidism should all be considered as potentially reversible causes. Unnecessary medications that may be causing bradycardia should be eliminated. Beta blockers, calcium channel blockers, and digoxin are some of the more common medications in use that may cause bradycardia. These drugs may have a wide range of indications in patients after MI and with chronic systolic dysfunction. If stopping the medication or decreasing the dose is an option, this should be tried first. If the medication is felt to be essential in patient management, a pacemaker may be indicated.

In patients with tachy-brady syndrome, alleviation of the tachycardia, whether it is atrial fibrillation or other forms of supraventricular tachyarrhythmias, can prevent bradycardia events. Treatment of the tachycardia can sometimes be accomplished with antiarrhythmic drug therapy or catheter ablation. If this cannot be achieved, permanent pacing may be necessary.

Hypoxia from decrease in blood flow to the SA node, which can occur with cardiac ischemia or MI, can lead to slowing of phase 4 depolarization and resultant bradycardia. Further ischemia and necrosis of pacemaker cells can cause irreversible sinus node disease. On occasion, reversal of ischemia with revascularization can alleviate bradycardia. Sinus pauses in the setting of tachy-brady syndrome may be eliminated if atrial tachyarrhythmias can be successfully treated. It is also important to recognize when bradycardia may be transient. Acute illness associated with episodes of extreme vagal tone may lead to transient SA node abnormalities. Typically this may be observed as sinus slowing, followed by transient sinus arrest and/or AV block. Although a pacemaker may be needed in extreme instances of prolonged arrest, recovery from the acute illness may make the pacemaker unnecessary in follow-up.

Sinus bradycardia is often observed after heart transplantation and cardiac surgery. In the case of heart transplantation, this may be because of accumulated amiodarone that affects the donor heart or ischemic injury to the SA node upon transplantation. If the SA nodal artery is injured at the time of right atriotomy during cardiac surgery, sinus arrest with junctional rhythm may be observed. Temporary pacing or pharmacologic support with beta-1 adrenergic agonists may be needed in these circumstances while awaiting SA nodal recovery.

In addition, sinus bradycardia and sinus pauses are common after spinal cord injury. The mechanism of bradycardia is enhanced parasympathetic tone and autonomic dysreflexia. Common triggers can be tracheal suctioning and turning the patient. Atropine and inotropes have shown mixed success. Adenosine blockade with theophylline or aminophylline can sometimes be successful. Temporary and sometimes permanent pacing may be necessary in extreme circumstances.

#### PERMANENT PACEMAKER IMPLANTATION

Pacing in SA nodal disease is indicated to alleviate symptoms of bradycardia. Consensus guidelines published by the American Heart Association (AHA)/American College of Cardiology (ACC)/

Heart Rhythm Society (HRS) outline the indications for the use of pacemakers and categorize them by class based on levels of evidence (**Fig. 244-6**). Since the first implementation of permanent pacing in the 1950s, many advances in technology have resulted in miniaturization, increased longevity of pulse generators, improvement in leads, and increased functionality. To better understand pacemaker therapy for bradycardias, it is important to be familiar with the fundamentals of pacemaker function.

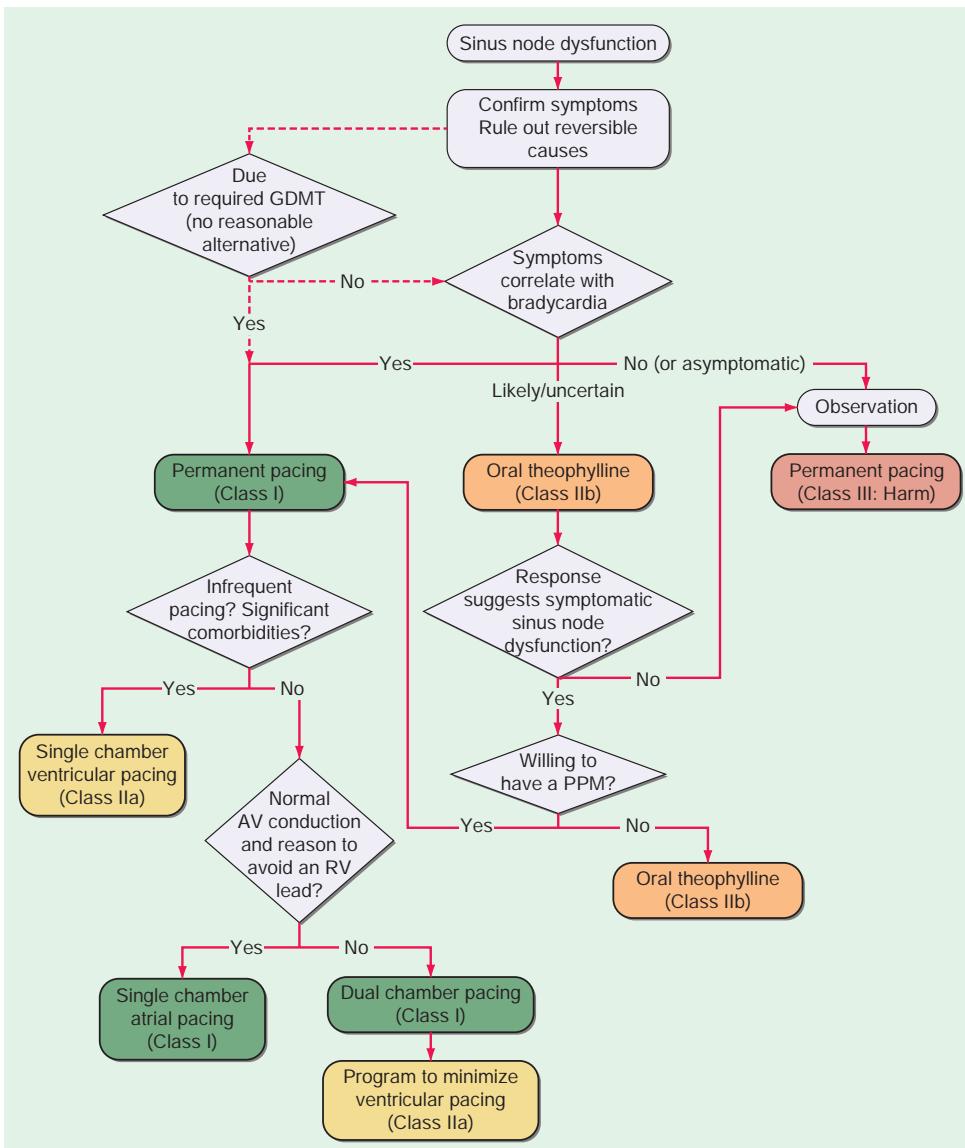
There is no established heart rate below which pacemaker treatment is indicated (**Table 244-2**). Well-conditioned athletes can have resting sinus rates well below 40 beats/min, and some individuals can have similar levels of bradycardia during sleep. Permanent pacing is typically not indicated for sleep-related pauses felt secondary to high vagal tone in the absence of other symptoms. Asymptomatic sinus bradycardia has not been associated with adverse outcomes and does not typically warrant permanent pacing. In situations such as asymptomatic sinus bradycardia, sinus pauses secondary to physiologically elevated parasympathetic tone, transient pauses during sleep, or asymptomatic SND where symptoms have been documented to occur in the absence of bradycardia, a pacemaker is generally not indicated.

Medications to improve heart rate in order to avoid PPM are very rarely utilized. Medications such as methylxanthines (e.g., theophylline) are sometimes utilized on a temporary basis when a pacemaker may need to be delayed due to unique circumstances such as active infection. In addition, oral theophylline may be considered to determine if an increase in heart rate is associated with improvement in symptoms in a patient with sinus bradycardia to suggest that a PPM may be beneficial. This latter strategy is rarely utilized in more equivocal situations.

PPM is the principal treatment for sinus node dysfunction and the decision to pursue this treatment is largely driven by a correlation between symptoms and bradycardia. The stronger the correlation between symptoms and bradycardia, the greater the likelihood of improvement. PPM is most commonly achieved through transvenous implantation of one or more leads through the left or right subclavian veins into the cardiac chambers. The leads are attached to a pacemaker generator that is placed subcutaneously in the pectoral chest region. Less commonly, pacing leads can be placed in the epicardium via surgical approaches including sternotomy or thoracotomy. This latter approach can be accomplished as a stand-alone procedure but is more commonly performed concomitantly during another primary cardiac surgery. Leadless pacemakers that are totally self-contained pacing devices can also be placed in the right ventricle to provide ventricular-based pacing. Some leadless pacemakers can also incorporate technology to sense atrial activity to attempt to coordinate atrial sensing with ventricular pacing. Currently, leadless pacemakers are only available for implant in the right ventricle. Although these devices can sense atrial activity and coordinate this with ventricular pacing (A-V synchrony), if atrial-based pacing is desired, a transvenous or epicardial atrial pacing lead is required.

A standard nomenclature for pacing mode programming utilizes a four-letter code. The first letter indicates the chamber(s) paced (O, none; A, atrium; V, ventricular; D, dual; S, single). The second letter indicates the chamber(s) sensed. The third letter is the response to a sensed event (O, none; I, inhibited; T, triggered; D, inhibition and triggered). The fourth letter refers to whether rate response (R) is turned on. Therefore a dual-chamber pacemaker programmed in a DDDR mode provides atrial and ventricular pacing. A and V sensing, can be inhibited or triggered by a sensed beat, and is programmed to provide rate responsiveness to activity via either a built-in accelerometer, minute ventilation sensor, or both. Rate response is essential for the treatment of CI as it attempts to mimic the natural physiologic increase in heart rate in response to exertion.

A single-chamber atrial pacemaker can be a consideration in patients with pure sinus node dysfunction who are felt to be at low risk for developing AV nodal block. However, fibrosis of the sinus



**FIGURE 244-6 Management of sinus node dysfunction.** Management of sinus node dysfunction begins with eliminating reversible causes and confirming whether symptoms correlate with bradycardia. If symptoms are clearly correlated, permanent pacing should be offered. If it is unclear, a trial of oral theophylline can be considered diagnostically. If there is no correlation between symptoms and bradycardia, then observation is appropriate. Class I recommendations should be performed or are indicated. Class IIa recommendations are considered reasonable to perform. Class IIb recommendations may be considered. Class III recommendations are associated with harm more than benefit. AV, atrioventricular; GDMT, guideline-directed management and therapy; PPM, permanent pacemaker; RV, right ventricular. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. Heart Rhythm 16:e128, 2019.)

node is associated with fibrosis of the AV node on pathology series in older patients and many patients with SND will develop AV node disease. Therefore, although a single-chamber atrial pacemaker

can be a consideration in younger patients with pure sinus node dysfunction, a majority of patients receiving a pacemaker for sinus node disease (particularly older individuals) often receive a dual-chamber pacemaker with backup ventricular pacing if needed.

Class I indications for pacing in SA node dysfunction include documented symptomatic bradycardia, SND-associated long-term drug therapy for which there is no alternative, and symptomatic CI. Class IIa indications include those outlined previously in which SND is suspected but not documented and for syncope of unexplained origin in the presence of major abnormalities of SA node dysfunction. Mildly symptomatic individuals with heart rates consistently <40 beats/min constitute a class IIb indication for pacing. Pacing is not indicated in patients with SA node dysfunction who do not have symptoms and in those in whom bradycardia is associated with the use of nonessential drugs.

**TABLE 244-2 Indications for Permanent Pacing in Sinus Node Dysfunction (SND)**

- Symptoms that are directly attributable to SND
- Symptomatic sinus bradycardia because of essential medication therapy for which there is no alternative treatment
- Tachy-brady syndrome and symptoms attributable to bradycardia
- Symptomatic chronotropic incompetence
- In patients with symptoms that are possibly attributable to SND, a trial of oral theophylline may be considered to increase heart rate and determine if permanent pacing may be beneficial

Source: FM Kusumoto et al: Heart Rhythm 16:e128, 2019.

## COMPLICATIONS RELATED TO PACEMAKER IMPLANTATION

Although pacemakers are highly reliable, they are subject to a number of complications related to implantation and electronic function. In adults, permanent pacemakers are most commonly implanted with access to the heart by way of the subclavian superior vena cava venous system. Rare, but possible, acute complications of transvenous pacemaker implantation include infection, hematoma, pneumothorax, cardiac perforation, diaphragmatic/phrenic nerve stimulation, and lead dislodgment. Limitations of chronic pacemaker therapy include infection, erosion, lead failure, and abnormalities resulting from inappropriate programming or interaction with the patient's native electrical cardiac function. Rotation of the pacemaker pulse generator in its subcutaneous pocket, either intentionally or inadvertently, often referred to as "twiddler's syndrome," can wrap the leads around the generator and produce dislodgment with failure to sense or pace the heart. The small size and light weight of contemporary pacemakers make this a rare complication. Transvenous leads are considered the least reliable component of permanent pacing systems. Enhancements in battery technology and component design have produced a pacing system small enough to be implanted in the heart without the need for a transvenous lead. The first "leadless" pacemakers were only appropriate for patients with indications for single-chamber ventricular (right ventricle) pacing. More recently these devices have been modified to detect mechanical atrial contraction, and thus can be programmed to preserve AV synchrony in patients with heart block but without SND.

### Acknowledgment

*David Spragg and Gordon Tomaselli contributed to this chapter in the 20th edition and some material from that chapter has been retained here.*

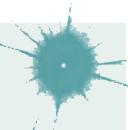
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245

## The Bradyarrhythmias: Disorders of the Atrioventricular Node

William H. Sauer, Bruce A. Koplan



Impulses generated in the sinoatrial (SA) node are conducted to the ventricles through the electrically and anatomically complex atrioventricular (AV) node. The AV node is specialized for slow conduction of the action potential to create a delay between atrial and ventricular activation. There is a similar pattern of arrangement of gap junctions and expression of connexins in the AV node as in the sinus node. This allows for weak electrical coupling in the center of the node to slow conduction and protect it from the periphery. This unique arrangement of gap junctions, along with extracellular matrix and fibroblasts, and a lack of conductance in adjacent valvular tissue allow the AV node to slow conduction and serve as the electrical "gatekeeper" to the ventricle.

As described in previous chapters, cells located in the AV node sit at a relatively higher resting membrane potential than surrounding atrial

and ventricular myocytes, exhibit spontaneous depolarization during phase 4 of the action potential, and have slower phase 0 depolarization (mediated by calcium influx in nodal tissue with a lack of the type of fast sodium channels found in atrial and ventricular myocytes) compared to ventricular tissue (mediated by sodium influx). Although the AV node has the potential for pacemaker activity, the normal automaticity rate is 20–60 beats/min, which is overridden by the higher intrinsic rate of the SA node (60–100 beats/min). Therefore, the AV node can provide backup heart rate when the SA node fails to depolarize. There is a progressive decrease in the frequency of spontaneous depolarization down the His and Purkinje fibers. This progressive decrease in rate of depolarization allows for unidirectional flow of impulses through the conduction system.

Bradycardia may occur when conduction across the AV node is compromised, resulting in slow ventricular rates. The consequences can be fatigue, syncope, and, if a reliable escape rhythm does not occur, death. Transient AV conduction block is common in the young and is most likely the result of high vagal tone found in up to 10% of young adults. Acquired and persistent failure of AV conduction is rare in healthy adult populations, with an estimated incidence of 1 per 5000 in the U.S. population per year. In the setting of myocardial ischemia, aging and fibrosis, or cardiac infiltrative diseases, however, persistent AV block is much more common. As with symptomatic bradycardia arising from SA node dysfunction, permanent pacing is the only reliable therapy for symptoms arising from AV conduction block.

## STRUCTURE AND PHYSIOLOGY OF THE AV NODE

The normal AV junctional area can be divided into a transition cell zone (which results from approaches from the atrium to the AV node), the compact AV node, and the penetrating part of the His bundle. Conduction from the SA node to the AV node occurs in a preferential manner via intra-atrial pathways with higher conduction velocity than the remainder of atrial tissue. The AV node itself is a small region (~1 × 3 × 5 mm) that lies beneath the right atrial endocardium at the apex of the triangle of Koch, a region defined by three landmarks: the coronary sinus ostium posteriorly, the septal tricuspid valve annulus anteriorly, and the tendon of Todaro superiorly. The AV node can be further subdivided into the lower nodal bundle and compact node. A rightward inferior node extension spreads along the tricuspid valve toward the coronary sinus, and the leftward nodal extension spreads from the compact node along the tendon of Todaro. In some people, there are two functional pathways in the AV node: a slow pathway located in the inferior node extension and a fast pathway that is less well defined but is superior to the slow pathway. The role of these pathways in supraventricular tachycardia is described in another chapter.

The compact AV node continues anteriorly and superiorly as the penetrating AV bundle where it traverses the central fibrous body in close proximity to the aortic, mitral, and tricuspid valve annuli. The penetrating AV bundle continues through the annulus fibrosis and emerges as the His bundle along the ventricular septum. The right bundle branch (RBB) emerges from the distal AV bundle and terminates to a band that traverses the right ventricle (moderator band). In contrast, the left bundle branch (LBB) is a broad subendocardial sheet of tissue on the septal left ventricle. The Purkinje fiber network emerges from the RBB and LBB and extensively ramifies on the endocardial surfaces of the right and left ventricles, respectively.

The cells that constitute the AV node complex are heterogeneous with a range of action potential profiles. The AV junction has distinct regions including a transitional cell zone (atrionodal cells), the compact AV node, and the cells of the penetrating part of the His bundle. In the transitional zones, the cells have an electrical phenotype between those of atrial myocytes and cells of the compact node. Atrionodal transitional connections exhibit *decremental conduction*, defined as slowing of conduction with increasingly rapid rates of stimulation. Myocytes that constitute the compact AV node are similar to sinus node myocytes, having a resting membrane potential of ~60 mV; exhibit action potentials with low amplitudes, slow upstrokes of phase 0

(<10 V/s), and spontaneous phase 4 diastolic depolarization; and have high-input resistance and relative insensitivity to external  $[K^+]$ . The action potential phenotype is explained by the complement of ionic currents expressed. AV nodal cells lack a robust inward rectifier potassium current ( $I_{K_1}$ ) and fast sodium current ( $I_{Na}$ ); L-type calcium current ( $I_{Ca-L}$ ) is responsible for phase 0; and phase 4 depolarization reflects the composite activity of the depolarizing currents—funny current ( $I_f$ ),  $I_{Ca-L}$ , T-type calcium current ( $I_{Ca-T}$ ), and sodium calcium exchanger current ( $I_{NCX}$ )—and the repolarizing currents—delayed rectifier ( $I_{Kr}$ ) and acetylcholine-gated ( $I_{KACH}$ ) potassium currents. Electrical coupling between cells in the AV node is tenuous due to the relatively sparse expression of gap junction channels (predominantly connexin-40) and increased extracellular volume.

The His bundle and the bundle branches are insulated from ventricular myocardium. The most rapid conduction in the heart is observed in Purkinje cells (1–3 m/s), with action potentials exhibiting a very rapid upstroke (phase 0), prolonged plateau (phase 2), and modest automaticity (phase 4 depolarization). Gap junctions, composed largely of connexin-40, are abundant, but bundles are not connected transversely to ventricular myocardium. The AV node is innervated by both sympathetic and parasympathetic autonomic input that can either slow or enhance conduction.

The blood supply to the penetrating AV bundle is from the AV nodal artery and first septal perforator of the left anterior descending coronary artery. The AV node artery arises from the right coronary artery (80–90% of the time) or the left circumflex (10%) with the assigned artery associated with the dominance of the coronary artery circulation. The bundle branches also have a dual blood supply from the septal perforators of the left anterior descending coronary artery (LBB) and proximal RBB) and branches of the posterior descending coronary artery. The AV node is highly innervated with postganglionic sympathetic and parasympathetic nerves; however, the bundle of His and distal conducting system are minimally influenced by autonomic tone.

## ELECTROCARDIOGRAPHIC DEFINITIONS OF AV CONDUCTION BLOCK (TABLE 245-1)

Conduction block in the AV node is classified based on the appearance on electrocardiography (ECG), which may also be a reflection of the location of block along the AV conduction axis. First-degree AV block involves a fixed prolongation of the PR interval (>200 ms). In first-degree AV block, delay usually occurs within the AV node, although the atria, His bundle, and Purkinje system may also be involved. Although the term *block* is a misnomer of sorts because electrical conduction is delayed and not interrupted, it remains in use. Second-degree AV block involves intermittent failure of conduction between the atrium and ventricle. There are two subtypes of second-degree AV block. Type I (Mobitz I, Wenckebach) AV block manifests as progressive prolongation of the PR interval prior to one or more “dropped” QRS complexes. Progressive shortening of the RR interval and “grouped beating” QRS complexes are classically seen in Mobitz I AV block. In addition,

comparison of the last PR interval before and the first PR interval after the dropped QRS complex will often reveal the greatest discrepancy of PR interval, making the diagnosis of Mobitz I AV block most evident. Mobitz I AV block typically involves the AV node, is hemodynamically stable, and in the absence of symptoms, does not typically require pacing. Type II second-degree AV block manifests on ECG as failed AV conduction preceded by fixed PR interval (no prolongation of PR interval prior to a dropped beat). Type II block has more serious implications, including a risk of sudden death. It is infranodal in location and associated with a less reliable escape rhythm. Permanent pacing is required. In the setting of 2:1 AV block, ECG differentiation of type I versus type II block is not possible. If the PR interval is <160 ms prior to the AV conduction and QRS is wider than normal, infranodal (type II) block is most likely. Complete heart block (third-degree block) involves complete AV dissociation with a ventricular rate that is slower than the atrial rate (Fig. 245-1).

In the absence of a preexisting bundle branch block, a wide QRS escape rhythm implies a block in the distal His or bundle branches; in contrast, a narrow QRS rhythm implies a block in the AV node or proximal His and an escape rhythm originating in the AV junction. Narrow QRS escape rhythms are typically faster and more stable than wide QRS escape rhythms and originate more proximally in the AV conduction system.

## ETIOLOGY OF AV CONDUCTION DISEASE

There are numerous causes of intrinsic AV node dysfunction. Fibrosis and sclerosis of the conduction system are the most common causes of acquired conduction disease, accounting for ~50% of AV block. Numerous conditions that may not be distinguishable from one another can lead to conduction system fibrosis. Senile degeneration of the conduction system is most commonly seen in the elderly and results from idiopathic fibrosis and calcification. Lev's disease results from proximal bundle branch fibrosis. Lenègre's disease results from a sclerodegenerative process that occurs in a younger age group and involves the more distal portions of the bundle branches. Calcification of the aortic valve annulus can encroach on the conduction system. Compared to aortic valve calcification, mitral calcification is less commonly a cause of AV block (Table 245-2).

## IATROGENIC CAUSES

AV block may also be from iatrogenic causes. Cardiac surgery, most commonly cardiac valve surgery, can result in damage to the AV conduction system, with the highest risk occurring in aortic valve and tricuspid valve surgery. Percutaneous transcatheter aortic valve replacement, septal myectomy, and alcohol septal ablation also carry a risk of AV block. Percutaneous catheter ablation for atrial arrhythmias, particularly AV nodal reentry tachycardia ablation, is associated with a 1% risk of AV block. Medications, including beta blockers, verapamil, diltiazem, and digoxin, are also common iatrogenic causes of AV block. Many patients with drug-induced AV block have preexisting conduction system disease. Iatrogenic AV block may occur rarely in the setting of thoracic radiation or chemotherapy. AV block is a rare complication of the surgical repair of ventricular septal defects (VSDs) or atrial septal defects (ASDs) but may complicate repairs of transposition of the great arteries.

## AV BLOCK IN THE SETTING OF MYOCARDIAL ISCHEMIA

Coronary artery disease may produce transient or persistent AV block. In the setting of coronary spasm, ischemia, particularly in the right coronary artery distribution, may produce transient AV block. In acute myocardial infarction (MI), AV block transiently develops in 10–25% of patients; most commonly, this is first- or second-degree AV block, but complete heart block (CHB) may also occur. Second-degree and higher-grade AV block tends to occur more often in inferior than in anterior acute MI; however, the level of block in inferior MI tends to be in the AV node with more stable, narrow escape rhythms. In contrast, acute anterior MI is associated with block in the distal AV nodal complex, His bundle, or bundle branches and results in wide complex,

**TABLE 245-1** Electrocardiographic Classification of Atrioventricular (AV) block

### First-Degree AV Block

All atrial impulses are conducted to the ventricle

PR interval is abnormally long (>200 ms)

AV delay usually occurs within the AV node

### Second-Degree AV Block (intermittent failure of conduction between atrium and ventricle)

Two subtypes

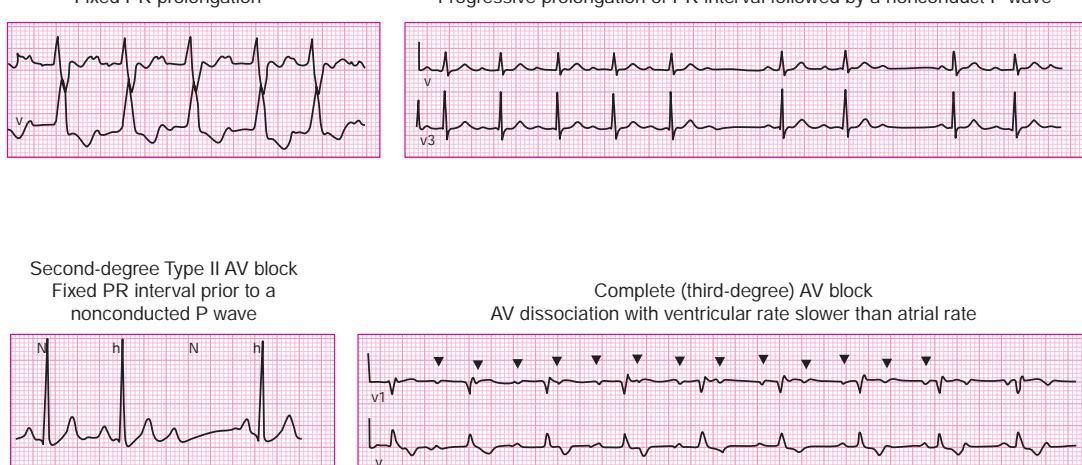
Type I/Mobitz I/Wenckebach block: progressive prolongation of the PR interval until loss of conduction occurs.

Type II/Mobitz II: fixed PR interval precedes loss of conduction

Usually associated with QRS widening

### Third-Degree AV Block (complete heart block)

Complete interruption of conduction between atria and ventricles



**FIGURE 245-1** Types of atrioventricular (AV) block. The upper left figure displays fixed prolongation of the PR interval. The upper right figure demonstrates Mobitz I block (Wenckebach AV block) manifested as progressive prolongation of the PR interval followed by a nonconducted P wave (“dropped beat”). The lower left figure displays AV block with P wave with no QRS complex and no associated PR prolongation prior to the dropped beat (Mobitz type II AV block). The lower right figure demonstrates complete heart block manifested as dissociation between P waves and QRS complexes (AV dissociation).

**TABLE 245-2 Causes of AV Block**

Fibrosis/sclerosis/calcification of the conduction system
Senile degeneration of the conduction system (Lev's disease)
Lenègre's disease
Calcification of the aortic valve annulus (mitral—less common)
Iatrogenic
After cardiac surgery (including valve surgery)
TAVR/alcohol septal ablation
Complication from catheter ablation
Medication (beta blockers, verapamil, diltiazem, digoxin)
Toxin/overdose/poisoning
Acute MI/coronary ischemia
Infectious causes
Lyme carditis
Bacterial endocarditis with perivalvular abscess
Viral myocarditis
Chagas' disease
Toxoplasmosis
Infiltrative heart disease/inflammatory disease
Sarcoidosis
Amyloid
Rheumatologic disease: reactive arthritis (Reiter's syndrome), SLE, RA, systemic sclerosis
Congenital AV block
Maternal lupus
Idiopathic congenital AV block
Congenital heart defects
Genetic
Endocrine (e.g., thyroid disease, hypoadosteronism)
Autoimmune disease
Neuromuscular disease (e.g., myotonic dystrophy, Kearns-Sayre syndrome, Erb's dystrophy)
Lymphoma
Enhanced vagal tone/neurocardiogenic

*Abbreviations:* AV, atrioventricular; MI, myocardial infarction; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TAVR, transcatheter aortic valve replacement.

unstable escape rhythms and a worse prognosis with high mortality rates.

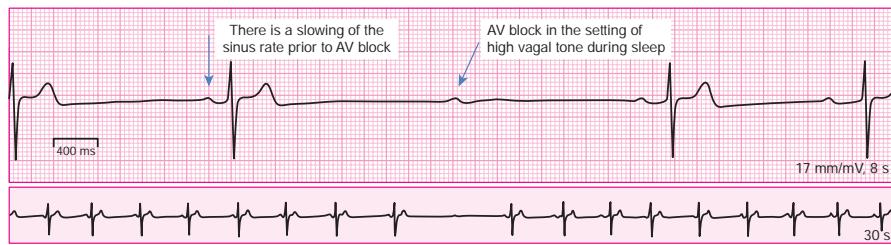
AV conduction abnormalities may be caused by either direct ischemia to the conduction system or enhanced autonomic tone (Bezold-Jarisch reflex). Conduction abnormalities can be considered based on infarct location, and this may also predict which conduction abnormalities may be reversible. High-grade AV block associated with inferior MI is often located proximal to the His bundle in 90% of patients. Narrow junctional escape typically occurs with rates >40 beats/min, and a temporary pacemaker is typically not required as the AV block is often reversible and successfully managed with pharmacologic therapy. High-grade AV block in the setting of anterior MI is typically indicative of extensive infarction, is more often distal to the AV node, and is associated with a high mortality rate. Temporary pacing in this circumstance is typically indicated. CHB in the setting of anterior MI may also be preceded by RBB block due to the arterial supply of the proximal RBB.

### INFECTIOUS CAUSES OF AV BLOCK

Infection can also cause AV block. AV block is a common manifestation of Lyme carditis due to infection with *Borrelia burgdorferi*. AV block is typically at the level of the AV node with narrow junctional escape rhythm >40 beats/min. Less commonly, conduction abnormalities can occur below the level of the AV node or in the sinus node. AV block typically improves within 1 week of antibiotic therapy, although a longer time frame can occur in some patients. AV block in the setting of infective endocarditis should raise concern for perivalvular abscess, which may necessitate surgical intervention. Viral myocarditis, Chagas' disease, and toxoplasmosis are less common infectious causes of AV block. Infiltrative heart disease such as cardiac sarcoid, amyloid, and hemochromatosis can present as AV block. Autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis, mixed connective tissue disease, and scleroderma, may cause AV block due to infiltration of the conduction system. Rare malignancies also may impair AV conduction.

### AUTONOMIC AND FUNCTIONAL CAUSES OF AV BLOCK

Functional causes of AV block (autonomic, metabolic/endocrine, and drug-related) tend to be reversible. Most other etiologies produce structural changes, typically fibrosis, in segments of the AV conduction



**FIGURE 245-2 Evidence of atrioventricular (AV) block during sleep.** During sleep, increased vagal tone leads to sinus bradycardia with associated Mobitz I (Wenckebach) AV block. See Fig. 245-1 for an explanation of Mobitz I block.

axis that are generally permanent. Heightened vagal tone during sleep or in well-conditioned individuals can be associated with all grades of AV block (**Fig. 245-2**).

Carotid sinus hypersensitivity, vasovagal syncope, and cough and micturition syncope may be associated with SA node slowing and AV conduction block. Transient metabolic and endocrinologic disturbances and a number of pharmacologic agents also may produce reversible AV conduction block.

### ACQUIRED AV BLOCK FROM FIBROSIS AND INFILTRATIVE CARDIOMYOPATHIES

Idiopathic progressive fibrosis of the conduction system is one of the more common and degenerative causes of AV conduction block. Aging is associated with degenerative changes in the summit of the ventricular septum, central fibrous body, and aortic and mitral annuli and has been described as “sclerosis of the left cardiac skeleton.” The process typically begins in the fourth decade of life and may be accelerated by atherosclerosis, hypertension, and diabetes mellitus. Accelerated forms of progressive familial heart block have been identified in families with mutations in the cardiac sodium channel gene (*SCN5A*) and other loci that have been mapped to chromosomes 1 and 19.

AV conduction block has been associated with heritable neuromuscular diseases, including the nucleotide repeat disease myotonic dystrophy, the mitochondrial myopathy Kearns-Sayre syndrome, and several of the monogenic muscular dystrophies.

### CONGENITAL AV BLOCK

Congenital AV block may be observed in complex congenital cardiac anomalies, such as transposition of the great arteries, ostium primum ASDs, VSDs, endocardial cushion defects, and some single-ventricle defects. Congenital AV block in the setting of a structurally normal heart has been seen in children born to mothers with SLE and other autoimmune diseases.

### DIAGNOSTIC TESTING

Patients with conduction abnormalities should be evaluated for the presence or absence of structural heart disease. Physical exam may reveal valvular heart disease. ECG may suggest concomitant disease that predisposes to conduction abnormalities. Echocardiography is also indicated to evaluate for structural heart disease including valvular abnormalities, ejection fraction, and ventricular wall motion. Because age-dependent progressive fibrosis of the conduction system is the most common cause, AV node block that develops at a younger age (<60 years) may warrant advanced imaging such as chest computed tomography (CT), cardiac magnetic resonance imaging (MRI), or CT/positron emission tomography (PET) scan to further evaluate for infiltrative heart disease such as sarcoidosis. Advanced imaging may also be warranted based on other factors in the history and testing that suggest the need for evaluation of infiltrative heart disease. Evaluation for cardiac ischemia should be driven by the clinical suspicion at presentation (e.g., symptoms of ischemia, ECG abnormalities, etc.) (**Fig. 245-3**).

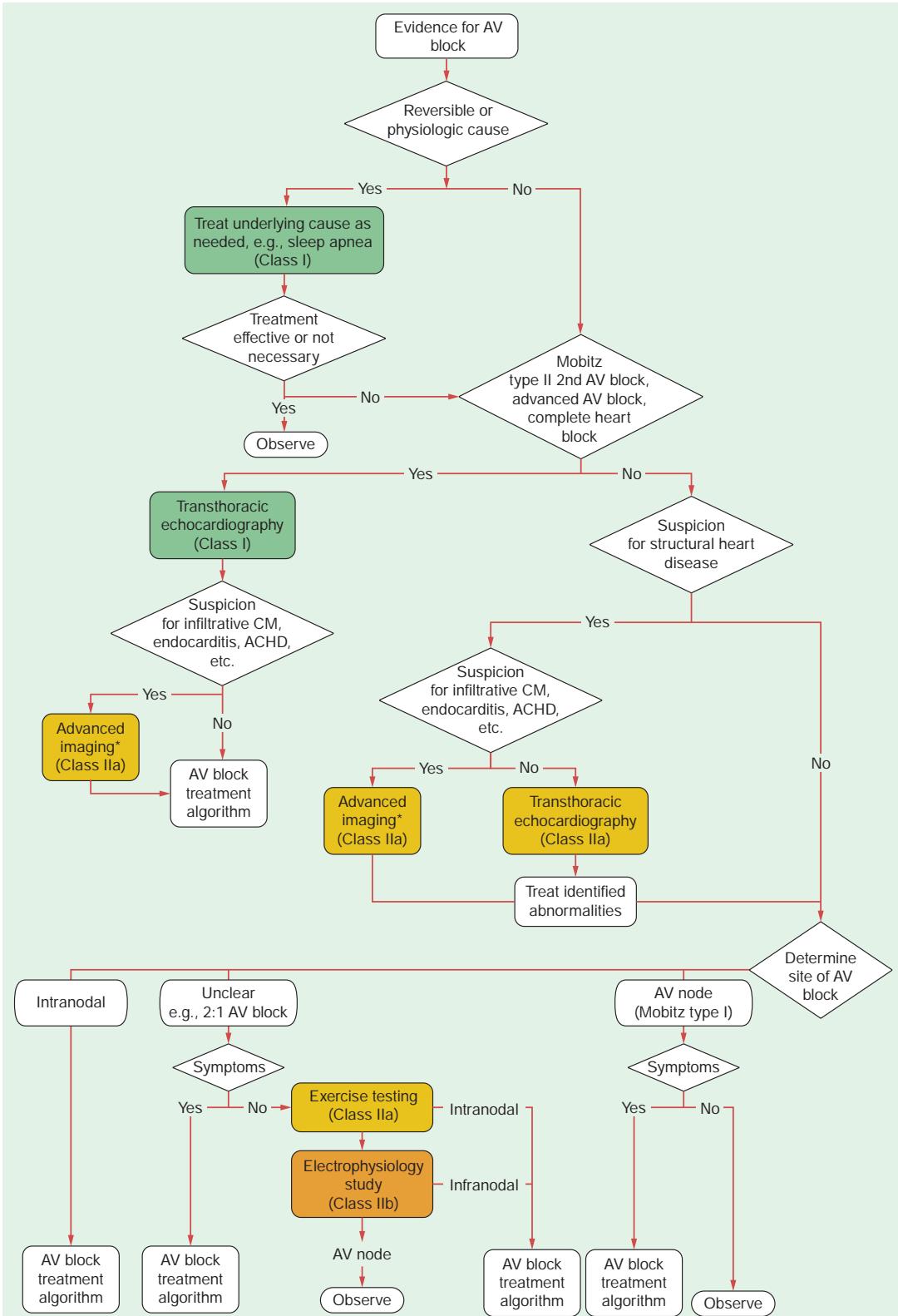
Diagnostic testing in the evaluation of AV block is aimed at determining the level of conduction block, particularly in asymptomatic patients, since the prognosis and therapy depend on whether the block is in or below the AV node. Vagal maneuvers, carotid sinus massage,

exercise, and administration of drugs such as atropine and isoproterenol may be diagnostically informative. Owing to the differences in the innervation of the AV node and infranodal conduction system, vagal stimulation and carotid sinus massage slow conduction in the AV node but have less of an effect on infranodal tissue and may even appear to improve conduction due to a reduced rate of activation of distal tissues. Conversely, atropine, isoproterenol, and exercise improve conduction through the AV node and may appear to impair infranodal conduction. In patients with congenital CHB and a narrow QRS complex, exercise typically increases heart rate; by contrast, those with acquired CHB, particularly with wide QRS, do not respond to exercise with an increase in heart rate.

Additional diagnostic evaluation, including electrophysiologic testing, may be indicated in patients with syncope and suspected high-grade AV block. This is particularly relevant if noninvasive testing does not reveal the cause of syncope or if the patient has structural heart disease with ventricular tachyarrhythmias as a cause of symptoms. Electrophysiologic testing provides more precise information regarding the location of AV conduction block and permits studies of AV conduction under conditions of pharmacologic stress and exercise. Recording of the His bundle electrogram by a catheter positioned at the superior margin of the tricuspid valve annulus provides information about conduction at all levels of the AV conduction axis. A properly recorded His bundle electrogram reveals local atrial activity, the His electrogram, and local ventricular activation; when it is monitored simultaneously with recorded body surface ECG traces, intra-atrial, AV nodal, and infranodal conduction times can be assessed. The time from the most rapid deflection of the atrial electrogram in the His bundle recording to the His electrogram (*AH interval*) represents conduction through the AV node and is normally <130 ms. The time from the His electrogram to the earliest onset of the QRS on the surface ECG (*HV interval*) represents the conduction time through the His-Purkinje system and is normally 55 ms (**Fig. 245-4**).

Rate stress produced by pacing can unveil abnormal AV conduction. Mobitz I second-degree AV block at short atrial paced cycle lengths is a normal response. However, when it occurs at atrial cycle lengths >500 ms (<120 beats/min) in the absence of high vagal tone, it is abnormal. Typically, type I second-degree AV block is associated with prolongation of the AH interval, representing conduction slowing and block in the AV node. AH prolongation occasionally is due to the effect of drugs (beta blockers, calcium channel blockers, digitalis) or increased vagal tone. Atropine can be used to reverse high vagal tone; however, if AH prolongation and AV block at long pacing cycle lengths persist, intrinsic AV node disease is likely. Type II second-degree block is typically infranodal, often in the His-Purkinje system. Block below the node with prolongation of the HV interval or a His bundle electrogram with no ventricular activation is abnormal unless it is elicited at fast pacing rates or short coupling intervals with extra stimulation. It is often difficult to determine the type of second-degree AV block when 2:1 conduction is present; however, the finding of a His bundle electrogram after every atrial electrogram indicates that block is occurring in the distal conduction system.

Intracardiac recording at an electrophysiologic study that reveals prolongation of conduction through the His-Purkinje system (i.e., long



**FIGURE 245-3** Initial evaluation of suspected atrioventricular (AV) block algorithm. \*Targeted advanced imaging—magnetic resonance imaging (MRI); amyloidosis, myocarditis, hemochromatosis, sarcoidosis, congenital heart disease (CHD), sinus of Valsalva aneurysm, aortic dissection, arrhythmogenic right ventricular cardiomyopathy, fluorodeoxyglucose-positron emission tomography (FDG-PET); sarcoidosis; technetium-99m pyrophosphate (Tc PYP) or 99m technetium 3,3-diphosphono-1,2-propanodicarboxylic acid (TC-DPD); transthyretin (TTR) amyloidosis; cardiac computed tomography (CT); CHD, sinus of Valsalva. ACHD, adult CHD; CM, cardiomyopathy. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. Heart Rhythm 16:e128, 2019.)



**FIGURE 245-4** High-grade atrioventricular (AV) block below the His. The AH interval is normal and is not changing before the block. Atrial and His bundle electrograms are recorded consistent with block below the distal AV junction. I, II, III, and V<sub>1</sub>, are surface ECG leads. HISp, HISd, and RVA are the proximal HIS, distal HIS, and right ventricular apical electrical recordings, respectively. A, H, and V represent the atrial, His, and ventricular electrograms on the His bundle recording, respectively. (Courtesy of Dr. Joseph Marine.)

HV interval) is associated with an increased risk of progression to higher grades of block and is generally an indication for pacing. In the setting of bundle branch block, the HV interval may reveal the condition of the unblocked bundle and the prognosis for developing more advanced AV conduction block. Prolongation of the HV interval in patients with asymptomatic bundle branch block is associated with an increased risk of developing higher-grade AV block. The risk increases with greater prolongation of the HV interval such that in patients with an HV interval >100 ms, the annual incidence of complete AV block approaches 10%, indicating a need for pacing. In patients with acquired CHB, even if intermittent, there is little role for electrophysiologic testing, and pacemaker implantation is almost always indicated.

## TREATMENT

### Acute Management of AV Conduction Block

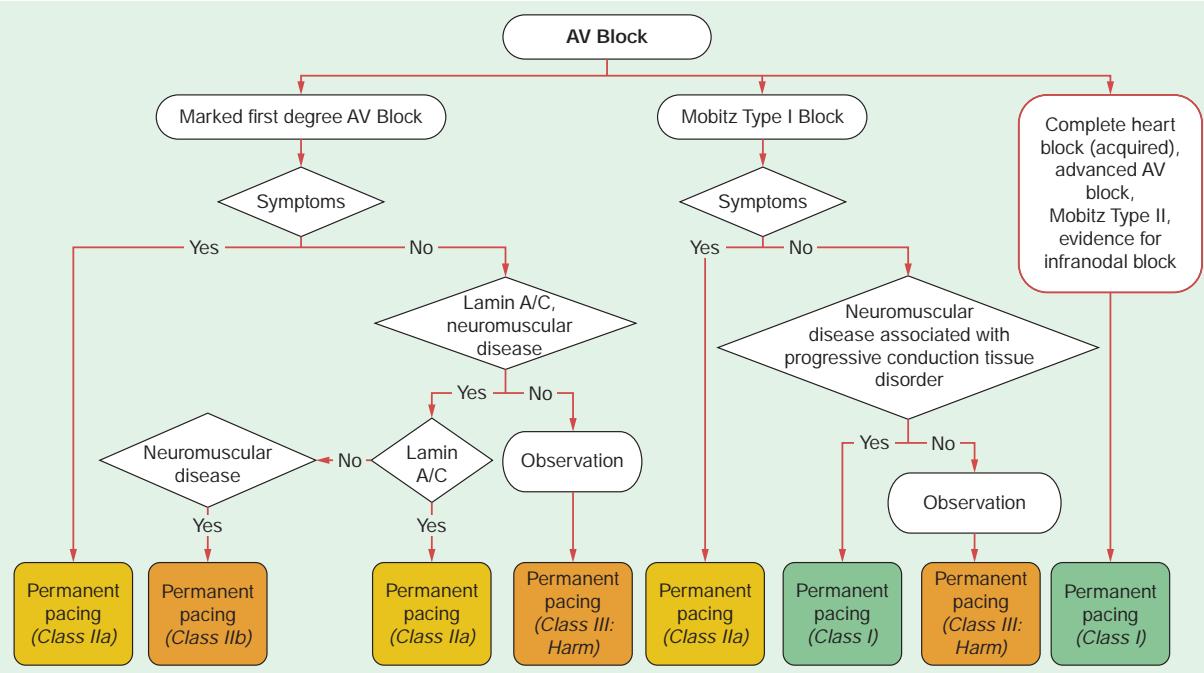
The first-line strategies for management of AV block should be to eliminate reversible causes and to determine the immediate safety and reliability of the heart rhythm (e.g., escape rhythm) and whether or not temporary or permanent pacing is warranted. The need for temporary pacing is determined by the symptoms of the patient, hemodynamic status, and the estimate of the level at which AV block is present. In a general sense, the lower in the conduction system that an escape rhythm is occurring, the lower is the reliability of the escape rhythm. A narrow-complex junctional escape of 45 beats/min with no symptoms does not warrant urgent temporary pacing, whereas a wide-complex (implying block lower in the conduction system) escape rhythm at 30 beats/min does. Elimination of unnecessary medications known to slow AV conduction (e.g., beta blockers, diltiazem, verapamil, digoxin), correction of electrolyte abnormalities, ischemia, and inhibition of excessive vagal tone may increase the heart rate. Adjunctive pharmacologic treatment

with atropine or isoproterenol may be useful if the block is in the AV node. When pacing is indicated, the most expeditious technique is the use of transcutaneous pacing, where pacing patches are placed anteriorly over the cardiac apex (cathode) and posteriorly between the spine and the scapula or above the right nipple (anode). Acutely, transcutaneous pacing is highly effective, but its duration is limited by patient discomfort and longer-term failure to capture the ventricle owing to changes in lead impedance. Transvenous temporary pacing is more reliable, and a pacing wire can be placed from the jugular, subclavian, or femoral venous system and advanced to the right ventricle, permitting stable temporary pacing.

AV conduction abnormalities may be reversible in certain circumstances including removal of unnecessary medication or toxins, correction of electrolyte abnormalities, relief of ischemia, treatment of certain infiltrative heart disease (e.g., immunosuppression in cardiac sarcoidosis), and treatment of sleep apnea in patients with nocturnal vagally mediated AV block. When symptomatic or infra-nodal AV block is not reversible, which is often the case, permanent pacing is warranted.

### PERMANENT PACEMAKER IMPLANTATION

The indications for pacing in AV conduction block are shown in Fig. 245-5. In patients with acquired Mobitz type II AV block, high-grade AV block, or third-degree AV block that is not reversible or physiologic, permanent pacing is recommended regardless of symptoms. For all other types of AV block, in the absence of conditions associated with progressive AV conduction abnormalities, permanent pacing should generally be considered only in the presence of symptoms that correlate with block. In patients with neuromuscular disease and other progressive cardiomyopathies affecting the conduction system, permanent pacemaker implantation is recommended for marked first-degree AV block and Mobitz I AV block. Pacemaker implantation should be performed in any patient



**FIGURE 245-5** Indications for pacing in patients with atrioventricular (AV) block. In patients presenting with AV block, the category of AV block should be determined (first-degree, second-degree, or complete heart block). In first-degree AV block, permanent pacing may be indicated in the setting of symptoms or higher-risk systemic disease such as neuromuscular disease or Lamin A/C cardiomyopathy. In Mobitz I AV block, pacing may be considered in the setting of symptoms or the additional disease mentioned with first-degree AV block. In complete heart block or Mobitz II AV block, permanent pacing is generally indicated. Class I recommendations should be performed or are indicated. Class IIa recommendations are considered reasonable to perform. Class IIb recommendations may be considered. Class III recommendations are associated with harm more than benefit. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Heart Rhythm* 16:e128, 2019.)

with symptomatic bradycardia and irreversible second- or third-degree AV block, regardless of the cause or level of block in the conducting system. Symptoms may include those directly related to bradycardia and low cardiac output or to worsening heart failure, angina, or intolerance to an essential medication. Pacing in patients with asymptomatic AV block should be individualized; situations in which pacing should be considered are patients with acquired CHB, particularly in the setting of cardiac enlargement; left ventricular dysfunction; and waking heart rates <40 beats/min. Patients who have asymptomatic second-degree AV block of either type should be considered for pacing if the block is demonstrated to be intra- or infra-His or is associated with a wide QRS complex. Pacing may be indicated in asymptomatic patients in special circumstances, in patients with profound first-degree AV block and left ventricular dysfunction in whom a shorter AV interval produces hemodynamic improvement, and in the setting of milder forms of AV conduction delay (first-degree AV block, intraventricular conduction delay) in patients with neuromuscular diseases that have a predilection for the conduction system, such as myotonic dystrophy and other muscular dystrophies and Kearns-Sayre syndrome.

AV block in acute MI is often transient, particularly in inferior infarction. The circumstances in which pacing is indicated in acute MI are persistent second- or third-degree AV block, particularly if symptomatic, and transient second- or third-degree AV block associated with bundle branch block. Pacing is generally not indicated in the setting of transient AV block in the absence of intraventricular conduction delays or in the presence of fascicular block or first-degree AV block that develops in the setting of preexisting bundle branch block. Fascicular blocks that develop in acute MI in the absence of other forms of AV block also do not require pacing.

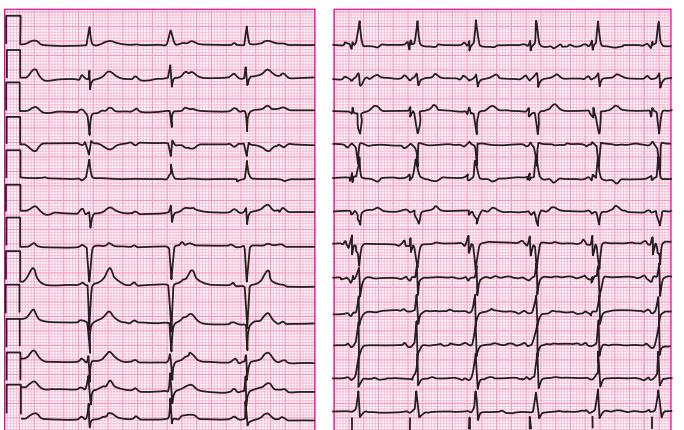
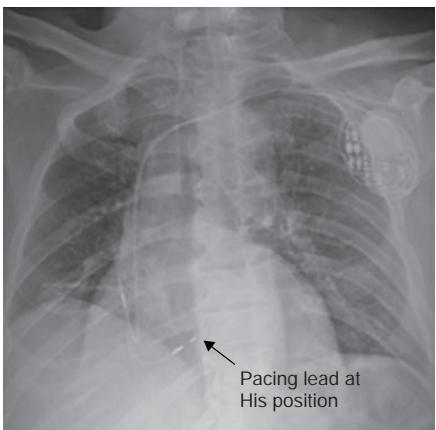
Distal forms of AV conduction block may require pacemaker implantation in certain clinical settings. Patients with bifascicular or trifascicular block and symptoms, particularly syncope that is not attributable to other causes, should undergo pacemaker

implantation. Permanent pacemaker implantation is indicated in asymptomatic patients with bifascicular or trifascicular block who experience intermittent third-degree block, type II second-degree AV block, or alternating bundle branch block. In patients with fascicular block who are undergoing electrophysiologic study, a markedly prolonged HV interval or block below the His at long cycle lengths also may constitute an indication for permanent pacing. Patients with fascicular block and the neuromuscular diseases previously described should also undergo pacemaker implantation.

#### SELECTION OF PACING MODE AND SYSTEM

In general, a pacing mode that maintains AV synchrony reduces complications of pacing such as pacemaker syndrome and pacemaker-mediated tachycardia. This is particularly true in younger patients; the importance of dual-chamber pacing in the elderly, however, is less well established, although AV synchrony in patients with sinus rhythm and AV block is typically desired.

**Physiologic Ventricular Pacing** In patients with left ventricular ejection fraction <50% and AV block who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time, techniques to provide more physiologic ventricular activation are preferred to right ventricular pacing to prevent heart failure. Cardiac resynchronization therapy (CRT) involves placement of an additional pacing lead in a lateral or anterolateral branch of the coronary sinus to allow for simultaneous right ventricle and lateral left ventricle pacing leading to a more physiologic left ventricular contraction. CRT pacing has been shown to improve outcomes and mortality in appropriately selected patients. Physiologic ventricular pacing has also been achieved with placement of a ventricular pacing lead in the region of the His bundle. His bundle pacing recruits the specialized conduction system, leading to a more physiologic cardiac contraction. In addition to His bundle pacing, left bundle branch area pacing in the proximal interventricular septal region has also been shown to achieve a more



**FIGURE 245-6 His bundle pacing.** The chest radiograph on the left shows a dual chamber pacemaker with a pacing lead in the right atrium (upper left) and a pacing lead in the region of the tricuspid valve in the His position. The electrocardiograms demonstrated intrinsic conduction with complete heart block on the left and atrial sensed, ventricular paced rhythm with a narrow QRS complex similar to the intrinsic QRS complex that results from pacing the His bundle and capturing the specialized conduction system of the heart.

physiologic pacing response. The selection of pacing lead location should be individualized (**Fig. 245-6**).

The availability of leadless miniaturized pacing systems may be appropriate in selected patients. Leadless pacemakers are completely self-contained devices that are implanted via the femoral vein into the right ventricle. The technology for these devices continues to evolve, and the most recent models are capable of detecting atrial mechanical contraction to allow for the preservation of AV synchrony. The device can provide single-chamber ventricular pacing in addition to containing technology that can sense atrial activity (utilizing the accelerometer in the pacemaker) to coordinate an atrial sensed, ventricular paced rhythm (AV synchrony). Leadless pacemakers can be particularly useful in patients with vascular access limitations. Because there is no intravascular pacing wire or implanted subcutaneous pacemaker generator, the long-term infection rate is lower and there is no risk of lead fracture (**Fig. 245-7**).

Several studies have failed to demonstrate a difference in mortality rate in older patients with AV block treated with a single- (VVI) compared with a dual- (DDD) chamber pacing mode. In some of the studies that randomized pacing mode, the risk of chronic atrial fibrillation and stroke risk decreased with physiologic pacing. In

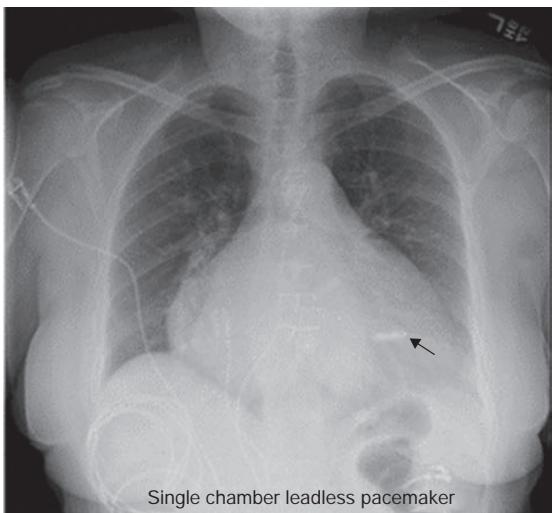
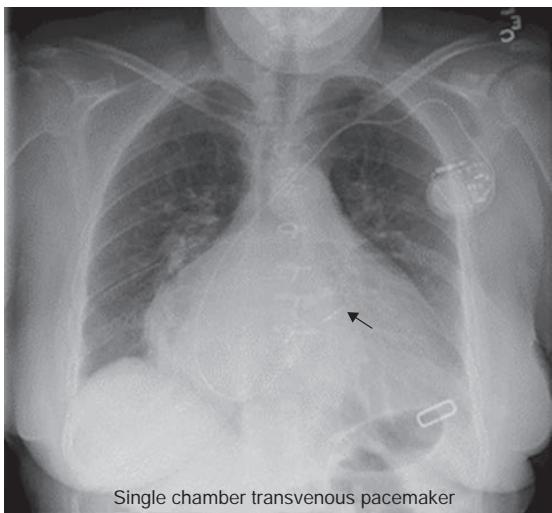
patients with sinus rhythm and AV block, the very modest increase in risk with dual-chamber pacemaker implantation appears to be justified to avoid the possible complications of single-chamber pacing.

#### Acknowledgment

David D. Spragg and Gordon F. Tomaselli contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

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**FIGURE 245-7 Types of pacemakers.** A single-chamber pacemaker with the pacing lead in the right ventricular outflow tract (arrow) is shown on the left. A single-chamber leadless pacemaker (arrow) is shown on the right.

# 246

## Approach to Supraventricular Tachyarrhythmias

William H. Sauer, Paul C. Zei



The most common arrhythmias that patients present with are part of a broad category defined by anatomic origin termed *supraventricular tachycardias* (SVTs). SVTs originate from or are dependent on conduction through the atrium or atrioventricular (AV) node to the ventricles. Most produce narrow QRS complex tachycardia (QRS duration <120 ms) characteristic of ventricular activation over the Purkinje system and thus are sometimes referred to as a narrow-complex tachycardias. The QRS morphology of the SVT is usually identical to the sinus rhythm QRS. Conduction block in the left or right bundle branch or activation of the ventricles from an accessory pathway produces a wide QRS complex during SVT that must be distinguished from ventricular tachycardia (VT). Mechanisms of supraventricular tachyarrhythmia can be divided into physiologic sinus tachycardia and pathologic tachycardia (**Table 246-1**).

Pathologic tachycardia can be further subclassified by mechanism as reentrant arrhythmias dependent on AV nodal conduction (e.g., AVNRT), large reentry circuits within the atrial tissue alone (e.g., atrial flutter), or focal atrial tachycardias that can be due to automaticity or small reentry circuits. The prognosis and treatment vary considerably depending on the mechanism and underlying heart disease. SVT can be of brief duration, termed *nonsustained*, or can be sustained such that an intervention, such as cardioversion, catheter ablation, or drug administration, is required for termination and maintenance of sinus rhythm. Episodes that occur with sudden onset and termination are referred to as paroxysmal. *Paroxysmal supraventricular tachycardia* (PSVT) refers to a family of tachycardias including AV node reentry, AV reciprocating tachycardia using an accessory pathway, and atrial tachycardia described in subsequent chapters (**Fig. 246-1**).

### CLINICAL PRESENTATION

Symptoms of supraventricular arrhythmia vary depending on the rate, duration, associated heart disease, and comorbidities and include palpitations, chest pain, dyspnea, diminished exertional capacity, and occasionally syncope. Rarely, a supraventricular arrhythmia precipitates cardiac arrest in patients with Wolff-Parkinson-White (WPW) syndrome or severe heart disease, such as hypertrophic cardiomyopathy.

### INITIAL EVALUATION

The diagnosis of SVT is most often entertained when evaluating a patient for arrhythmia-related symptoms or when evidence of ventricular preexcitation is seen on an electrocardiogram (ECG) as an outpatient. Diagnosis of SVT requires obtaining an ECG at the time of symptoms (**Fig. 246-2**). Ventricular preexcitation on the resting ECG suggests AV reciprocating tachycardia using an accessory pathway. When the arrhythmia is ongoing at the time of recording, the ECG usually establishes or suggests the diagnosis. In the urgent care or inpatient setting, treatment of SVT will often involve vagal maneuvers or carotid sinus massage (CSM) to achieve AV block (**Table 246-2**). In the appropriate patient, CSM should be used cautiously, if at all, if there is concern for carotid atherosclerosis that may be embolized during manipulation. If this is unsuccessful, the administration of 6 or 12 mg of adenosine to cause transient AV block is usually successful in terminating an AV nodal-dependent SVT or diagnosing a non-AV nodal-dependent SVT such as atrial tachycardia or atrial flutter. There are some atrial tachycardias that are adenosine sensitive, and thus,

### TABLE 246-1 Mechanisms of Supraventricular Tachyarrhythmia

#### Physiologic Sinus Tachycardia

*Defining feature:* normal sinus mechanism precipitated by exertion, stress, exogenous or endogenous stimulants, concurrent illness

#### Pathologic Supraventricular Tachycardia (SVT)

##### A. Tachycardias originating from the atrium

*Defining feature:* tachycardia may continue despite beats that fail to conduct to the ventricles, indicating that the atrioventricular (AV) node is not participating in the tachycardia circuit

###### 1. Inappropriate sinus tachycardia

*Defining feature:* tachycardia from the normal sinus node area that occurs without an identifiable precipitating factor as a result of dysfunctional autonomic regulation

###### 2. Focal atrial tachycardia (AT)

*Defining feature:* regular atrial tachycardia with defined P wave; may be sustained, nonsustained, paroxysmal, or incessant; frequent sites of origin occur along the valve annuli of left or right atrium, pulmonary veins, coronary sinus musculature, superior vena cava

###### 3. Atrial flutter and macroreentrant atrial tachycardia

*Defining feature:* macroreentry reflected as organized atrial activity on an electrocardiogram (ECG), commonly seen as sawtooth flutter waves at rates typically faster than 200 beats/min

###### 4. Atrial fibrillation

*Defining feature:* chaotic rapid atrial electrical activity with variable ventricular rate; the most common sustained cardiac arrhythmia in older adults

###### 5. Multifocal atrial tachycardia

*Defining feature:* multiple discrete P waves often seen in patients with pulmonary disease during acute exacerbations of pulmonary insufficiency

##### B. AV nodal reentry tachycardia (AVNRT)

*Defining feature:* paroxysmal regular tachycardia with P waves visible at the end of the QRS complex or not visible at all; the most common paroxysmal sustained tachycardia in healthy young adults; more common in women

##### C. Tachycardias associated with accessory atrioventricular pathways

###### 1. Orthodromic AV reciprocating tachycardia (AVRT)

*Defining feature:* paroxysmal sustained tachycardia similar to AV nodal reentry; during sinus rhythm, evidence of ventricular preexcitation may be present (Wolff-Parkinson-White syndrome) or absent (concealed accessory pathway)

###### 2. Preexcited tachycardia

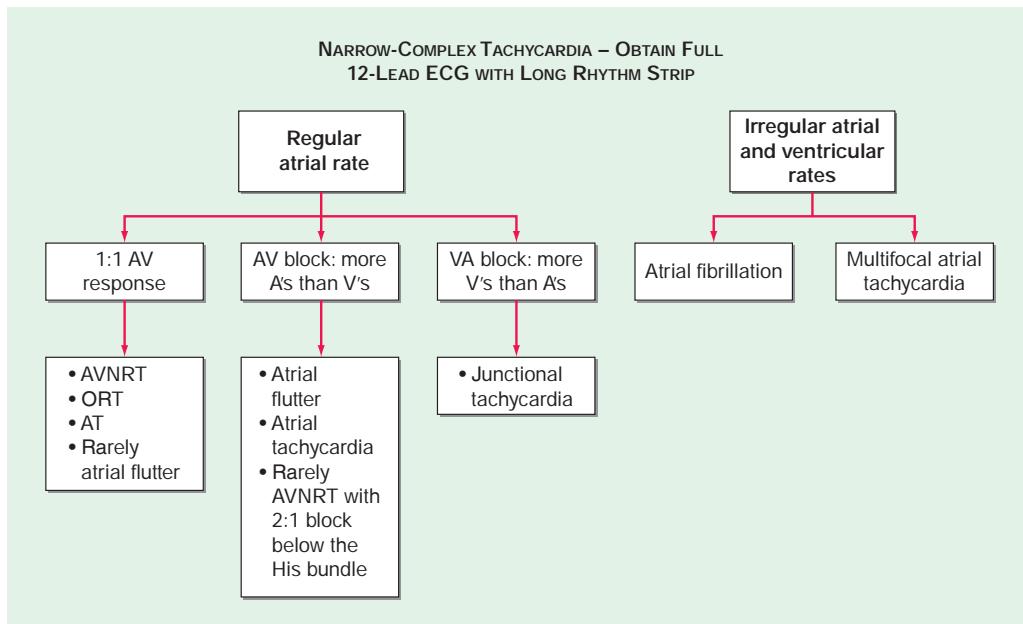
*Defining feature:* wide QRS tachycardia with QRS morphology similar to ventricular tachycardia

- Antidromic AV reciprocating tachycardia—regular paroxysmal tachycardia
- Atrial fibrillation with preexcitation—irregular wide-complex or intermittently wide-complex tachycardia, some with dangerously rapid rates faster than 250/min
- Atrial tachycardia or flutter with preexcitation

termination of an SVT with adenosine does not exclude this potential diagnosis.

For transient arrhythmias, ambulatory ECG recording is warranted. Patients will often have access to ECG recording devices, such as a watch or smartphone-enabled electrogram recording electrode pair. Therefore, a patient may have the ECG diagnosis before seeing a physician (**Fig. 246-3**).

Exercise testing is useful for assessing exercise-related symptoms and potentially evoking the arrhythmia. Additional evaluation for underlying cardiac disease and to exclude potentially dangerous arrhythmias should be performed based on the clinical scenario. Occasionally, an invasive electrophysiology study is warranted to provoke the arrhythmia with pacing, confirm the mechanism, and risk stratify the patient, but most commonly, this is performed at the time of intended catheter ablation to treat the arrhythmia.

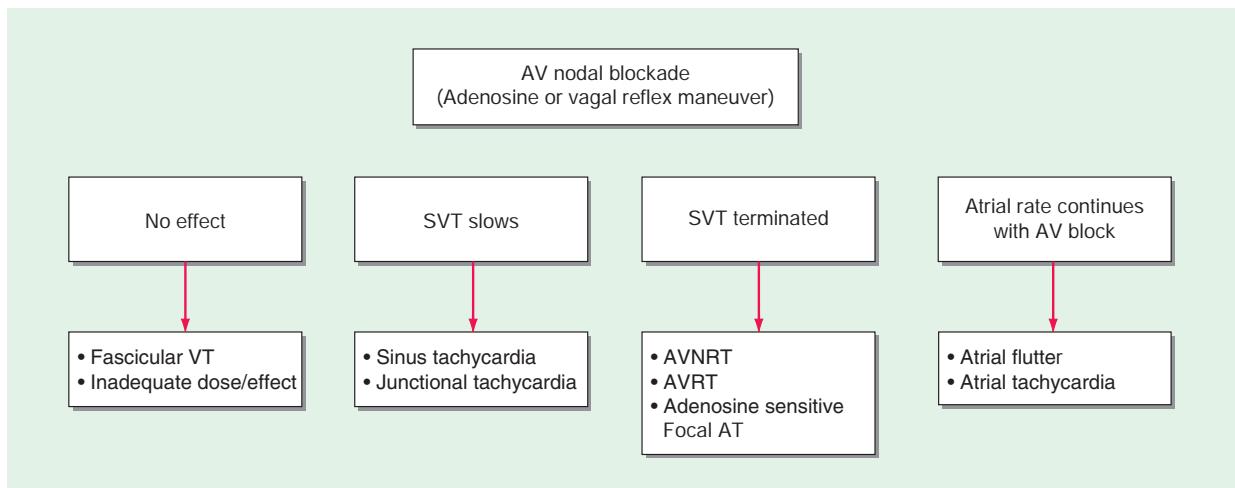


**FIGURE 246-1** Diagnostic possibilities based on the appearance of the 12-lead electrocardiogram (ECG) recorded during an episode of supraventricular tachycardia (SVT). AT, focal atrial tachycardia; AVNRT, atrioventricular (AV) nodal reentry tachycardia; ORT, orthodromic AV reentry tachycardia.

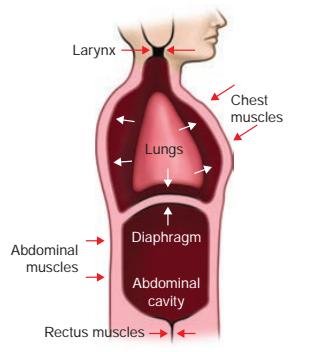
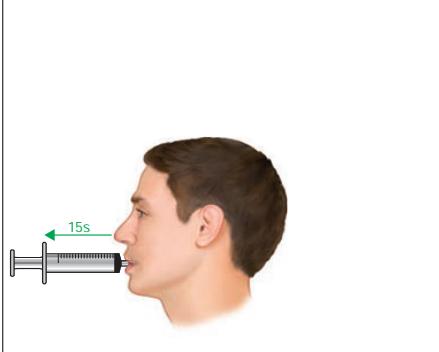
Paroxysmal SVT is most commonly encountered in patients who do not have structural heart disease. Other supraventricular arrhythmias, particularly atrial fibrillation, are often associated with a variety of heart diseases. At initial evaluation, history and examination should assess possible underlying heart disease. Any abnormal findings may warrant further cardiac evaluation.

The most common SVT is sinus tachycardia in response to physiologic stress, such as exercise, but it can also be a manifestation of acute illness. The first step in diagnosis of SVT is to consider the possibility of sinus tachycardia. Therapy is then determined by

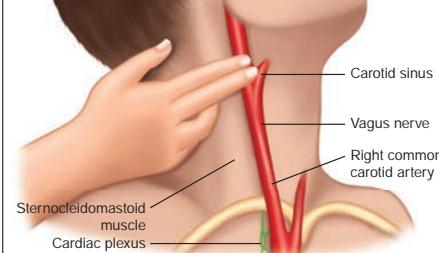
the clinical findings and probable diagnosis. If sinus tachycardia is diagnosed, treatment of the underlying inciting cause is the primary approach. If the arrhythmia is ongoing and is not due to sinus tachycardia, initial assessment determines whether immediate therapy is needed to terminate the arrhythmia or slow the rate. Arrhythmias that cause hypotension, impaired consciousness, angina, or heart failure warrant immediate therapy, guided by the type of arrhythmia. Treatment options for specific types of SVT are discussed in more detail in subsequent chapters and include pharmacologic and procedural interventions.



**FIGURE 246-2** Diagnostic effect of increasing atrioventricular (AV) node blockade with vagal maneuvers, carotid sinus massage, adenosine, verapamil, or beta blockers. AT, focal atrial tachycardia; AVNRT, atrioventricular nodal reentry tachycardia; AVRT, atrioventricular reciprocating tachycardia; SVT, supraventricular tachycardia.

		
Holding breath while bearing down to increase intrathoracic pressure	Breathing hard into a syringe against pressure to increase intrathoracic pressure	Raise legs abruptly to increase venous return

		
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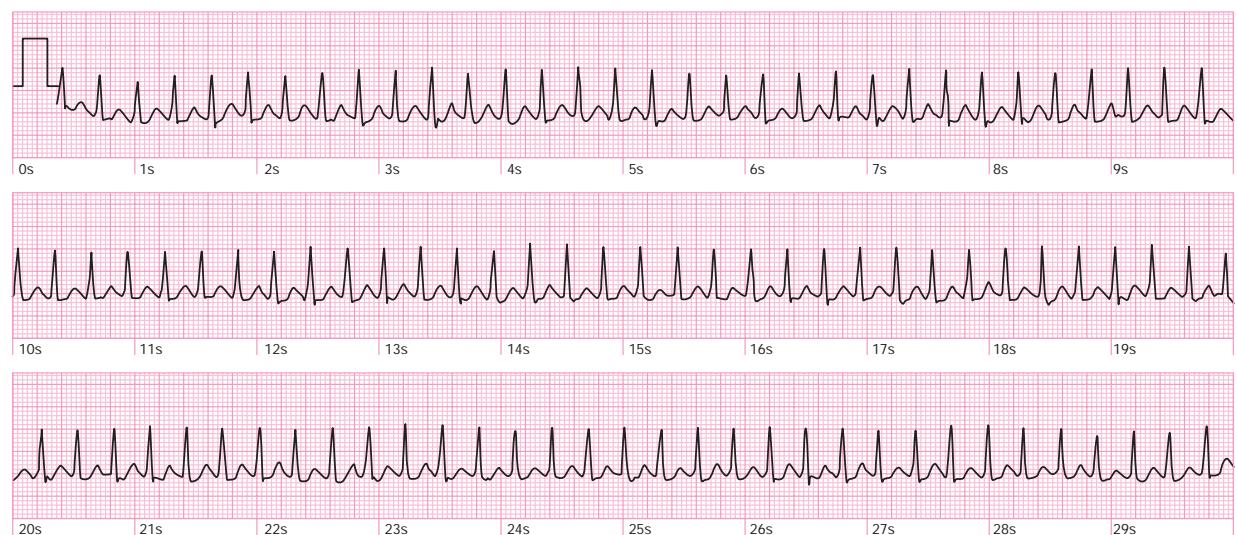
#### Heart Rate Over 120 —♥ 200 BPM Average

This ECG was not checked for AFib because your heart rate was over 120 BPM.

If you repeatedly get this result or you're not feeling well, you should talk to your doctor.

#### Reported Symptoms

- Rapid pounding, or fluttering heartbeat
- Chest tightness or pain
- Fainting



25 mm/s, 10 mm/mV, Lead I, 511Hz, iOS 12.1.4, watchOS 5.1.3, Watch4,2 — The waveform is similar to a Lead I ECG. For more information, see Instructions for Use.

FIGURE 246-3 Narrow-complex tachycardia recorded by a consumer wearable monitor (Apple watch). Afib, atrial fibrillation; ECG, electrocardiogram.

## Acknowledgment

Gregory F. Michaud and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

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# 247

## Physiologic and Nonphysiologic Sinus Tachycardia

William H. Sauer, Paul C. Zei

The sinus node is composed of a group of cells located in the lateral superior aspect of the junction between the right atrium and superior vena cava, within the superior aspect of the thick ridge of muscle known as the crista terminalis where the posterior smooth atrial wall derived from the sinus venosus meets the trabeculated anterior portion of the right atrium. Patients with sinus tachycardia will often seek medical attention with the uncomfortable awareness of their heartbeat as their chief complaint. Often, an arrhythmia is suspected because of the similar constellation of symptoms that accompanies supraventricular and ventricular tachycardia or atrial and ventricular ectopy. However, a careful review of the 12-lead electrocardiogram (ECG) reveals a characteristic P wave originating from the superior and lateral aspect of the right atrium with a positive deflection in leads I, II, and III and

a biphasic morphology in lead V<sub>1</sub>. Sinus P waves are characterized by a frontal plane axis directed inferiorly and leftward, with positive P waves in leads II, III, and aVF; a negative P wave in aVR; and an initially positive biphasic P wave in V<sub>1</sub>. Normal sinus rhythm has a range of rates between 60 and 100 beats/min (Fig. 247-1).

## PHYSIOLOGIC SINUS TACHYCARDIA

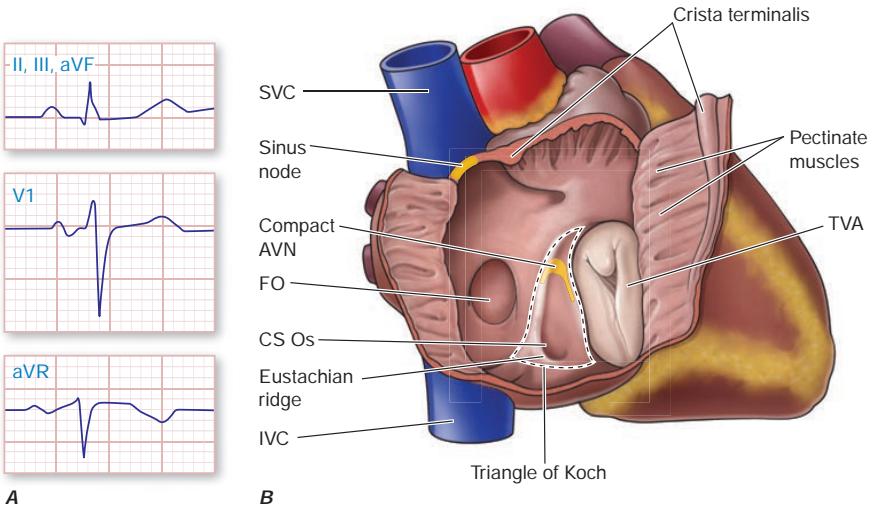
Sinus tachycardia (>100 beats/min) typically occurs in response to sympathetic stimulation and vagal withdrawal, whereby the rate of spontaneous depolarization of the sinus node increases and the focus of earliest activation within the node typically shifts more leftward and closer to the superior septal aspect of the crista terminalis, thus producing taller P waves in the inferior limb leads when compared to normal sinus rhythm. Sinus bradycardia is defined as rates <60 beats/min; however, bradycardia can be normal during sleep and in fit individuals.

Sinus tachycardia is considered physiologic when it is an appropriate response to exercise, stress, or illness. Sinus tachycardia can be difficult to distinguish from focal atrial tachycardia (see below) that originates near the sinus node. A causative factor (e.g., exertion) and a gradual rate increase favor a diagnosis of sinus tachycardia, whereas abrupt tachycardia onset and offset favor atrial tachycardia (Fig. 247-2).

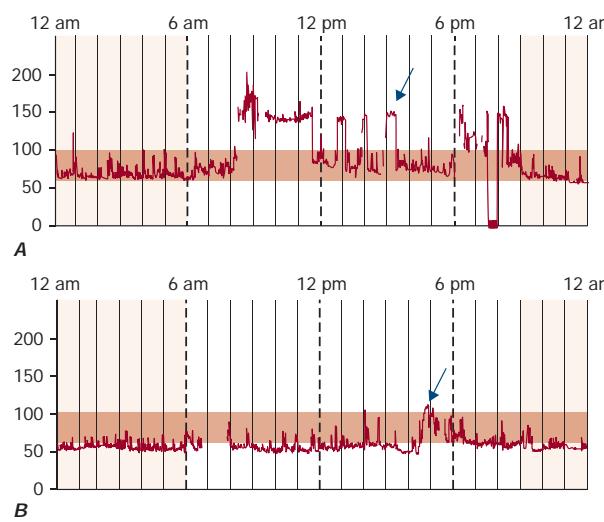
The distinction can be difficult and occasionally requires extended ECG monitoring or invasive electrophysiology study. Treatment for physiologic sinus tachycardia is aimed at the underlying condition, but frequently, no therapy is necessary. Consideration to abnormal thyroid conditions and anemia should be given in patients with sinus tachycardia as these represent reversible causes. In addition, structural and functional cardiovascular abnormalities can present as sinus tachycardia, especially pulmonary embolism, and thus must be ruled out before considering sinus tachycardia as nonphysiologic. Finally, as sinus rate varies widely between individuals, a relatively elevated sinus rate (whether at rest or during exercise) without underlying cause, particularly without symptoms, typical does not warrant treatment (Table 247-1).

## NONPHYSIOLOGIC SINUS TACHYCARDIA

*Inappropriate sinus tachycardia* is an uncommon condition in which the sinus rate increases spontaneously at rest or out of proportion to physiologic stress or exertion and is within a spectrum of ill-defined conditions associated with autonomic dysregulation. The underlying mechanism remains elusive, but it may be related to imbalance between



**FIGURE 247-1** Right atrial anatomy pertinent to normal sinus rhythm and supraventricular tachycardia. **A.** Typical P-wave morphology during normal sinus rhythm based on standard 12-lead electrocardiogram. There is a positive P wave in leads II, III, and aVF and a biphasic, initially positive P wave in aVR. **B.** Right atrial anatomy seen from a right lateral perspective with lateral wall opened to view the septum. AVN, atrioventricular node; CS Os, coronary sinus ostium; FO, fossa ovalis; IVC, inferior vena cava; TVA, tricuspid valve annulus.



**FIGURE 247-2** Outpatient telemetry monitor in a patient with intermittent atrial tachycardia (**A**) and normal physiologic sinus tachycardia (**B**).

sympathetic and parasympathetic inputs to the sinus node, altered membrane automaticity of sinus node cells, or a combination of both. Affected individuals are often women in the third or fourth decade of life. Fatigue, dizziness, and even syncope may accompany palpitations, which can be disabling. Additional symptoms of chest pain, headaches, and gastrointestinal upset are common. Inappropriate sinus tachycardia must be distinguished from appropriate sinus tachycardia and from focal atrial tachycardia arising from a region near the sinus node. The distinction between physiologic sinus tachycardia due to an anxiety disorder and inappropriate sinus tachycardia can be difficult. Therapy is often ineffective or poorly tolerated. Careful titration of beta blockers and/or calcium channel blockers may reduce symptoms. Clonidine and serotonin reuptake inhibitors have also been used. Ivabradine, a drug that blocks the  $I_f$  current that causes spontaneous sinus node depolarization, is approved in the United States for use in heart failure, but it has also been effective in the treatment of inappropriate sinus tachycardia. Catheter ablation of the sinus node to modify and thereby decrease the sinus rate has been performed, but long-term control of symptoms is usually poor and can result in a permanent pacemaker requirement due to resultant symptomatic bradycardia or chronotropic incompetence (Fig. 247-3).

*Postural orthostatic tachycardia syndrome (POTS)* is characterized by symptomatic sinus tachycardia that occurs with postural change

**TABLE 247-1 Common Causes of Sinus Tachycardia**

#### Physiologic Causes

Emotion, physical exercise, sexual intercourse, pain, pregnancy

#### Pathologic Causes

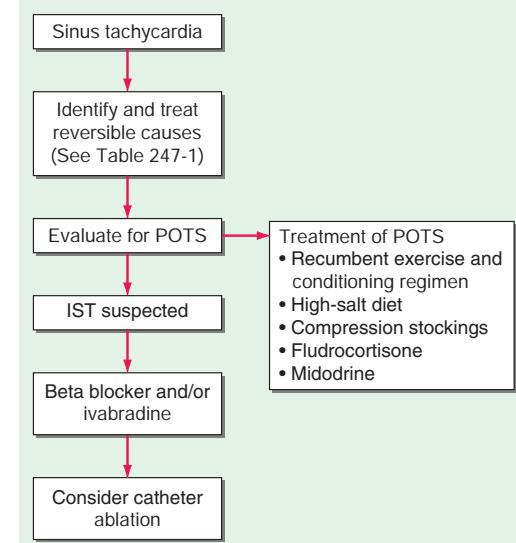
Anxiety, panic attack, anemia, fever, dehydration, infection, malignancies, hyperthyroidism, hypoglycemia, pheochromocytoma, Cushing's disease, diabetes mellitus with evidence of autonomic dysfunction, pulmonary embolus, myocardial infarction, pericarditis, valve disease, decompensated heart failure, shock, alcohol withdrawal

#### Drugs

Epinephrine, norepinephrine, dopamine, dobutamine, atropine,  $\beta$ -adrenergic receptor agonists (salbutamol), methylxanthines, doxorubicin, daunorubicin, beta blocker withdrawal, caffeine, alcohol

#### Illicit Drugs

Amphetamines, cocaine, lysergic acid diethylamide, psilocybin, ecstasy, cocaine



**FIGURE 247-3 Evaluation and treatment of sinus tachycardia.** For the patient who presents with sinus tachycardia, reversible causes of appropriate sinus tachycardia must be excluded and treated as indicated. Otherwise, evaluation for a spectrum of syndromes resulting in inappropriate sinus tachycardia should be undertaken. Potential directed therapies are shown. IST, inappropriate sinus tachycardia; POTS, postural orthostatic tachycardia syndrome.

from a supine position to standing. The sinus rate increases by 30 beats/min or to >120 beats/min within 10 min of standing and in the absence of hypotension. Symptoms are often similar to those in patients with inappropriate sinus tachycardia. POTS is sometimes due to autonomic dysfunction following a viral illness and may resolve spontaneously over 3–12 months. Volume expansion with salt supplementation, oral fludrocortisone, compression stockings, and the  $\alpha$ -agonist midodrine, often in combination, can be helpful. Exercise training has also been shown to improve symptoms and should be a part of a treatment strategy to reduce symptoms. While it is sometimes difficult to differentiate inappropriate sinus tachycardia from POTS, recognition of these distinct clinical syndromes is critical for treatment. Sinus node modification will be ineffective for the treatment of POTS. Likewise, treatment strategies aimed at increasing blood pressure will not be appropriate for inappropriate sinus tachycardia.

#### Acknowledgment

Gregory F. Michaud and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

#### FURTHER READING

Brugada J et al: 2019 ESC guidelines for the management of patients with supraventricular tachycardia. The task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) Developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 41:655, 2020.

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# 248

## Focal Atrial Tachycardia

William H. Sauer, Paul C. Zei

The underlying mechanisms of focal atrial tachycardia (AT) include abnormal automaticity, triggered automaticity, or a small reentry circuit in diseased atrial tissue. The term *focal* is used to differentiate this form of atrial tachycardia from typical and atypical atrial flutter but does not define a mechanism of the arrhythmia. ATs can originate from most regions of the atria, including atrial tissue extending into a pulmonary vein, the coronary sinus, or vena cava. It can be sustained, nonsustained, paroxysmal, or incessant. Focal AT accounts for ~10% of paroxysmal supraventricular tachycardia (PSVTs) in patients referred for catheter ablation. Nonsustained focal AT is commonly observed on ambulatory electrocardiogram (ECG) recordings, and the prevalence increases with age. Treatment is not recommended for asymptomatic nonsustained atrial tachycardia identified on ECG monitoring. However, frequent atrial ectopy and nonsustained AT are often precursors to more significant arrhythmias such as atrial fibrillation and atrial flutter. Nonsustained, frequent atrial ectopy or short bursts of AT may be symptomatic and require therapy similar to that required for focal AT (**Fig. 248-1**).

AT can occur in the absence of structural heart disease or may be associated with any condition that causes atrial fibrosis, including prior catheter ablation. Areas of fibrosis can act as a nidus for abnormal automaticity from damaged cells or microreentry within zones of slow conduction within and on the border of fibrotic areas. Sympathetic stimulation is a promoting factor, and the emergence of AT can be a sign of underlying illness. AT with atrioventricular (AV) block may occur in digitalis toxicity. Symptoms from AT are highly variable but similar to other supraventricular tachycardias (SVTs), and incessant AT can cause tachycardia-induced cardiomyopathy.

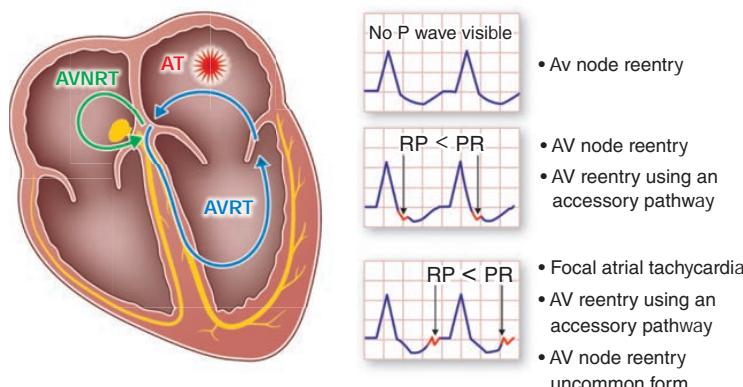
AT typically presents with 1:1 AV conduction or with AV block in a Wenckebach or fixed (e.g., 2:1 or 3:1) pattern. Because it is not dependent on AV nodal conduction, AT will not terminate with AV block, and the atrial rate will not be affected, which distinguishes AT from most AV nodal-dependent SVTs, such as AV nodal reentry and AV reentry using an accessory pathway (see below). A so-called warm-up phase when the atrial activation rate increases after initiation

or a cool-down phase when the rate slows prior to termination also favors AT rather than AV nodal-dependent SVT, as this is a common observation with triggered automaticity. P waves are often discrete, with an intervening isoelectric segment, in contrast to atrial flutter and macroreentrant AT because atrial activation from a focal source occurs through a small portion of the tachycardia cycle (**Fig. 248-2**).

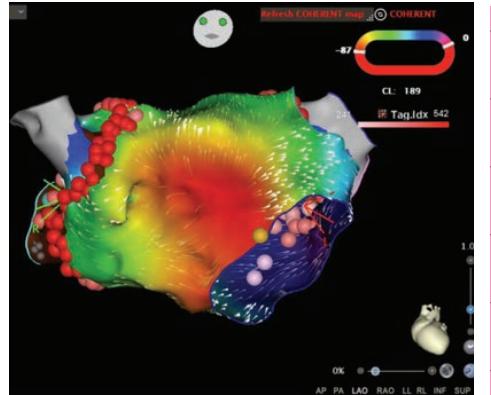
When 1:1 conduction to the ventricles is present, the arrhythmia can resemble sinus tachycardia typically with a P-R interval shorter than the R-P interval, particularly when sympathetic tone results in rapid AV nodal conduction. It can be distinguished from sinus tachycardia by the P-wave morphology, which usually differs from sinus P waves depending on the location of the focus. Focal AT tends to originate in areas of complex atrial anatomy, such as the crista terminalis, valve annuli, atrial septum, and atrial muscle extending along cardiac thoracic veins (superior vena cava, coronary sinus, and pulmonary veins), and the location can often be estimated by the P-wave morphology. AT from the atrial septum will frequently have a narrower P-wave duration than sinus rhythm. AT from the left atrium will usually have a monophasic, positive P wave in lead V<sub>1</sub> and negative P waves in I and aVL, indicating an activation wavefront away from the left atrial free wall. AT that originates from superior atrial locations, such as the superior vena cava or superior pulmonary veins, will be positive in the inferior limb leads II, III, and aVF, whereas AT from a more inferior location, such as the ostium of the coronary sinus, will inscribe negative P waves in these same leads. When the focus is in the superior aspect of the crista terminalis, close to the sinus node, however, the P wave will resemble that of sinus tachycardia. Abrupt onset and offset then favor AT rather than sinus tachycardia. Depending on the atrial rate, the P wave may fall on top of the T wave, or during 2:1 conduction, it may fall coincident with the QRS. Maneuvers that increase AV block, such as carotid sinus massage, Valsalva maneuver, or administration of AV nodal-blocking agents, such as adenosine, are useful to create AV block that will expose the P wave.

Acute management of sudden-onset, sustained AT is the same as for other forms of PSVT, but the response to pharmacologic therapy is variable, likely depending on the mechanism (**Fig. 248-3**).

For AT due to reentry, administration of adenosine or vagal maneuvers may transiently increase AV block without terminating tachycardia. Some ATs terminate with a sufficient dose of adenosine, consistent with triggered activity as the mechanism. Cardioversion can be effective in some but fails in others because of immediate recurrence, suggesting automaticity as the mechanism in these cases.



**FIGURE 248-1** Common mechanisms underlying paroxysmal supraventricular tachycardia along with typical R-P relationships. **A.** Schematic showing a four-chamber view of the heart with atrioventricular (AV) node and specialized conduction tissue (His-Purkinje) in yellow. Atrial tachycardia (AT; red circuit) is confined completely to atrial tissue. Atrioventricular nodal reentry tachycardia (AVNRT; green circuit) uses AV nodal and perinodal atrial tissue. Atrioventricular reentry tachycardia (AVRT; blue circuit) uses atrial and ventricular tissue, accessory pathway between the ventricle and atrium, AV node, and His-Purkinje tissue as part of the reentry circuit. **B.** Typical relation of the P wave to QRS, commonly described as the R-P to P-R relationship, for the different tachycardia mechanisms.



**FIGURE 248-2** Focal atrial tachycardia. In the right panel, a surface 12-lead electrocardiogram shows focal intermittent atrial tachycardia. Note the discrete P waves, with isoelectric segments between, as well as the sinus rhythm. The left panel shows an electroanatomic map of the same focal atrial tachycardia originating from the anterior interatrial septum, as viewed in an anterior-posterior (AP) view of the left atrium obtained during electrophysiology study and ablation. The colors represent the timing of local electrical activation during each tachycardia atrial activation, showing a focal early (red) site. Additional markers of white “flecks” represent conduction direction, demonstrating activation of the atrium dispersing from this focal site. Of note, the pink and red dots represent ablation lesions, in this case, for pulmonary vein isolation. (Adapted from J Brugada et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J 41:655, 2020.)

Beta blockers and calcium channel blockers may slow the ventricular rate by increasing AV block, which can improve tolerance of the arrhythmias, but large doses are sometimes required. Potential precipitating factors and intercurrent illness should be sought and corrected. Underlying heart disease should be considered and excluded.

For patients with recurrent episodes, beta blockers, calcium channel blockers such as diltiazem or verapamil, and antiarrhythmic drugs such as flecainide, propafenone, disopyramide, sotalol, and amiodarone can be effective, but potential toxicities and adverse effects often warrant avoidance of long-term use.

Catheter ablation targeting the AT focus is effective in >80% of patients and is recommended for recurrent symptomatic AT when drugs fail or are not desired or for incessant AT causing tachycardia-induced cardiomyopathy. Although AT is often a precursor to atrial

fibrillation or atrial flutter, the associated risk for stroke and hence indications for long-term anticoagulation are unclear but not considered equivalent.

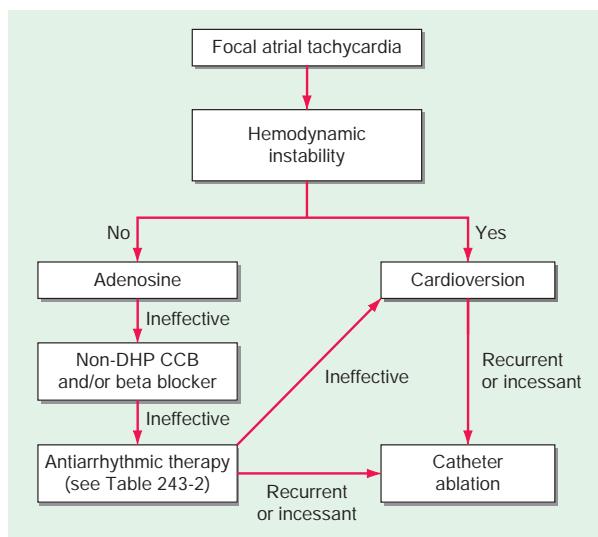
#### Acknowledgment

Gregory F. Michaud and William G. Stevenson contributed to this chapter in the 20th edition and some material from that chapter has been retained here.

#### FURTHER READING

Brugada J et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the Management of Patients with Supraventricular Tachycardia of the European Society of Cardiology (ESC) developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 41:655, 2020.

Callans DJ: *Josephson's Clinical Cardiac Electrophysiology: Techniques and Interpretations*, 6th ed. Philadelphia, Wolters Kluwer, 2021.



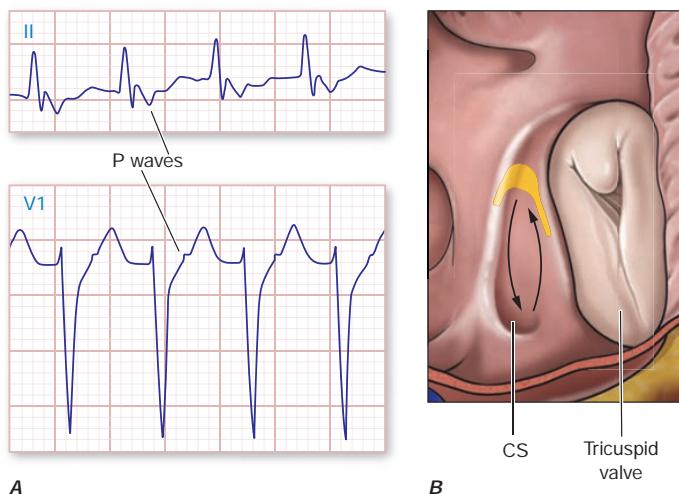
**FIGURE 248-3** Clinical approach and treatment algorithm for management of focal atrial tachycardia. CCB, calcium channel blocker; DHP, dihydropyridine. (Adapted from J Brugada et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) [published correction appears in Eur Heart J. 2020 Nov 21;41(44):4258]. Eur Heart J 41:655, 2020.)

## 249 Paroxysmal Supraventricular Tachycardias

William H. Sauer, Paul C. Zei



In this chapter, sustained supraventricular tachycardias (SVTs) dependent on the atrioventricular (AV) node are discussed. These include AV nodal reentry tachycardia (AVNRT), junctional tachycardia, AV reciprocating tachycardia (AVRT) utilizing an accessory pathway, and a group of additional various SVTs that involve an accessory pathway, termed *preexcited tachycardias*. The term *SVT* encompasses a broad group of tachyarrhythmias based on anatomic origin and technically includes sinus tachycardia, atrial tachycardia (AT), atrial flutter, and atrial fibrillation; however, for the purposes of describing an organized approach to diagnosis and treatment of SVT, a separate discussion for these non-AV nodal-dependent SVTs are discussed elsewhere.



**FIGURE 249-1** Atrioventricular (AV) node reentry. **A.** Leads II and V<sub>1</sub> are shown. P waves are visible at the end of the QRS complex and are negative in lead II and may give the impression of S waves in the inferior limb leads II, III, and aVF and an R' in lead V<sub>1</sub>. **B.** Stylized version of the AV nodal reentry circuit within the triangle of Koch (see Fig. 247-1) that involves AV node and its extensions along with perinodal atrial tissue. CS, coronary sinus.

## ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA

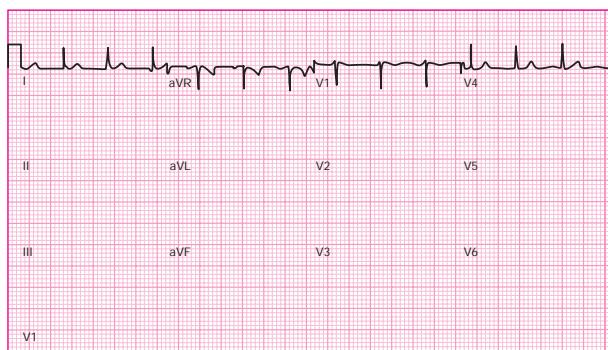
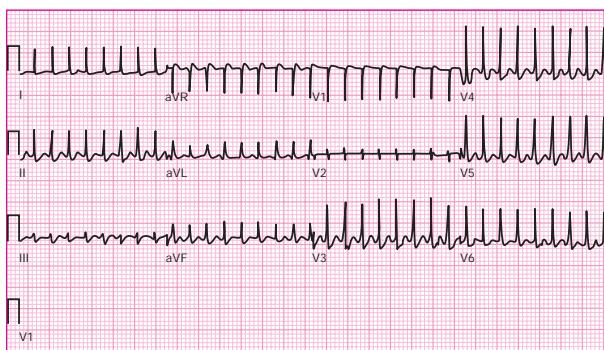
AVNRT is the most common form of paroxysmal supraventricular tachycardia (PSVT), representing ~60% of cases referred for catheter ablation. It most commonly manifests in the second to fourth decades of life, often in women. It is often well tolerated, but rapid tachycardia, particularly in the elderly, may cause angina, pulmonary edema, hypotension, or syncope. It is not usually associated with structural heart disease. In patients without associated heart disease, AVNRT is not a life-threatening arrhythmia; however, it may cause significant symptoms.

The mechanism is reentry involving the AV node and the perinodal atrium, made possible by the existence of multiple pathways for conduction from the atrium into the AV node that are capable of conduction in two directions (Fig. 249-1).

Most forms of AVNRT utilize a slowly conducting AV nodal pathway (right inferior extension) that extends from the compact AV node near the His bundle, inferiorly along the tricuspid valve annulus to the floor of the coronary sinus. The reentry wavefront propagates up this slowly conducting pathway to the compact AV node and then exits from the fast pathway at the top of the AV node. The path back to the slow pathway probably involves the left atrial septum, which has connections to the coronary sinus musculature. More unusual forms of AVNRT utilize a left inferior extension that connects to the compact AV node through the roof of the coronary sinus or, in extremely rare

cases, directly from the mitral valve annulus avoiding the coronary sinus musculature altogether. In typical forms, the conduction time from the compact AV node region to the atrium is similar to that from the compact node to the His bundle and ventricles, such that atrial activation occurs at about the same time as ventricular activation. The P wave is therefore inscribed during, slightly before, or slightly after the QRS and can be difficult to discern. Often the P wave is seen at the end of the QRS complex as a pseudo-r' in lead V<sub>1</sub> and pseudo-S waves in leads II, III, and aVF (Fig. 249-2).

More unusual forms of AVNRT have P waves falling later, anywhere between QRS complexes, in which case, an inverted P wave is seen in the inferior limb leads with the inverted P wave seen in the subsequent T wave. The rate can vary with sympathetic tone through its effect on the conduction time of AV nodal tissues. Simultaneous atrial and ventricular contraction results in atrial contraction against a closed tricuspid valve, producing a cannon A wave visible in the jugular venous pulse often perceived as a fluttering sensation in the neck. Elevated venous pressures may also lead to release of natriuretic peptides that cause posttachycardia diuresis. In contrast to ATs, maneuvers or medications that produce AV nodal block terminate the arrhythmia. Acute treatment is the same as for other forms of PSVT (discussed below). Whether ongoing therapy is warranted depends on the severity of symptoms and frequency of episodes. Reassurance and instruction as to how to perform the Valsalva maneuver or other vagal nerve stimulating maneuvers to terminate episodes are sufficient for many patients.



**FIGURE 249-2** Atrioventricular nodal reentry tachycardia with retrograde P waves before and after adenosine termination.

Administration of an oral beta blocker, verapamil, or diltiazem at the onset of an episode can be used to facilitate termination. Chronic therapy with these medications or flecainide is an option if prophylactic therapy is needed. Catheter ablation of the slow AV nodal pathway is recommended for patients with recurrent or severe episodes or when drug therapy is ineffective, not tolerated, or not desired by the patient. Catheter ablation is curative in >95% of patients. The major risk is AV block requiring permanent pacemaker implantation, which occurs in <1% of patients.

## JUNCTIONAL TACHYCARDIA

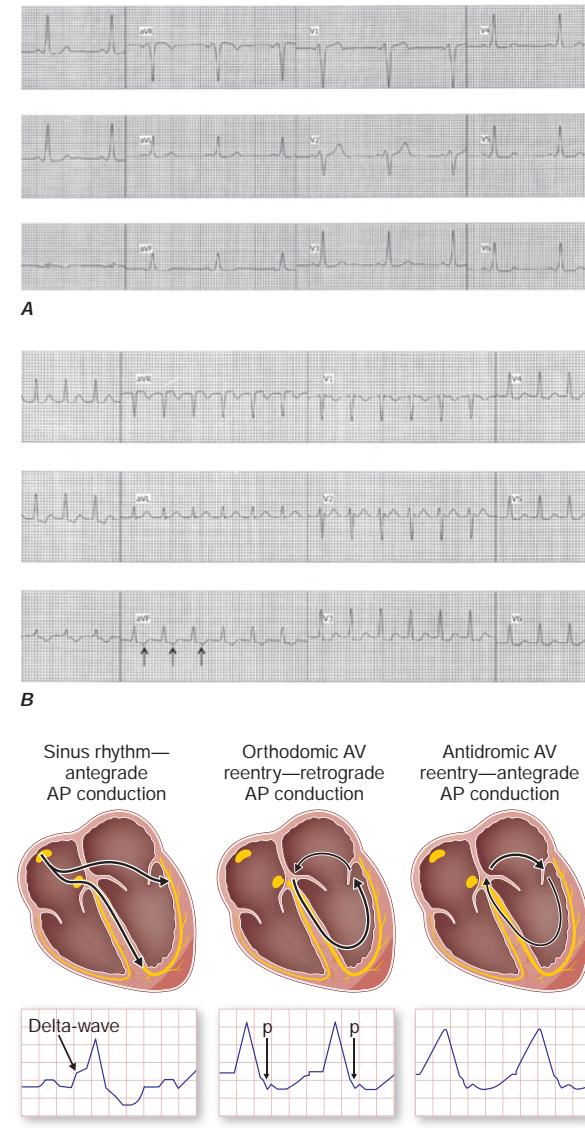
Junctional ectopic tachycardia (JET) is due to automaticity within the AV node. It is rare in adults and more frequently encountered as an incessant tachycardia in children, often in the perioperative period of surgery for congenital heart disease. It presents as a narrow QRS tachycardia, often with ventriculoatrial (VA) block, such that AV dissociation is present. JET can occur as a manifestation of increased adrenergic tone and may be seen after administration of isoproterenol, particularly after catheter ablation in the perinodal region. It may also occur for a short period of time after ablation for AVNRT. *Accelerated junctional rhythm* is a junctional automatic rhythm between 50 and 100 beats/min. Initiation may occur with gradual acceleration in rate, suggesting an automatic focus, or after a premature ventricular contraction, suggesting a focus of triggered automaticity. VA conduction is usually present, with P-wave morphology and timing such that it resembles AVNRT at a slow rate. It can be related to increased sympathetic tone and may produce palpitations. It usually does not require specific therapy.

## ACCESSORY PATHWAYS AND THE WOLFF-PARKINSON-WHITE SYNDROME

Accessory pathways (APs) occur in 1 in 1500–2000 people and are associated with a variety of arrhythmias including narrow-complex PSVT, wide-complex tachycardias, and, rarely, sudden death. Most patients have structurally normal hearts, but APs are associated with Ebstein's anomaly of the tricuspid valve and forms of hypertrophic cardiomyopathy including *PRKAG2* mutations, Danon's disease, and Fabry's disease (Fig. 249-3).

APs are abnormal connections that allow conduction between the atrium and ventricle across the AV ring. They are present from birth and are due to failure of complete partitioning of atrium and ventricle by the fibrous AV rings. They occur across either an AV valve annulus or the septum, most frequently between the left atrium and free wall of the left ventricle, followed by posteroseptal, right free wall, and anteroseptal locations. If the impulse from the sinus node conducts through the AP to the ventricle (antegrade) before the impulse conducts through the AV node and His bundle, then the ventricles are preexcited during sinus rhythm, and the electrocardiogram (ECG) shows a short P-R interval (<0.12 s), slurred initial portion of the QRS (delta wave), and prolonged QRS duration produced by slow conduction through direct activation of ventricular myocardium over the AP. The morphology of the QRS and delta wave is determined by the AP location and the degree of fusion between the excitation wavefronts from conduction over the AV node and conduction over the AP (Fig. 249-4).

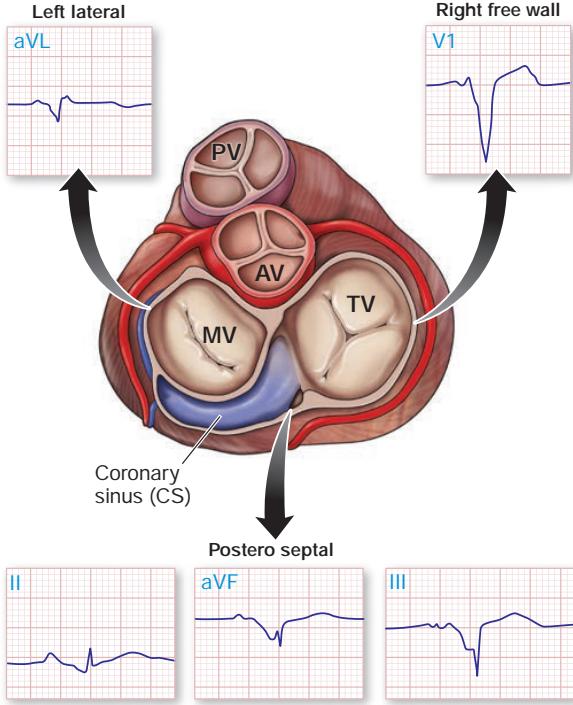
Right-sided pathways preexcite the right ventricle, producing a left bundle branch block-like configuration in lead V<sub>1</sub>, and often create marked preexcitation because of relatively close proximity of the AP to the sinus node (Fig. 249-4). Left-sided pathways preexcite the left ventricle and may produce a right bundle branch-like configuration in lead V<sub>1</sub>, and a negative delta wave in aVL, indicating initial depolarization of the lateral portion of the left ventricle that can mimic Q waves of lateral wall infarction (Fig. 249-4). Because of the relatively large distance between the sinus node and left free wall APs, preexcitation may be minimal or absent on 12-lead ECG. Preexcitation due to an AP at the diaphragmatic surface of the heart, typically in the paraseptal region, produces delta waves that are negative in leads III and aVF,



**FIGURE 249-3** Wolff-Parkinson-White (WPW) syndrome. **A.** A 12-lead electrocardiogram in sinus rhythm (SR) of a patient with WPW demonstrating short P-R interval, delta waves, and widened QRS complex. This patient had an anteroseptal location of the accessory pathway (AP). **B.** Orthodromic atrioventricular (AV) reentry in a patient with WPW syndrome using a posteroseptal AP. Note the P waves in the ST segment (arrows) seen in lead III and normal appearance of QRS complex. **C.** Three most common rhythms associated with WPW syndrome: sinus rhythm demonstrating antegrade conduction over the AP and AV node; orthodromic AV reentry tachycardia (AVRT) using retrograde conduction over the AP and antegrade conduction over the AV node; and antidromic AVRT using retrograde conduction over the AV node and antegrade conduction over the AP.

mimicking the Q waves of inferior wall infarction (Fig. 249-4). Preexcitation can be intermittent and disappear during exercise as conduction over the AV node accelerates and may take over ventricular activation completely.

Wolff-Parkinson-White (WPW) syndrome is defined as a preexcited QRS during sinus rhythm and episodes of PSVT. There are a number of variations of APs that may not cause preexcitation and/or arrhythmias. Concealed APs allow only retrograde conduction, from ventricle to atrium, so no preexcitation is present during sinus rhythm, but SVT can occur. Other unusual forms of APs occur. Fasciculoventricular



**FIGURE 249-4** Potential locations for accessory pathways in patients with Wolff-Parkinson-White syndrome and typical QRS appearance of delta waves that can mimic underlying structural heart disease such as myocardial infarction or bundle branch block. AV, aortic valve; MV, mitral valve; PV, pulmonary valve; TV, tricuspid valve.

connections between the His bundle and ventricular septum produce preexcitation but do not cause arrhythmia, probably because the circuit is too short to promote reentry. Atriofascicular pathways, also known as Mahaim fibers, probably represent a duplicate AV node and His-Purkinje system that connect the right atrium to fascicles of the right bundle branch and produce a wide-complex tachycardia having a left bundle branch block configuration.

### ATRIOVENTRICULAR RECIPROCATING TACHYCARDIA

The most common tachycardia caused by an AP is the PSVT designated *orthodromic AV reciprocating tachycardia*. The circulating reentry waveform propagates from the atrium anterogradely over the AV node and His-Purkinje system to the ventricles and then reenters the atria via retrograde conduction over the AP. The QRS is narrow or may have typical right or left bundle branch block, but without preexcitation during tachycardia. Because excitation through the AV node and AP are necessary, AV or VA block results in tachycardia termination. During sinus rhythm, preexcitation is seen if the pathway also allows anterograde conduction. Most commonly, during tachycardia, the R-P interval is shorter than the P-R interval and can resemble AVNRT. Unlike typical AVNRT, P waves always follow the QRS and are never simultaneous with a narrow QRS complex because the ventricles must be activated before the reentry waveform reaches the AP and conducts back to the atrium. The morphology of the P wave is determined by the pathway location, but it can be difficult to assess because it is usually inscribed during the ST segment. The P wave in posteroseptal APs is negative in leads II, III, and aVF, similar to that of AV nodal reentry, but P-wave morphology differs from AV nodal reentry for pathways in other locations. Occasionally, an AP conducts extremely slowly in the retrograde direction, resulting in tachycardia with a long R-P

interval, similar to most ATs. These pathways are usually located in the septal region and have negative P waves in leads II, III, and aVF. Slow AP conduction facilitates reentry, often leading to nearly incessant tachycardia, known as *permanent junctional reciprocating tachycardia* (PJRT). Tachycardia-induced cardiomyopathy can occur. Without an invasive electrophysiology study, it may be difficult to distinguish this form of orthodromic AV reentry from atypical AV nodal reentry or AT.

### PREEXCITED TACHYCARDIAS

Preexcited tachycardia occurs when the ventricles are activated by antegrade conduction over the AP. The most common mechanism is *antidromic AV reciprocating tachycardia* in which activation propagates from atrium to ventricle via the AP and then conducts retrogradely to the atria via the His-Purkinje system and the AV node (or rarely a second AP). The wide QRS complex is produced entirely via ventricular excitation over the AP because there is no contribution of ventricular activation over more rapidly conducting specialized His-Purkinje fibers. This tachycardia is often indistinguishable from monomorphic ventricular tachycardia. The presence of preexcitation in sinus rhythm suggests the diagnosis.

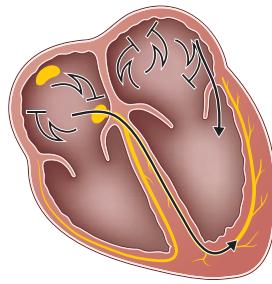
Preexcited tachycardia also occurs if an AP allows antegrade conduction to the ventricles during AT, atrial flutter, atrial fibrillation (AF), or AV nodal reentry, otherwise known as bystander AP conduction. AF and atrial flutter are potentially life-threatening if the AP allows very rapid repetitive conduction (Fig. 249-5).

Approximately 25% of APs causing preexcitation allow minimum R-to-R intervals of <250 ms during AF and are associated with a higher risk of inducing ventricular fibrillation and sudden death. Preexcited AF presents as a wide-complex, very irregular rhythm. During AF, the ventricular rate is determined by the conduction properties of the AP and AV node. The QRS complex can appear quite bizarre and change on a beat-to-beat basis due to the variability in the degree of fusion from activation over the AV node and AP, or all beats may be due to conduction over the AP. Ventricular activation from the Purkinje system may depolarize the ventricular aspect of the AP and prevent atrial wavefront conduction over the AP. Slowing AV nodal conduction without slowing AP conduction can thereby facilitate AP conduction and dangerously accelerate the ventricular rate. Administration of AV nodal-blocking agents, including oral or intravenous verapamil, diltiazem, beta blockers, intravenous adenosine, and intravenous amiodarone, is contraindicated during preexcited AF. Rapid preexcited tachycardia should be treated with electrical cardioversion or intravenous procainamide or ibutilide, which may terminate the arrhythmia or slow the ventricular rate.

### MANAGEMENT OF PATIENTS WITH ACCESSORY PATHWAYS

Acute management of orthodromic AV reentry is discussed below for PSVT. Patients with WPW syndrome may have wide-complex tachycardia due to antidromic AV reentry, orthodromic AV with bundle branch block, or a preexcited tachycardia, and treatment depends on the underlying rhythm. Initial patient evaluation should include assessment for aggravating factors, including intercurrent illness and factors that increase sympathetic tone. Examination should focus on excluding underlying heart disease. An echocardiogram is reasonable to exclude Ebstein's anomaly and forms of hypertrophic cardiomyopathy that can be associated with APs.

Patients with preexcitation who have symptoms of arrhythmia are at risk for developing AF and sudden death if they have an AP that allows rapid antegrade conduction. The risk of cardiac arrest is in the range of 2 per 1000 patients in adults but is likely greater in children. An invasive electrophysiology study is recommended to assess whether the pathway can support dangerously rapid heart rates if AF were to occur, and it is usually combined with potentially curative catheter ablation. Catheter ablation is warranted for recurrent arrhythmias



**FIGURE 249-5** Preexcited atrial fibrillation (AF) due to conduction over a left free wall accessory pathway (AP). The electrocardiogram shows rapid irregular QRS complexes that represent fusion between conduction over the atrioventricular node and left free wall AP. Shortest R-R intervals between preexcited QRS complexes of <250 ms, as in this case, indicate a risk of sudden death with this arrhythmia.

when drugs are ineffective, not tolerated, or not desired by the patient. Efficacy is in the range of 95% depending on the location of the AP. Serious complications occur in <3% of patients but can include AV block, cardiac tamponade, thromboembolism, coronary artery injury, and vascular access complications. Procedure mortality is <1 in 1000 patients. Ambulatory monitoring or exercise testing is often used to gain reassurance that the AP is not high risk, evaluating for abrupt loss of conduction (preexcitation) at physiologic heart rates consistent with a low-risk pathway, but this is not completely reliable. Gradual loss of AP conduction with increased sympathetic tone does not reliably indicate low risk since this can occur as AV nodal conduction time shortens, and therefore, the possibility of rapid antegrade AP conduction is not excluded definitively.

For patients with concealed APs or known low-risk APs causing orthodromic AVRT, chronic therapy is guided by symptoms and frequency of events. Vagal maneuvers may terminate episodes, as may a dose of beta blocker, verapamil, or diltiazem taken at the onset of an episode. Chronic therapy with these agents or flecainide can reduce the frequency of episodes in some patients.

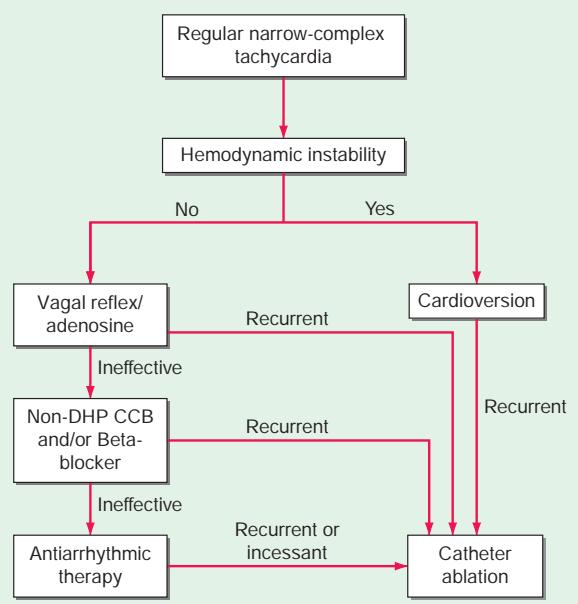
Adults who have preexcitation but no arrhythmia symptoms have a risk of sudden death estimated to be 1 per 1000 patient-years. Electrophysiology study is usually advised for people in occupations for which an arrhythmia occurrence would place them or others at risk, such as police, military, and pilots, or for individuals who desire

evaluation for risk. Routine follow-up without therapy is reasonable in others. Children are at greater risk of sudden death, ~2 per 1000 patient-years.

## TREATMENT

### Paroxysmal Supraventricular Tachycardia

Acute management of narrow QRS PSVT is guided by the clinical presentation. Continuous ECG monitoring should be implemented, and a 12-lead ECG should always be obtained when possible, since this may be useful in determining the mechanism. In the presence of hypotension with unconsciousness or respiratory distress, QRS-synchronous direct current cardioversion is warranted, but this is rarely needed, because intravenous adenosine works promptly in most situations (see below). For stable individuals, initial therapy takes advantage of the fact that most PSVTs are dependent on AV nodal conduction (AV nodal reentry or orthodromic AV reentry) and, therefore, likely to respond to sympatholytic and vagotonic maneuvers and drugs. As these are administered, the ECG should be continuously recorded because the response can establish the diagnosis. AV block with only transient slowing of tachycardia may expose ongoing P waves, indicating AT or atrial flutter as the mechanism (**Fig. 249-6**).



**FIGURE 249-6** Treatment algorithm for patients presenting with hemodynamically stable paroxysmal supraventricular tachycardia. CCB, calcium channel blocker; DHP, dihydropyridine.

Carotid sinus massage is reasonable provided the risk of carotid vascular disease is low, as indicated by absence of carotid bruits and no prior history of stroke. A Valsalva maneuver should be attempted in cooperative individuals, and if effective, the patient can be taught to perform this maneuver as needed. If vagal maneuvers fail or cannot be performed, intravenous adenosine will terminate the vast majority of PSVT episodes by transiently blocking conduction in the AV node. Adenosine may produce transient chest pain, dyspnea, and anxiety. It is contraindicated in patients with prior cardiac transplantation due to potential hypersensitivity due to surgical sympathetic denervation. It can theoretically aggravate bronchospasm. Adenosine precipitates AF, which is usually brief, in up to 15% of patients, so it should be used cautiously in patients with WPW syndrome in whom AF may produce hemodynamic instability. Intravenous beta blockers and calcium channel blockers (verapamil or diltiazem) are also effective but may cause hypotension before and after arrhythmia termination and have a longer duration of action. These agents can also be given orally and can be taken by the patient on an as-needed basis to slow ventricular rate and facilitate termination by Valsalva maneuver.

The differential diagnosis of wide-complex tachycardia includes ventricular tachycardia, PSVT with bundle branch block aberrancy, and preexcited tachycardia (see above). In general, these should be managed as ventricular tachycardia until proven otherwise. If the tachycardia is regular and the patient is stable, a trial of intravenous adenosine is reasonable. Very irregular wide-complex tachycardia is most likely preexcited AF or flutter (see above) and should be managed with cardioversion, intravenous procainamide, or ibutilide. If the diagnosis of PSVT with aberrancy is unequivocal, as may be the case in patients with prior episodes, treatment for PSVT with vagal maneuvers and adenosine is reasonable. In all cases, continuous ECG monitoring should be implemented, and emergency cardioversion and defibrillation should be available.

#### Acknowledgment

Gregory F. Michaud and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

#### FURTHER READING

Brugada J et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) Developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 41:655, 2020.

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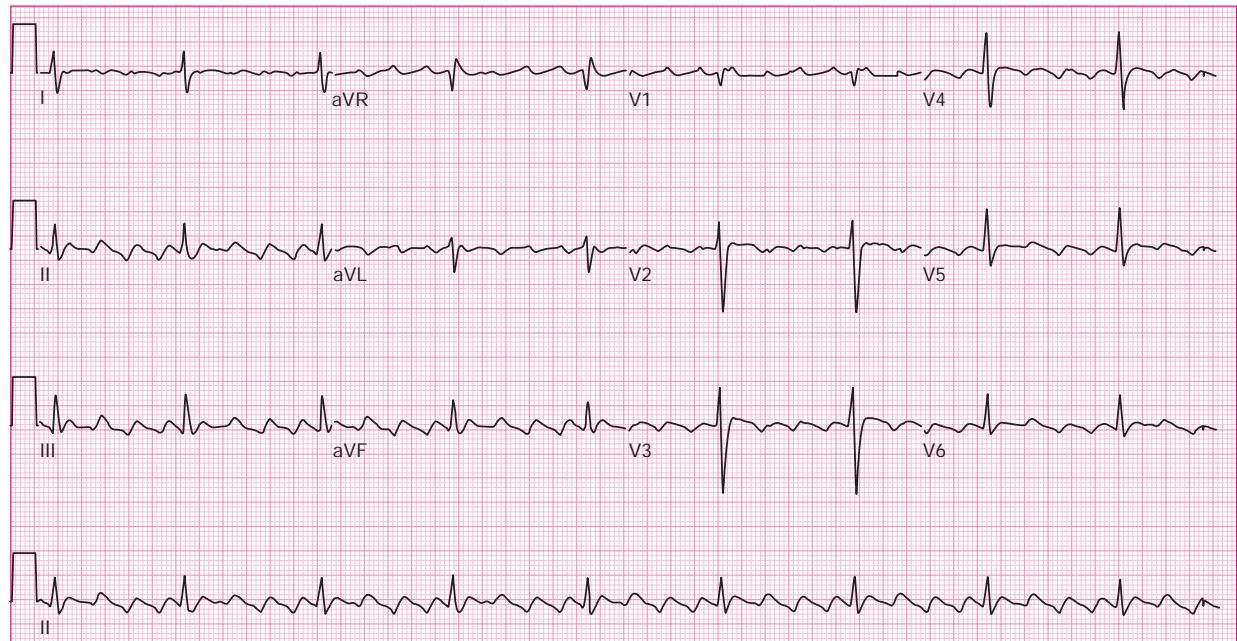
## Common Atrial Flutter and Macroreentrant and Multifocal Atrial Tachycardias

William H. Sauer, Paul C. Zei

**Macroreentrant atrial tachycardia** is due to a large anatomic reentry circuit, often associated with areas of scar in the atria. **Common or typical right atrial flutter** is due to a circuit pathway around the tricuspid valve annulus, bounded anteriorly by the annulus and posteriorly by functional conduction block in the crista terminalis. The waveform passes between the inferior vena cava and the tricuspid valve annulus, known as the sub-Eustachian or cavotricuspid isthmus, where it is susceptible to interruption by catheter ablation. Thus, common atrial flutter is also known as *cavotricuspid isthmus-dependent atrial flutter*. This circuit most commonly revolves in a counterclockwise direction (as viewed looking toward the tricuspid annulus from the ventricular apex), which produces the characteristic negative sawtooth flutter waves in leads II, III, and aVF and positive P waves in lead V<sub>1</sub>. When the direction is reversed, clockwise rotation produces the opposite P-wave vector in those leads. The atrial rate is typically 240–300 beats/min but may be slower in the presence of atrial disease or antiarrhythmic drugs. It often conducts to the ventricles with 2:1 AV block, creating a regular tachycardia at 130–150 beats/min, with P waves that may be difficult to discern from the T wave. Maneuvers that increase AV nodal block will typically expose flutter waves, allowing diagnosis. AV nodal disease or AV nodal-blocking agents may render the conduction ratio between atrium and ventricle higher, resulting in more obvious flutter waves (**Fig. 250-1**).

Common right atrial flutter often occurs in association with atrial fibrillation and often with atrial scar from senescence or prior cardiac surgery. Right-sided cardiac or pulmonary vascular disease may also predispose to common right atrial flutter. Some patients with atrial fibrillation treated with an antiarrhythmic drug, particularly flecainide, propafenone, or amiodarone, will present with atrial flutter rather than fibrillation, since these agents slow atrial conduction velocity and can promote reentry, in addition to suppressing ectopic atrial triggers.

Macroreentrant atrial tachycardias (ATs) that are not dependent on conduction through the cavotricuspid isthmus are referred to as **atypical atrial flutters**. They can occur in either atrium and are almost universally associated with areas of atrial scar. Right atrial atypical flutter often occurs after cardiac surgery if an atriotomy is performed in the right atrium as part of the surgery. Left atrial flutter and perimitral left atrial flutter are commonly seen after extensive left atrial ablation for atrial fibrillation or atrial surgery. The clinical presentation is similar to common atrial flutter but with different P-wave morphologies. They can be difficult to distinguish from focal AT, and in most cases, the mechanism can only be confirmed by an electrophysiology study (**Fig. 250-2**).



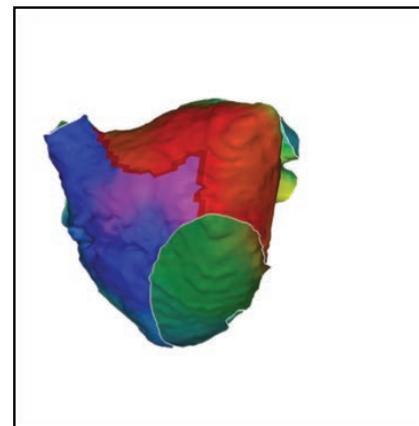
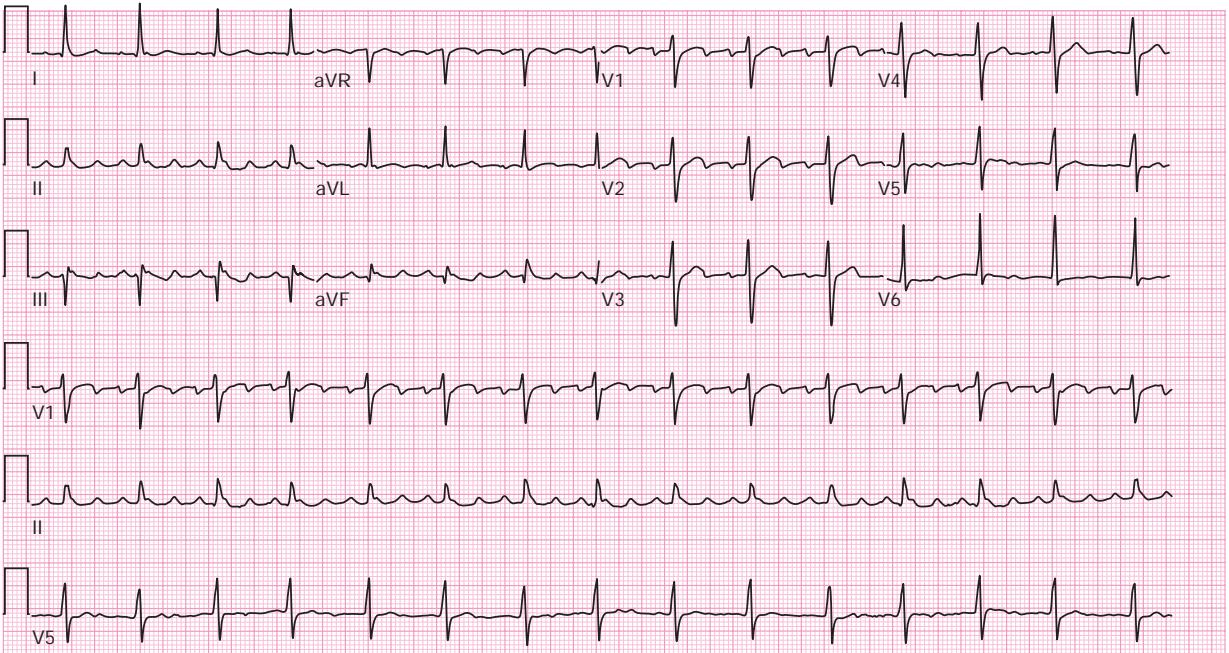
**FIGURE 250-1** Electrocardiogram (ECG) and electroanatomic map of typical flutter. In the *upper panel*, a 12-lead ECG of typical atrial flutter is shown. Note the sawtooth pattern of atrial activation, with negative flutter (F) waves, as well as 4:1 atrioventricular (AV) conduction during flutter. In the *lower panel*, counterclockwise (more common, left portion of the panel) and clockwise typical, cavotricuspid isthmus (CTI)-dependent atrial flutter is shown on electroanatomic maps. These maps of the electrical activation pattern during flutter were obtained during electrophysiologic study and catheter ablation, viewed from the vantage point of the right ventricle through the tricuspid valve. Colors refer to local activation time, demonstrating a complete timing of the electrical circuit around the peritricuspid RA.

## ATRIAL FLUTTER

Initial management of atrial flutter is similar to that for atrial fibrillation, discussed in more detail in [Chap. 251](#). Electrical cardioversion is warranted for hemodynamic instability or severe symptoms. Otherwise, rate control can be achieved with administration of AV nodal-blocking agents, but this is often more difficult than for atrial fibrillation. The risk of thromboembolic events is thought to be similar to that associated with atrial fibrillation, and hence, management of stroke risk is similar to the approach for atrial fibrillation. Anticoagulation is warranted prior to conversion for episodes >48 h in duration

and chronically for patients at increased risk of thromboembolic stroke based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system (see [Chap. 251](#) and [Table 251-2](#)).

For a first episode of atrial flutter, conversion to sinus rhythm without subsequent chronic use of an antiarrhythmic drug therapy is reasonable. For recurrent episodes, antiarrhythmic drug therapy with sotalol, dofetilide, disopyramide, and amiodarone may be considered, but >70% of patients experience recurrences. For recurrent episodes of common atrial flutter, catheter ablation of the cavotricuspid isthmus abolishes the arrhythmia in >95% of patients with a low risk of



**FIGURE 250-2** Electrocardiogram (ECG) and electroanatomic map of mitral annular flutter after pulmonary vein isolation. In the *upper panel*, a 12-lead surface ECG demonstrates atypical atrial flutter. Note the flutter wave morphology with positively deflected flutter waves in the inferior leads (II, III, aVF), with 3:1 atrioventricular (AV) conduction. In the *lower panel*, the corresponding electroanatomic map obtained during electrophysiologic study and catheter ablation is shown. This panel shows the left atrium (LA) from the vantage point of the left ventricle, through the mitral valve. Colors refer to local activation time, demonstrating a complete timing of the electrical circuit around the peri-mitral valve LA tissues. (Adapted from Fig. 245-1 in the 20th edition of Harrison's Principles of Internal Medicine.)

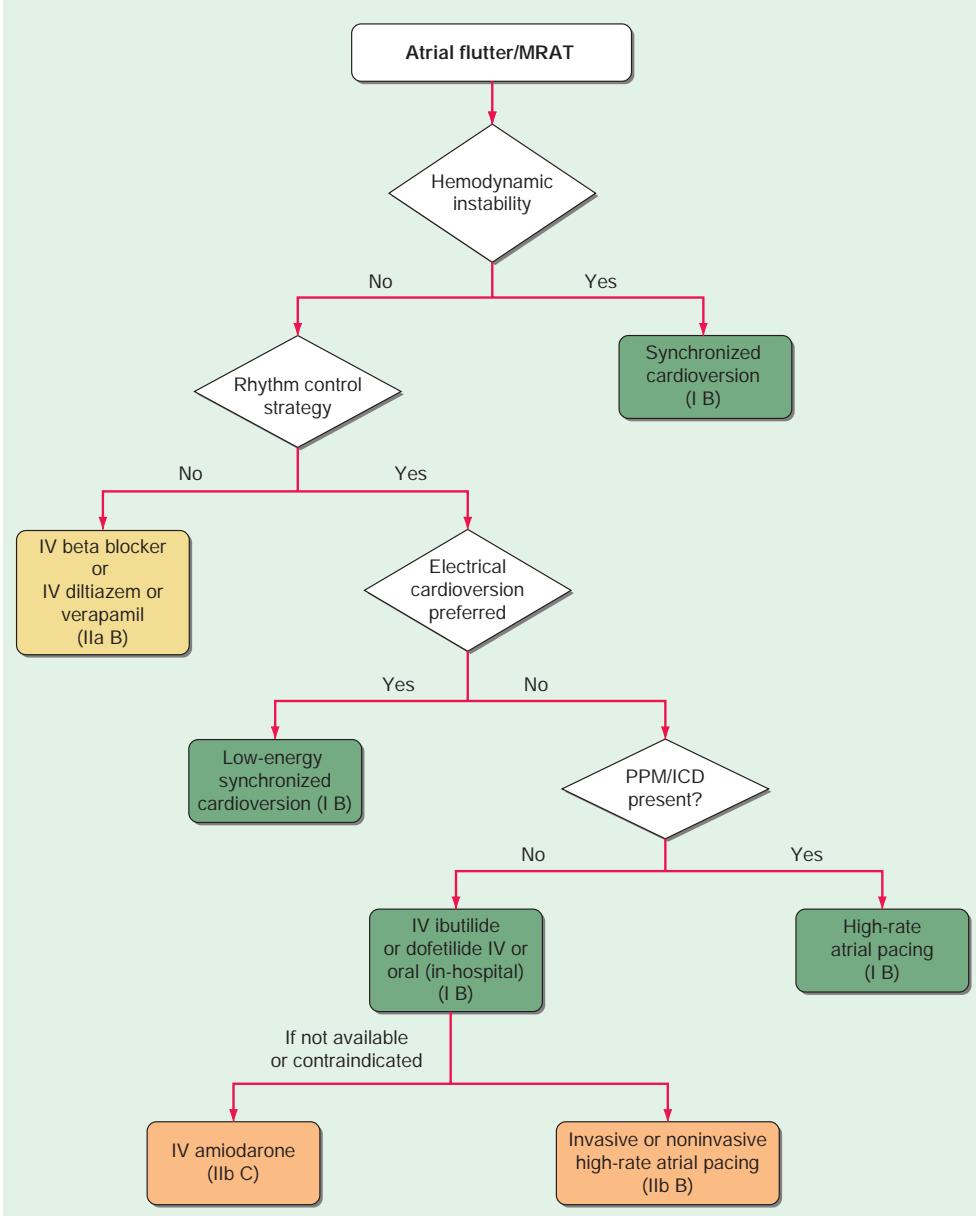
complications that are largely related to vascular access and rarely heart block. Therefore, catheter ablation for atrial flutter can be considered as first-line therapy. Approximately 50% of patients presenting with atrial flutter develop atrial fibrillation within 5 years after diagnosis, which is an important consideration in patients with a high-risk profile for thromboembolism. In general, patients with atrial flutter are treated identically to those with atrial fibrillation in terms of recommendations for anticoagulation for stroke prevention (Fig. 250-3).

### MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal AT (MAT) is characterized by a rhythm with at least three distinct P-wave morphologies with rates typically between 100 and 150 beats/min. Unlike atrial fibrillation, there are clear isoelectric

intervals between P waves and the atrial rate is slower. The mechanism is likely triggered automaticity from multiple atrial foci. It is usually encountered in patients with chronic pulmonary disease and acute illness (Fig. 250-4).

Therapy for MAT is directed at treating the underlying disease and correcting any metabolic abnormalities. Electrical cardioversion is ineffective. The calcium channel blockers verapamil or diltiazem may slow the atrial and ventricular rate. Patients with severe pulmonary disease often do not tolerate beta blocker therapy. MAT may respond to amiodarone, but long-term therapy with this agent is usually avoided due to its toxicities, particularly pulmonary fibrosis. The associated risk of thromboembolism in MAT remains unclear but is not considered to be the same as atrial fibrillation or atrial flutter.



**FIGURE 250-3** Approach to the patient with atrial flutter or macroreentrant atrial tachycardia (MRAT). ICD, implantable cardioverter-defibrillator; PPM, permanent pacemaker. (Adapted from FM Kusumoto et al: *Heart Rhythm* 16:e128, 2019.)



**FIGURE 250-4** Multifocal atrial tachycardia. Rhythm strip obtained from a patient with severe pulmonary disease during an acute illness. Arrows note three distinct P-wave morphologies.

**Acknowledgment**

*Gregory F. Michaud and William G. Stevenson contributed to this chapter in the 20th edition and some material from that chapter has been retained here.*

**FURTHER READING**

Brugada J et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 41:655, 2020.

Callans DJ: *Josephson's Clinical Cardiac Electrophysiology: Techniques and Interpretations*, 6th ed. Philadelphia, Wolters Kluwer, 2021.

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AF is the most common sustained arrhythmia; as a result, it is a major public health issue. Prevalence increases with age, with >95% of AF patients >60 years of age. The prevalence in humans over age 80 is ~10%. The lifetime risk of developing AF for men aged 40 years old is ~25%. AF is slightly more common in men than women and more common in whites than blacks. Risk factors for developing AF in addition to age and underlying cardiac disease include hypertension, diabetes mellitus, cardiac disease, family history of AF, obesity, and sleep-disordered breathing. AF is not a benign condition, with a 1.5- to 1.9-fold increased risk of mortality after controlling for underlying cardiac disease. Perhaps the most important consequence of AF is a significantly increased risk of stroke compared to the general population, causing ~25% of all strokes. The risk of dementia is increased in patients with AF, as is the risk of MRI-detected asymptomatic embolic infarct. AF, most often when ventricular rate remains uncontrolled for prolonged periods, increases the risk of developing congestive heart failure and cardiomyopathy. Moreover, as a corollary, patients with underlying heart disease, in particular cardiomyopathy and congestive heart failure, are at higher risk for developing AF. AF is a marker for worsened morbidity and mortality in patients with existing heart disease, although the precise extent of the independent risk increase associated with AF in heart disease is unclear. AF may, on occasion, be associated with an identifiable precipitating factor, such as hyperthyroidism, acute alcohol intoxication, myocardial infarction, pulmonary embolism, pericarditis, and cardiac surgery, where AF occurs in up to 30% of patients postoperatively.

AF is clinically most typically defined by the pattern of episodes. Paroxysmal AF is defined as a pattern of AF episodes that occur spontaneously and terminate with a relatively short duration, most commonly defined as 7 days or less. Persistent AF refers to AF that occurs continuously for >7 days but <1 year, whereas long-standing persistent AF refers to AF that has been persistent for >1 year. These descriptors for AF correlate with the underlying pathophysiology of AF. AF tends to be a progressive condition, with, at this point, no definitive "cure" that will completely eliminate AF durably in a predictable fashion. The pathophysiology of AF, however, remains incompletely understood. Most data support a multifactorial process that leads to the development of manifest AF. Clinical and epidemiologic studies have demonstrated that, in addition to cardiovascular disease, obesity,

**251****Atrial Fibrillation**

William H. Sauer, Paul C. Zei

**PATHOPHYSIOLOGY AND EPIDEMIOLOGY**

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by seemingly disorganized, rapid, and irregular atrial electrical activation, resulting in loss of organized atrial mechanical contraction. These rapid and irregular electrical signals input into the atrioventricular (AV) node, which determines ventricular activation and rate. The conducted ventricular rate is variable, resulting in an irregular, usually rapid ventricular rate, ranging typically between 110 and 160 beats/min in most. In some patients, the sustained ventricular rate can exceed 200 beats/min, whereas in others with either high vagal tone or AV nodal conduction disease, the ventricular rate may be excessively slow (Fig. 251-1).

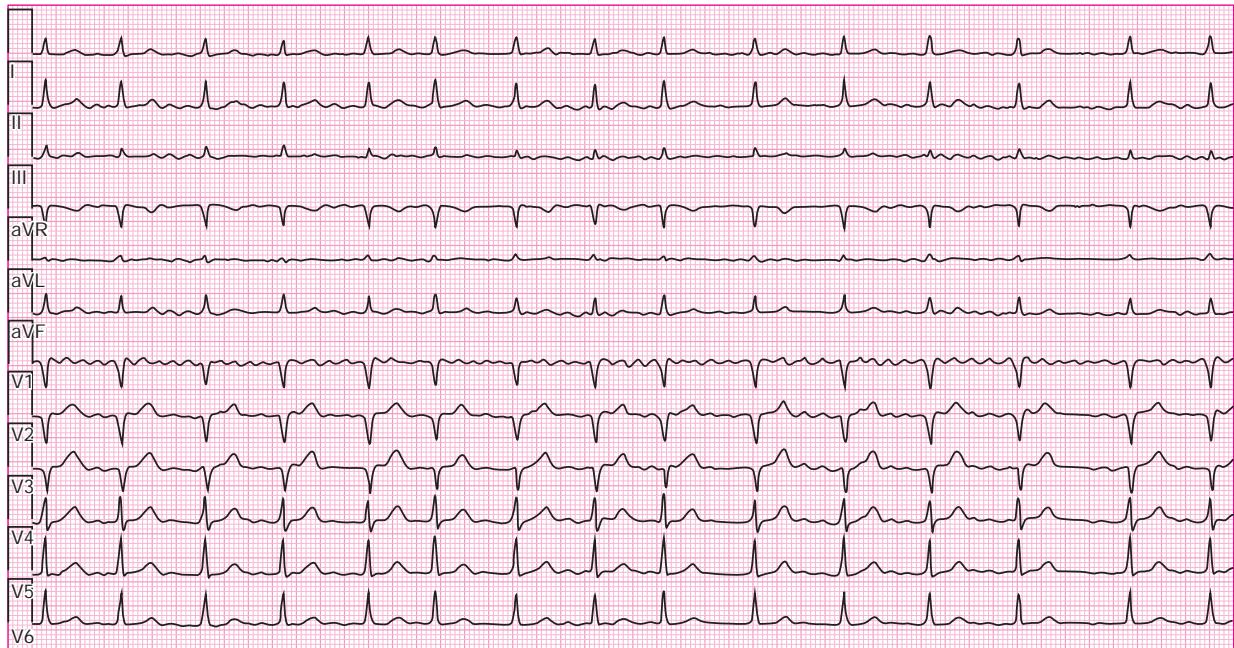
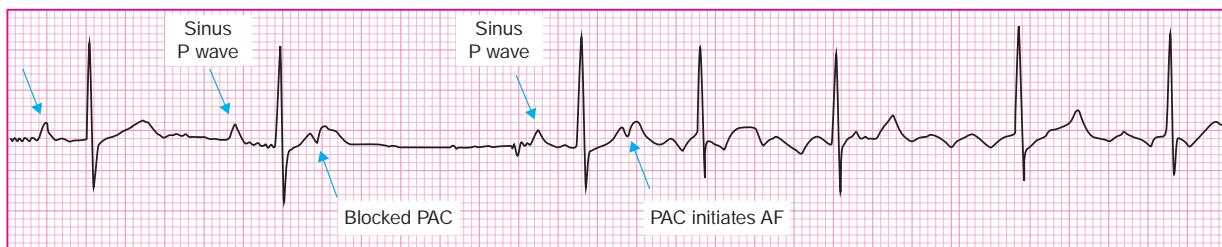


FIGURE 251-1 Electrocardiogram of an irregularly irregular heart rhythm without discernable P waves. The disorganized atrial activation is best appreciated in lead V<sub>1</sub>, for this patient.



**FIGURE 251-2** Surface electrocardiogram (ECG) of atrial ectopy initiating atrial fibrillation (AF). In this single-lead surface ECG recording, the tracing begins with two conducted sinus beats. A nonconducted premature atrial contraction (PAC) (labeled “blocked PAC”) is shown after the second QRS complex. After the next sinus P wave and QRS, an ectopic beat (PAC) initiates fibrillation, as demonstrated by (somewhat organized) erratic atrial activity and an irregular ventricular response.

hypertension, diabetes mellitus, and sleep-disordered breathing are associated with higher risk of developing AF. The proposed pathophysiology suggests a “final common pathway” of these risk factors leading to electrophysiologic changes in atrial tissues. Alterations in regulation of membrane channels and other proteins result in abnormal electrical excitability. Atrial tissues, in particular pulmonary vein musculature, exhibit enhanced automaticity, resulting in ectopic beats (premature atrial contractions), as shown in Fig. 251-2. Bouts of rapid atrial ectopy may then initiate either atrial tachycardia or frank AF. Additional cellular and, eventually, tissue remodeling results in abnormal conduction properties throughout the atria, including, in particular, shortening of atrial tissue refractory periods. This enables sustained AF through a combination of rapid automaticity-based “drivers” and areas of functional reentry. Further remodeling leads to the development of fibrosis and left atrial enlargement (Table 251-1).

These functional and anatomic changes in atrial tissues appear to correlate with the progression of clinical AF. AF tends to be a progressive disease in most, although exceptions occur. Typically, for a period of time, patients experience sporadic ectopic beats, likely originating from the pulmonary veins, preceding the onset of frank AF.

Other regions of the atria have been demonstrated to produce ectopic depolarizations that may trigger AF; these include the muscular tissue sleeves within the superior vena cava, coronary sinus, or the remnant of the vein of Marshall. When enough frequent bursts of ectopic beats/tachycardia and/or changes in underlying substrate support the maintenance of AF for short periods, the patient develops episodes of paroxysmal AF. In the untreated patient, over time, as electrical and remodeling continues to progress, episodes of paroxysmal AF may be prolonged to the point of not terminating spontaneously, the hallmark of persistent AF. After further remodeling, not only do patients continue on to long-standing persistent AF but

also the efficacy of therapeutic interventions to restore sinus rhythm diminishes.

## CLINICAL PRESENTATION AND MANIFESTATIONS

The clinical manifestations of AF result from (1) symptoms related to the irregular, often rapid but sometimes slow ventricular rates that result; (2) the hemodynamic consequences of altered cardiac function; (3) the consequences of cardioembolic phenomena; and/or (4) the impact of AF on cardiovascular function over time. AF is diagnosed by electrocardiogram (ECG), either by 12-lead standard ECG or limited lead ambulatory monitor ECG, with findings of lack of organized atrial activity (no P wave), with an irregular ventricular response. The role of screening populations for AF is evolving with the use of wearable monitors and home ECG capabilities.

With irregular, rapid ventricular rates, there is variable cardiac displacement and contraction, resulting in the sensation of palpitations and awareness of the heartbeat, when of course, in a normal rhythm, most humans do not sense each and every heartbeat. Interestingly, many patients are, for the most part, unaware of the irregular ventricular beating for unknown reasons.

During AF, there is loss of the contribution of atrial systole to overall cardiac output and, with irregular ventricular rates, variable ventricular filling and, as a consequence, variable stroke volume. The resultant impact on overall cardiac output may result in exercise intolerance, fatigue, weakness, presyncope, or dyspnea. In patients with underlying cardiac disease, the additional hemodynamic compromise resulting from AF may result in exacerbation of the disease and/or symptoms. Patients with hypertrophic cardiomyopathy, coronary artery disease, heart failure with either depressed or preserved ejection fraction, or amyloidosis are particularly susceptible. In patients with concomitant

**TABLE 251-1** Categorization of Atrial Fibrillation (AF) by Clinical Temporal Characteristics and Associated Features

	PAROXYSMAL AF	PERSISTENT AF	LONG-STANDING PERSISTENT AF
Definition	Episodes self-terminate or via CV in <7 d	Episodes do not self-terminate in <7 d	Persistent AF >1 year
LA size	Normal to mildly enlarged	Mild to severely enlarged	Typically, severely enlarged
LA scar burden	Low	Moderate	High
Efficacy of AAD	Often effective	Not as effective	Usually refractory
When to offer ablation?	First-line therapy reasonable	First-line appropriate but usually offered after AAD failure	After AAD failure, not always a good option
Ablation technique	PV isolation alone usually effective	PV isolation and any identified non-PV AF source	PV isolation; additional ablation for substrate modification likely needed

*Note:* With paroxysmal, persistent, and long-standing persistent AF, definitions are based on duration of events and diagnosis overall. These categorizations correlate with LA size, LA scar burden, and resultant efficacy of medical and ablative therapies.

*Abbreviations:* AAD, antiarrhythmic drugs; CV, cardioversion; LA, left atrium; PV, pulmonary vein.

AV nodal conduction disease, bradycardia during AF may result in presyncope or syncope. Pauses at the time of spontaneous conversion from AF to sinus rhythm, a manifestation of sinus node dysfunction that commonly occurs in patients with AF, may result in presyncope or syncope as well.

With the loss of atrial mechanical contraction, blood stasis may promote *in situ* thrombosis, which, when embolized, may result in a range of clinical consequences, most importantly, ischemic stroke. Thrombus formation occurs primarily in the left atrial appendage. Over time, recurrent thromboembolism to the brain, even if asymptomatic, may result in debilitating neurologic sequelae. An increased risk of dementia in patients with AF may be the consequence of this phenomenon.

In patients with prolonged periods of rapid ventricular rates resulting from AF, there is risk of developing a tachycardia-induced cardiomyopathy, with associated depressed left ventricular function. Tachycardia-induced myopathy appears generally to be reversible once ventricular rates are controlled. In patients with long-standing persistent AF, the atria, especially the left atrium, tend to be more dilated and to contain a higher burden of fibrotic, noncontractile atrial tissue. More recently, the hemodynamic consequences of a noncompliant, fibrotic left atrium, including elevated left atrial filling pressures, volume overload, and congestive heart failure, have been described as “stiff left atrial syndrome.”

## TREATMENT

### Atrial Fibrillation

The treatment and management of the patient with AF centers on three aims: (1) control of patient symptoms through a strategy of rate control and/or rhythm control; (2) appropriate mitigation of thromboembolism risk; and (3) addressing modifiable risk factors for progression of AF. In the acute onset of AF, if significant hemodynamic compromise, pulmonary edema, or evidence of coronary ischemia is present, emergent cardioversion is recommended. Electrical cardioversion can be achieved with a QRS synchronous shock, preferably in a sedated patient, or via pharmacologic cardioversion, most typically with the intravenous administration of the class III antiarrhythmic ibutilide. Ibutilide should be avoided in patients with baseline prolonged QT interval or severe left ventricular dysfunction, given the risk of torsades des pointes. In the hemodynamically stable patient with new-onset AF, therapy should focus on control of ventricular rate to prevent hemodynamic sequelae, consideration of anticoagulation to mitigate thromboembolic risk, and consideration of restoration and maintenance of sinus rhythm—a so-called rhythm control strategy. If restoration of sinus rhythm is being considered, a more immediate risk of thromboembolism must be factored into the management strategy. Although there is a lack of definitive data, it is presumed that if the presenting episode of AF is >48 h or if the episode duration is unknown, there is risk for precipitating a thromboembolic complication through cardioversion, whether electrical or pharmacologically achieved. Therefore, in this circumstance, the patient should be either initiated on anticoagulation, with cardioversion deferred for at least 4 weeks after uninterrupted anticoagulation, or evaluated to exclude the presence of left atrial appendage thrombus. Most commonly, transesophageal echocardiography (TEE) is used to evaluate for left atrial appendage thrombus, although computed tomography (CT) angiography has been demonstrated to have excellent sensitivity and specificity as well.

### CARDIOVERSION AND ANTICOAGULATION

The major source of thromboembolism and stroke in AF is formation of thrombus in the left atrial appendage where flow is relatively stagnant, although thrombus occasionally forms in other locations as well. Following conversion from prolonged AF to sinus rhythm, atrial mechanical function can be delayed for weeks, such that thrombi can form even during sinus rhythm. When AF has been present for >48 h and in patients at high risk for thromboembolism,

such as those with mitral stenosis or hypertrophic cardiomyopathy, conversion to sinus rhythm is associated with an increased risk of thromboembolism. Thromboembolism can occur soon or several days after restoration of sinus rhythm if appropriate anticoagulation measures are not taken.

*Cardioversion within 48 h of the onset of AF* is common practice in patients who have not been anticoagulated, provided that they are not at high risk for stroke due to a prior history of embolic events, rheumatic mitral stenosis, or hypertrophic cardiomyopathy with marked left atrial enlargement. These low-risk patients with occasional episodes of AF can be instructed to notify their physician when AF occurs to arrange for cardioversion to be done within 48 h.

*If the duration of AF exceeds 48 h or is unknown,* there is greater concern for thromboembolism after cardioversion, even in patients considered low risk ( $\text{CHA}_2\text{DS}_2\text{-VASc}$  of 0 or 1 [see below]) for stroke. There are two approaches to mitigate the risk related to cardioversion. One option is to anticoagulate continuously for 3 weeks before and a minimum of 4 weeks after cardioversion. A second approach is to start anticoagulation and perform a TEE or high-resolution cardiac CT scan to detect the presence of thrombus in the left atrial appendage. If thrombus is absent, cardioversion can be performed and anticoagulation continued for a minimum of 4 weeks to allow time for recovery of atrial mechanical function. In either case, cardioversion of AF is associated with a substantial risk of recurrence, which may not be symptomatic. Longer-term maintenance of anticoagulation is considered based on the patient's individual risk for stroke, commonly assessed using the  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score.

### ACUTE RATE CONTROL

The goal of rate control in AF is to allow more diastolic filling time, improving cardiac output and reducing patient symptoms. In the longer term, adequate rate control will minimize the risk of congestive heart failure and tachycardia-induced cardiomyopathy. Acute rate control can be achieved with beta blockers and/or the calcium channel blockers verapamil and diltiazem administered either intravenously or orally, as warranted by the urgency of the clinical situation. Digoxin has been used for many years for rate control, particularly in patients susceptible to congestive heart failure, because it lacks the negative inotropic effect seen in calcium channel blockers and beta blockers. It acts synergistically with beta blockers and calcium channel blockers and, therefore, may be useful as an added agent when rate control is inadequate. However, recent evidence suggests increased mortality with its use, and so its utilization has declined.

### CHRONIC RATE CONTROL

For patients who remain in AF chronically, the goal of rate control is to both alleviate symptoms and prevent deterioration of ventricular function from excessive rates. -Adrenergic blockers and calcium channel blockers are often used either alone or in combination. Exertion-related symptoms are often an indication of inadequate rate control. Rate should be assessed with exertion and medications adjusted accordingly. Adequate rate control is defined as a resting heart rate of <80 beats/min that increases to <100 beats/min with light exertion, such as walking. If it is difficult to slow the ventricular rate to that degree, allowing a resting rate of up to 110 beats/min is acceptable provided it does not cause symptoms and ventricular function is normal; however, periodic assessment of ventricular function is warranted because some patients develop tachycardia-induced cardiomyopathy.

If adequate rate control in AF is difficult to achieve, further consideration should be given to restoring sinus rhythm (see below). Catheter ablation of the AV junction to create permanent AV block and implantation of a permanent pacemaker reliably achieve rate control without the need for AV nodal-blocking agents, a so-called “ablate and pace” strategy. These patients not only remain in AF but also become dependent on the pacemaker to support ventricular

rate. The typical pacing configuration with placement of a ventricular lead in the right ventricular apex may induce dyssynchronous ventricular activation that can depress ventricular function in some patients. Biventricular pacing or direct pacing of the His bundle or left bundle branch may be used to minimize the degree of ventricular dyssynchrony.

### STROKE PREVENTION IN ATRIAL FIBRILLATION

Thromboembolic complications, in particular, stroke, are the most significant and potentially life-threatening sequelae of AF. Therefore, appropriate stroke prevention strategies are a key aspect of AF management. The mainstay of stroke prevention is continuous anticoagulation therapy, most commonly using an oral medication. Specific patient populations have a high risk of stroke, including patients with hypertrophic cardiomyopathy, mitral stenosis, and prior stroke history, and therefore, anticoagulation is recommended, barring contraindications. AF in patients without mitral stenosis is commonly referred to as nonvalvular AF. In the majority of patients with AF, the decision about whether a stroke prevention regimen is indicated is largely based on an assessment of stroke risk, balanced by the risk of the preventative therapy. The risk of stroke appears to be most accurately predicted by the presence of underlying risk factors known to increase stroke risk. The CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system (Fig. 251-3) is a widely used tool to estimate stroke risk. Anticoagulation is currently recommended in the United States for patients with a score of 1, unless the lone risk factor is female gender. Stroke risk increases with increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc score, such that annual stroke risk may be as high as nearly 20% without anticoagulation. On the other hand, anticoagulation carries a risk of serious and potentially life-threatening bleeding complications, in particular, intracranial hemorrhage and gastrointestinal bleed. Bleeding risk is often assessed using the HAS-BLED scoring system (Fig. 251-3). If bleeding risk is deemed

to be outweighed by stroke risk, anticoagulation is recommended. It is important to note that the perceived burden of AF has not been shown to predict stroke risk. The approach to patients with paroxysmal AF is therefore the same as for persistent AF. It is recognized that many patients who appear to have infrequent AF episodes based on office visits often have asymptomatic episodes that put them at risk. Absence of AF during periodic monitoring is not sufficient to indicate low risk. The role of continuous monitoring with implanted recorders or pacemakers as a guide for anticoagulation in patients with a borderline risk profile is not clear.

The options for anticoagulation are the oral factor Xa inhibitors apixaban, edoxaban, or rivaroxaban; the oral antithrombin inhibitor dabigatran; and the vitamin K antagonist warfarin.

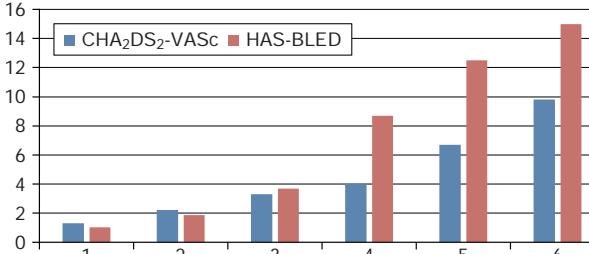
Antiplatelet agents alone are generally not sufficient. In non-valvular AF warfarin reduces the annual risk of stroke by 64% compared to placebo and by 37% compared to antiplatelet therapy. Patients with AF with an increased risk of stroke also have an increased risk of venous thromboembolism, which appears to be lower with oral anticoagulation. The direct-acting anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban were noninferior to warfarin in individual trials of nonvalvular AF patients, and intent-to-treat analysis of pooled data suggests superiority to warfarin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and intracranial hemorrhage. Warfarin is required for patients with rheumatic mitral stenosis or mechanical heart valves. The newer, direct-acting anticoagulants have not been tested in rheumatic heart disease, and a direct thrombin inhibitor did not prevent thromboembolism in patients with mechanical heart valves. Warfarin can be an inconvenient agent that requires several days to achieve a therapeutic effect (prothrombin time [PT]/international normalized ratio [INR] >2), requires monitoring of PT/INR to adjust dose, and has many drug and food interactions that can hinder patient compliance and render maintaining a therapeutic effect challenging. The direct-acting agents are easier to use and achieve reliable anticoagulation promptly without requiring dosage adjustment based on blood tests. Dabigatran, rivaroxaban, and apixaban have renal excretion, cannot be used with severe renal insufficiency (creatinine clearance <15 mL/min), and require dose adjustment for modest renal impairment, which is of particular concern in the elderly, who are at increased bleeding risk. Limited experience with apixaban demonstrates safety and efficacy in patients undergoing chronic hemodialysis for end-stage kidney disease. Excretion can also be influenced by P-glycoprotein inducers and inhibitors. Warfarin anticoagulation can be reversed by administration of fresh frozen plasma, prothrombin complex concentrate, and vitamin K. Reversal agents are available for dabigatran (idarucizumab), and Xa inhibitors are available (andexanet alfa), and both are administered intravenously. These agents may be pro-thrombotic and administration must be judicious. The antiplatelet agents aspirin and clopidogrel are inferior to warfarin for stroke prevention in AF and do not have less risk of bleeding. Clopidogrel combined with aspirin is better than aspirin alone for stroke prevention, but this combination is inferior to warfarin and has a greater bleeding risk than aspirin alone.

Bleeding is the major risk of anticoagulation. Major bleeding requiring transfusion and intracranial bleeding occur in ~1% of patients per year with warfarin. Direct-acting anticoagulants appear to have a lower risk of intracranial bleeding compared with warfarin without sacrificing protective effects against thromboembolism. Risk factors for bleeding include age >65–75 years, heart failure, renal insufficiency, prior bleeding, and excessive alcohol or nonsteroidal anti-inflammatory drug use. In patients who require dual antiplatelet therapy (e.g., aspirin and clopidogrel) after coronary or peripheral arterial stenting, there is a substantially increased bleeding risk when standard oral anticoagulation with warfarin or a direct-acting anticoagulant is added. The optimal combination of agents for patients with AF who also require antiplatelet therapy remains unclear.

Chronic anticoagulation is contraindicated in some patients due to bleeding risks. Because most atrial thrombi likely originate

CHA <sub>2</sub> DS <sub>2</sub> -VASc		HAS-BLED	
Risk Criteria			
Congestive heart failure	1	Hypertension	1
Age >75	2	Abnormal renal or liver function	1 each
Hypertension	1	Bleeding diasthesia	1
Diabetes mellitus	1	Labile INR (on warfarin)	1
Prior stroke or TIA	2	Age >65	1
Vascular disease	1	Drugs or alcohol	1 each
Age >65	1		
Sex category (F)	1		

Annual Stroke or Major Bleeding Rate (%) as a Function of Score



**FIGURE 251-3 CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED Systems.** The CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system gives a point for each outlined stroke risk factor, whereas the HAS-BLED scoring system gives a point for each bleeding risk factor, as outlined in the table. In the chart below the table, the corresponding risk of stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc) or major bleed event (HAS-BLED) is plotted as a percent risk per annum as a function of score. F, female; INR, international normalized ratio; TIA, transient ischemic attack.

**TABLE 251-2 Novel Oral Anticoagulant Dosing**

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Standard dose	150 mg bid	20 mg qd	5 mg bid	60 mg qd
Reduced dose	110 mg bid	15 mg qd	2.5 mg bid	30 mg qd
Dose reduction criteria	Dabigatran 110 mg bid in patients with: age ≥ 80 years, concomitant use of verapamil, or increased bleeding risk	Creatine clearance 15–49 mL/min	At least 2 of 3 criteria: age ≥ 80 years, body weight ≥ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 mol/L)	If any of the following: creatinine clearance 30–50 mL/min, body weight ≥ 60 kg, or concomitant use of dronedarone, cyclosporine, erythromycin, or ketoconazole

Note: As of publication, four novel oral anticoagulants are available and indicated for stroke prevention for atrial fibrillation. The standard dosing, reduced dosing, and criteria for reduced dosing are shown for each agent.

in the left atrial appendage, surgical removal of the appendage, combined with atrial maze surgery, may be considered for patients undergoing surgery, although removal of the appendage has not been unequivocally shown to reduce the risk of thromboembolism. Percutaneously deployed devices that occlude or ligate the left atrial appendage are also available, appear to be noninferior to warfarin in reducing stroke risk, and are considered in patients who have a high risk of thromboembolism but serious bleeding risk from chronic oral anticoagulation (**Table 251-2**).

### RHYTHM CONTROL

The decision to administer antiarrhythmic drugs or perform catheter ablation to attempt maintenance of sinus rhythm (commonly referred to as the *rhythm control strategy*) is mainly guided by patient symptoms and preferences regarding the benefits and risks of therapies. In general, patients who maintain sinus rhythm have better survival than those who continue to have AF. This may be because continued AF is a marker of disease severity. In older randomized trials, administration of antiarrhythmic medications to maintain sinus rhythm did not improve survival or symptoms compared to a rate control strategy, and the drug therapy group had more hospitalizations. Disappointing efficacy and toxicities of available antiarrhythmic drugs and patient selection bias may be factors that influenced the results of these trials. Recently, a randomized trial evaluating an early rhythm control strategy (within 1 year of initial presentation) compared to standard rate control demonstrated a reduction in cardiovascular events, including death from cardiovascular causes and stroke. Differences between this study and earlier randomized trials that failed to show a significant difference in outcomes in rate versus rhythm control included the use of catheter ablation and a high adherence rate to anticoagulation despite apparent rhythm control. In patients with heart failure due to depressed left ventricular function, a catheter ablation-based strategy to maintain sinus rhythm appears to provide mortality benefit compared with a medical rhythm control strategy. In a broader population of patients with AF, a large, randomized, prospective study comparing catheter ablation rhythm control medications demonstrated a nonsignificant trend toward reduced hospitalizations and improved mortality, mostly driven by patients with heart failure.

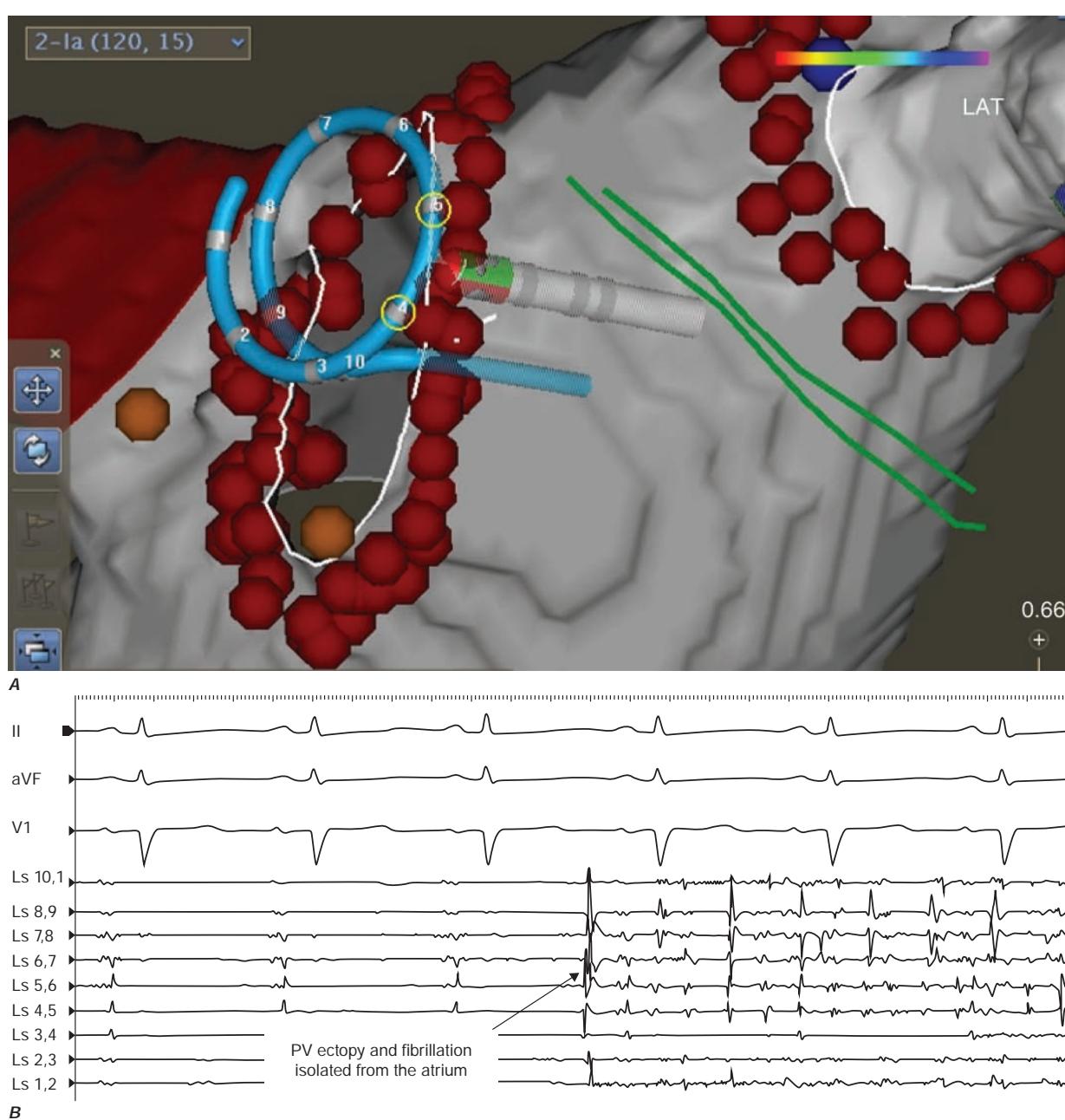
A rhythm control strategy is usually selected for patients with symptomatic paroxysmal AF, recurrent episodes of symptomatic persistent AF, AF with difficult rate control, and AF that has resulted in depressed ventricular function or that aggravates heart failure. A rhythm control strategy is more likely to be favored in younger patients than in sedentary or elderly patients in whom rate control is more easily achieved. Even if sinus rhythm is apparently maintained, anticoagulation is recommended according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk profile because asymptomatic episodes of AF are common. Following a first episode of persistent AF, a strategy using AV nodal-blocking agents, cardioversion, and anticoagulation is reasonable, in addition to addressing possible aggravating factors. If recurrences are infrequent, periodic cardioversion is reasonable. However, if a patient has frequent symptomatic AF despite rate control, then a rhythm control strategy incorporating catheter ablation and/or antiarrhythmic medications is indicated.

Based on recent randomized trial data demonstrating superiority of ablation over medications for maintenance of sinus rhythm and benefits of an early rhythm control strategy, there is a trend toward offering ablation earlier in the course of treatment, especially for individuals with paroxysmal AF.

**Pharmacologic Therapy for Maintaining Sinus Rhythm** The goal of pharmacologic therapy is to maintain sinus rhythm or reduce episodes of AF. Risks and side effects of antiarrhythmic drugs are a major consideration in selecting therapy. Drug therapy can be instituted once sinus rhythm has been established or in anticipation of cardioversion. However, antiarrhythmic medications may in some instances pharmacologically cardiovert the patient into sinus rhythm. Therefore, an appropriate anticoagulation strategy approach similar to electrical cardioversion is recommended, particularly at the time of initiation of therapy. -Adrenergic blockers and calcium channel blockers help control ventricular rate, improve symptoms, and possess a low-risk profile, but have low efficacy for preventing or terminating AF episodes. Class I sodium channel-blocking agents (e.g., flecainide, propafenone, disopyramide) are options for patients without significant structural heart disease, but negative inotropic and proarrhythmic effects warrant avoidance in patients with coronary artery disease or heart failure. The class III agents sotalol and dofetilide can be administered to patients with coronary artery disease or structural heart disease but have ~3% risk of inducing excessive QT prolongation and torsades de pointes. Dofetilide should be initiated only in a hospital with ECG monitoring, and many physicians take this approach with sotalol as well. Dronedarone increases mortality in patients with heart failure or long-standing persistent AF. All of these agents have modest efficacy in patients with paroxysmal AF, of whom ~30–50% will benefit. Amiodarone is more effective, maintaining sinus rhythm in approximately two-thirds of patients. It can be administered to patients with heart failure and coronary artery disease. However, >40% of patients experience amiodarone-related toxicities during long-term therapy, and thus, careful monitoring of potential toxicities, including liver, lung, and thyroid abnormalities, must be accompanied with this therapy.

**Catheter And Surgical Ablation for Maintaining Sinus Rhythm** Successful catheter ablation avoids antiarrhythmic drug toxicities, but procedural risks and efficacy depend on operator experience. For patients with previously untreated but recurrent paroxysmal AF, catheter ablation has superior efficacy compared to antiarrhythmic drug therapy, and ablation is even more clearly superior to antiarrhythmic drugs for patients who have recurrent AF despite drug treatment. Long-term control of AF is more difficult to achieve in patients with persistent AF, likely because of more extensive atrial abnormalities and associated greater comorbidities in these patients (**Fig. 251-4**).

Catheter ablation involves percutaneous venous access (typically via the femoral veins), transatrial septal puncture, and radiofrequency ablation or cryoablation to electrically isolate the left atrial regions around the pulmonary vein antra, abolishing the ability of triggering foci in these regions to initiate AF and also likely impacting the substrate for reentry in the left atrium. Extensive areas of ablation are required, and gaps in healed ablation areas

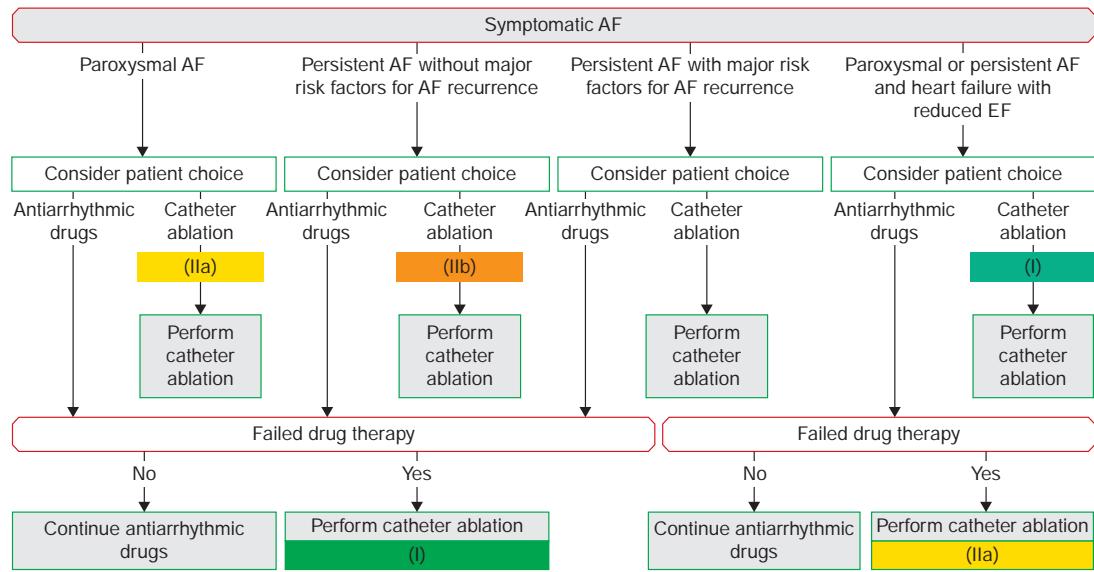


**FIGURE 251-4** *A.* Electroanatomic map superimposed on an MRI reconstruction of a left atrium with mapping catheter in the left common pulmonary vein and ablation catheter at the pulmonary vein-left atrium junction. *B.* Spontaneous pulmonary vein (PV) ectopy initiating fibrillatory conduction contained within the isolated vein.

or emergence of new trigger sites outside the pulmonary veins necessitate a repeat procedure in 10–30% of patients. Several alternative energy sources to create ablative lesions are being evaluated for ablation of AF and other arrhythmias, including laser, external beam radiation, and pulsed field electroporation.

In patients with paroxysmal AF, sinus rhythm is maintained for >1 year after a single ablation procedure in ~70% of patients and is achieved in >90% of patients after multiple procedures in some studies. Many patients become more responsive to antiarrhythmic drugs or become less symptomatic with a reduced AF burden after a pulmonary vein isolation procedure, and thus, repeat ablation may not be required for symptom control in some. Ablation is less effective in patients with persistent AF, particularly long-standing

persistent AF, especially when associated with more extensive cardiac disease, comorbidities, and evidence of left atrial enlargement. More extensive ablation is often required, targeting areas that likely support reentry and/or AF maintenance and regions outside but adjacent to the pulmonary venous antra. There is no proven strategy for selecting ablation targets outside the pulmonary vein antral regions, and a variety of approaches have been pursued. Ablation of areas of rapid activity during AF and creation of ablation lines to block conduction across regions of the atria have not been proven to improve outcomes in unselected patients. Other ablation targets include non-pulmonary vein foci that fire in response to high-dose isoproterenol, areas of atrial fibrosis, and regions with repetitive rotational or focal activation during AF. More than one ablation



**FIGURE 251-5 Rhythm control strategy for symptomatic atrial fibrillation (AF).** This chart outlines the guideline-based management of patients with symptomatic atrial fibrillation. As outlined in Table 251-1, the first step is determination of the temporal nature of the patient's AF (paroxysmal vs persistent) and any associated risk factors for AF recurrence, such as left atrial anatomic dimensions. A decision is then made regarding medical versus catheter ablation-based rhythm control, with recommendations for when to consider catheter ablation based on guideline recommendations (class IIa for paroxysmal, IIb for persistent without major risks for recurrence, or AF of any sort in patients with heart failure with reduced ejection fraction [EF], class I). Note the importance of patient choice, as well as the subsequent decisions to consider catheter ablation if drugs have failed. (G Hindricks et al: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J 42:17, 2020. (Translated and) Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.)

procedure is often required to maintain sinus rhythm in patients with persistent and long-standing persistent AF because of lack of lesion durability and complex atrial substrate with non-pulmonary vein sources that may be incompletely treated at the initial ablation session (Fig. 251-5).

Catheter ablation has a 2–7% risk of major procedure-related complications, with the long-term trend suggesting steady improvement in complication rates. Complication rates are clearly lowest with high-volume operators and centers. Complications including stroke (0.5–1%), cardiac tamponade (1%), phrenic nerve palsy, bleeding from femoral access sites, and fluid overload with heart failure, which can emerge 1–3 days after the procedure. It is important to recognize the potential for delayed presentation of some complications. Ablation within the PV can lead to PV stenosis, presenting weeks to months after the procedure with dyspnea or hemoptysis. The esophagus abuts the posterior wall of the left atrium where it is subject to injury, and esophageal ulcers can form immediately after the procedure and may rarely lead to a fistula between the left atrium and esophagus (estimated incidence of <0.1%) that presents as endocarditis and stroke 10 days to 3 weeks after the procedure. Early diagnosis of atrioesophageal fistula is important because delayed diagnosis leads to likely death. Diagnosis is made by chest CT scan with water-soluble oral and IV contrast. Endoscopy should be avoided in patients with a suspected fistula because of the risk of air/esophageal fluid embolus. Definitive repair of the atrioesophageal fistula with emergent surgery is required.

Surgical ablation of AF is most frequently performed concomitant with cardiac valve or coronary artery surgery and less commonly as a stand-alone procedure. However, for patients with persistent AF, surgical or hybrid procedures (a combination of a surgical and catheter-based approach, most often in separate procedures) appear to have comparable efficacy to catheter ablation. Risks include sinus node injury requiring pacemaker implantation and higher morbidity with surgical ablation. Surgical removal of the left atrial appendage may reduce stroke risk, although thrombus can form in the remnant of the appendage or if the appendage is not completely ligated.

## RISK FACTORS FOR AND LIFESTYLE IMPACT ON ATRIAL FIBRILLATION

There is strong evidence that AF is associated with obesity, hypertension, alcohol use, and sleep apnea. Aggressive treatment of these risk factors can substantially reduce AF episodes in some patients and is warranted in all patients, as additional benefits to the patient are likely beyond AF improvement. The amount of exercise appears to have a complex relationship with the risk of AF development. In males, a U-shaped curve exists, where AF risk is high among those with sedentary lifestyles and those who participate extensively in endurance athletics such as long-distance running or cycling. Moderate exercise appears to confer a lower risk of AF. On the other hand, in females, a linear relationship exists between exercise and AF risk, with risk of AF decreasing continuously with increasing exercise activity. Although caffeine intake is often invoked as a risk for AF development or as a trigger for AF episodes in patients with a known AF diagnosis, large cohort studies have demonstrated, in contrast, a modest decrease in AF risk with modest caffeine intake. Other proposed risk factors are being evaluated, including psychological stress. Genetic predisposition to AF is seen in those with first-degree relatives with AF, and a small subset of AF patients can be determined to have a familial form of AF.

There is emerging emphasis on an integrated approach to management of AF patients, with coordinated management of risk factor modification, stroke prevention, rate control, rhythm control, and management of associated comorbidities of critical importance.

### Acknowledgment

Gregory F. Michaud and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

### FURTHER READING

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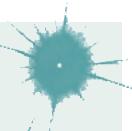
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## 252

## Approach to Ventricular Arrhythmias

William H. Sauer, Usha B. Tedrow



There are myriad types of ventricular arrhythmias (VAs), affecting patients with normal hearts and those with structural heart disease ranging from benign to life-threatening. An understanding of an approach to these arrhythmias is critical to being appropriately parsimonious with benign forms, while understanding an approach to the malignant forms.

### TYPES OF VAS

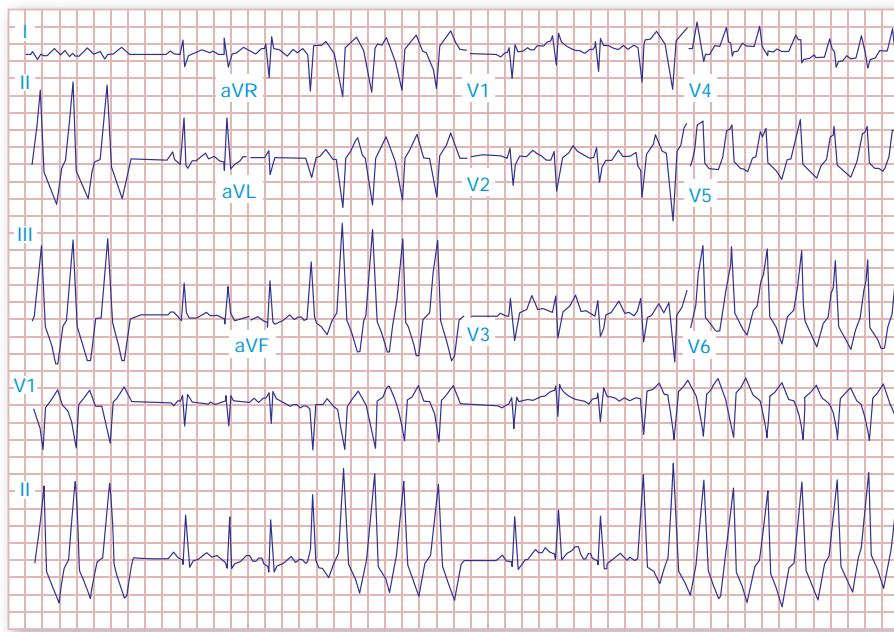
VAs can arise from focal sites of origin or from reentrant circuits. Focal VAs can originate from myocardial or Purkinje cells capable of automaticity or triggered activity. Reentrant VAs often involve areas of scar such as old myocardial infarction or a cardiomyopathic process. Less commonly, diseased Purkinje conduction pathways can also result in reentrant circuits. VAs are characterized by their electrocardiographic appearance and duration. Conduction away from the ventricular focus or reentrant circuit exit, propagating through the ventricular myocardium, is slower than activation of the ventricles over the normal Purkinje system. For this reason, the QRS complex duration during VAs will be wide, typically  $>0.12$  s, though there are unusual situations that can arise with narrow QRS duration as well.

**Premature ventricular beats** (also referred to as a *premature ventricular contractions* [PVCs]) are single ventricular beats that fall earlier than the next anticipated supraventricular beat (Fig. 252-1). PVCs that originate from the same focus will have the same QRS morphology and are referred to as unifocal (Fig. 252-1A). PVCs that originate from different ventricular sites have different QRS morphologies and are referred to as multifocal (Fig. 252-1B). Two consecutive ventricular beats are ventricular couplets.

**Ventricular tachycardia** (VT) is three or more consecutive beats at a rate faster than 100 beats/min. Three or more consecutive beats at slower rates are designated an idioventricular rhythm. VT that terminates spontaneously within 30 s is designated *nonsustained*, whereas sustained VT persists for  $>30$  s or is terminated by an active intervention, such as administration of an intravenous medication, external cardioversion, antitachycardia pacing, or a shock from an implanted cardioverter defibrillator (Fig. 252-2).



**FIGURE 252-1** **A.** Unifocal premature ventricular contractions (PVCs) at bigeminal frequency. Trace shows electrocardiogram lead 1 and arterial pressure (Art. Pr.). Sinus rhythm beats are followed by normal arterial waveform. The arterial pressure following premature beats is attenuated (arrows) and imperceptible to palpation. The pulse in this patient is registered at half the heart rate. **B.** Multifocal PVCs. The two PVCs shown have different morphologies. **C.** Example of accelerated idioventricular rhythm. (See text for details.)



**FIGURE 252-2** Repetitive monomorphic nonsustained ventricular tachycardia (VT) of right ventricular outflow tract origin. The VT has a left bundle branch block pattern with inferior axis with tall QRS complexes in the inferior leads.

*Monomorphic* VT has the same QRS complex from beat to beat, indicating that the activation sequence is the same from beat to beat and that each beat likely originates from the same source (Fig. 252-3A). The initial site of ventricular activation largely determines the sequence of ventricular activation. Therefore, the QRS morphology of PVCs and monomorphic VT provides an indication of the site of origin within the ventricles (Fig. 252-4). The likely origin often suggests whether an arrhythmia is idiopathic or associated with structural disease. Arrhythmias that originate from the right ventricle or septum result in late activation of much of the left ventricle, thereby producing a prominent S wave in V<sub>1</sub> referred to as a left bundle branch block-like configuration. Arrhythmias that originate from the free wall of the left ventricle have a prominent positive deflection in V<sub>1</sub>, thereby producing a right bundle branch block-like morphology in V<sub>1</sub>. The frontal plane axis of the QRS is also useful. An axis that is directed inferiorly, as indicated by dominant R waves in lead II, III, and AVF, suggests initial activation of the cranial portion of the ventricle, whereas a frontal plane axis that is directed superiorly (dominant S waves in II, III, and AVF) suggests initial activation at the inferior wall.

Very rapid monomorphic VT has a sinusoidal appearance, also called *ventricular flutter*, because it is not possible to distinguish the QRS complex from the T wave (Fig. 252-3B). Relatively slow *sinusoidal* VTs have a wide QRS indicative of slowed ventricular conduction (Fig. 252-3C). Hyperkalemia, toxicity from excessive effects of drugs that block sodium channels (e.g., flecainide, propafenone, or tricyclic antidepressants), and severe global myocardial ischemia are possible causes.

*Polymorphic* VT has a continually changing QRS morphology indicating a changing ventricular activation sequence. Polymorphic VT that occurs in the context of congenital or acquired prolongation of the QT interval often has a waxing and waning QRS amplitude, creating a characteristic shifting axis referred to as *torsades des pointes* after the classic ballet sequence (Fig. 252-3D).

*Ventricular fibrillation* (VF) has continuous irregular activation with no discrete QRS complexes. Monomorphic or polymorphic VT may transition to VF in susceptible patients. Cardiac ischemia is the most common cause of VF (Fig. 252-3E).

The term *idiopathic ventricular arrhythmia* generally refers to PVCs or VT that occurs in patients with a normal electrocardiogram (ECG),

without structural heart disease, and not associated with an underlying genetic syndrome or risk of sudden death.

## CLINICAL MANIFESTATIONS

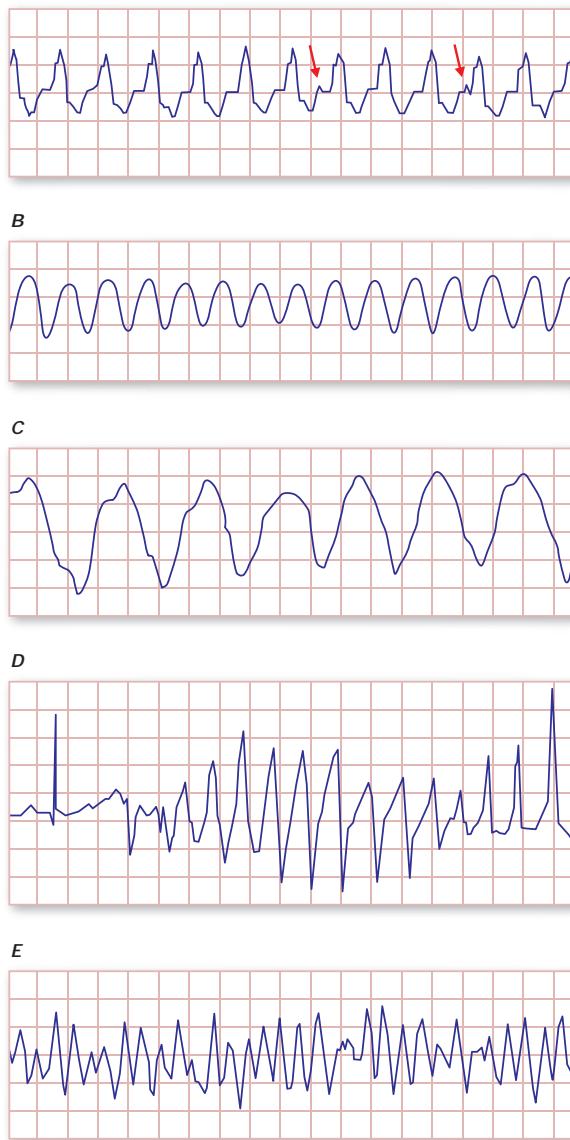
Common symptoms of VAs include palpitations, dizziness, exercise intolerance, episodes of lightheadedness, syncope, or sudden cardiac arrest leading to sudden death if not resuscitated. VAs can also be asymptomatic and encountered unexpectedly as an irregular pulse or heart sounds on examination or may be seen on a routine ECG, exercise test, or cardiac ECG monitoring. Occasionally when every other beat is a PVC (*bigeminy*), pulse measurements for heart rate can be erroneously low (*pseudobradyarrhythmia*) because the PVCs may not generate a separate pulse wave.

Syncope is a concerning symptom, particularly when occurring without prodrome, during exercise, or in the setting of abnormal ECG or structural heart disease. Such episodes can be due to VT that produces severe hypotension, warranting concern for risk of cardiac arrest and sudden death with arrhythmia recurrence. Although benign processes such as reflex-mediated neurocardiogenic (vasovagal) episodes and orthostatic hypotension are the most common causes of syncope, it is important to consider the possibility of underlying heart disease or a genetic syndrome causing VT. When these are suspected, hospitalization for further evaluation and monitoring is often appropriate.

Sustained VT may present as a wide QRS complex tachycardia that must be distinguished from supraventricular tachycardia with aberrancy (Chap. 246). Symptoms can be minor but more commonly include hypotension with syncope and even imminent cardiac arrest. Sustained VT may degenerate to VF, particularly if it is rapid and polymorphic. Many patients who are at risk for VT have known heart disease, and many have an implantable cardioverter defibrillator (ICD). In patients with an ICD, VT episodes may cause transient lightheadedness, palpitations, or syncope followed by a shock from the ICD (see below).

## EVALUATION OF PATIENTS WITH DOCUMENTED OR SUSPECTED VENTRICULAR ARRHYTHMIAS

There are several important considerations that guide evaluation of patients with documented or suspected cardiac arrhythmias. First, establish whether a VA is the cause of the symptoms or clinical



**FIGURE 252-3** **A.** Monomorphic ventricular tachycardia (VT) with dissociated P waves (short arrows). **B.** Ventricular flutter. **C.** Sinusoidal VT due to electrolyte disturbance or drug effects. **D.** Polymorphic VT resulting from prolongation of QT interval (torsade de pointe VT). **E.** Ventricular fibrillation. (See text for details.)

presentation. Second, determine whether the arrhythmia is associated with a cardiac disease, and establish the prognostic significance of that disease and, in particular, whether it is associated with a risk of sudden cardiac death. Finally, define the likelihood of arrhythmia recurrence and the symptoms and risk imposed by the recurrence. The risks of cardiac arrest and sudden cardiac death are largely determined by the cause of the arrhythmia and the associated underlying heart disease.

The diagnosis of VAs can be established by recording the arrhythmia on an ECG, by an ambulatory or implanted cardiac monitor, by an implanted rhythm management device such as a pacemaker or ICD, or in some cases, initiation of the arrhythmia during an electrophysiologic study. A 12-lead ECG of the arrhythmia should be obtained when possible and often provides clues to the potential site of origin and possible presence of underlying heart disease (see above) (Fig. 252-4).

For patients with sustained wide-complex tachycardia, initial management is guided by the patient's hemodynamic stability. The approach

to sustained wide-complex tachycardia is discussed in **Chap. 254**. The management of VT that causes cardiac arrest is discussed in **Chap. 306**. Once hemodynamic stability is restored, further management is guided by the possibility of a recurrence and the risk imposed by a recurrence.

### EVALUATION OF THE PATIENT WITH ARRHYTHMIA SYMPTOMS

When symptoms are intermittent, initial evaluation aims to establish symptom severity, provocative factors, and presence of underlying heart disease. Syncope or near syncope raises concern that an arrhythmia is causing episodes of hypotension and that there may be a risk of cardiac arrest. Symptoms that occur with exertion suggest arrhythmias that are provoked by sympathetic stimulation but can also be related to exertional ischemia in patients with coronary artery disease, although non-arrhythmia causes must also be considered. A past history of any cardiac disease is important. A review of all medications is relevant. Medications that prolong the QT interval predispose to polymorphic VT (**Chap. 255**). Adrenergic stimulants can provoke PVCs.

Family history should determine the presence of premature coronary artery disease, cardiomyopathy, or cardiac arrhythmias, particularly a history of sudden death. Family history may also suggest that a possibility of a genetic cause of an arrhythmia warrants careful consideration. Details of premature deaths are relevant. Sudden death victims are often said to have died of a “massive heart attack” despite absence of definite confirmation of thrombotic myocardial infarction and when other causes such as arrhythmia may have been possible.

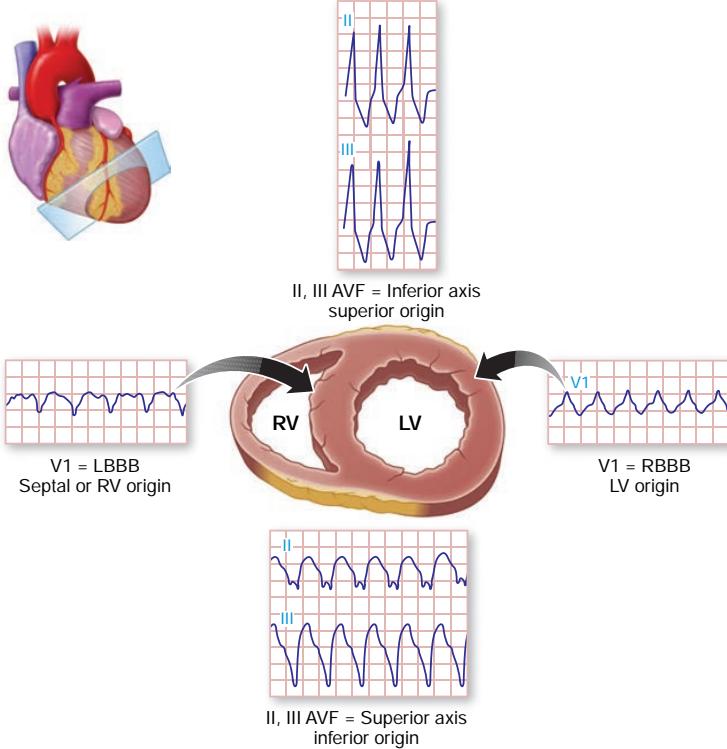
The physical examination focuses on evidence of structural heart disease with assessment of pulse, jugular venous pressure, lung fields, and cardiac auscultation. Stigmata of neuromuscular disease or dysmorphic features may suggest a genetic arrhythmia syndrome.

A 12-lead ECG should be obtained even if the patient is not having symptoms at the time of evaluation. Occasionally, premature ventricular beats will be detected. Patients with benign idiopathic arrhythmias usually have a completely normal ECG during sinus rhythm. Any ECG abnormality warrants further evaluation. Particularly relevant findings include Q waves that indicate prior myocardial infarction, which may have been silent, and ventricular hypertrophy, which may indicate hypertrophic cardiomyopathy or other ventricular disease. An ECG finding is the major diagnostic manifestation of several genetic arrhythmia syndromes in patients without structural heart disease, including the long QT syndrome, Brugada syndrome, and short QT syndrome.

If there is suspicion for structural heart disease, cardiac imaging is warranted to assess ventricular function and structure. Transthoracic echocardiography is most frequently employed for initial evaluation. Depressed ventricular function increases concern for a risk of sudden death and warrants further evaluation to establish the cause, which may be cardiomyopathy, coronary artery disease, or valvular heart disease. Ventricular thickening may indicate hypertrophic cardiomyopathy or infiltrative diseases such as amyloidosis. Cardiac MRI with gadolinium contrast imaging provides similar assessment but also can detect areas of ventricular scar, evident as regions of delayed hyperenhancement, which are usually present in patients who have sustained monomorphic VT (**Fig. 252-5**). The nature and location of abnormalities are helpful in assessing the type of heart disease. Evaluation to exclude atherosclerotic coronary artery disease should be performed in patients at risk, guided by age and other risk factors.

### TREATMENT OPTIONS FOR VENTRICULAR ARRHYTHMIAS

Treatment of VAs is guided by the severity and frequency of symptoms. For some, reassurance and removal of aggravating factors (e.g., caffeine) are all that is needed. For arrhythmias associated with a sudden death risk, ICD implantation is usually indicated and will provide a “safety net” to terminate life-threatening VT or VF, preventing sudden death but without preventing the arrhythmia. When suppression of the arrhythmia is required, antiarrhythmic drug therapy or catheter ablation is a major consideration.



**FIGURE 252-4** Site of ventricular tachycardia origin based on QRS morphology. (See text for details.) LBBB, left bundle branch block; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle.

## -ADRENERGIC BLOCKERS

Many VAs are sensitive to sympathetic stimulation, and -adrenergic stimulation also diminishes the electrophysiologic effects of many membrane-active antiarrhythmic drugs. The safety of -blocking agents makes them the first choice of therapy for most VAs. They are particularly useful for exercise-induced arrhythmias and idiopathic arrhythmias but have limited efficacy for most arrhythmias associated with heart disease. Bradyarrhythmias and negative inotropic effects are the major cardiac adverse effects.

## CALCIUM CHANNEL BLOCKERS

The nondihydropyridine calcium channel blockers diltiazem and verapamil can be effective for some idiopathic VTs. The risk of proarrhythmia is low, but they have negative inotropic and vasodilatory effects that can aggravate hypotension.

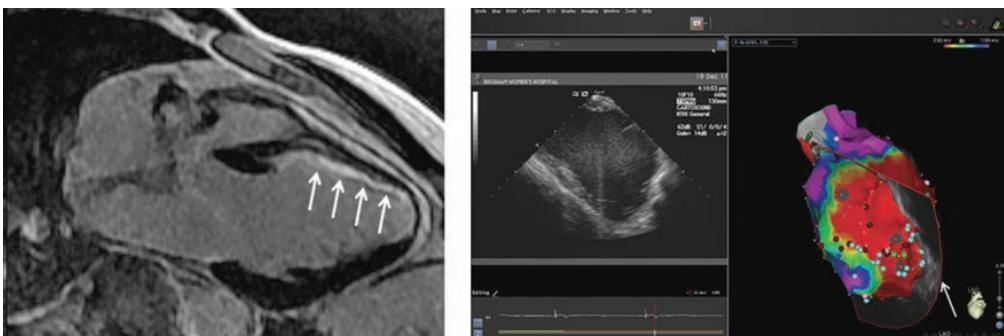
## SODIUM CHANNEL-BLOCKING AGENTS

Drugs whose major effect is mediated through sodium channel blockade include mexiletine, quinidine, disopyramide, flecainide, and propafenone, which are available for chronic oral therapy. Blockade of the fast inward sodium current has been referred to as a class I antiarrhythmic drug effect. Antiarrhythmic actions are the result of depressing cardiac conduction and membrane excitability. Conduction slowing can be manifest as a prolongation of QRS duration. Lidocaine, quinidine, and procainamide are available as intravenous formulations. Quinidine, disopyramide, and procainamide also have potassium channel-blocking effects that prolong the QT interval (class III antiarrhythmic drug action), contributing to

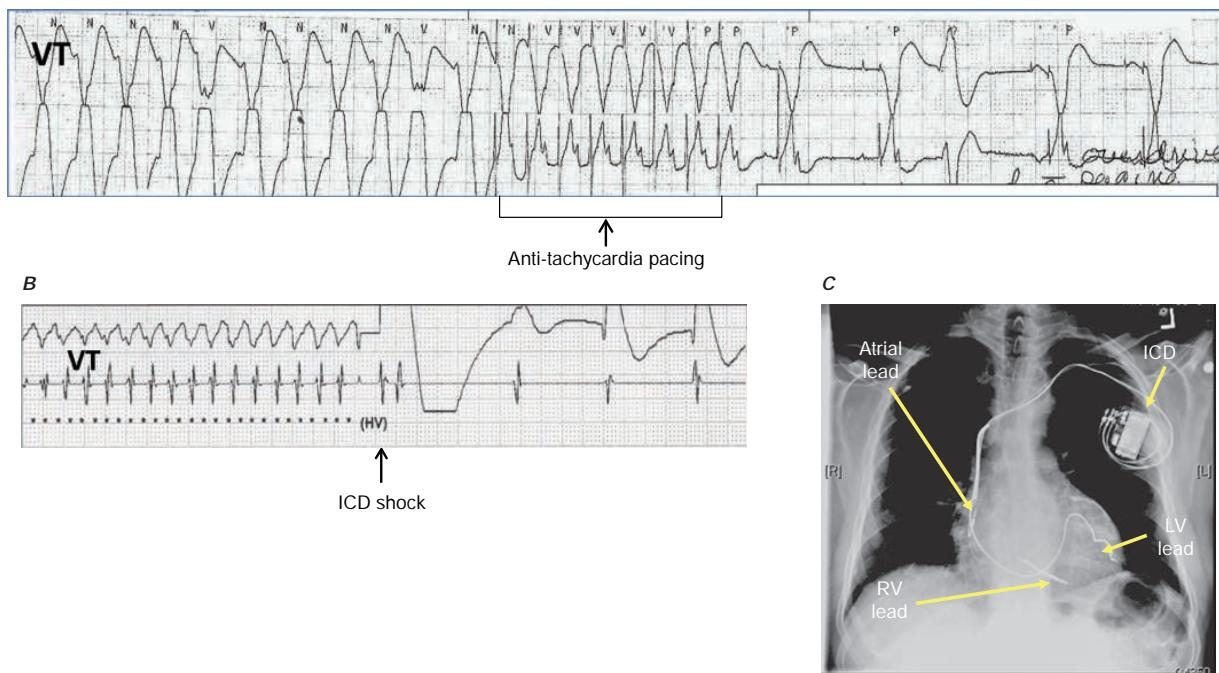
their antiarrhythmic effect. These agents have potential proarrhythmic effects and, with the possible exception of quinidine, also have negative inotropic effects that may have contributed to the increased mortality observed when some were administered chronically to patients with prior myocardial infarction. Long-term therapy is generally avoided in patients with structural heart disease but may be used to reduce symptomatic arrhythmias in patients with ICDs.

## POTASSIUM CHANNEL BLOCKING AGENTS

Sotalol and dofetilide block the delayed rectifier potassium channel  $I_{Kr}$ , thereby prolonging action potential duration (QT interval) and the cardiac refractory period, known as the class III antiarrhythmic drug effect. Sotalol also has nonselective -adrenergic-blocking activity. It has been



**FIGURE 252-5** Imaging studies of the left ventricle (LV) used to assist ablation for ventricular tachycardia (VT). Left panel is an MRI image of a longitudinal section demonstrating thinning of the anterior wall and late gadolinium enhancement in a subendocardial scar (white arrows). The middle panel shows a two-dimensional image of the LV in long axis corresponding to the sector through the mid-LV (arrow in figure on right panel) obtained by an intracardiac echocardiography probe positioned in the right ventricle. An electroanatomic three-dimensional map of the LV in the left anterior oblique projection is displayed in the right panel. The purple areas depict areas of normal voltage ( $>1.5$  mV). Blue, green, and yellow represent progressively lower voltages, with the red areas indicating scar ( $<0.5$  mV). Channels of viable myocardium with slow conduction within the scar are identified with the light blue dots. Areas of ablation delivered to regions involved in reentrant VT are indicated by maroon dots.



**FIGURE 252-6** Implantable cardioverter defibrillator (ICD) and therapies for ventricular arrhythmias. **A**, A monomorphic ventricular tachycardia (VT) is terminated by a burst of pacing impulses at a rate faster than VT (anti-tachycardia pacing). **B**, A rapid VT is converted with a high-voltage shock (arrow). The chest x-ray in the panel **C** shows the components of an ICD capable of biventricular pacing. ICD generator in the subcutaneous tissue of the left upper chest, pacing leads in the right atrium and the left ventricular (LV) branch of the coronary sinus (LV lead) and a pacing/defibrillating lead in the right ventricle (RV lead) are shown.

shown to have a modest effect on reducing ICD shocks due to ventricular and atrial arrhythmias. Proarrhythmia due to the polymorphic VT torsade de pointe that is associated with QT prolongation occurs in 3–5% of patients. Both sotalol and dofetilide are excreted via the kidneys, necessitating dose adjustment or avoidance in renal insufficiency. These drugs must be avoided in patients with other risk factors for torsade de pointe, including QT prolongation, hypokalemia, and significant bradycardia.

### AMIODARONE

Amiodarone blocks multiple cardiac ionic currents and has sympatholytic activity. It is the most effective antiarrhythmic drug for suppressing VAs. It is administered intravenously for life-threatening arrhythmias. During chronic oral therapy, electrophysiologic effects develop over several days. It is more effective than sotalol in reducing ICD shocks and is often used for VAs in patients with heart disease. Bradyarrhythmias are the major cardiac adverse effect. Ventricular proarrhythmia can occur, but torsade de pointe VT is rare. Noncardiac toxicities are a major problem and contribute to drug discontinuation in at least a third of patients during long-term therapy. Hyper- and hypothyroidism are related to the iodine content of the drug. Pneumonitis or pulmonary fibrosis occurs in ~1% of patients. Photosensitivity is common, and neuropathy and ocular toxicity can occur. Systematic monitoring is recommended during chronic therapy including assessment for thyroid, liver, and pulmonary toxicity. Intravenous administration of amiodarone via a peripheral vein for >24 h can cause severe peripheral thrombophlebitis. Dronedarone has structural similarities to amiodarone but without the iodine moiety. Efficacy for VAs is poor, and dronedarone increases mortality in patients with heart failure, so dronedarone is not typically used for treatment of VAs.

### IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

ICDs detect sustained VT, largely based on heart rate, and then terminate the arrhythmia. In transvenous devices, VF is terminated by a shock applied between a lead in the right ventricle and the ICD pulse generator. The lead can provide pacing for bradycardia if needed. This

transvenous form of ICD has the disadvantages of vascular occlusion, risk of lead fracture, endocarditis in the event of infection, and difficulty with removal. Monomorphic VT can also be terminated by a burst of rapid pacing faster than the VT, known as antitachycardia pacing (ATP) (Fig. 252-6A). If ATP fails or is not a programmed treatment, as is often the case for rapid VT or VF, a shock is delivered (Fig. 252-6B). ICDs can also be subcutaneous, without a transvenous lead. The rhythm is also sensed by this lead, in a manner similar to a surface ECG. The lead is placed overlying the left chest with a coil parallel to the sternum. Only shocks can be delivered from a subcutaneous ICD, and pacing is not possible. No matter the type of ICD, shocks are painful if the patient is conscious. ICDs are highly effective for termination of VT. The most common ICD complication is the delivery of unnecessary therapy (either ATP or shocks) in response to an inappropriately detected rapid supraventricular tachycardia or electrical noise as a result of an ICD lead fracture or electromagnetic interference from an external source. ICDs record and store electrograms from arrhythmia episodes that can be retrieved by interrogation of the ICD, which can be performed remotely and communicated via Internet. This assessment is critical after an ICD shock to determine the arrhythmia diagnosis and exclude an unnecessary therapy. Device infection is an important problem long term and occurs in ~1% of patients. This risk may be less for subcutaneous implants.

ICDs decrease mortality in patients at risk for sudden death due to structural heart diseases. In all cases, ICDs are recommended only if there is also expectation for survival of at least a year with acceptable functional capacity. The exception is in cases of patients with end-stage heart disease who are awaiting cardiac transplantation outside the hospital or who have left bundle branch block QRS prolongation such that they are likely to have improvement in ventricular function with cardiac resynchronization therapy from a biventricular ICD (Fig. 252-6C). In these cases, an ICD may be warranted despite guarded prognosis. A wearable ICD system with electrodes incorporated into a vest and an external battery pack is also available for short-term use in patients pending decision regarding a permanent implanted system.

Despite prompt termination of VT or VF by an ICD, the occurrence of these arrhythmias predicts subsequent increased mortality and risk of heart failure. Occurrence of VT or VF should therefore prompt assessment for potential causes including worsening heart failure, electrolyte abnormalities, and ischemia. Repeated shocks, even if appropriate, often induce posttraumatic stress disorder. Antiarrhythmic drug therapy, most commonly amiodarone, or catheter ablation is often required for suppression of recurrent arrhythmias. Antiarrhythmic drug therapy can alter the VT rate and the energy required for defibrillation, thereby necessitating programming changes in the ICD's algorithms for detection and therapy.

### CATHETER ABLATION FOR VT

Catheter ablation is usually performed by applying radiofrequency (RF) current to cause thermal injury by resistive heating of cardiac tissue responsible for the arrhythmia. An electrode catheter with an electroanatomic mapping system is used to map local electrical activity to identify the ventricular myocardium that is causing the arrhythmia, referred to as the arrhythmia substrate. The size and location of the arrhythmia substrate determine the ease and likely effectiveness of the procedure, as well as the potential complications. When the arrhythmia originates from the endocardium, as is most commonly the case, it can be reached from an endovascular approach via a femoral vein or artery. Less commonly, arrhythmias originate from the subepicardium, and percutaneous pericardial puncture, similar to pericardiocentesis, is required to insert a catheter into the pericardial space for mapping and ablation. In patients with scar-related VT due to prior infarction or cardiomyopathy, ablation targets abnormal regions in the scar. Because these scars often contain multiple reentry circuits over relatively large regions, extensive areas of ablation are required, and these areas are often identified as regions of low voltage displayed on anatomic reconstructions of the ventricle (Fig. 252-5).

Catheter ablation is often performed in patients with recurrent VAs associated with poor cardiac function, and the procedure-related mortality in this situation is 0.5–3%. Outcomes are better for patients with prior infarction and VT than for patients with nonischemic cardiomyopathies in which the scar locations are more variable and often intramural or subepicardial. Ablation can be lifesaving for patients with very frequent or incessant VT. Methods of delivering ablative energy to intramural areas or areas requiring very extensive ablation are under development. These include needle catheters capable of delivering ablative energy into intramural sources. Stereotactic body radiation therapy (SBRT), classically used for treating thoracic tumors, has been used to direct radiation therapy to a specific portion of the scar substrate to noninvasively ablate VT with encouraging early studies.

Idiopathic VTs and PVCs that occur in the absence of structural heart disease usually originate from a small focus, for which catheter ablation typically has a higher success rate for preventing recurrent arrhythmia. Long-term arrhythmia-free survival in these patients is excellent.

### ARRHYTHMIA SURGERY

When antiarrhythmic drug therapy and catheter ablation fail or are not an option, surgical cryoablation, often combined with aneurysmectomy, can be effective therapy for recurrent VT due to prior myocardial infarction and has also been used successfully in a few patients with nonischemic heart disease. Few centers now maintain the expertise for this therapy, though some use this therapy as an adjunct to ventricular assist device implantation.

### Acknowledgment

*Roy M. John and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.*

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253

## Premature Ventricular Contractions, Nonsustained Ventricular Tachycardia, and Accelerated Idioventricular Rhythm

William H. Sauer, Usha B. Tedrow

Ventricular ectopic beats are very common and may be identified during outpatient or inpatient telemetry monitoring either due to symptoms of palpitations or as an incidental finding. In most cases, ventricular ectopy, presenting as premature ventricular contractions (PVCs), nonsustained ventricular tachycardia (NSVT), and accelerated idioventricular rhythm (AIVR), is asymptomatic and does not require specific treatment. While most commonly benign when presenting in patients with structurally normal hearts and normal ECGs, these ventricular arrhythmias can rarely be associated with structural heart disease and a risk of sudden death.

### PREMATURE VENTRICULAR CONTRACTIONS AND NON-SUSTAINED VT

PVCs are very common and can be due to enhanced automaticity, triggered automaticity, or reentry. PVCs are often sensitive to sympathetic stimulation and can be a sign of increased sympathetic tone, myocardial ischemia, hypoxia, electrolyte abnormalities, or underlying heart disease. During myocardial ischemia or in association with other structural heart disease, PVCs can be a harbinger of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF).

The electrocardiogram (ECG) characteristics of the arrhythmia are often suggestive of whether structural heart disease is present. PVCs with smooth uninterrupted contours and sharp QRS deflections may suggest an ectopic focus in relatively normal myocardium, whereas broad notching and slurred QRS deflections may suggest a diseased myocardial substrate. The QRS morphology also suggests the likely site of origin within the ventricle. PVCs that have a dominant S wave in  $V_1$ , referred to as a left bundle branch block-like configuration, originate from the right ventricle or interventricular septum. Those with a dominant R wave in  $V_1$  originate from the left ventricle. A superior frontal plane axis (negative in II, III, aVF) indicates initial depolarization of the inferior wall (diaphragmatic aspect of the heart), whereas an inferior frontal plane axis (positive in II, III, aVF) indicates an origin in the cranial aspect of the heart. The location of arrhythmia origin often suggests the nature of underlying heart disease. Most common ventricular arrhythmias that are not associated with structural heart disease have a left bundle branch block-like configuration. PVCs with a right bundle branch block configuration are more likely to be associated with structural heart disease. Multiple morphologies of PVCs (multifocal PVCs) are also more likely to indicate structural heart disease or a myopathic

**1916** disease process. In patients with heart disease, greater frequency and complexity (couplets and NSVT) of these arrhythmias are associated with more severe disease.

## PVCs AND NSVT DURING ACUTE ILLNESS

These arrhythmias are often encountered in patients who are being evaluated in the emergency department or who have been hospitalized and are on a cardiac monitor. When encountered during acute illness or as a new finding, evaluation should focus on detection and correction of potential aggravating factors and causes, specifically myocardial ischemia, ventricular dysfunction, and electrolyte abnormalities, most commonly hypokalemia. If there is a suspicion of underlying heart disease, then this should be evaluated. Otherwise, asymptomatic PVCs and NSVT in the hospitalized patient do not indicate any specific treatment outside the patient's presenting illness.

## PVCs AND NSVT IN PATIENTS WITHOUT HEART DISEASE

Idiopathic ventricular arrhythmias frequently originate from the left or right ventricular outflow tracts near the valve annuli, giving rise to PVCs or VT that have a left bundle branch block-like configuration, with an inferiorly directed frontal plane axis, as discussed below. Other regions that give rise to PVCs in normal hearts include the papillary muscles and fascicular tissue. NSVT from a benign idiopathic source is usually monomorphic, with rates <200 beats/min. NSVT that is very rapid, polymorphic, or with a first beat that occurs prior to the peak of the T wave ("short-coupled") is uncommon and should prompt concern and careful evaluation for underlying disease or genetic syndromes associated with sudden death.

A family history of sudden death should prompt evaluation for genetic syndromes associated with sudden death, including cardiomyopathy, long QT syndrome, and arrhythmogenic right ventricular cardiomyopathy (ARVC) (see below). Any abnormality on the 12-lead ECG warrants further evaluation. Repolarization abnormalities are seen in a number of genetically determined syndromes associated with sudden death, including the long QT syndrome, Brugada syndrome, ARVC, and hypertrophic cardiomyopathy (Fig. 253-1). Structural abnormalities such as mitral valve prolapse and mitral annular disjunction can be associated with papillary muscle PVCs and sudden death. An echocardiogram is often necessary to assess ventricular function,

wall motion abnormalities, and valvular heart disease. Contrast-enhanced cardiac magnetic resonance imaging (MRI) is also useful for this purpose and for the detection of ventricular scarring that is the substrate for sustained VT. Exercise stress testing should be performed in patients with effort-related symptoms and for those at risk for coronary artery disease.

## TREATMENT OF IDIOPATHIC ARRHYTHMIAS

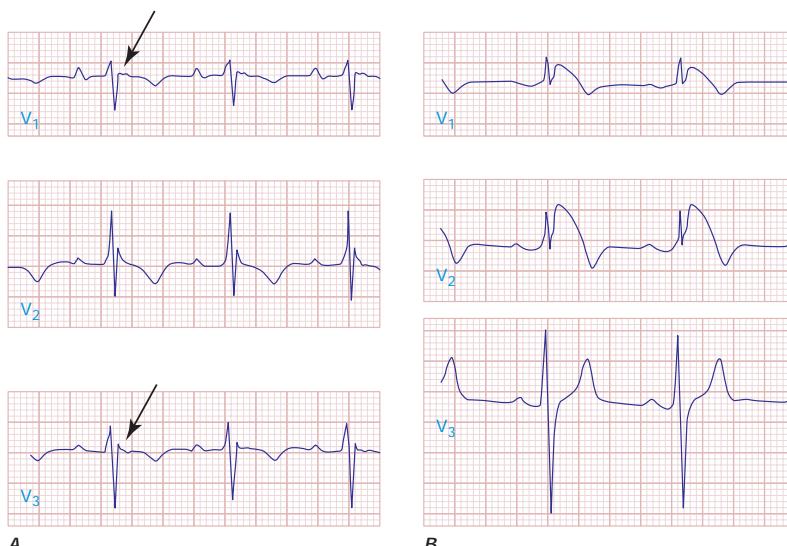
For PVCs and NSVT in the absence of structural heart disease or a genetic sudden death syndrome, no specific therapy is needed unless the patient has significant symptoms or evidence that frequent PVCs are depressing ventricular function (see below). Reassurance that the arrhythmia is benign is often sufficient to allow the patient to cope with the symptoms, which will often wax and wane in frequency over years. Avoiding stimulants, such as caffeine and alcohol, is helpful in some patients. If symptoms require treatment,  $\beta$ -adrenergic blockers and nondihydropyridine calcium channel blockers (verapamil and diltiazem) are sometimes helpful. If these fail, more membrane active antiarrhythmic drugs and catheter ablation are options. The antiarrhythmic agents flecainide, propafenone, mexiletine, and amiodarone can be effective, but the potential for side effects warrants careful consideration prior to prescribing these agents for long-term use. Catheter ablation is effective at suppressing this arrhythmia in ~90% of patients. Failure of ablation is usually due to inability to provoke the arrhythmia for mapping in the electrophysiology laboratory or if the site of origin is near a vital structure, such as the coronary arteries or His-Purkinje system, or is not accessible due to a site of origin deep within the myocardium.

## PVCs AND NSVT ASSOCIATED WITH ACUTE CORONARY SYNDROMES

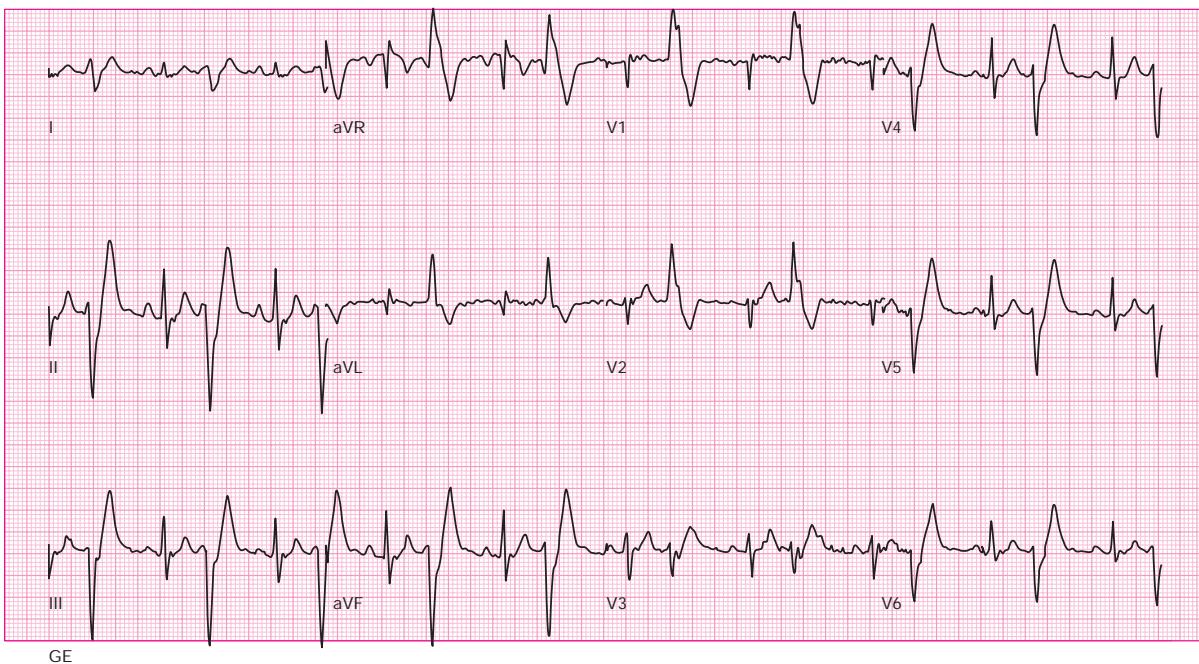
In the peri-infarct period, PVCs and NSVT are common and can be an early manifestation of ischemia and a harbinger of subsequent VF. Treatment with  $\beta$ -adrenergic blockers and correction of hypokalemia and hypomagnesemia reduce the risk of VF. Routine administration of antiarrhythmic drugs such as lidocaine or amiodarone does not reduce mortality and is not indicated for suppression of PVCs or asymptomatic NSVT but may be implemented transiently if an episode of sustained VT or VF occurs, with the goal of reducing the likelihood of a subsequent episode.

Following recovery from acute myocardial infarction (MI), frequent PVCs (typically >10 PVCs/h), repetitive PVCs with couplets, and NSVT are markers for depressed ventricular function and increased mortality, but routine antiarrhythmic drug therapy to suppress these arrhythmias has not been shown to improve mortality. Therefore, amiodarone is an option for treatment of symptomatic arrhythmias in this population when the potential benefit outweighs its potential toxicities.  $\beta$ -Adrenergic blockers reduce sudden death but have limited effect on spontaneous arrhythmias.

For survivors of an acute MI, an implantable cardioverter defibrillator (ICD) reduces mortality in certain high-risk groups: patients who have survived >40 days after the acute MI and have a left ventricular ejection fraction of <30%, or who have an ejection fraction <35% and have symptomatic heart failure (functional class II or III); and patients >5 days after MI who have a reduced left ventricular ejection fraction, NSVT, and inducible sustained VT or VF on electrophysiologic testing. ICDs do not reduce total mortality when routinely implanted early after MI and have not been demonstrated to improve mortality when implanted early after coronary artery revascularization.



**FIGURE 253-1** Electrocardiogram leads depicting Brugada syndrome. Precordial chest leads V<sub>1</sub>–V<sub>3</sub> showing typical abnormalities of arrhythmogenic right ventricular cardiomyopathy (ARVC) (**A**) and Brugada syndrome (**B**). In ARVC, there is T inversion and delayed ventricular activation manifest as epsilon waves (arrows). Panel **B** shows ST elevation in V<sub>1</sub> and V<sub>2</sub> typical of the Brugada syndrome.



**FIGURE 253-2** Ventricular bigeminy with premature ventricular contractions (PVCs) originating from the posteromedial papillary muscle. Twelve-lead electrocardiogram showing normal sinus rhythm with ventricular bigeminy. The PVCs have a right bundle branch block configuration in V<sub>1</sub>, with superiorly directed axis. The leads V<sub>4</sub>–V<sub>6</sub> are negative. The configuration is consistent with a PVC origin in the posteromedial papillary muscle of the left ventricle.

### PVCs AND NSVT ASSOCIATED WITH DEPRESSED VENTRICULAR FUNCTION AND HEART FAILURE

PVCs and NSVT are common in patients with depressed ventricular function and heart failure and are markers for disease severity and increased mortality, but antiarrhythmic drug therapy to suppress these arrhythmias has not been shown to improve survival. The use of antiarrhythmic drugs whose major action is blockade of the cardiac sodium channel (flecainide, propafenone, mexiletine, quinidine, and disopyramide) is avoided in patients with structural heart disease because of a risk of proarrhythmia and negative inotropic effects. Amiodarone suppresses ventricular ectopy and reduces sudden death but does not improve overall survival. ICDs are the major therapy to protect against sudden death in patients at high risk and are recommended for those with a left ventricular ejection fraction <35% and New York Heart Association class II or III heart failure, in whom they reduce mortality from 36 to 29% over 5 years.

### PVC AND NSVT ASSOCIATED WITH OTHER CARDIAC DISEASES

Ventricular ectopy is associated with increased mortality in patients with hypertrophic cardiomyopathy or with congenital heart disease associated with right or left ventricular dysfunction. In these patients, management is similar to that for patients with ventricular dysfunction. Pharmacologic suppression of the arrhythmia has not been shown to improve mortality. ICDs are indicated for patients considered at high risk for sudden cardiac death.

### PVC-INDUCED VENTRICULAR DYSFUNCTION

Very frequent ventricular ectopy and repetitive NSVT can depress ventricular function, possibly through an effect similar to chronic tachycardia or by inducing ventricular dyssynchrony. Depression of ventricular function rarely occurs unless PVCs account for at least 10–20% of total beats over a 24-h period, and only a minority of patients with PVCs will have a reversible cardiomyopathy. Often the PVCs are idiopathic and unifocal, most commonly originating from the

outflow tract regions or left ventricular papillary muscles (Fig. 253-2), where they can be targeted for ablation.

Other sites of origin such as the mitral and tricuspid valve annuli, right ventricular moderator band, and even the epicardial surface of the heart also occur (Fig. 253-3). The factors that can potentially predict development of heart failure and increased risk of adverse outcomes include PVC frequency, characteristics of the PVC morphology, and timing of the PVC coupling interval. In addition, the presence of late gadolinium enhancement on cardiac MRI may suggest the presence of an additional underlying cardiomyopathic process. The degree of expected recovery of ventricular function with PVC suppression is difficult to predict. Even in the setting of known underlying cardiomyopathy, controlling frequent ventricular ectopy can be helpful to improve ejection fraction and improve other factors such as delivery of resynchronization pacing.

### ACCELERATED IDIOVENTRICULAR RHYTHMS

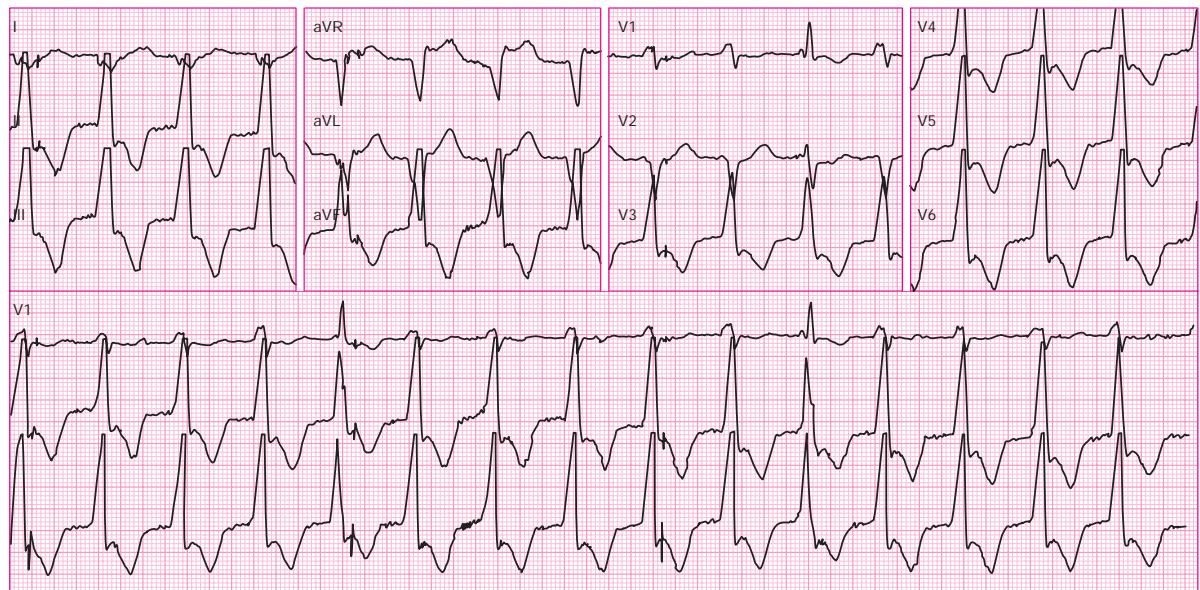
Three or more ventricular beats at a rate slower than 100 beats/min are termed an AIVR (Fig. 253-4). Automaticity is the likely mechanism, although in some rare cases, a reentrant circuit utilizing diseased myocardium can cause AIVR. Idioventricular rhythms are common during acute MI and may emerge during sinus bradycardia. Often, they are not symptomatic, but hemodynamic compromise may occur with the loss of atrioventricular synchrony in susceptible patients. Atropine may be administered to increase the sinus rates if this is a concern. This rhythm is also common in patients with cardiomyopathies or sleep apnea. It can also be idiopathic, often emerging when the sinus rate slows during sleep. Therapy should target any underlying cause and correction of bradycardia. Specific antiarrhythmic therapy for asymptomatic idioventricular rhythm is not necessary.

### FUTURE DIRECTIONS

Recently, it has been appreciated that inflammation plays a role in the genesis of PVCs in specific patients with inflammatory cardiomyopathies and even in inherited cardiomyopathies. The roles of early identification of this process and targeted treatment are areas of active research.



**FIGURE 253-3 Catheter ablation of premature ventricular contractions (PVCs) from the left ventricular outflow tract.** Shown is an electroanatomic map on the left and PVC morphology with superimposed pacing morphology on the right. The left ventricle is seen from the atrial side (posteriorly), and an ablation catheter is seen passing through the aortic valve at the top of the electroanatomic map and contacting the anterolateral portion of the left ventricular outflow tract. Maroon dots are ablation lesions that have been delivered at the site of interest. Pacing from the site of interest generates a QRS complex very similar to the clinical PVC as seen on the right.



**FIGURE 253-4 Accelerated idioventricular rhythm.** Shown is an example of a slow regular wide-complex rhythm. Fusion beats are seen on complexes 4 and 10, which are more positive in lead  $V_1$  and narrower than the rest of the beats. These features are consistent with an accelerated idioventricular rhythm.

## Acknowledgment

Roy M. John and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

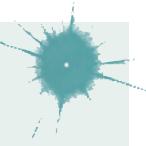
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# 254

## Sustained Ventricular Tachycardia

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Sustained monomorphic ventricular tachycardia (VT) is a ventricular arrhythmia with a wide QRS lasting for 30 s or requiring an intervention for termination. Each QRS complex resembles the others, indicating either a site of origin from either an automatic focus or fixed reentry circuit. In structural heart disease, the substrate is most often an area of patchy replacement fibrosis due to infarction, fibrosis, inflammation, or prior cardiac surgery that creates anatomic or functional reentry pathways. Less commonly, VT is related to reentry or automaticity in diseased conduction pathways in the Purkinje system. While scar-related reentrant VTs are associated with risk of sudden death, idiopathic VT is a more benign form of VT that occurs in structurally normal hearts and can be due to a focal region of automaticity in the myocardium or reentry involving a portion of the Purkinje system.

The clinical presentation varies depending on the rate of the arrhythmia, underlying cardiac function, and autonomic adaptation in response to the arrhythmia. Rapid VT can produce hypotension that may present as syncope, particularly in patients with significant ventricular dysfunction. In contrast, patients with normal cardiac function might tolerate their sustained VT, even presenting with simple palpitations, despite rapid rates. Monomorphic VT that is rapid or associated with structural heart disease may eventually deteriorate to ventricular fibrillation (VF), which may be the initial cardiac rhythm recorded at the time of resuscitation of an out-of-hospital cardiac arrest.

## DIAGNOSIS

Sustained monomorphic VT (**Table 254-1**) has to be distinguished from other causes of uniform wide QRS tachycardia. These include supraventricular tachycardia with left or right bundle branch block aberrant conduction, supraventricular tachycardias conducted to the ventricles over an accessory pathway, and rapid cardiac pacing, appropriate or inappropriate, in a patient with a ventricular pacemaker or defibrillator. In the presence of known heart disease, VT is the most likely diagnosis of a wide QRS tachycardia, independent of QRS morphology. When left ventricular (LV) function is depressed or there is evidence of structural myocardial disease, scar-related reentry is the most likely cause of sustained monomorphic VT. Scars are suggested by pathologic Q waves on the electrocardiogram (ECG), segmental LV or right ventricular wall motion abnormalities on echocardiogram or

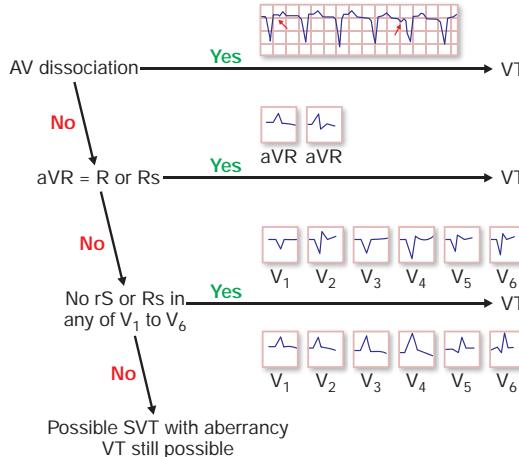
## TABLE 254-1 Sustained Ventricular Arrhythmias

1. **Idiopathic ventricular tachycardia (VT) without structural heart disease**
  - A. Outflow tract origin
    - Right ventricular (RV) outflow tract: left bundle branch block pattern in  $V_1$  with inferior axis (tall QRS in inferior leads) and late transition in the precordial leads
    - Left ventricular (LV) outflow tract: similar inferiorly directed axis but with early precordial transition with prominent R wave in  $V_2-V_3$
  - B. LV fascicular VT: Typical right bundle branch block pattern in  $V_1$  with sharp intrinsicoid deflection and left axis deviation (arising from left posterior fascicle in its most common form)
  - C. Papillary muscle VT
    - Postero medial: atypical right bundle branch block pattern in  $V_1$  with monophasic R wave and left axis deviation
    - Anterolateral: atypical right bundle branch block pattern in  $V_1$  with positive deflection in lead III and negative deflection in lead I
2. **Ischemic cardiomyopathy**
  - Monomorphic VT is common with prior large myocardial infarction
  - Polymorphic VT and ventricular fibrillation (VF) should prompt ischemia evaluation
3. **Nonischemic cardiomyopathy**
  - Fibrotic scars can cause monomorphic VT, especially with sarcoidosis or other inflammatory cardiomyopathies, Chagas' disease, and familial arrhythmogenic cardiomyopathies such as Lamin A/C genetic cardiomyopathy
  - Polymorphic VT and VF can also occur independently or related to degeneration of monomorphic VT
4. **Arrhythmogenic RV cardiomyopathy**
  - Monomorphic VT usually of RV origin (left bundle branch morphology in  $V_1$ )
  - Polymorphic VT and VF can occur independently or related to degeneration of monomorphic VT
5. **Repaired tetralogy of Fallot**
  - Monomorphic VT of RV origin (usually left bundle branch morphology in  $V_1$ )
6. **Hypertrophic cardiomyopathy**
  - Polymorphic VT or ventricular fibrillation
  - Less commonly, monomorphic VT associated with myocardial scars, particularly apical aneurysms
7. **Genetic arrhythmia syndromes**
  - A. Long QT syndrome
    - Torsades des pointes VT
  - B. Brugada syndrome
    - Ventricular fibrillation episodes, often nocturnal
  - C. Catecholaminergic polymorphic VT
    - Polymorphic VT or bidirectional VT
  - D. Short QT and early repolarization syndromes
    - Ventricular fibrillation
8. **Idiopathic polymorphic VT or ventricular fibrillation**
  - Usually triggered by recurrent premature ventricular contractions; the most common site of origin is the left posterior fascicle (right bundle branch block/left anterior fascicular block pattern)

nuclear imaging, and areas of delayed gadolinium enhancement during magnetic resonance imaging (MRI).

Hemodynamic stability during the arrhythmia does not help distinguish between VT and other mechanisms of wide-complex tachycardia. A number of ECG criteria have been evaluated to distinguish supraventricular tachycardia with aberrancy from VT. The presence of ventriculoatrial (VA) dissociation is a reliable marker for VT, provided the atrial rate is slower than the ventricular rate. Sometimes, P waves can be difficult to define, and the VA relationship cannot be assessed in a patient with an ongoing atrial arrhythmia such as atrial fibrillation. A P wave following each QRS does not exclude VT because 1:1 conduction from ventricle to atrium can occur. A monophasic R wave or RS complex in aVR or concordance from  $V_1$  to  $V_6$  of monophasic R or S waves is also relatively specific for VT (**Fig. 254-1**). A number of other QRS morphology criteria have also been described, but

### VT versus Supraventricular Tachycardia (SVT) with Aberrancy



**FIGURE 254-1** Algorithm for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia with aberrancy. AV, atrioventricular.

all have limitations and are not very reliable in patients with severe heart disease. In patients with known bundle branch block, the same QRS morphology during tachycardia as during sinus rhythm suggests supraventricular tachycardia rather than VT, but even this is not absolutely reliable. Patients with reentry involving the bundle branches of the Purkinje system can have a VT morphology that resembles their native QRS in sinus rhythm. An electrophysiologic study is sometimes required for definitive diagnosis. Occasionally, noise and movement artifacts on telemetry recordings can simulate VT. Prompt recognition can avoid unnecessary tests and interventions.

### TREATMENT AND PROGNOSIS

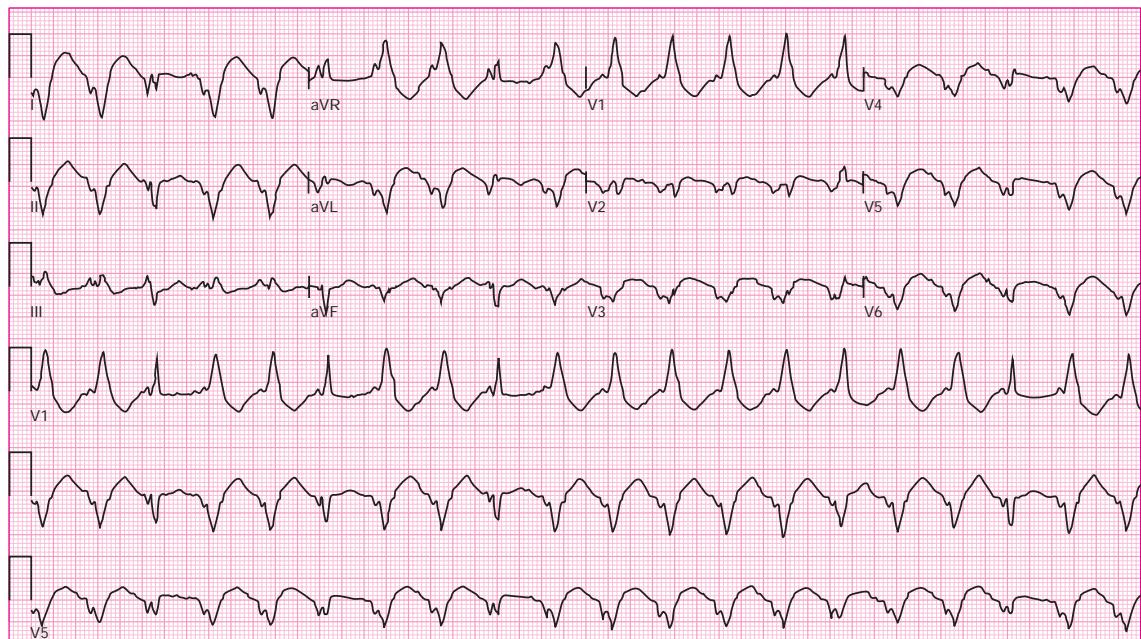
Initial management follows Advanced Cardiac Life Support (ACLS) guidelines. If hypotension, impaired consciousness, or pulmonary edema is present, QRS synchronous electrical cardioversion should be performed, ideally after sedation if the patient is conscious. For

stable tachycardia, a trial of adenosine is reasonable as this may clarify a supraventricular tachycardia with aberrancy. Adenosine should not be used if the patient has a heart transplant or if the wide-complex rhythm is irregular or unstable. Intravenous amiodarone is the drug of choice if heart disease is present. Following restoration of sinus rhythm, hospitalization and evaluation to define underlying heart disease are required. Assessment of cardiac biomarkers for evidence of myocardial infarction (MI) is appropriate, but acute MI is rarely a cause of sustained monomorphic VT. Elevations in troponin or creatine kinase (CK)-MB are more likely to indicate myocardial damage that is secondary to hypotension and ischemia from fixed coronary lesions during the VT. Subsequent management is determined by the underlying heart disease and frequency of VT. If VT recurs frequently or is incessant, administration of antiarrhythmic medications or catheter ablation may be required to restore stability. More commonly, sustained monomorphic VT occurs as a single episode but with a high risk of recurrence. Implantable cardioverter defibrillators (ICDs) are warranted for secondary prevention of sudden death in patients who present with sustained VT associated with structural heart disease (Fig. 254-2).

### SUSTAINED MONOMORPHIC VT IN SPECIFIC DISEASES

#### CORONARY ARTERY DISEASE

Patients who present with sustained monomorphic VT associated with coronary artery disease typically have a history of a remote prior large MI. Patients typically present years after the acute infarct with a remodeled ventricle and markedly depressed LV function. Even when there is biomarker evidence of acute MI, a preexisting scar from previous MI should be suspected as the cause of the VT. Infarct scars provide a durable substrate for sustained VT, and up to 70% of patients have a recurrence of the arrhythmia within 2 years. Scar-related reentry is not usually dependent on recurrent acute myocardial ischemia, so coronary revascularization is unlikely to prevent recurrent VT, although it may be appropriate for treatment of angina or other indications. Depressed ventricular function, which is a risk factor for sudden death, is usually present. Implantation of an ICD is clearly indicated for secondary prevention provided that there is a reasonable expectation of survival for 1 year with acceptable functional status. Compared with



**FIGURE 254-2** Monomorphic ventricular tachycardia in a patient with prior myocardial infarction. Shown is a wide-complex tachycardia. Complexes 3, 6, 9, and 18 are narrower and are examples of fusion beats, proving ventriculoatrial (VA) dissociation and proving that this rhythm is in fact ventricular tachycardia.

antiarrhythmic drug therapy. ICDs reduce annual mortality from 12.3 to 8.8% and lower arrhythmic deaths by 50% in patients with hemodynamically significant sustained VT or a history of cardiac arrest. Antiarrhythmic drugs may have some utility for palliation of VT symptoms and prevention of ICD therapies, such as shocks and antitachycardia pacing; however, without an ICD, these drugs do not improve survival.

Following ICD implantation, patients with depressed ejection fraction remain at risk for clinical heart failure, recurrent ischemic events, and recurrent VT, with a 5-year mortality that exceeds 30%. Attention to guideline-directed medical therapy for patients with heart failure and coronary artery disease, including -adrenergic blocking agents and angiotensin-converting enzyme inhibitors, is important.

ICD therapies, whether shocks or antitachycardia pacing, constitute an adverse event for the patient and are associated with increased rates of heart failure, mortality, and psychological stress. For this reason, recurrent VT episodes in patients with an ICD warrant treatment with medications or catheter ablation. In a randomized study of catheter ablation versus escalated medical therapy (Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs [VANISH]), patients receiving catheter ablation fared better than those receiving increasing doses of antiarrhythmic drugs, in particular, amiodarone. Another randomized trial (BERLIN VT) examined a preventative versus deferred ablation strategy in patients who had not yet failed an antiarrhythmic drug. This trial was stopped early for futility, with more procedural complications but fewer VT episodes in the catheter ablation group. For this reason, the most recent consensus statement most strongly recommends catheter ablation for patients with ischemic cardiomyopathy failing or intolerant of antiarrhythmic drugs but also allows for consideration of catheter ablation when long-term therapy with an antiarrhythmic drug (such as amiodarone, which has significant long-term toxicities) is not desired.

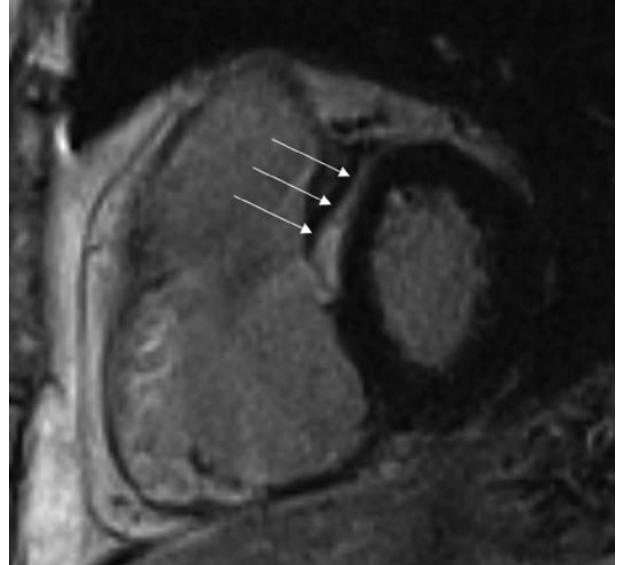
### NONISCHEMIC DILATED CARDIOMYOPATHY

Sustained monomorphic VT associated with nonischemic cardiomyopathy is usually due to scar-related reentry. The etiology of scar is often unclear, but progressive replacement fibrosis is the likely cause. Patients with nonischemic cardiomyopathy (NICM) have historically been presumed to have a postviral etiology, although increasingly, genetic causes are found in many. Inflammatory etiologies (myocarditis, sarcoidosis) are also increasingly appreciated. On cardiac MRI, scars are detectable as areas of delayed gadolinium enhancement and are more often intramural (Fig. 254-3) or subepicardial in location as compared with patients with prior MI. Scars that cause VT are often located adjacent to a valve annulus and can occur in either ventricle. Any cardiomyopathic process can cause scars and VT, but cardiac sarcoidosis, Chagas' disease, and cardiomyopathy due to Lamin A/C mutations are particularly associated with monomorphic VT. An ICD is indicated for patients with a history of sustained VT, syncope, or New York Heart Association class II or III heart failure symptoms, with additional drugs or catheter ablation for control of recurrent VT. In addition, for patients with malignant familial arrhythmogenic cardiomyopathies, an ICD may be considered earlier in the clinical course.

Overall, there are fewer studies of catheter ablation for VT in NICM. Reported success rates are lower than VT ablation in ischemic cardiomyopathy in most observational series. Additionally, inability to reproduce the clinical VT at ablation attempts and epicardial and intramural reentry circuits are important causes of failure of endocardial VT ablation in NICM. Imaging with MRI or computed tomography (CT) scans with late contrast administration to define areas of fibrosis can be useful to guide ablation.

### ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare genetic disorder most commonly due to mutations in genes encoding for cardiac desmosomal proteins; however, it is increasingly appreciated that other cardiomyopathic processes may produce a similar phenotype. Approximately 50% of patients have a familial transmission with autosomal dominant inheritance. A less common,



**FIGURE 254-3** Cardiac magnetic resonance image (MRI). Shown is an MRI of the heart with the right ventricle on the left and the left ventricle on the right. Between the ventricles (*arrows*) is a stripe of late gadolinium enhancement, indicating midmyocardial fibrosis in the interventricular septum. This type of scar pattern is often seen in patients with nonischemic cardiomyopathies and ventricular tachycardia.

autosomal recessive form is classically associated with cardiocutaneous syndromes that include Naxos disease and Carvajal syndrome. The former is most commonly related to mutations in plakophilin-2 and plakoglobin, while the latter is most commonly due to a mutation in desmoplakin. Patients are typically diagnosed between the second and fifth decades with palpitations, syncope, or cardiac arrest owing to sustained monomorphic VT, although polymorphic VT can also occur. Fibrosis and fibrofatty replacement most commonly involve the right ventricular myocardium and provide the substrate for reentrant VT that usually has a left bundle branch block-like configuration in ECG lead  $V_1$ , consistent with the right ventricular origin, and can resemble idiopathic VT. The sinus rhythm ECG suggests the disease in >85% of patients, most often showing T-wave inversions in  $V_1-V_3$ . Delayed activation of the right ventricle may cause a widened QRS (>110 ms) in the right precordial leads ( $V_1-V_3$ ) and a prolonged S-wave upstroke in those leads and, occasionally, a notched deflection at the end of the QRS known as an epsilon wave. Cardiac imaging may show right ventricular enlargement or areas of abnormal motion or reveal areas of scar on contrast-enhanced MRI.

LV involvement can occur and can occasionally precede manifest right ventricular disease. Clinical heart failure is rare except in late stages, and survival to advanced age can be anticipated provided that VT can be controlled. An ICD is recommended. When VT is exercise induced, it may respond to -adrenergic blockers and limiting exercise. Sotalol, flecainide, and amiodarone have been used to reduce ventricular arrhythmias. Catheter ablation prevents or reduces VT episodes in 70% of patients, but epicardial mapping and ablation are often required.

### ADULT CONGENITAL HEART DISEASE

Among all patients with adult congenital heart disease (ACHD), sustained monomorphic VT is quite rare. However, the most common substrate for sustained VT is seen in those with repairs of a ventricular septal defect, in particular tetralogy of Fallot (TOF). The prevalence of VT after TOF repair is estimated to be 3–14%, and risk of sudden cardiac death may reach as high as 1% per year in adulthood by the fourth or fifth decade of life. The greatest risk for ventricular arrhythmias is posed via two potential mechanisms: (1) those who have undergone repair involving a ventriculotomy and (2) those with long-standing



**FIGURE 254-4 Idiopathic monomorphic ventricular tachycardia (VT).** This is a 12-lead electrocardiogram showing the onset of idiopathic VT in a young patient without structural heart disease. The VT has a left bundle branch block configuration in  $V_1$ , and an inferiorly directed axis consistent with an outflow tract origin. Note that the narrow (normal sinus) beats have a normal QRS configuration, consistent with the patient's lack of structural heart disease.

hemodynamic overload causing ventricular dysfunction and/or hypertrophy independent of surgical incisions.

Monomorphic VT in TOF most commonly occurs in stereotyped circuits due to reentry around areas of surgically created scar in the right ventricle. Factors associated with VT risk include age  $>5$  years at the time of repair, high-grade ventricular ectopy, inducible VT on an electrophysiologic study, abnormal right ventricular hemodynamics, and sinus rhythm QRS duration  $>180$  ms. An ICD is usually warranted for patients who have a spontaneous episode of VT, but ICDs are also considered for patients with multiple risk factors. Catheter ablation or antiarrhythmic drug therapy is used to control recurrent episodes.

### BUNDLE BRANCH REENTRY VT

Reentry through the Purkinje system occurs in ~5% of patients with monomorphic VT in the presence of structural heart disease. The reentry circuit typically revolves retrograde via the left bundle and anterograde down the right bundle, thereby producing VT that has a left bundle branch block configuration. The VT QRS morphology may closely resemble the QRS morphology in sinus rhythm. Catheter ablation of the right bundle branch abolishes this VT. Bundle branch reentry is usually associated with severe underlying heart disease. Other scar-related VTs are often present and often require additional therapy.

### IDIOPATHIC MONOMORPHIC VT

Idiopathic VT in patients without structural heart disease usually presents with palpitations, lightheadedness, and, rarely, syncope. Episodes and can be provoked either by sympathetic stimulation or acute withdrawal of sympathetic tone, as in the immediate postexercise period. The QRS morphology of the arrhythmia suggests the diagnosis (see below). The sinus rhythm ECG is normal. Family history suggests no familial cardiomyopathy or sudden death. Cardiac imaging, including echocardiography and cardiac MRI, shows normal ventricular function and no evidence of ventricular scar. Occasionally, a patient with structural heart disease is found to have concomitant idiopathic VT unrelated to the structural disease, in which case, the underlying disease should be treated as per the guidelines, separate from the VT. Repeated bursts of nonsustained VT, which may occur incessantly, are known as repetitive monomorphic VT and can cause a tachycardia-induced cardiomyopathy with depressed ventricular function

that recovers after suppression of the arrhythmia. Sudden death in isolated idiopathic VT is rare, and an ICD is not recommended.

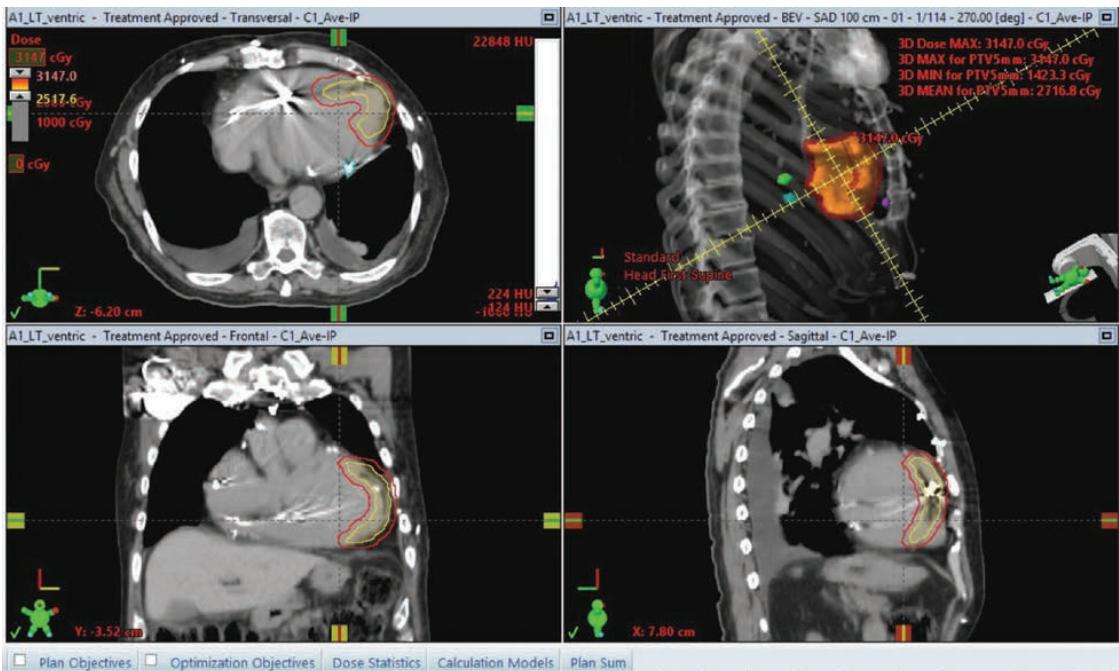
Outflow tract VTs originate from a focus near the pulmonic or aortic valve annuli, usually with features consistent with triggered automaticity. The arrhythmia may present with sustained VT, nonsustained VT, or premature ventricular contractions (PVCs). Most originate in the right ventricular outflow tract, which gives rise to VT that has a left bundle branch block configuration in  $V_1$ , and an axis that is directed inferiorly, with tall R waves in II, III, and aVF. Idiopathic VT can also arise in the LV outflow tract or in sleeves of myocardium that extend along the aortic root. LV origin is suspected when lead  $V_1$  or  $V_2$  has prominent R waves. Although this typical outflow tract QRS morphology favors idiopathic VT, some cardiomyopathies, notably ARVC, can cause PVCs or VT from this region. Excluding these diseases is an initial focus of evaluation (Fig. 254-4).

LV fascicular VT, sometimes referred to as Belhassen's VT or verapamil-sensitive VT, is the second most common form of idiopathic VT after outflow tract VTs. It often presents with sustained VT that has a right bundle branch block-like configuration and is negative in the inferior leads. It is often exercise induced and occurs more often in men than women. The mechanism was originally thought to be focal but has been demonstrated to be due to a small reentry circuit in or near the septal ramifications of the LV Purkinje system. There can be an LV false tendon associated with this rhythm.

Other sites of origin for idiopathic VT exist, including papillary muscles, mitral and tricuspid valve annuli, and the moderator band in the right ventricle. Even focal sites from the epicardial surface have been described. The presence of VT from these more unusual sites should prompt even more careful assessment for structural heart disease.

### MANAGEMENT OF IDIOPATHIC VT

Treatment is required for symptoms or when frequent or incessant arrhythmias depress ventricular function. Symptoms can be controlled with medications including beta blockers, calcium channel blockers, and sodium channel blockers such as flecainide. Although flecainide is not typically recommended in patients with structural heart disease, it has been used successfully to resolve tachycardia-induced cardiomyopathy in the setting of idiopathic PVCs and VT. Catheter ablation is also



**FIGURE 254-5** Stereotactic body radiation therapy. Shown is a planning computed tomography scan for noninvasive cardiac ablation delivered with stereotactic radiation. The region of interest is determined by analysis of presenting arrhythmias, underlying structural heart disease, and proximity to adjacent structures such as coronary arteries, the phrenic nerve, and the gastrointestinal tract. Radiation is delivered to the chosen treatment volume in order to create conduction block in the culprit scar region.

indicated for control of symptoms, has an overall success rate of 80%, and is recommended for those with symptomatic VT in whom medications are ineffective or not preferred by the patient. Efficacy and risks of catheter ablation vary with the specific site of origin of the VT, being most favorable for arrhythmias originating in the right ventricular outflow tract. Failure of ablation is most often due to inability to initiate the arrhythmia for mapping in the electrophysiology laboratory.

LV interfascicular VT can be terminated by intravenous administration of verapamil, although chronic therapy with oral verapamil is not always effective. Catheter ablation is recommended if -adrenergic blockers or calcium channel blockers are ineffective or not desired.

## FUTURE DIRECTIONS

Treatment of monomorphic VT, especially in the setting of structural heart disease, is an important cause of morbidity and mortality. Limitations of current therapies include toxicities of antiarrhythmic drugs and inability to successfully perform catheter ablation of the substrate for arrhythmias. Advances in imaging and intracardiac mapping techniques are likely to improve success rates over time. In addition, the inability of ablative energy to reach deep intramural substrates is a current limitation. Innovations in delivery of ablative energy, including bipolar ablation, needle catheter ablation, and electroporation, are ongoing. In addition, noninvasive ablation is a promising area of investigation. Proton beam or stereotactic radiation can be used to target VTs identified by advanced cardiac imaging or by a multielectrode ECG vest. Early multicenter studies suggest durable control of VT with noninvasive ablation (Fig. 254-5).

### Acknowledgment

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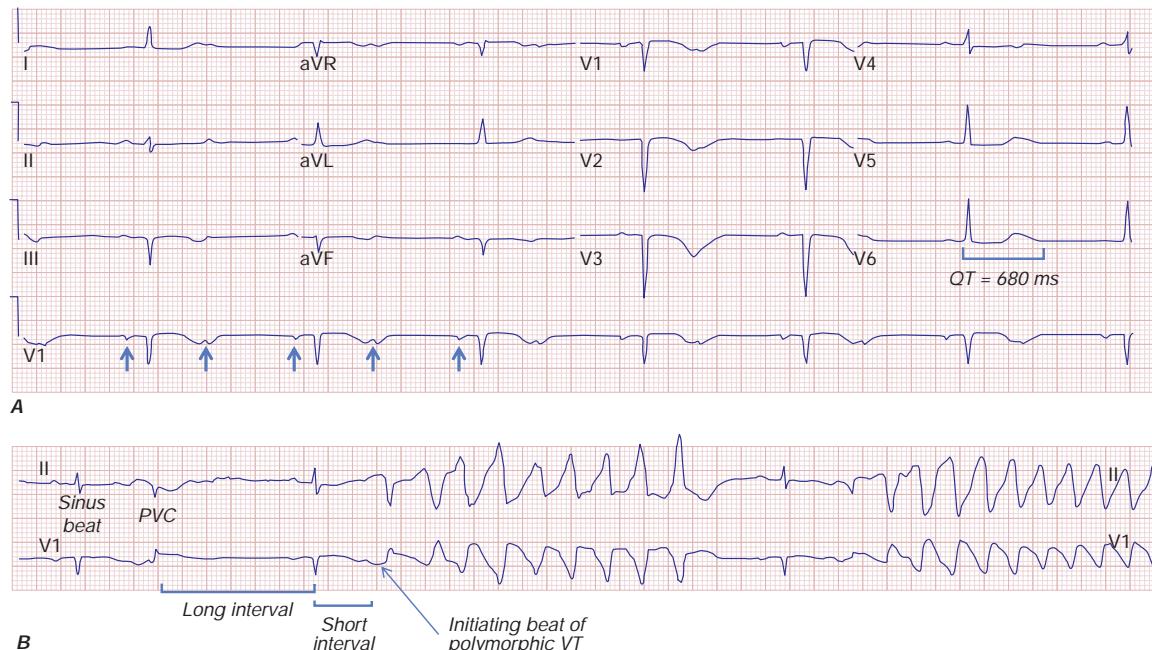
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## Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

William H. Sauer, Usha B. Tedrow

### POLYMORPHIC VENTRICULAR TACHYCARDIA

Sustained polymorphic ventricular tachycardia (VT) has a continuously changing QRS configuration from beat to beat, indicating a continually changing ventricular activation sequence. However, unlike sustained monomorphic VT, polymorphic VT does not necessarily indicate a fixed structural abnormality or focus of automaticity. Reentry can occur with continually changing reentrant paths, spiral wave reentry, and multiple automatic foci as potential mechanisms. This type of reentry



**FIGURE 255-1** Torsades des pointes ventricular tachycardia (VT) in a patient with bradycardia and marked QT prolongation. **A.** Twelve-lead electrocardiogram showing 2:1 atrioventricular block (P waves marked by blue arrows) with a heart rate of 40 beats/min and QT interval of 680 ms and corrected QT of 550 ms. **B.** The bottom panel shows a telemetry rhythm strip with periods of self-limiting torsades des pointes polymorphic VT. Following a normally conducted sinus beat, a premature ventricular contraction (PVC) causes a compensatory pause, leading to a long RR interval. A PVC after the next sinus beat initiates VT. This is the classic pause-dependent mode of initiation of torsades des pointes VT with long-short intervals.

can occur near fibrotic areas of myocardium, potentiated by proximity to damaged Purkinje cells or ventricular hypertrophy. Abnormal transmural dispersion of repolarization can occur in the setting of channelopathies or antiarrhythmic drugs in the absence of structural heart disease. Sustained polymorphic VT usually degenerates into ventricular fibrillation (VF). Polymorphic VT is typically seen in association with acute myocardial infarction or ischemia (MI), ventricular hypertrophy, and a number of genetic mutations that affect cardiac ion channels.

### POLYMORPHIC VT ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION/ISCHEMIA

Acute MI or ischemia is a common cause of polymorphic VT and should be the initial consideration in management. Approximately 10% of patients with acute MI develop VT that degenerates to VF, likely related to reentry through the infarct border zone. The risk is greatest in the first hour of acute MI. More rarely, surviving Purkinje cells with automaticity can initiate polymorphic VT. Following defibrillation as per the Advanced Cardiac Life Support (ACLS) guidelines, management is as for acute MI. -Adrenergic blockers, correction of electrolyte abnormalities, and prompt myocardial reperfusion are required. Repeated episodes of polymorphic VT may suggest ongoing MI and warrant assessment of adequacy of myocardial reperfusion. Polymorphic VT and VF that occur within the first 48 h of acute MI are associated with greater in-hospital mortality, but patients who survive past hospital discharge are not at increased risk for arrhythmic sudden death. Long-term therapy for postinfarct ventricular arrhythmia is determined by residual left ventricular (LV) function, with an implantable cardioverter defibrillator (ICD) indicated for persistent severe LV dysfunction (LV ejection fraction <35%).

### REPOLARIZATION ABNORMALITIES AND GENETIC ARRHYTHMIA SYNDROMES

#### ACQUIRED LONG QT SYNDROME

Abnormal prolongation of the QT interval is associated with the polymorphic VT torsades des pointes. The VT often has a characteristic

initiation sequence of a premature ventricular beat that induces a pause, followed by a sinus beat that has a longer QT interval and interruption of the T wave by the premature ventricular contraction (PVC) that is the first beat of the polymorphic VT (Fig. 255-1). This characteristic initiation is termed *pause-dependent*. Causes of QT prolongation include electrolyte abnormalities, bradycardia, and a number of medications that block repolarizing potassium currents, notably the antiarrhythmic drugs sotalol, dofetilide, and ibutilide, but also a number of other medications used for noncardiac diseases, including erythromycin, pentamidine, haloperidol, phenothiazines, and methadone. Individual susceptibility may be related to genetic polymorphisms or mutations that influence repolarization. The website [crediblemeds.org](http://crediblemeds.org) is an excellent resource for the clinician to determine whether a given medication has been reported to prolong the QT interval.

Patients typically present with near-syncope, syncope, or cardiac arrest. Sustained episodes degenerate to VF requiring defibrillation. PVCs and nonsustained VT often precede episodes of sustained VT. Intravenous administration of 1–2 g of magnesium sulphate usually suppresses recurrent episodes. If magnesium alone is ineffective, increasing heart rate with isoproterenol infusion or pacing, to a rate of 100–120 depolarizations/min as required to suppress PVCs, usually suppresses VT recurrences. These maneuvers allow time for correction of associated electrolyte disturbance (hypokalemia and hypocalcemia) and bradycardia and removal of any causative drugs (Table 255-1). Drug interactions that elevate levels of the offending agent are often a precipitating factor. Patients who experience a polymorphic VT induced by QT prolongation should be considered to have a susceptibility to the arrhythmia and should avoid all future exposure to medications known to prolong the QT interval.

#### CONGENITAL LONG QT SYNDROME

The congenital long QT syndrome (LQTS) is caused by mutations in genes coding for cardiac ion channels responsible for ventricular repolarization. The corrected QT (QTc) is typically prolonged to >440 ms in men and 460 ms in women. Symptoms are due to torsades des pointes VT. Several forms of congenital LQTS have been identified, but three groups of mutations that lead to LQTS-1, LQTS-2, and LQTS-3

**TABLE 255-1 Causes of QT Prolongation and Torsades des Pointes**

1. Congenital long QT syndromes
Long QT syndrome type 1: Reduced repolarizing current $I_{Ks}$ due to mutation in <i>KCNQ1</i> gene
Long QT syndrome type 2: Reduced repolarizing current $I_{Kr}$ due to mutation in <i>KCNH2</i> gene
Long QT syndrome type 3: Delayed inactivation of the $I_{Na}$ due to mutations in <i>SCN5A</i> gene
Others: Several other types of long QT syndromes have been described; long QT syndrome types 1, 2, and 3 account for 80–90% of cases
2. Electrolyte abnormalities: Hypokalemia, hypomagnesemia, hypocalcemia
3. Drug-induced acquired prolongation of QT interval
Antiarhythmic drugs
Class IA: Quinidine, disopyramide, procainamide
Class III: Sotalol, dofetilide, ibutilide, dofetilide
Antibiotics
Macrolides: Erythromycin, clarithromycin, azithromycin
Fluoroquinolones: Levofloxacin, moxifloxacin
Trimethoprim-sulfamethoxazole
Clindamycin
Pentamidine
Chloroquine
Antifungals: Ketoconazole, itraconazole
Antivirals: Amantadine
Antipsychotics
Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, zimelidine, ziprasidone
Tricyclic and tetracyclic antidepressants
Antihistamines (histamine 1-receptor antagonists)
Astemizole, diphenhydramine, hydroxyzine
Other drugs
Citrate (massive blood transfusions)
Cocaine
Methadone
Hydroxychloroquine
4. Cardiac conditions
Myocardial ischemia and infarction
Myocarditis
Marked bradycardia
Stress cardiomyopathy
5. Endocrine disorders
Hypothyroidism
Hyperparathyroidism
Pheochromocytoma
Hyperaldosteronism
6. Intracranial disorders
Subarachnoid hemorrhage
Thalamic hematoma
Cerebrovascular accident
Encephalitis
Head injury
7. Nutritional disorders
Anorexia nervosa
Starvation
Liquid protein diets
Gastroplasty and ileojejunostomy bypass
Celiac disease

syndromes account for 90% of cases. The most frequently encountered mutations (LQTS-1 and LQTS-2) are due to abnormalities of potassium channels, but mutations affecting the sodium channel (LQTS-3) and calcium channels have also been described.

Typical presentation is with syncope or cardiac arrest, usually during childhood. In LQTS-1, episodes tend to occur during exertion,

particularly swimming. In LQTS-2, sudden auditory stimuli or emotional upset predisposes to events. In LQTS-3, sudden death tends to occur during sleep. Asymptomatic patients may be discovered in the course of family screening or on a routine electrocardiogram (ECG). Genotyping can be helpful for family screening and to provide reassurance regarding the diagnosis. Correlations of genotype with risk and response to therapy are beginning to emerge. In most patients with LQTS-1 or LQTS-2, adequate doses of beta-blocker therapy (the non-selective agents nadolol and propranolol are favored) are sufficient protection from arrhythmia episodes. Markers of increased risk include QTc interval exceeding 500 ms, female gender, and a history of syncope or cardiac arrest. Recurrent syncope despite beta-blocker therapy or a high-risk profile merits consideration of an ICD. Avoidance of QT-prolonging drugs is critical for all patients with LQTS, including those who are genotype positive but have normal QT intervals.

## SHORT QT SYNDROME

Short QT syndrome is very rare compared to LQTS. The QTc is <360 ms and usually <300 ms. The genetic abnormality causes a gain of function of the potassium channel ( $I_{Kr}$ ) or reduced inward depolarizing currents. The abnormality is associated with atrial fibrillation, polymorphic VT, and sudden death.

## BRUGADA SYNDROME

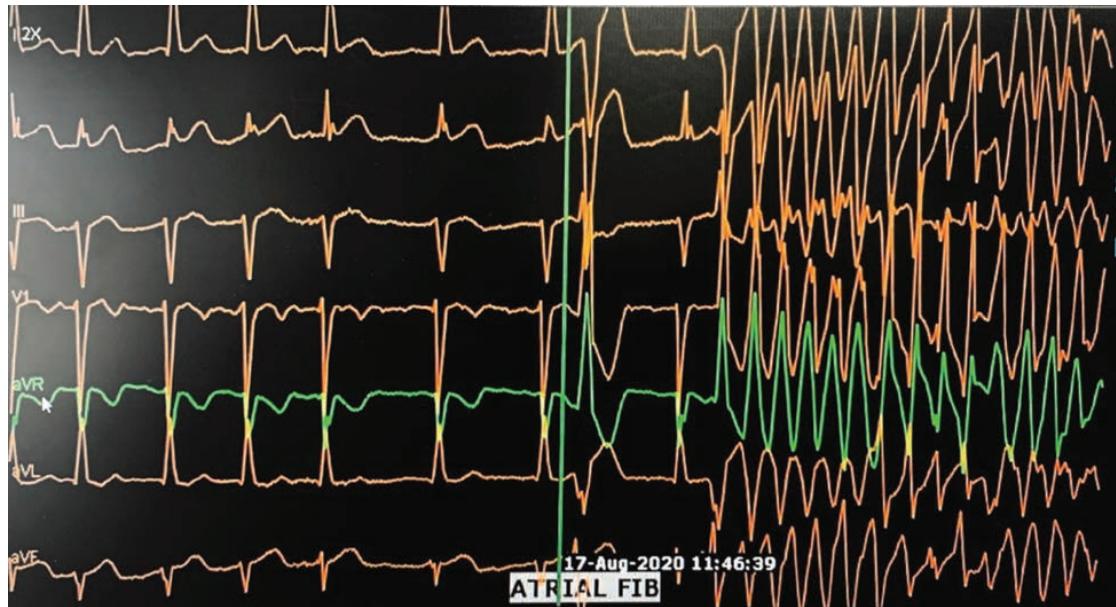
Brugada syndrome is a rare syndrome characterized by >0.2 mV of ST-segment elevation with a coved ST segment and negative T wave in more than one anterior precordial lead ( $V_1$ – $V_3$ ) (see Fig. 253-1) and episodes of syncope or cardiac arrest due to polymorphic VT in the absence of structural heart disease. Cardiac arrest may occur during sleep or be provoked by febrile illness. Males are more commonly affected than females. Mutations involving cardiac sodium channels are identified in ~25% of cases. Distinction from patients with similar ST elevation owing to LV hypertrophy, pericarditis, myocardial ischemia or MI hyperkalemia, hypothermia, right bundle branch block, and arrhythmogenic right ventricular cardiomyopathy is often difficult. Furthermore, the characteristic ST-segment elevation can wax and wane over time and may become pronounced during acute illness and fever. Administration of the sodium channel-blocking drugs flecainide, ajmaline, or procainamide can augment or unmask ST elevation in affected individuals. An ICD is indicated for individuals who have had unexplained syncope or been resuscitated from cardiac arrest. Quinidine and catheter ablation of abnormal regions in the epicardial right ventricular free wall have been used successfully to suppress frequent episodes of VT.

## EARLY REPOLARIZATION SYNDROME

Patients resuscitated from VF who have no structural heart disease or other identified abnormality have a higher prevalence of J-point elevation with notching in the terminal QRS. A family history of sudden death is present in some patients, suggesting a potential genetic basis. J-point elevation is also seen in some patients with the Brugada syndrome and is associated with a higher risk of arrhythmias. An ICD is recommended for those who have had prior cardiac arrest. It should be noted that J-point elevation is commonly seen as a normal variant in patients without arrhythmias, and in the absence of specific symptoms, the clinical relevance is not known.

## CATECHOLAMINERGIC POLYMORPHIC VT

This rare familial syndrome is due to mutations in the cardiac ryanodine receptor and, less commonly, the sarcoplasmic calcium binding protein calsequestrin 2. These mutations result in abnormal sarcoplasmic calcium handling and polymorphic ventricular arrhythmias that resemble those seen with digitalis toxicity. The VT is polymorphic or has a characteristic alternating QRS morphology termed bidirectional VT. Patients usually present during childhood with exercise or emotion-induced palpitations, syncope, or cardiac arrest. -Adrenergic blockers (e.g., nadolol and propranolol) and an ICD are usually recommended. Verapamil, flecainide, or surgical left cardiac sympathetic denervation reduces or prevents recurrent VT in some patients. The use of ICDs is controversial because of the fear that an ICD shock could initiate a



**FIGURE 255-2** Fascicular ectopy triggering ventricular fibrillation. Shown is a multilead monitor from a patient with recent inferoposterior myocardial infarction and surgical revascularization. Purkinje fibers can often survive acute infarction due to greater cellular glycogen stores and oxygenation from the left ventricular cavity. Upon revascularization, these now surviving but poorly coupled Purkinje fibers can trigger premature ventricular contractions and ventricular fibrillation as shown in this strip.

vicious cycle of adrenergic output and escalated ventricular arrhythmias, leading to death.

### HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder, occurring in 1 in 500 individuals, and is a prominent cause of sudden death before the age of 35 years. Sudden death can be due to polymorphic VT/VF. Rarely, sustained monomorphic VT occurs related to areas of ventricular scar, most commonly in patients who develop an apical aneurysm. Risk factors for sudden death in this disease include young age, nonsustained VT, failure of blood pressure to increase during exercise, recent (within 6 months) syncope, ventricular wall thickness >3 cm, and possibly the severity of LV outflow obstruction. An ICD is generally indicated for high-risk subjects, but the specific risk profile warranting an ICD continues to be debated. Surgical myectomy, performed to relieve outflow obstruction, has been associated with a sudden death rate of <1% per year. The reported annual rate of sustained VT or sudden death after transcoronary ethanol septal ablation done to relieve outflow obstruction has been reported to range between 1 and 5%.

### GENETIC DILATED CARDIOMYOPATHIES

Genetic dilated cardiomyopathies account for 30–40% of cases of nonischemic dilated cardiomyopathies. Some are associated with muscular dystrophy. Autosomal dominant, recessive, X-linked, and mitochondrial inheritance patterns are recognized. Mutations in genes coding for structural proteins of the nuclear lamina (Lamin A/C) and the *SCN5A* gene are particularly associated with conduction system disease and ventricular arrhythmias. Patients can experience polymorphic VT and cardiac arrest or develop areas of scar causing sustained monomorphic VT. ICDs are recommended for those who have had a sustained VT, are at high risk due to significantly depressed ventricular function (LV ejection fraction <35% and associated with heart failure), or have a malignant family history of sudden death.

### VENTRICULAR FIBRILLATION

VF is characterized by disordered electrical ventricular activation without identifiable QRS complexes (**Fig. 255-2**). Spiral wave reentry

and multiple circulating reentry wavefronts are possible mechanisms. Sustained polymorphic or monomorphic VT that degenerates to VF is a common cause of out-of-hospital cardiac arrest. Treatment follows ACLS guidelines with defibrillation to restore sinus rhythm. If resuscitation is successful, further evaluation is performed to identify and treat underlying heart disease and potential causes of the arrhythmia, including the possibility that monomorphic or polymorphic VT could have initiated VF. If a transient reversible cause such as acute MI is not identified, therapy to reduce the risk of sudden death with an ICD is often warranted.

### FUTURE DIRECTIONS

The role for catheter ablation in polymorphic VT and VF is rapidly evolving, with some investigators making use of simultaneous electrical recordings from basket catheters to define critical sites for the arrhythmia and correlating these with detailed cardiac imaging to identify typical vulnerable sites for ablation.

### Acknowledgment

Roy M. John and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

### FURTHER READING

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## Electrical Storm and Incessant Ventricular Tachycardia

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### ELECTRICAL STORM

Electrical storm or ventricular tachycardia (VT) storm refers to the occurrence of three or more episodes of VT or ventricular fibrillation (VF) within 24 h requiring intervention for termination. This severe electrical instability is associated with a high mortality and requires prompt therapeutic intervention. Electrical storms occur in 4% of patients with a primary prevention implantable cardioverter defibrillator (ICD) but in as many as 20% of patients with a history of known VT or resuscitated sudden death. Catheter ablation in electrical storms can be life-saving.

### INCESSANT VT

VT is designated incessant when VT continues to recur shortly after electrical, pharmacologic, or spontaneous conversion to sinus rhythm (**Fig. 256-1**). Typically, VT is monomorphic. Rarely, a slow incessant monomorphic VT will fail detection by an ICD because it falls outside of the programmed detection parameters. If the arrhythmia is hemodynamically stable acutely, patients can present with symptoms of gradual cardiac decompensation. VT may become incessant due to the proarrhythmic effect of an antiarrhythmic drug such as amiodarone or a sodium channel blocker such as flecainide. Hemodynamic support may be required acutely until the precipitating factors can be corrected. Urgent catheter ablation is often warranted.

### MANAGEMENT OF PATIENTS PRESENTING WITH ICD SHOCKS

A substantial number of patients who receive an ICD can be expected to have an arrhythmia that is terminated by the ICD, either by a shock or antitachycardia pacing. Although this is an expected event, it can be a sign of impending instability, deterioration of cardiac function, or emergence of a new arrhythmia and therefore requires evaluation. Interrogation of the ICD is crucial after a patient reports a shock or symptoms of arrhythmia to confirm that the therapy was indeed delivered for a ventricular arrhythmia and not for lead malfunction or an atrial arrhythmia. After a shock and in the absence of other symptoms to suggest arrhythmia or ischemia, patients have the option of waiting until the next working day or using remote monitoring to transmit device interrogation data to their physician. However, occurrence of multiple ICD shocks constitutes a medical emergency and warrants immediate medical attention by activating the emergency medical system. Patients should never drive to the hospital themselves after receiving a shock from their ICD.

Spontaneous arrhythmias, particularly those that are converted with a shock, are associated with a subsequent increased risk of death and hospitalization in patients with depressed ventricular function.

The occurrence of an arrhythmia, therefore, warrants a reevaluation for possible decline in cardiac function, emergence of ischemia, or intercurrent illness.

If the ICD therapy is appropriate for VT or VF, consideration is given to whether therapy is warranted to reduce further episodes with either antiarrhythmic drug therapy or catheter ablation. Patients who have a rare episode of VT that is appropriately terminated and who have no other evidence of instability may not need any additional therapy, particularly if the VT is terminated by antitachycardia pacing rather than a shock. Shocks reduce quality of life and can lead to posttraumatic stress disorder. In many patients, the possibility of a shock can be reduced with appropriate ICD programming. Studies have shown that antitachycardia pacing effectively terminates >70% of VT episodes, even when VT is very rapid. Most ICDs can be programmed to attempt overdrive pace termination during capacitor charge. If the arrhythmia then terminates, the shock is aborted. Appropriate programming of antitachycardia pacing is therefore critical for reducing shocks. For patients implanted with ICDs as primary prevention, programming of VF detection zones >220 beats/min significantly reduces unnecessary and inappropriate shocks. Long detection times will also help avoid unnecessary therapies for VT episodes liable to terminate spontaneously.

Recurrent symptomatic episodes of VT or VF (**Fig. 256-2**) warrant specific therapy with antiarrhythmic drugs or ablation as discussed for the specific arrhythmia. The beta blockers sotalol and amiodarone are the most common pharmacologic options. Amiodarone combined with beta blockers is more effective than sotalol or beta blockers alone. It is important to recognize that although VT/VF episodes may represent a deterioration of clinical status in these patients, interventions to control the arrhythmia itself may have adverse effects on outcome. Most antiarrhythmic drugs have the potential to induce bradycardia to the point of requiring pacing from the ICD that, in itself, may have deleterious effects on ventricular function. Catheter ablation is an important option for patients with monomorphic VT.

### MANAGEMENT OF THE PATIENT WITH ELECTRICAL STORM

Patients should be adequately sedated to allay anxiety and provide pain relief. Recurrent VT/VF is treated using standard Advanced Cardiac Life Support guidelines; treatment includes the use of medications such as beta blockers, amiodarone, and lidocaine with correction of any metabolic abnormalities. Recordings from electrocardiogram (ECG) monitoring or an implanted ICD are important to assess whether VT is monomorphic or polymorphic. The initiation and termination of tachycardia in the stored ICD electrograms may also suggest possible precipitating or aggravating factors. Sedation or general anesthesia should be considered for suppression of recurrent hemodynamically unstable ventricular arrhythmia. Percutaneous stellate ganglion block and upper thoracic epidural anesthesia may reduce cardiac sympathetic outflow and have been used to restore stability in some patients. Rarely, mechanical ventricular support with extracorporeal membrane oxygenation, percutaneous left ventricular assist device, or intra-aortic balloon pump may be considered (**Fig. 256-3**).

In addition to this global strategy of stabilizing the heart rhythm, reducing sympathetic drive, and relieving any triggering mechanisms for the management of electrical storm, there are some specific



**FIGURE 256-1** Example of incessant monomorphic ventricular tachycardia (VT). In the initial portion of this electrocardiogram tracing, monomorphic VT is present. A train of antitachycardia pacing (area bracketed by arrows) that is initiated at the fourth VT complex results in ventricular capture with fusion by the eighth beat and termination of VT at cessation of pacing. The patient has underlying atrial fibrillation. Multifocal premature ventricular contractions are present. VT similar in morphology to the initial VT restarts spontaneously toward the latter part of the trace (arrow).



**FIGURE 256-2** Multiple implantable cardioverter defibrillator (ICD) shocks from a subcutaneous ICD. Shown is a tracing from a patient with a subcutaneous ICD with recurrent episodes of ventricular fibrillation. The first five lines show gradually increasing amounts of ventricular ectopy and then ventricular fibrillation on the sixth line, which is terminated by a shock (thunderbolt) on the ninth line. The sequence repeats itself, and the patient receives a second shock that successfully terminates the arrhythmia.

Electrical storm treatments			
Speed of Deployment	Stabilize rhythm	Relieve triggers	Reduce sympathetic drive
Rapid	• Defibrillation • Amiodarone • Lidocaine	• Electrolyte management • Volume removal • Coronary revascularization	• Beta blockers • Sedation and intubation • Anxiolytics
	• Quinidine • Ranolazine • Procainamide • Catheter ablation	• Overdrive pacing • Mechanical support (ECMO/IABP)	• Stellate ganglion block (SGB)
		• Consideration of biopsy/anti-inflammatory therapies	• Cardiac surgical sympathetic denervation
Delayed			

**FIGURE 256-3** Global strategy for managing electrical storm. Shown are considerations for stabilization of electrical storm with medication strategies and procedures. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

therapies to be considered for patients with unique electrophysiologic substrate (Fig. 256-4).

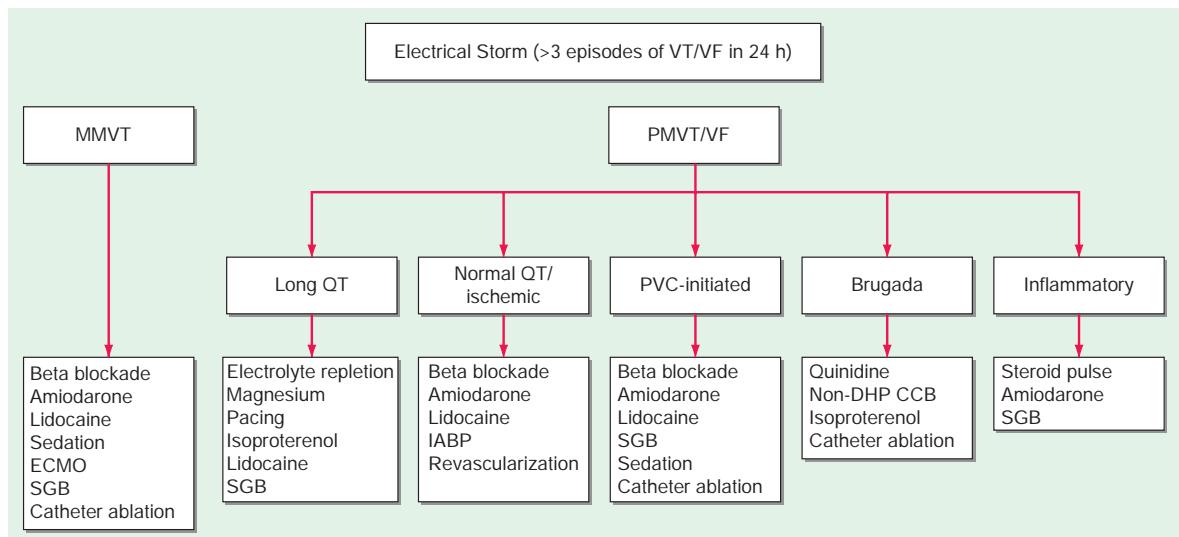
### VT/VF IN THE SETTING OF MYOCARDIAL ISCHEMIA

Ischemia should be considered especially if polymorphic VT or VF is identified as the primary arrhythmia. If electrical storm is occurring in the setting of an acute coronary syndrome, emergent revascularization and alleviation of anginal symptoms should be attempted. Within the infarcted myocardium, surviving Purkinje cells can exhibit triggered automaticity and lead to recurrent episodes of polymorphic VT/VF requiring frequent cardioversions before and after revascularization. Catheter ablation of premature ventricular contractions (PVCs) that are observed to repeatedly initiate the arrhythmia can be effective (Fig. 256-5).

pacing support should be considered. Isoproterenol can be used to increase patient's sinus rate, but there is the possibility of increased ectopy with high doses of isoproterenol possibly exacerbating ventricular arrhythmias. Although lidocaine can reduce the QT interval, other antiarrhythmic agents should be avoided because of their effect on repolarization.

### BRUGADA SYNDROME

If the QT interval is not prolonged and a Brugada pattern of Rsr' with ST elevation in leads V<sub>1</sub> or V<sub>2</sub> is seen on resting ECG, administration of quinidine and/or isoproterenol may abolish recurrent polymorphic VT/VF episodes. Nondihydropyridine calcium channel blockers and isoproterenol have also been used to reduce arrhythmic events. An epicardial substrate-based catheter ablation over the right ventricular



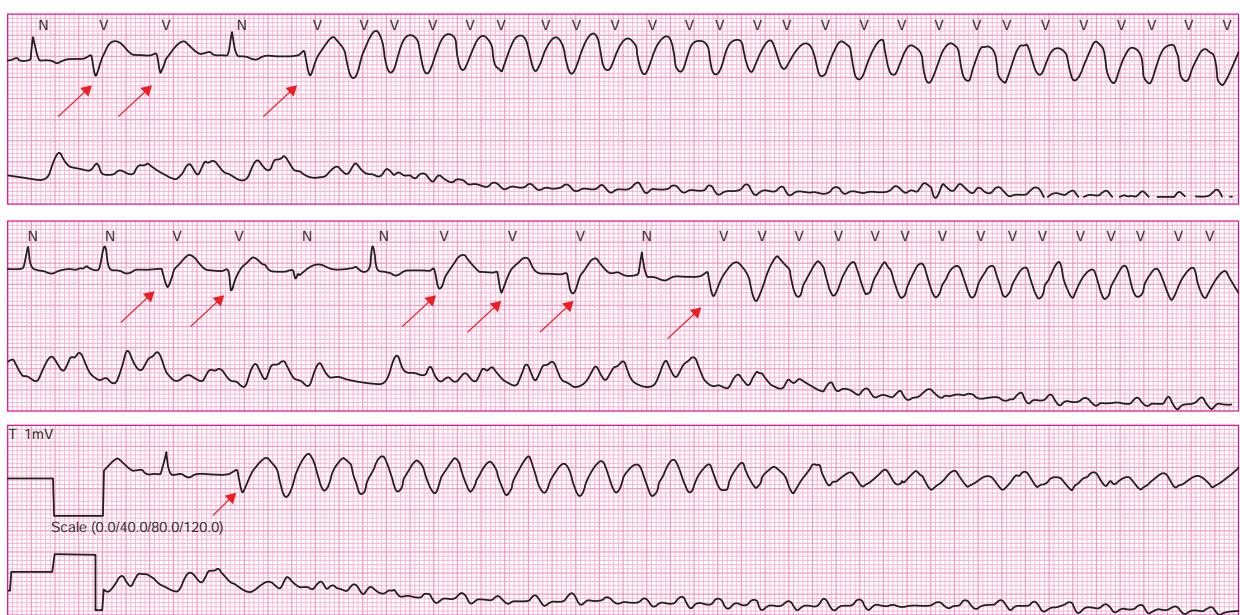
**FIGURE 256-4** Management algorithm for electrical storm. Shown is a suggested strategy for managing electrical storm based on the underlying rhythm and substrate. CCB, calcium channel blocker; DHP, dihydropyridine; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MMVT, monomorphic ventricular tachycardia; PMVT, polymorphic ventricular tachycardia; PVC, premature ventricular contraction; SGB, stellate ganglion block; VF, ventricular fibrillation; VT, ventricular tachycardia.

### PVC-INITIATED POLYMORPHIC VT/VF

Similar to the post-myocardial infarction electrical storm, patients without myocardial infarction or ischemia can have PVC-initiated polymorphic VT/VF storm. This idiopathic form of VF is usually caused by triggering PVCs originating from fascicular tissue or papillary muscles. Often, the ventricular ectopy is from scarred myocardial tissue detected on cardiac magnetic resonance imaging. Catheter ablation is indicated for this condition when antiarrhythmic medication is ineffective.

### ACQUIRED OR CONGENITAL LONG QT SYNDROME

If QT prolongation causing torsades des pointes (TdP) is possible, intravenous magnesium should be administered for its immediate effect on repolarization. In addition, electrolyte repletion, especially potassium, should be aggressively pursued. Increasing the heart rate can sometimes normalize the QT interval, and thus, pharmacologic or



**FIGURE 256-5** Premature ventricular contraction (PVC)-triggered ventricular fibrillation (VF) after myocardial infarction electrical storm. Shown is a series of monitoring strips from a patient with VF occurring in a PVC-triggered fashion after myocardial infarction. A single electrocardiogram lead and the blood pressure tracings are shown. The triggering PVCs are indicated with red arrows. The VF results in prompt hemodynamic collapse as evidenced by the blood pressure tracing.

outflow tract has been described as a strategy for drug-refractory ventricular tachyarrhythmias in Brugada syndrome.

#### INFLAMMATORY CARDIOMYOPATHY

If the patient has no known previous cardiac disease, consideration should be given to an inflammatory myocarditis causing the frequent ventricular arrhythmias. Giant cell myocarditis, cardiac sarcoidosis, and certain viral myocarditis can present with VT/VF storm. An endomyocardial biopsy should be considered to potentially identify new-onset inflammatory cardiomyopathies that may require urgent anti-inflammatory therapy. Once the acute episode is controlled, strategies to prevent recurrent VT or VF should be considered.

#### Acknowledgment

Roy M. John and William G. Stevenson contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

#### FURTHER READING

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Cronin EM et al: 2019 HRS/EHRA/APHRS/LAHS expert consensus statement on catheter ablation of ventricular arrhythmias. *EP Europe* 21:1143, 2019.

Jalife J, Stevenson W (eds): *Zipes and Jalife's Cardiac Electrophysiology: From Cell to Bedside*, 8th ed. Philadelphia, Elsevier, 2021.

## Section 4 Disorders of the Heart, Muscles, Valves, and Pericardium

257

### Heart Failure: Pathophysiology and Diagnosis

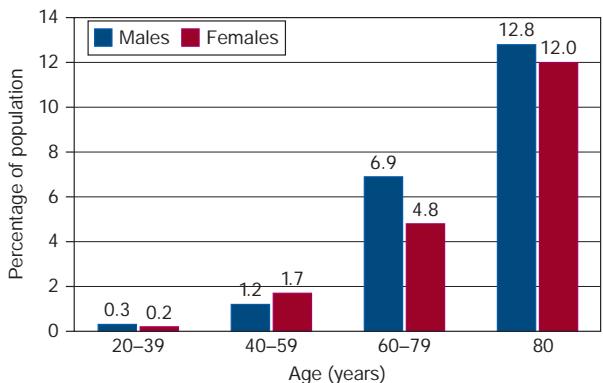
Michael M. Givertz, Mandeep R. Mehra



#### CLINICAL DEFINITIONS, EPIDEMIOLOGY, AND PHENOTYPES

##### DEFINITIONS

Heart failure (HF) is a common final pathway for most chronic cardiovascular diseases including hypertension, coronary artery disease, and valvular heart disease. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and Heart Failure Society of America (HFSA) guidelines define HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood leading to cardinal manifestations of dyspnea, fatigue, and fluid retention. The European Society of Cardiology's (ESC) definition emphasizes typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) and signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. Because some patients present without signs or symptoms of volume overload, the term *heart failure* is preferred over the older term *congestive heart failure*. *Cardiomyopathy* and *left ventricular dysfunction* are more general terms that describe disorders of myocardial structure and/or function, which may lead to HF. In pathophysiologic terms, HF has been defined as a syndrome



**FIGURE 257-1 Prevalence of heart failure.** Prevalence of heart failure among U.S. adults 20 years of age by sex and age, from the National Health and Nutrition Examination Survey (NHANES), 2013–2016. (Source: SS Virani et al: *Circulation* 141:e139, 2020.)

characterized by elevated cardiac filling pressure and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction.

**Chronic heart failure** describes patients with longstanding (e.g., months to years) symptoms and/or signs of HF typically treated with medical and device therapy as described in [Chap. 258](#). **Acute heart failure**, previously termed acute decompensated HF, refers to the rapid onset or worsening of symptoms of HF. Most episodes of acute HF result from worsening of chronic HF, but ~20% are due to new-onset HF that can occur in the setting of acute coronary syndrome, acute valvular dysfunction, hypertensive urgency, or postcardiotomy syndrome. Similarly, **acute pulmonary edema** in HF describes a clinical scenario in which a patient presents with rapidly worsening signs and symptoms of pulmonary congestion, typically due to severe elevation of left heart filling pressure.

## EPIDEMIOLOGY

**Global Incidence and Prevalence** HF is a major cause of morbidity and mortality worldwide. An estimated 6.2 million American adults are being treated for HF, with >600,000 new cases diagnosed each year. Globally, >26 million people are affected by HF. The prevalence of HF increases significantly with age, occurring in 1–2% of the population aged 40–59 years and up to 12% of adults >80 years old ([Fig. 257-1](#)). The lifetime risk of HF at age 55 years is 33% for men and 28% for women. Projections show that the prevalence of HF in the United States will increase by 46% from 2012 to 2030. Between 1980 and 2000, the number of HF hospitalizations rose steadily in both men and women to ~1 million per year. However, according to the most recent AHA statistics, hospitalizations decreased from 1,020,000 in 2006 to 809,000 in 2016. While prevalence of HF continues to rise, incidence may be decreasing due to improved recognition and treatment of cardiovascular disease and its comorbidities as well as disease prevention. However, as rates of obesity rise globally, these favorable trends in HF incidence may reverse.

There are distinct racial and ethnic differences in HF epidemiology ([Fig. 257-2](#)). In community-based

studies, blacks have the highest risk of developing HF, followed by Hispanic, white, and Chinese Americans. These differences are attributed to disparities in risk factors (e.g., obesity, hypertension, diabetes), socioeconomic status, and access to health care. Similarly, studies have shown that age-adjusted rates of HF hospitalization are highest for black men, followed by black women, white men, and white women. Accurate data on HF prevalence from emerging nations are lacking. As developing nations undergo socioeconomic development, the epidemiology of HF is becoming similar to that of Western Europe and North America, with coronary artery disease emerging as the most common cause of HF.

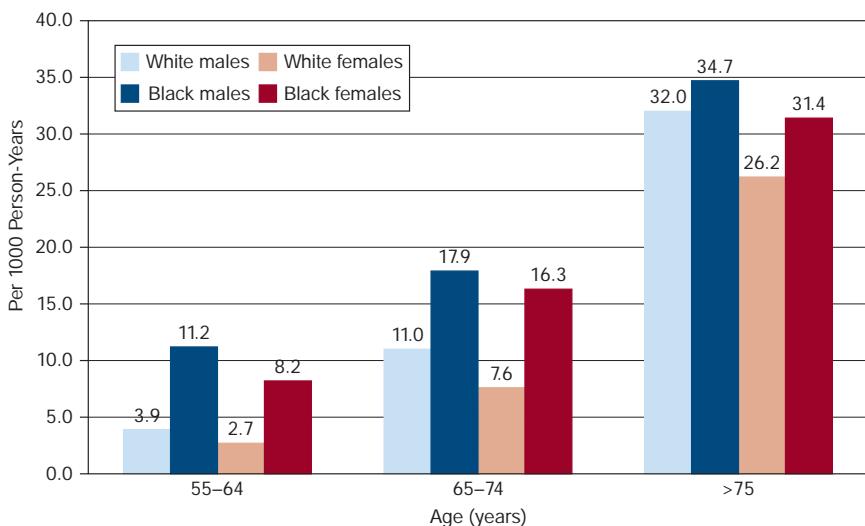
**Morbidity and Mortality** In primary care, the overall 5-year survival following the diagnosis of HF is ~50%. For patients with severe HF, the 1-year mortality may be as high as 40%. In the United States, 1 in 8 deaths list HF on the death certificate. The majority of these patients die of cardiovascular causes, most commonly progressive HF or sudden cardiac death. A number of clinical and laboratory parameters are independent predictors of mortality ([Table 257-1](#)). In a population-based study, hospitalizations were common after an HF diagnosis, with 83% hospitalized at least once, and 67%, 54%, and 43% hospitalized at least two, three, and four times, respectively. Following an HF admission, mortality rates range from 8–14% at 30 days to 26–37% at 1 year to up to 75% at 5 years. Readmission with HF is also common, ranging from 20–25% at 60 days to nearly 50% at 6 months. With each subsequent admission, the risk of death rises. There are racial disparities in outcomes with blacks having higher case-fatality rates compared to whites. Despite these statistics, the overall prognosis for patients with HF is improving due to treatment of risk factors and increased use of guideline-directed therapies.

**Costs** The overall cost of HF care is high (estimated \$30.7 billion in the United States in 2012) and rising. Projections for 2030 are that hospitalization costs for HF in the United States will increase to \$70 billion. Indirect costs due to lost work and productivity may equal or exceed this amount. The global economic burden of HF in 2012 was estimated at \$108 billion, with direct costs accounting for 60%. For pediatric patients with acute HF, inpatient costs are estimated at nearly \$1 billion annually and rising.

## PHENOTYPES AND CAUSES

### HF with Reduced Versus Preserved Ejection Fraction

Epidemiologic studies have shown that approximately one-half of patients who develop HF have reduced left ventricular ejection fraction (EF;



**FIGURE 257-2 Incidence of heart failure.** First acute heart failure annual event rates per 1000 from Atherosclerosis Risk in Communities (ARIC) Community Surveillance by sex and race in the United States from 2005 to 2014. (Source: SS Virani et al: *Circulation* 141:e139, 2020.)

**TABLE 257-1 Independent Predictors of Adverse Outcomes in Heart Failure**

Clinical	Male sex Increasing age Diabetes mellitus Chronic kidney disease Coronary artery disease Advanced NYHA class <sup>a</sup> Presence of third heart sound or elevated JVP Decreased exercise capacity Cardiac cachexia Depression
Structural	Reduced left ventricular ejection fraction Reduced right ventricular ejection fraction Increased ventricular volumes and mass Secondary mitral or tricuspid regurgitation
Hemodynamic	Elevated pulmonary capillary wedge pressure Reduced cardiac index Reduced peak oxygen consumption Pulmonary hypertension Diastolic dysfunction
Biochemical	Worsening renal function Hyponatremia Hyperuricemia Elevated cardiac biomarkers (troponin and natriuretic peptides) Elevated plasma neurohormones (norepinephrine, renin, aldosterone, and endothelin-1)
Electrophysiologic	Tachycardia Widened QRS interval or LBBB Atrial fibrillation Ventricular ectopic activity Ventricular tachycardia and sudden death

<sup>a</sup>See Table 257-4.

Abbreviations: JVP, jugular venous pressure; LBBB, left bundle branch block; NYHA, New York Heart Association.

40%) while the other half have near-normal or preserved EF ( 50%). Because most patients with HF (regardless of EF) have abnormalities in both systolic and diastolic function, the older terms of *systolic heart failure* and *diastolic heart failure* have fallen out of favor. Classifying patients based on their EF (HF with reduced EF [HF<sub>r</sub>EF] vs HF with preserved EF [HF<sub>p</sub>EF]) is important due to differences in demographics, comorbidities, and response to therapies (Chap. 258). Underlying causes of HF may be associated with reduced or preserved EF and include disorders of the coronary arteries, myocardium, pericardium, heart valves and great vessels (Table 257-2). The diagnosis of HF<sub>p</sub>EF is often more challenging due to the need to rule out noncardiac causes of shortness of breath and/or fluid retention.

**HF with Recovered EF** A subgroup of patients who are diagnosed with HFrEF and treated with guideline-directed therapy have rapid or gradual improvement in EF to the normal range and are referred to as having HF with recovered EF (HF<sub>rec</sub>EF). Predictors of HF<sub>rec</sub>EF include younger age, shorter duration of HF, nonischemic etiology, smaller ventricular volumes, and absence of myocardial fibrosis. Specific clinical examples include fulminant myocarditis, stress cardiomyopathy, peripartum cardiomyopathy, and tachycardia-induced cardiomyopathy, as well as reversible toxin exposures such as chemotherapy, immunotherapy, or alcohol. Despite recovery of EF, patients may remain symptomatic due to persistent abnormalities in diastolic function or exercise-induced pulmonary hypertension. For patients who become asymptomatic, withdrawal of therapy can lead to recurrence of HF symptoms and decrease in EF. In general, prognosis of patients with HF<sub>rec</sub>EF is superior to that of patients with either HFrEF or HF<sub>p</sub>EF.

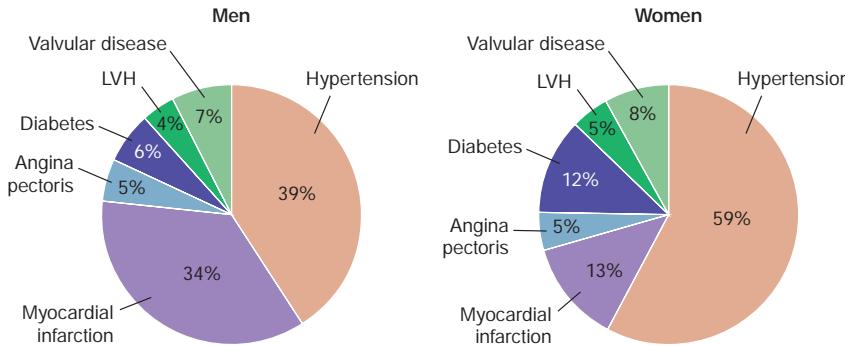
**TABLE 257-2 Selected Causes of Heart Failure**

Heart Failure with Reduced Ejection Fraction	
Coronary artery disease Myocardial infarction Myocardial ischemia	Nonischemic cardiomyopathy Infiltrative disorders Familial disorders Tachycardia induced
Valvular heart disease Aortic stenosis or regurgitation Mitral or tricuspid regurgitation	Toxic cardiomyopathy Chemotherapy, immunotherapy Drugs such as hydroxychloroquine Alcohol, cocaine
Congenital heart disease Intracardiac shunts Repaired defects Systemic right ventricular failure	Chronic lung/pulmonary vascular disease Cor pulmonale Pulmonary arterial hypertension
Infectious Chagas HIV	Autoimmune disease Giant cell myocarditis Lupus myocarditis
Heart Failure with Preserved Ejection Fraction	
Hypertension	Coronary artery disease
Valvular heart disease Aortic stenosis Mitral stenosis	Restrictive cardiomyopathy Amyloidosis Sarcoidosis Hemochromatosis Glycogen storage disease
Hypertrophic cardiomyopathy	Radiation therapy
Constrictive pericarditis	Aging
Myocarditis	Endomyocardial fibroelastosis
Obesity	
High-Output Heart Failure	
Thyrotoxicosis	Arteriovenous shunt
Obesity	Cirrhosis
Anemia	Vitamin B deficiency (beriberi)
Chronic lung disease	Myeloproliferative disorder

Abbreviation: HIV, human immunodeficiency virus.

**Heart Failure with Mildly Reduced EF (HFmrEF)** Patients with HF and an EF between 40 and 50% represent an intermediate group that are often treated for risk factors and comorbidities and with guideline-directed medical therapy similar to patients with HFrEF. They are felt to have primarily mild systolic dysfunction, but with features of diastolic dysfunction. They may also include either patients with reduced EF who experience improvement in their EF or those with initially preserved EF who suffer a mild decline in their systolic performance. Unlike the ACCF/AHA and HFS guidelines, the ESC guideline has identified HFmrEF as a separate group in order to stimulate research into underlying characteristics, pathophysiology, and treatment.

**Acquired Versus Familial, Congenital, and Other Disorders** In developed countries, coronary artery disease is responsible for approximately two-thirds of the cases of HF, with hypertension as a principal contributor in up to 75% and diabetes mellitus in 10–40% (Fig. 257-3). While most cardiovascular disease underlying HF is acquired in mid and later life (Chaps. 261, 273, and 277), a wide range of congenital and inherited disorders leading to HF may be diagnosed in children and younger adults. It is currently estimated that >1.4 million U.S. adults are living with congenital heart disease (CHD), which surpasses the number of children with CHD. In general, adults with CHD who develop HF can be divided into one of three pathophysiologic groups: uncorrected defects with late presentation due to missed diagnosis, nonintervention, or lack of access to care; repaired or palliated defects with late valvular and/or ventricular failure; or failing single-ventricle physiology. In addition, each adult with CHD often presents with unique anatomic and physiologic challenges that affect HF and its treatment.



**FIGURE 257-3 Population attributable risk of heart failure (HF) incidence.** Based on longitudinal data from the Framingham Heart Study, the risk factors contributing most significantly to the population attributable risk (PAR) of HF in men were previous myocardial infarction and hypertension (in men, both represented equal contributions to HF PAR). In contrast, hypertension was the risk factor accounting for the majority of total PAR in women. In women, previous myocardial infarction accounted for only 13% of the PAR of HF compared with 34% in men. PAR values are developed based on individual calculations for each variable using hazard ratio and prevalence statistics. Thus, they may not, in aggregate equal 100%. LVH, left ventricular hypertrophy. (From MM Givertz, WS Colucci: Heart failure. In Peter Libby, Essential Atlas of Cardiovascular Disease, 2009, Current Medicine Group. Reproduced with permission of SNCSC.)

Inherited cardiomyopathies are also increasingly recognized in adults presenting with HF. These include more common disorders, such as hypertrophic and arrhythmogenic cardiomyopathies, and lesser known heart muscle disease related to pathogenic variants in genes encoding lamin and titin, muscular dystrophies, and mitochondrial disease. Most forms of familial cardiomyopathy are inherited in an autosomal dominant fashion. Society guidelines have been published documenting the importance of taking a detailed family history and indications for (and limitations of) clinical genetic testing.

A myriad of systemic diseases with cardiac and extracardiac manifestations (e.g., amyloidosis, sarcoidosis), autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), infectious diseases (e.g., Chagas, HIV), and drug toxicities (chemotherapy, other prescribed or illicit agents) can result in HF with either reduced or preserved EF. In Africa and Asia, rheumatic heart disease remains a major cause of HF, especially in the young. Finally, disorders associated with a high cardiac output state (e.g., anemia, thyrotoxicosis) are seldom associated with HF in the absence of underlying structural heart disease. However, diagnosis and treatment of high-output HF will be missed if not considered in the differential diagnosis of patients with predisposing conditions (e.g., cirrhosis, end-stage renal disease with arteriovenous fistula, Paget's disease, or nutritional deficiency such as beriberi).

## PATOPHYSIOLOGY

### PROGRESSIVE DISEASE

HFrEF is a progressive disease that typically involves an index event followed by months to years of structural and functional cardiovascular remodeling (Fig. 257-4). The primary event may be sudden in onset, such as an acute myocardial infarction; more gradual, as occurs in the setting of chronic pressure or volume overload; inherited, as seen with genetic cardiomyopathies; or congenital disease. Despite an initial reduction in cardiac performance, patients may be asymptomatic or mildly symptomatic for prolonged periods due to the activation of compensatory mechanisms (described below) that ultimately contribute to disease progression.

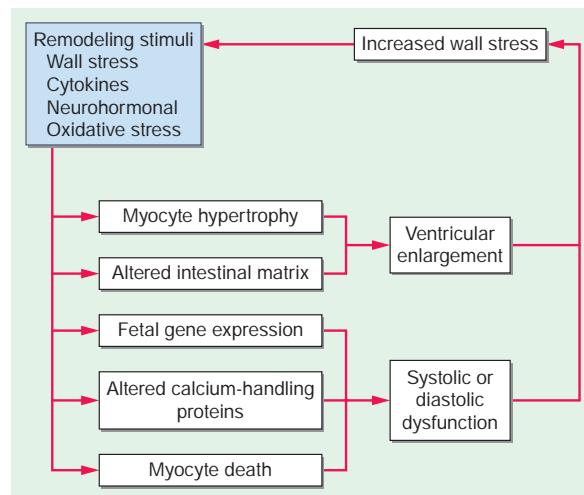
**Ventricular Remodeling** As demonstrated in both animal and human studies, different patterns of ventricular remodeling occur in response to excess cardiac workload. Concentric hypertrophy, in which increased mass is out of proportion to chamber volume, effectively reduces wall stress under conditions of pressure overload (e.g., hypertension, aortic stenosis). By contrast, an increase in cavity size or volume (eccentric hypertrophy) occurs in volume overload conditions (e.g., aortic regurgitation, mitral regurgitation). In both forms of remodeling, an increase in ventricular mass is accompanied at the cellular level by myocyte hypertrophy and interstitial

fibrosis, at the protein level by alteration in calcium-handling and cytoskeletal function, and at the molecular level by re-expression of fetal genes (Table 257-3). In addition to cell loss from necrosis, myocytes that are unable to adapt to remodeling stimuli may be triggered to undergo apoptosis or programmed cell death. Further impairment in pump function and increased wall stress in the face of systemic vasoconstriction and loss of neurohormonal adaptation (discussed below) can lead to afterload mismatch. These events feed back on remodeling stimuli, setting up a cycle of deleterious processes resulting in clinical HF.

While our understanding of ventricular remodeling in HFrEF is well supported by animal and human studies, the mechanisms underlying HFpEF are less clear. The original descriptions of HFpEF focused on diastolic dysfunction as the primary mediator of HF signs and symptoms as exemplified in older women with hypertension. At the myocyte level, impaired uptake of cytosolic calcium into the sarcoplasmic reticulum by reductions in adenosine triphosphate explained abnormalities in myocardial relaxation. As different phenotypes of HFpEF have emerged, many pathophysiologic processes other than diastolic dysfunction have been implicated in disease progression, including vascular stiffness, renal dysfunction, sodium avidity, and metabolic inflammation related to regional adiposity. Furthermore, biologic alterations including oxidative stress and impaired nitric oxide signaling leading to nitratoses may play a role in disease activity and inform future therapies.

### MECHANISMS OF DISEASE PROGRESSION

A number of compensatory mechanisms become activated during the development of HF and contribute to disease progression. Our



**FIGURE 257-4 Remodeling stimuli in heart failure.** Chronic hemodynamic stimuli such as pressure and volume overload lead to ventricular remodeling through increases in myocardial wall stress, inflammatory cytokines, signaling peptides, neuroendocrine signals, and oxidative stress. The myocardium responds with adaptive as well as maladaptive changes. Reexpression of fetal contractile proteins and calcium handling proteins may contribute to impaired contraction and relaxation. Myocytes unable to adapt might be triggered to undergo programmed cell death (apoptosis). The net result of these changes is further impairment in pump function and increased wall stress, thus completing a vicious cycle that leads to further progression of myocardial dysfunction. (From MM Givertz, WS Colucci: Heart failure. In Peter Libby, Essential Atlas of Cardiovascular Disease, 2009, Current Medicine Group. Reproduced with permission of SNCSC.)

**TABLE 257-3 Mechanisms of Ventricular Remodeling****Changes in Myocyte Biology**

- Abnormal excitation-contraction coupling and crossbridge interaction
- Fetal gene expression (e.g.,  $\beta$ -myosin heavy chain)
- $\beta$ -Adrenergic receptor desensitization
- Myocyte hypertrophy
- Impaired cytoskeletal proteins

**Changes in Myocardial Makeup**

- Myocyte necrosis, apoptosis, and autophagy
  - Interstitial and perivascular fibrosis
  - Matrix degradation
- Changes in Ventricular Geometry**
- Ventricular dilation and wall thinning
  - Increased sphericity and displacement of papillary muscles
  - Atrioventricular valve regurgitation

understanding of these mechanisms derives from preclinical studies, *in vivo* human studies, and randomized clinical trials demonstrating benefit of therapies targeted to attenuating or reversing these biologic processes.

**Neurohormonal Activation** Activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) plays a critical role in the development and progression of HF. Initially, neurohormonal activation leads to increases in heart rate, blood pressure, and cardiac contractility and retention of sodium and water to augment preload and maintain cardiac output at rest and during exercise. Over time, these unchecked compensatory responses lead to excessive vasoconstriction and volume retention, electrolyte and renal abnormalities, baroreceptor dysfunction, direct myocardial toxicity, and cardiac arrhythmias. At the tissue level, neurohormonal activation contributes to remodeling of the heart, blood vessels (atherosclerosis), kidneys, and other organs (Fig. 257-5) and the development of symptomatic HF. Landmark clinical trials in HF have demonstrated that antagonism of the RAAS and SNS with renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and beta blockers attenuates or reverses ventricular and vascular remodeling and reduces morbidity and mortality (Chap. 258).

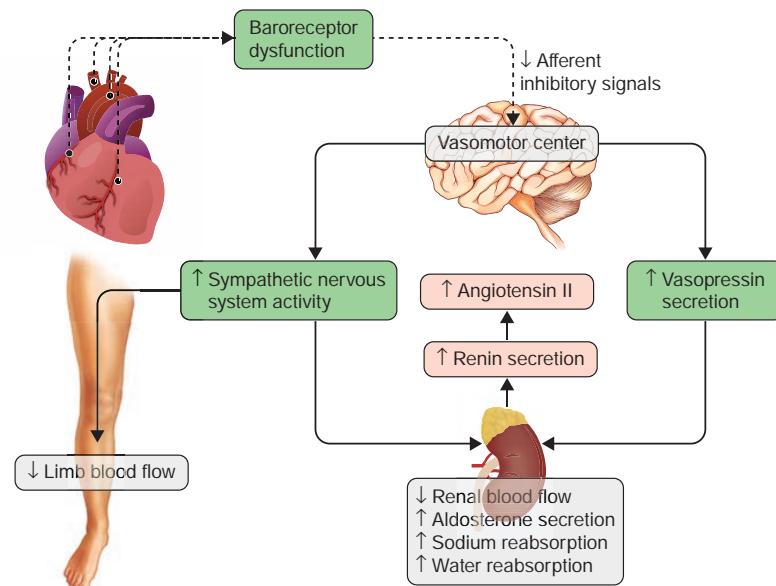
**Vasodilatory Hormones** While RAAS and SNS activation contributes to disease progression in HF, a number of counterregulatory hormones are upregulated and exert beneficial effects on the heart, kidney, and vasculature. These include the natriuretic peptides (atrial natriuretic peptide [ANP] and B-type natriuretic peptide [BNP]), prostaglandins (prostaglandin E<sub>1</sub> [PGE<sub>1</sub>] and prostacyclin [PGI<sub>2</sub>]), bradykinin, adrenomedullin, and nitric oxide. ANP and BNP are stored and released primarily from the atria and ventricles, respectively, in response to increased stretch or pressure. Beneficial actions are mediated through stimulation of guanylate cyclase and include systemic and pulmonary vasodilation, increased sodium and water excretion, inhibition of renin and aldosterone, and baroreceptor modulation. Bradykinin and natriuretic peptides are inactivated by neprilysin, a membrane bound

peptidase, which explains in part the beneficial clinical impact of angiotensin receptor-neprilysin inhibition in HF (Chap. 258). As described below, natriuretic peptide levels can be used to assist in the diagnosis and risk stratification of patients with HF.

**Endothelin, Inflammatory Cytokines, and Oxidative Stress**

Endothelin is a potent vasoconstrictor peptide with growth-promoting effects that may play an important role in pulmonary hypertension and right ventricular failure. Endothelin is released from a variety of vascular and inflammatory cells within the pulmonary circulation and myocardium in response to increased pressure and has direct deleterious effects on the heart, leading to myocyte hypertrophy and interstitial fibrosis. Unlike RAAS and SNS inhibition, however, endothelin blockade has not been shown to slow the progression of clinical HF but is beneficial for treatment of pulmonary arterial hypertension (Chap. 283). Other factors that have the potential to cause or contribute to ventricular remodeling in HF include inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL) 1 and reactive oxygen species such as superoxide. Potential sources of these biologically active substances are the liver and gastrointestinal tract, as described below. The role of anti-inflammatory and antioxidant therapies remains unproven.

**Novel Biologic Targets** Sodium-glucose cotransporter-2 (SGLT-2) is a protein located on the proximal tubule of the kidney that is responsible for reabsorption of up to 90% of filtered glucose. In patients with HF, activity of SGLT-2 contributes to sodium and water retention, endothelial dysfunction, abnormal myocardial metabolism, and impaired calcium handling. Inhibitors of SGLT-2 were developed for the treatment of type 2 diabetes mellitus to take advantage of their glycosuric and metabolic effects (Chap. 404). Subsequent large clinical trials in cardiovascular disease including HF (with or without overt diabetes mellitus) have demonstrated not only safety of these agents



**FIGURE 257-5 Activation of neurohormonal systems in heart failure.** Decreased cardiac output in heart failure (HF) results in an “unloading” of high-pressure baroreceptors (circles) in the left ventricle, carotid sinus, and aortic arch, which in turn causes reduced parasympathetic tone. This decrease in afferent inhibition results in a generalized increase in efferent sympathetic tone and nonosmotic release of arginine vasopressin from the pituitary. Vasopressin is a powerful vasoconstrictor that also leads to reabsorption of free water by the kidney. Afferent signals to the central nervous system also activate sympathetic innervation of the heart, kidney, peripheral vasculature, and skeletal muscles. Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention, peripheral vasoconstriction, myocyte hypertrophy, cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure, they also result in end-organ changes in the heart and circulation. (Modified from A Nohria et al: *Atlas of Heart Failure: Cardiac Function and Dysfunction*, 4th ed, WS Colucci [ed]. Philadelphia, Current Medicine Group, 2002, p. 104, and J Hartuvee, DL Mann: *Nat Rev Cardiol* 14:30, 2017.)

(as required by the U.S. Food and Drug Administration) but also, more importantly, beneficial effects on morbidity and mortality. Whether benefits of SGLT-2 inhibitors in HF are due primarily to diuretic effects or to effects on cardiac and vascular remodeling, proarrhythmia, renal function, and/or metabolic function or inflammation remains to be determined. Another pathway that is downregulated in HF and contributes to endothelial dysfunction involves cyclic guanosine monophosphate (cGMP). Oral soluble guanylate cyclase stimulators enhance the cGMP pathway and exert beneficial myocardial and vascular effects in experimental and clinical HF.

**Dyssynchrony and Electrical Instability** In up to one-third of patients with HF, disease progression is associated with prolongation of the QRS interval. Electrical dyssynchrony in the form of left bundle branch block (LBBB) or intraventricular conduction delay results in abnormal ventricular contraction. As discussed in *Chap. 258*, correction of electrical dyssynchrony with left or biventricular pacing can improve contractile function, decrease mitral regurgitation, and reverse ventricular remodeling. In patients with symptomatic HFrEF and LBBB on guideline-directed medical therapy, cardiac resynchronization therapy is indicated to reduce morbidity and mortality. Other forms of electrical instability, including atrial fibrillation with inadequate rate control and frequent premature ventricular complexes, can also contribute to worsening HF. In addition to the direct impact of tachycardia and irregular rhythm on disease progression, the link between these arrhythmias and cardiac remodeling (atrial and ventricular) involves increased wall stress, neurohormonal activation, and inflammation.

**Secondary Mitral Regurgitation** A large number of patients with HFrEF demonstrate evidence of mitral regurgitation. This occurs due to a distortion in the mitral valve apparatus and includes the effects of various pathophysiologic mechanisms including reduced contractile force, which leads to decreased coaptation of the leaflets, a spherical shape of the ventricle that influences length and function of the chordal-papillary muscle structure, increased dimension of the mitral annulus (and inability of the annulus to contract during systole) with reduced leaflet alignment, and dilation of the posterior wall of the left atrium, which distorts the posterior leaflet of the valve. This worsening in regurgitant volume contributes to progression in HF and adversely influences prognosis. Ensuring that this vicious cycle is interrupted is now a therapeutic target in HF. Some success has been noted by treating the mitral valve using transcatheter techniques when patients are carefully selected after exposure to optimal medical therapy when residual and significant secondary mitral regurgitation persists.

### CARDIORENAL AND ABDOMINAL INTERACTIONS

An important concept underlying the pathophysiology of HF recognizes the systemic nature of disease. Thus, while the primary hemodynamic problem in HF is related to abnormalities in myocardial function (preload, afterload, and contractility), many of the presenting signs and symptoms are related to end-organ failure, including dysfunction of the kidneys, liver, and lungs. The heart and kidney interaction increases circulating volume, worsens symptoms of HF, and results in disease progression, referred to as the cardiorenal syndrome. Traditionally, this relationship was deemed to be a consequence of an impairment in forward flow (cardiac output) leading to a decrease in renal arterial perfusion, worsening renal function, and neurohormonal activation with release of arginine vasopressin, resulting in water and sodium retention. However, evidence has emerged that renal dysfunction may not be adequately explained simply by arterial underfilling and a decline in cardiac output. Systemic venous congestion in HF with increased backward pressure may be operative in determining the development of the cardiorenal syndrome, and relief of venous congestion is associated with significant improvement in renal function in HF. Increased intraabdominal pressure, as noted in right-sided HF, and a rise in abdominal congestion are correlated with renal dysfunction in worsening HF. The interaction is not only confined to the renal component of the abdominal compartment but also involves the liver and spleen. The splanchnic veins serve as a blood reservoir and actively

function in regulation of cardiac preload during changes in volume status, regulated by transmural pressure changes or mechanisms of systemic sympathetic activation. The liver and spleen participate in determining volume regulation in HF in addition to several additional interactive pathways. Splanchnic congestion results in portal vein distension and activation of the hepatorenal reflex as well as the splenorenal reflex, which induces renal vasoconstriction. Thus, decongestion in HF by diuretic therapy or mechanical means such as ultrafiltration reduces volume, but also facilitates a decrease in pressure within the abdominal compartment, and this combination of therapeutic effect may serve to improve renal function in HF.

### GUT CONGESTION, THE MICROBIOME, AND INFLAMMATION

As noted above, circulating levels of proinflammatory cytokines are elevated in a number of cardiovascular disease states, including HF, and have been associated with disease progression. While the primary source of inflammation is unknown, emerging evidence suggests that an alteration in gut microbial composition and loss of microbial diversity may play an important role. The potential role of gut congestion and also altered gut microbial composition may propagate the chronic state of inflammation and immune system dysregulation, eventually leading to progression of HFrEF. Lipopolysaccharide (LPS) is a gram-negative bacterial cell wall product whose levels are increased in patients with HF and increased intestinal permeability during periods of congestion, and reduced with diuretic treatment. LPS is a strong stimulator of the immune system and can lead to dysregulated systemic inflammation via macrophage activation. Resulting increases in cytokines such as TNF-, IL-1, and IL-6 in these pathways can cause progressive loss of cardiac function and also contribute to cardiac cachexia. A mechanistic link has been shown between gut microbe-dependent generation of trimethylamine N-oxide derived from specific dietary nutrients such as choline and carnitine and poor outcomes in patients with both acute and chronic HF. Microbe-generated uremic toxins, such as indoxyl sulfate, may play an important role in the development of HF, particularly in interaction with renal insufficiency. Thus, bowel ischemia and/or congestion depending on HF severity may be associated with morphologic and functional alterations in the intestines and result in bacterial endotoxemia and a proinflammatory state.

### HIGH-OUTPUT STATES

Although most patients with HF, with either reduced or preserved EF, have low or normal cardiac output (CO) accompanied by elevated systemic vascular resistance (SVR), a minority of patients with HF present with a high-output state with low SVR (*Table 257-2*). High-output states by themselves are seldom responsible for HF, but their development in the presence of underlying cardiovascular disease can precipitate HF. For example, chronic anemia is associated with high CO when hemoglobin reduces significantly, for example, to a level that is 8 g/dL. An increase in vasodilatory metabolites and arteriolar vasodilation in response to decreased oxygen-carrying capacity of the blood in addition to a decrease in blood viscosity contributes to low SVR. Even when severe, anemia rarely causes high-output HF in the absence of a specific cardiac abnormality such as ischemic or valvular heart disease. Patients with end-stage renal disease (*Chap. 312*) are at particular risk of developing high-output HF when chronic anemia is exacerbated by increased flow through an arteriovenous fistula. In a contemporary series of patients with high-output HF, the most common causes were obesity (31%), liver disease (23%), arteriovenous shunts (23%), lung disease (16%), and myeloproliferative disorders (8%).

### EVALUATION

#### HISTORY

**Symptoms of Congestion: Pulmonary Versus Systemic** The most common symptoms of HF are related to volume overload with elevation in pulmonary and/or systemic venous pressures. Shortness of breath is a cardinal manifestation of left HF and may arise with increasing severity as exertional dyspnea, orthopnea, paroxysmal nocturnal

**TABLE 257-4** New York Heart Association Functional Classification

FUNCTIONAL CLASS	LIMITATION	CLINICAL ASSESSMENT
Class I	None	Ordinary physical activity does not cause undue fatigue, dyspnea, palpitations, or angina.
Class II	Slight	Comfortable at rest. Ordinary physical activity (e.g., carrying heavy packages) may result in fatigue, dyspnea, palpitations, or angina.
Class III	Marked	Comfortable at rest. Less than ordinary physical activity (e.g., getting dressed) leads to symptoms.
Class IV	Severe	Symptoms of heart failure or angina are present at rest and worsened with any activity.

dyspnea, and dyspnea at rest. Mechanisms of dyspnea include pulmonary venous congestion and transudation of fluid into the interstitium and/or alveoli, leading to decreased lung compliance, increased airway resistance, hypoxemia, and ventilation/perfusion mismatch. Stimulation of juxtagapillary J receptors leading to an increased ventilatory drive and reduced blood flow to respiratory muscles may cause lactic acidosis and a sensation of dyspnea. The New York Heart Association (NYHA) functional classification (**Table 257-4**) may be used to categorize patients based on the amount of effort required to provoke breathlessness. Notably, however, NYHA class does not correlate well with other objective measures of cardiac structure (e.g., left ventricular size, EF) or function (e.g., peak oxygen consumption).

Orthopnea refers to dyspnea that occurs in the recumbent position and is due to redistribution of fluid from the abdomen and lower body into the chest, increased work of breathing due to decreased lung compliance, and, in patients with ascites or hepatomegaly, elevation of the diaphragm. Orthopnea typically occurs in the awake patient within 1–2 min of lying down and may be relieved by raising the head and chest with pillows or an adjustable bed. With more severe HF, patients may end up sleeping in a recliner chair or sitting up, although for some, orthopnea may diminish as symptoms of right HF appear. Orthopnea may be accompanied by nocturnal cough related to pulmonary congestion.

Paroxysmal nocturnal dyspnea (PND) refers to episodes of shortness of breath that awaken a patient suddenly from sleep with feelings of anxiety and suffocation and require sitting upright for relief. In contrast to orthopnea, PND usually occurs after prolonged recumbency, is less predictable in occurrence, and may require 30 min or longer in the upright position for relief. Episodes are often accompanied by coughing and wheezing (so-called cardiac asthma) thought to be due to increased bronchial arterial pressure leading to airway compression and interstitial pulmonary edema causing increased airway resistance. Acute pulmonary edema, due to marked elevation of the pulmonary capillary wedge pressure, is manifested by severe shortness of breath and pink, frothy sputum (**Chap. 305**). Cheyne-Stokes respiration and central sleep apnea may precipitate episodes of PND in HF and are related to increased sensitivity of the respiratory center to arterial PCO<sub>2</sub> and a prolonged circulatory time. Unlike obstructive sleep apnea, which can be treated with positive airway pressure therapy, central sleep apnea has no proven therapy beyond the directed treatment of HF (**Chap. 297**).

In contrast to symptoms of left HF due to pulmonary venous congestion, symptoms of right HF are typically related to systemic venous congestion. Weight gain and lower extremity edema may be the initial manifestations followed by a range of gastrointestinal symptoms due to edema of the bowel wall and hepatic congestion. Abdominal bloating, anorexia, and early satiety are common. Some patients develop right upper quadrant pain related to stretching of the hepatic capsule with nausea and vomiting. When these symptoms are associated with abnormal liver function tests (see below), misdiagnosis of biliary tract disease may occur. For patients with refractory right HF, the development of massive edema involving the entire body with recurrent pleural effusions and/or ascites is termed *anasarca*.

**TABLE 257-5** Precipitating Factors in Heart Failure

Patient-Related
Excess exertion or emotional stress
Excess fluid and/or sodium intake
Nonadherence with medications
Heavy alcohol use
Provider-Related
Recommended use of medications that cause salt and water retention (e.g., NSAIDs)
Prescribed use of medications with negative inotropic properties (e.g., CCBs)
Unrecognized congestion and inadequate use of diuretics
Heart Failure-Related
Uncontrolled hypertension
Mycardial ischemia or infarction
Atrial or ventricular arrhythmias
Pulmonary embolism
Other Disease States
Systemic infection
Worsening renal or hepatic failure
Hyperthyroidism
Untreated sleep apnea
Anemia

Abbreviations: CCB, calcium channel blocker; NSAID, nonsteroidal anti-inflammatory drug.

**Symptoms of Reduced Perfusion** Some patients with advanced HF present with symptoms related to decreased CO, sometimes referred to as *low-output syndrome*. Fatigue and weakness, particularly of the lower extremities, are nonspecific symptoms that can occur with exertion or at rest. Pathophysiology includes reduced blood flow to exercising muscles due to endothelial dysfunction and increased SVR from neurohormonal activation. Chronic alterations in skeletal muscle structure and metabolism have also been demonstrated. In older patients with HF and cerebrovascular disease, reduced systemic perfusion may result in mental dullness, depressed affect, and confusion. In addition to low CO, fatigue may be caused by volume depletion, hyponatremia, iron deficiency, and medications (e.g., beta blockers).

**Other Symptoms** Patients with HF may present with mood disturbances and poor sleep, both of which may be exacerbated by nocturnal dyspnea and obstructive and/or central sleep apnea. Nocturia due to improved CO and renal perfusion in the supine position, in addition to delayed diuretic effects, can also contribute to sleep disturbances. Oliguria due to severe reductions in renal blood flow may be a sign of advanced-stage HF.

**Precipitating Factors** Patients with HF may be asymptomatic or mildly symptomatic either because the cardiac impairment is mild or because compensatory mechanisms help to balance or normalize cardiac function. Symptoms of HF may develop when one or more precipitating factors increase cardiac workload and disrupt the balance in favor of decompensation. Specific factors may be identified in 50–90% of admissions and can be divided into patient-related factors, provider-related factors, HF-related disease states, and other causes (**Table 257-5**). Inability to recognize and correct these factors promptly may lead to persistent HF despite adequate treatment.

## PHYSICAL EXAMINATION

**General Appearance** Most patients with mild-moderate HF will appear well nourished and comfortable at rest. Even patients with more advanced disease may be in no distress after resting for a few minutes but may demonstrate dyspnea with minimal exertion such as walking across the room. In contrast, patients with severe HF may need to sit upright and appear anxious, diaphoretic, and dyspneic at rest with

**TABLE 257-6 Definition of Cardiac Cachexia**

- Edema-free weight loss of at least 5% in 12 months or less in the presence of underlying illness (or a BMI <20 kg/m<sup>2</sup>) and at least three of the following criteria:
- Decreased muscle strength (lowest tertile)
  - Fatigue (physical and/or mental weariness resulting from exertion)
  - Anorexia (limited food intake [<70% of usual] or poor appetite)
  - Low fat-free BMI (lean tissue depletion by DEXA <5.45 in women and <7.25 in men)
  - Abnormal biochemistry:
    - Increased inflammatory markers (CRP >5.0 mg/L, IL-6 >4.0 pg/mL)
    - Anemia (hemoglobin <12 g/dL)
    - Low serum albumin (<3.2 g/dL)

**Abbreviations:** BMI, body mass index; CRP, C-reactive protein; DEXA, dual-energy x-ray absorptiometry; IL, interleukin.

**Source:** Modified from WJ Evans et al: Clin Nutr 27:793, 2008.

pallor due to anemia or duskeness due to low output. Other signs of severe HF include cool extremities and peripheral cyanosis. Cardiac cachexia (**Table 257-6**), defined partially as unintentional edema-free weight loss of >5% over 12 months, may be observed in patients with longstanding, severe HF as bitemporal or upper body muscle wasting. Contributing factors include poor oral intake due to anorexia, decreased fat absorption due to bowel wall edema, and catabolic/metabolic imbalance from activation of inflammatory cytokines (see above) and dysregulation of the growth hormone–insulin-like growth factor 1 pathway. Rarely, scleral icterus and jaundice may result from severe right HF.

**Vital Signs** With new-onset HF, heart rate rises and blood pressure may initially be increased due to sympathetic activation. In patients with chronic HF on guideline-directed medical therapy, resting heart rate ideally should be <70–75 beats/min, and blood pressure should be in the normal to low-normal range. An irregular rhythm may be due to atrial fibrillation or flutter or frequent premature atrial or ventricular complexes. Severe HF may be associated with hypotension and narrow pulse pressure along with a rapid, thready pulse. An alternatingly strong and weak pulse, known as *pulsus alternans*, is attributed to reduced left ventricular contraction in every other cardiac cycle due to incomplete recovery causing alternation in the left ventricular stroke volume. Respiratory rate may be normal at rest but may increase on lying down or on minimal exertion. Advanced HF may be associated with periodic breathing or Cheyne-Stokes respirations. The patient is usually unaware of the altered breathing pattern, but family members or friends may become alarmed or attribute this incorrectly to anxiety. Oxygen saturation is typically normal on room air unless there is acute pulmonary edema, underlying CHD with shunting, severe pulmonary arterial hypertension, or concomitant acute or chronic lung disease. A low-grade fever resulting from cytokine activation may occur in severe HF and subside when compensation is restored.

**Jugular Venous Pulse** Examination of the jugular veins provides an estimate of the right atrial pressure. Typically, the patient is examined at a 45° angle, and jugular venous pressure (JVP) is quantified in centimeters of water by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5. In patients with mild right HF, JVP may be normal at rest (~8 cmH<sub>2</sub>O) but increase with compression of the right upper quadrant. *Hepatogastroreflux* is elicited by applying firm continuous pressure over the liver for 15–30 s while observing the neck veins. The patient must breathe normally and not strain during the maneuver. Higher levels of venous pressure approaching the angle of the jaw are common in chronic right HF. If significant tricuspid regurgitation is present, prominent V waves and Y descents may be noted. The *abdominojugular test*, defined as an increase in right atrial pressure during 10 s of firm midabdominal compression followed by an abrupt drop on pressure release, suggests elevated left-sided filling pressure. A rise in JVP with inspiration or Kussmaul's sign may be due to severe biventricular HF and is a marker of poor outcome.

**Lung Examination** Pulmonary rales result from transudation of fluid from the intravascular space into the alveoli and airways. In general, rales are heard at the lung bases, but in severe HF or acute pulmonary edema, they may be heard throughout the lung fields. Wheezing and rhonchi can occur with congestion of the bronchial mucosa and sometimes lead to a misdiagnosis (and inappropriate treatment) of asthma or chronic obstructive pulmonary disease (COPD). Rales may be absent in patients with longstanding HF and chronically elevated pulmonary capillary wedge pressures due to increased lymphatic drainage, which prevents spillage from the interstitium into the alveoli. In biventricular or predominant right HF, bilateral pleural effusions are recognized as dullness to percussion and decreased breath sounds at the bases. When pleural effusions are unilateral, they typically involve the right side.

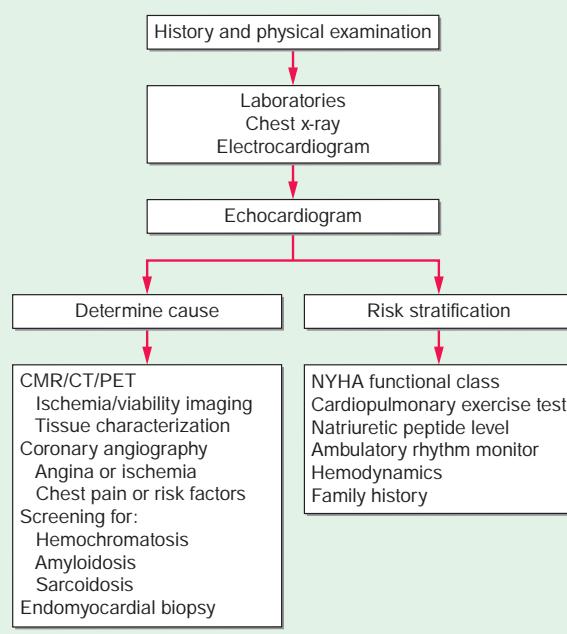
**Cardiac Examination** As discussed above, chronic HF with ventricular remodeling is accompanied by cardiac enlargement. The apical impulse is displaced downward and to the left and may be diffuse in dilated cardiomyopathy or sustained in pressure overloaded states such as aortic stenosis. In biventricular or severe right HF, a right ventricular heave or parasternal lift may be palpated along the left sternal border. Uncommonly, a palpable third heart sound may be present. In patients with HFrEF precordial palpation is often normal. On auscultation, an S<sub>3</sub> gallop is most commonly present in patients with volume overload and tachycardia, suggests severe hemodynamic compromise, and carries negative prognostic significance. An S<sub>4</sub> gallop is not specific to HF but may be present in patients with HFrEF due to hypertension. Holosystolic murmurs of mitral and tricuspid regurgitation are present in the setting of advanced HF, often in the absence of structural valvular abnormalities. In patients with secondary pulmonary hypertension, a loud pulmonary component of the second heart sound may be heard.

**Abdomen and Extremities** Hepatomegaly is an early sign of systemic venous congestion. The liver edge may be tender due to stretching of the capsule, but with progression of right HF, tenderness may disappear. The liver edge may be pulsatile in patients with tricuspid regurgitation. Longstanding hepatic congestion may result in cardiac cirrhosis with congestive splenomegaly and mild-moderate ascites. The presence of massive ascites should lead to a search for other causes such as constrictive pericarditis or primary liver failure. Dependent lower extremity edema is common in chronic HF and is typically symmetric and pitting. Over time, chronic edema may cause reddening and induration of the skin, become weeping, or lead to cellulitis. Anasarca is used to describe massive, generalized edema involving the legs, sacrum, and abdominal wall. In patients with acute HF or younger adults with chronic HF, lower extremity edema may be absent despite marked systemic venous hypertension. Unilateral lower extremity edema may be due to deep venous thrombosis, prior trauma, or history of vein harvest for bypass surgery. Nonpitting edema that does not respond to increasing doses of diuretics may represent lymphedema that requires alternative diagnostic workup and treatment.

## DIAGNOSIS

The diagnosis of HF is relatively straightforward when the patient presents with typical signs and symptoms; however, the signs and symptoms of HF are neither specific nor sensitive. It is therefore important for clinicians to have a high index of suspicion for HF, particularly in patients who are at increased risk, including older patients with underlying cardiovascular disease and those with comorbidities such as hypertension, diabetes, and chronic kidney disease. In this setting, additional laboratory testing and imaging should be performed (**Fig. 257-6**).

**Routine Laboratories** Standard laboratory testing in patients with HF includes a comprehensive metabolic panel, complete blood count, coagulation studies, and urinalysis. Selected patients should have assessment for diabetes, dyslipidemia, and thyroid function. Blood urea nitrogen and creatinine levels are often elevated in moderate-severe HF due to reduced renal blood flow and/or increased renal venous pressure. Worsening renal function (**Chaps. 310 and 311**) due to



**FIGURE 257-6 Initial assessment of patients presenting with heart failure.** The initial evaluation starts with a thorough history and physical examination, focusing on detection of comorbidities including hypertension, diabetes, and dyslipidemia. In addition, identification of valvular heart disease, vascular disease, history of mediastinal radiation, or exposure to cardiotoxins (e.g., chemotherapy, alcohol, or illicit drugs) may help determine underlying cause. A family history of sudden death, heart failure, arrhythmias, or cardiomyopathy is also useful. Routine laboratory evaluation (see text) should also be performed. Chest x-ray is useful to detect cardiomegaly and fluid overload and to rule out pulmonary disease. A 12-lead electrocardiogram should be performed to detect abnormalities of cardiac rhythm and conduction, left ventricular hypertrophy, and evidence of myocardial ischemia or infarction. Two-dimensional echocardiography with Doppler imaging is indicated to assess cardiovascular structure and function and detect abnormalities of the myocardium, heart valves, or pericardium. Further imaging and laboratory studies aimed at identifying a specific cause of cardiomyopathy depend on information obtained from the history and physical examination. In all patients, risk stratification should be performed to assess severity of illness, guide therapy, and provide prognosis to patient and family. CMR, cardiac magnetic resonance imaging; CT, computed tomography; NYHA, New York Heart Association; PET, positron emission tomography.

diuretics, RAAS inhibitors, and noncardiac medications (e.g., nonsteroidal anti-inflammatory drugs) is also common. Proteinuria may be present in the setting of longstanding hypertension or diabetes or suggest an underlying systemic disease. Chronic right HF with congestive hepatomegaly can lead to modest elevations in transaminases, alkaline phosphatase, and bilirubin that should not be confused with biliary tract disease. Marked elevation in transaminases and lactic acid suggest cardiogenic shock with severe low output. In patients with cardiac cirrhosis, hypoalbuminemia may exacerbate fluid accumulation, whereas hyperammonemia contributes to altered mental status. In general, inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein, and uric acid are nonspecific and do not aid in the diagnosis of HF. Other laboratories, including antinuclear antibodies, rheumatoid factor, serum free light chains, serum protein electrophoresis, ferritin, ceruloplasmin, hepatitis C, and HIV, are reserved for targeted testing.

Electrolyte abnormalities seen in HF include hyponatremia due to sodium restriction, diuretic therapy, and vasopressin-mediated free water retention. Hyponatremia is a negative prognostic indicator at the time of HF hospitalization and predicts decreased long-term survival (Table 257-1). Hypokalemia is most often due to thiazide or loop diuretics given without oral potassium supplementation but may also result from increased aldosterone levels. Hyperkalemia may result from marked reductions in glomerular filtration rate and is exacerbated by

use of RAAS inhibitors and potassium-sparing diuretics (**Chap. 258**). Hypo- or hyperkalemia may lead to atrial or ventricular arrhythmias. Hypophosphatemia and hypomagnesemia are commonly associated with chronic alcohol use.

Anemia is not diagnostic of HF, but when present, it may exacerbate underlying ischemic heart disease and should be corrected. Rarely, severe anemia may cause high-output HF typically in the presence of underlying cardiovascular disease. The presence of iron deficiency (with or without anemia) is increasingly recognized in patients with chronic HF and has been attributed to decreased gut absorption, impaired hepatic storage, and chronic blood loss. Repletion with IV iron results in improved symptoms and exercise capacity and reduced HF hospitalizations, but its effect on survival remains uncertain.

**Chest X-Ray** Major abnormalities on chest imaging associated with left HF include enlarged cardiac silhouette (cardiothoracic ratio >0.5) and pulmonary venous congestion. Early radiologic signs of acute HF include upper zone venous redistribution and thickening of interlobular septa. When the pulmonary capillary wedge pressure is moderate to severely elevated, alveolar edema can present as diffuse haziness extending downward toward the lower lung fields. The absence of these findings in patients with chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid. Pleural effusions of varying size and distribution are common in biventricular HF. Chest x-ray can also be used to identify noncardiac causes of dyspnea (e.g., pneumonia, COPD).

**Electrocardiogram** No specific electrocardiographic (ECG) pattern is diagnostic of HF. Rather, the ECG may provide important information regarding presence of underlying cardiac disease. For example, left ventricular hypertrophy and left atrial enlargement suggest HFrEF due to hypertension, aortic stenosis, or hypertrophic cardiomyopathy. The presence of Q waves or infarction is suggestive of ischemic heart disease, whereas Q waves with reduced QRS voltage (pseudo-infarct pattern) may be seen with restrictive or infiltrative cardiomyopathies (e.g., amyloid). Conduction system disease should raise concern for cardiac sarcoid or Chagas cardiomyopathy in the right clinical setting.

Paroxysmal or persistent atrial fibrillation is present in up to 40% of patients with chronic HF and is an indication for anticoagulation. Premature ventricular complexes (PVCs) and nonsustained ventricular tachycardia can reflect worsening HF and are markers of increased risk. Conversely, frequent PVCs can cause cardiomyopathy that may be treated successfully with ablation (**Chap. 253**). Finally, determination of the QRS width and presence of LBBB is used to ascertain whether the patient may benefit from cardiac resynchronization therapy.

**Noninvasive Imaging** Noninvasive cardiac imaging (**Chap. 241**) is essential for the diagnosis, evaluation, and management of HF. Two-dimensional echocardiography provides an accurate and rapid determination of ventricular size and function and valvular morphology and function and can detect intracavitary thrombi and pericardial effusions. When left ventricular ejection fraction (LVEF) is 50%, systolic function is deemed to be normal. Myocardial strain rate imaging using speckle tracking can add incremental value to LVEF and carries prognostic value. Doppler techniques can be used to estimate CO, pulmonary artery pressures, and valve areas, and may detect abnormalities in left ventricular diastolic filling in patients with HFrEF. For patients with end-stage HF, echocardiography is critical for assessment of right ventricular function before and after mechanical circulatory support and heart transplant. Transesophageal echocardiogram is indicated to rule out atrial thrombi prior to cardioversion and can assess aortic or mitral valve pathology in planning for transcatheter valvular replacement or repair.

Cardiac magnetic resonance imaging (CMR) has emerged as a highly accurate and quantitative tool for evaluation of left ventricular mass, volumes, and function and for determining specific causes of HF (e.g., ischemic cardiomyopathy, myocarditis, amyloidosis, hemochromatosis). CMR is particularly helpful in defining multiple anatomic and functional abnormalities in adults with CHD. Serial CMR studies can assess ventricular remodeling in response to therapy and are useful

in clinic research. For patients who cannot undergo CMR (e.g., due to implantable devices), cardiac computed tomography (CT) is particularly helpful to rule out pericardial disease or left ventricular apical thrombus. While limited by availability and cost, cardiac positron emission tomography (PET) plays a role in evaluating the extent of ischemia or infarction in patients with coronary artery disease and, in the case of sarcoid, can reliably determine the severity and distribution of cardiac inflammation.

**Cardiopulmonary Exercise Testing** While not routinely performed in HF, cardiopulmonary exercise testing using a symptom-limited, ramp protocol can provide an objective assessment of peak functional capacity in patients being evaluated for mechanical circulatory support or heart transplant (Chap. 260). Several parameters including absolute and percent-predicted peak oxygen consumption ( $\text{VO}_2$ ) and ventilatory efficiency (assessed by the  $\text{VE}/\text{VCO}_2$  slope) are independent predictors of survival. Additional data including heart rate and blood pressure response to exercise and exercise-induced arrhythmias can also be assessed. This test may also be useful in defining the cause of dyspnea when the diagnosis is uncertain.

**Biomarkers** Circulating levels of natriuretic peptides are useful, adjunctive tools in the diagnosis of HF. BNP and N-terminal pro-BNP (NT-proBNP) are released from the atria and ventricles in response to increased wall stress. Patients with HFrEF tend to have higher levels than patients with HFpEF, whereas levels may be falsely low in obesity. In ambulatory patients with dyspnea, the measurement of BNP or NT-proBNP is useful to support clinical decision-making regarding the diagnosis of HF, especially in the setting of clinical uncertainty or with concomitant lung disease. Moreover, natriuretic peptide levels can be used to establish disease severity and prognosis in chronic HF and may help to guide optimal dosing of medical therapy in stable outpatients. Importantly, many noncardiac factors, including age, female sex, and chronic kidney disease, increase natriuretic peptide levels. Other cardiovascular diseases including atrial fibrillation, pulmonary embolism, and pulmonary arterial hypertension can also increase BNP levels. Galectin-3 and soluble ST2 are newer biomarkers that have been approved for assessment of prognosis in HF but are not widely used. Biomarkers of renal injury require further study in HF.

**Invasive Studies** In the intensive care setting, assessment of cardiac filling pressures and CO may be necessary to differentiate cardiogenic from noncardiogenic pulmonary edema and manage hemodynamic instability. Placement of a pulmonary artery catheter can be performed safely at the bedside and used to determine response to intravenous vasoactive and diuretic therapy in severe HF. Simultaneous measurement of right and left heart filling pressures in the cardiac catheterization laboratory can be used to distinguish restrictive cardiomyopathy from constrictive pericarditis. Coronary angiography is indicated to exclude ischemic heart disease as an underlying, potentially reversible cause of left ventricular dysfunction. The management of coronary artery disease in the setting of chronic HF is discussed in Chaps. 274–276. If echocardiographic windows are suboptimal, left ventriculography can provide an assessment of left ventricular size and function and severity of mitral regurgitation. The role of right ventricular endomyocardial biopsy in the management of HF and cardiomyopathy remains controversial. Indications include detection of myocarditis, diagnosis of cardiac amyloidosis and chemotherapy-related left ventricular failure, and screening for cardiac allograft rejection following heart transplant.

## COMORBIDITIES

### DIABETES

Type 2 diabetes mellitus is a risk factor for the development of HF (Table 257-7) and increases the risk of morbidity and mortality in patients with established disease. In ambulatory HF cohorts, the prevalence of diabetes ranges from 10 to 40%, with prevalence even higher in patients hospitalized with HF. When the two diseases coexist, patients are at increased risk for adverse outcomes, worse quality of life, and higher costs of care. Recent data from cardiovascular outcomes trials

**TABLE 257-7 Mechanisms That Contribute to Development of Heart Failure in Patients with Type 2 Diabetes Mellitus**

Altered myocardial substrate
Abnormal mitochondrial bioenergetics
Oxidative stress and inflammation
Lipotoxicity
Endoplasmic reticulum stress
Impaired insulin signaling
$\beta_2$ -Adrenergic receptor signaling
G protein-coupled receptor kinase 2 signaling
RAAS activation
Advanced glycation end products
Autophagy

Abbreviation: RAAS, renin-angiotensin-aldosterone system.

Source: Reproduced with permission from TA Zelniker: Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol* 75:422, 2020.

demonstrate that HF is a critical outcome in patients with diabetes and that glucose-lowering therapies can impact morbidity and mortality. As discussed above, SGLT-2 inhibitors in particular have not only been shown to be safe in patients with HF but can also improve renal function and decrease the risk of hospitalization and death. Use of other guideline-directed medical therapy is indicated in patients with HF regardless of diabetes status.

### SLEEP APNEA

Sleep-disordered breathing is common in HF, with increased incidence of both obstructive sleep apnea and central sleep apnea (Chap. 297). The pathophysiologic link between these disorders has been studied in both animal models and humans and includes increased afterload, decreased preload, intermittent hypoxia, and sympathetic activation. Increase in sympathetic tone can provoke ischemia and arrhythmias and complicate blood pressure management. Approximately one-third of patients with HF and sleep-disordered breathing have central sleep apnea, which is associated with increased mortality independent of other known risk factors. In patients with HFrEF and obstructive sleep apnea, continuous positive airway pressure has been shown to improve quality of life, decrease blood pressure and arrhythmias, and increase EF. Unlike obstructive sleep apnea, there is no proven therapy for central sleep apnea, although the role of nocturnal oxygen is currently being tested.

### OBESITY

Similar to diabetes, obesity is both a risk factor for the development of HF and highly prevalent in patients with HF. In particular, obesity is common in patients with HFpEF and complicates the assessment of volume status in both ambulatory and inpatient settings. Unlike diabetes, the risk of morbidity and mortality in obese patients with HF is complex. The obesity paradox refers to the observation that obese patients diagnosed with HF have a more favorable prognosis than patients with low or even normal body mass index. While weight loss has been shown to improve quality of life and exercise capacity and may contribute to reverse ventricular remodeling in patients with HF, the impact on survival is unknown.

### DEPRESSION

Depression is an independent risk factor for adverse outcomes in HF (Table 257-1), especially in older women. The mechanisms underlying this risk remain unknown but may involve neuroendocrine dysfunction and systemic inflammation, as well as contributions from poor sleep, decreased appetite, and adverse effects of medications and alcohol. The AHA recommends screening for depression among patients with cardiovascular disease including HF using validated patient health questionnaires. Selective serotonin reuptake inhibitors are safe for treating depression in HF but do not appear to affect the natural history of disease. The effect of cognitive behavioral therapy and the collaborative care model, as well as newer therapies such as transcranial

**TABLE 257-8 Differential Diagnosis of Heart Failure**

SYMPTOM OR SIGN	DIFFERENTIAL DIAGNOSIS
Dyspnea	Chronic lung disease Pulmonary arterial hypertension Neuromuscular disease Anemia Iron-deficiency anemia
Edema	Venous insufficiency Nephrotic syndrome Deep vein thrombosis Lymphedema
Ascites	Hepatic cirrhosis Portal vein thrombosis Malignant carcinomatosis
Pleural effusion(s)	Chronic infection Lung cancer Collagen vascular or rheumatologic disease
Jugular venous distension	Constrictive pericarditis Pericardial effusion Superior vena cava syndrome

magnetic stimulation, on HF morbidity and mortality requires further study.

## DIFFERENTIAL DIAGNOSIS

Many symptoms and signs suggesting HF may be caused by other conditions (**Table 257-8**). In a patient with dyspnea, the clinician must distinguish cardiac from pulmonary causes, although the differentiation may be difficult. For example, orthopnea may be a well-established symptom in some patients with severe chronic lung disease. Patients with underlying pulmonary disease may also experience episodic shortness of breath during sleep that mimics PND. In chronic lung disease, this is usually due to accumulation of tracheobronchial secretions and is relieved by coughing and expectoration, whereas in cardiac disease, the patient has to sit upright. Wheezing caused by bronchoconstriction may be a prominent symptom when left ventricular failure supervenes in individuals with reactive airways disease. Patients with cardiac asthma may be more likely to exhibit diaphoresis and varying degrees of cyanosis compared to patients with bronchial asthma. Differentiating dyspnea related to HF versus pulmonary disease may be impossible when the diseases coexist, a situation that is common in chronically ill older patients with active or prior smoking. Following effective diuresis, pulmonary function tests may help to determine the predominant cause of dyspnea. In ambulatory patients with advanced HF, cardiopulmonary exercise testing can also help to make this distinction. Finally, a very low BNP or NT-proBNP level may be helpful in excluding HF as the cause of dyspnea in nonobese patients.

Apart from pulmonary disease, HF needs to be distinguished from conditions in which congestion results from abnormal salt and water retention but in which cardiac structure and function are normal (e.g., renal failure) and from noncardiac causes of pulmonary edema (e.g., acute respiratory distress syndrome). Non-HF causes of lower extremity edema such as venous insufficiency, lymphedema, and obesity should also be considered.

### Acknowledgement

Dr. Douglas L. Mann and Dr. Murali Chakinala contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

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## Heart Failure: Management

**Akshay S. Desai, Mandeep R. Mehra**



Clinical management of patients with heart failure (HF) varies widely based on the clinical phenotype at presentation. Those in the earliest stage of disease with asymptomatic ventricular dysfunction (American College of Cardiology [ACC]/American Heart Association [AHA] stage B) may be amenable to treatment with neurohormonal antagonists, including angiotensin-converting inhibitors and  $\beta$ -adrenergic receptor antagonists, with the goal of facilitating ventricular recovery and preventing the development of clinical HF (not further discussed). Those with symptomatic HF (ACC/AHA stage C) comprise a heterogeneous group in whom the approach to therapy is differentiated largely based on measurement of the left ventricular ejection fraction. Data from prospective, randomized clinical outcomes trials enrolling patients with symptomatic chronic HF and reduced ejection fraction (HFrEF) has provided a rich evidence base that supports the efficacy of stepped pharmacologic therapy with neurohormonal antagonists, including renin-angiotensin-aldosterone system (RAAS) antagonists, neprilysin inhibitors,  $\beta$ -adrenergic receptor antagonists, and mineralocorticoid receptor antagonists, as a complement to device-based treatment with cardiac resynchronization therapy and implantable cardioverter-defibrillators. By contrast, treatment of patients with symptomatic chronic HF and preserved ejection fraction (HFpEF) has remained heavily symptom-focused owing to the lack of evidence to support specific pharmacologic therapies to modify disease progression. Even with effective therapy, patients with both HFrEF and HFpEF are at risk for clinical deterioration, typically as a consequence of progressive sodium and fluid retention that fuels the development of congestive symptoms and acute decompensated HF (ADHF). Management of these exacerbations (frequently hospital-based) is heavily focused on hemodynamic stabilization, decongestion, and institution of appropriate disease-modifying therapy in the transition back to chronic ambulatory management. Recurrent episodes of ADHF despite careful longitudinal follow-up and effective treatment may signal the onset of an advanced or refractory HF phenotype (ACC/AHA stage D) in which the risk of mortality from sudden death or end-stage HF is high, and consideration of salvage therapies including cardiac transplant or mechanical circulatory support may be appropriate prior to escalation of palliative measures (**Chap. 260**).

## HEART FAILURE WITH PRESERVED EJECTION FRACTION

### GENERAL PRINCIPLES

Although clinical trials of renin-angiotensin-aldosterone antagonists, digoxin, -adrenergic receptor blockers, and neprilysin inhibitors have been conducted in patients with HFpEF, none has conclusively demonstrated a mortality reduction. In the absence of specific pharmacologic therapies proven to improve clinical outcomes, management of patients with HFpEF is therefore focused on improving symptoms and effort tolerance through lifestyle modification, control of congestion, stabilization of heart rhythm (particularly in those with atrial fibrillation), control of blood pressure to guideline-recommended targets, and management of comorbidities that may contribute to disease progression (including, for example, obesity, obstructive lung disease, obstructive sleep apnea, diabetes/insulin resistance, anemia, iron deficiency, and chronic kidney disease).

### CLINICAL TRIALS IN HFpEF

Attempts to export the benefits of drugs that improve clinical outcomes in patients with HFrEF, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), -adrenergic receptor blockers, digoxin, and mineralocorticoid receptor antagonists, to those with HFpEF have generally been unsuccessful. The Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM) Preserved study showed a statistically significant reduction in HF hospitalizations but no difference in all-cause mortality in patients with HFpEF who were treated with the ARB candesartan. Similarly, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial demonstrated no differences in the composite of cardiovascular death or HF hospitalization during treatment with the ARB irbesartan compared with placebo. Apparent early benefits of the ACE inhibitor perindopril on HF hospitalizations and functional capacity in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study were attenuated over longer-duration follow-up. The Digitalis Investigation Group (DIG) Ancillary Trial found no impact of digoxin on all-cause mortality or on all-cause or cardiovascular hospitalization among patients with chronic HF, ejection fraction (EF) >45%, and sinus rhythm, although a modest reduction in HF hospitalizations was noted. Although no dedicated study of beta blockers has been conducted in HFpEF, the subgroup of elderly patients with prior hospitalization and HFpEF enrolled in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial of nebivolol, a vasodilating beta blocker, did not appear to experience significant reductions in all-cause or cardiovascular mortality.

With regard to *mineralocorticoid receptor antagonists*, which have potent antifibrotic effects in HFrEF, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial explored the potential benefit of spironolactone compared to placebo in HFpEF. This trial demonstrated no improvement in the primary composite endpoint of cardiovascular death, HF hospitalizations, or aborted cardiac arrest but did show a reduction in HF hospitalizations among those allocated to spironolactone. Post hoc analyses of the study suggested significant regional differences in the baseline characteristics, event rates, adverse effects, and adherence to spironolactone among patients randomized in Russia and the Republic of Georgia compared with those randomized in the Americas that raised concerns about study conduct in Russian and Georgian sites. Apparent reductions in cardiovascular death and HF hospitalization associated with spironolactone among the subgroup of patients randomized in the Americas suggest that these study design issues may have obscured a signal of spironolactone benefit. These data have supported a weak recommendation for spironolactone in patients with HFpEF who meet the inclusion criteria for the TOPCAT trial and are at low risk for adverse effects, including hyperkalemia and worsening renal function, in the most recent U.S. and European guidelines. However, the results of the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study in which spironolactone improved echocardiographic

indices of diastolic dysfunction but failed to improve exercise capacity, symptoms, or quality-of-life (QOL) measures highlight the need for further study. Ongoing trials, including the registry-based Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRRIT-HFpEF) (SPIRRIT-HFpEF; clinicaltrials.gov identifier NCT02901184) and the randomized Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity and Mortality in Participants with Heart Failure and Left Ventricular Ejection Fraction Greater than or Equal to 40% (FINEARTS-HF, clinicaltrials.gov identifier: NCT04435626) may provide additional insight in this regard.

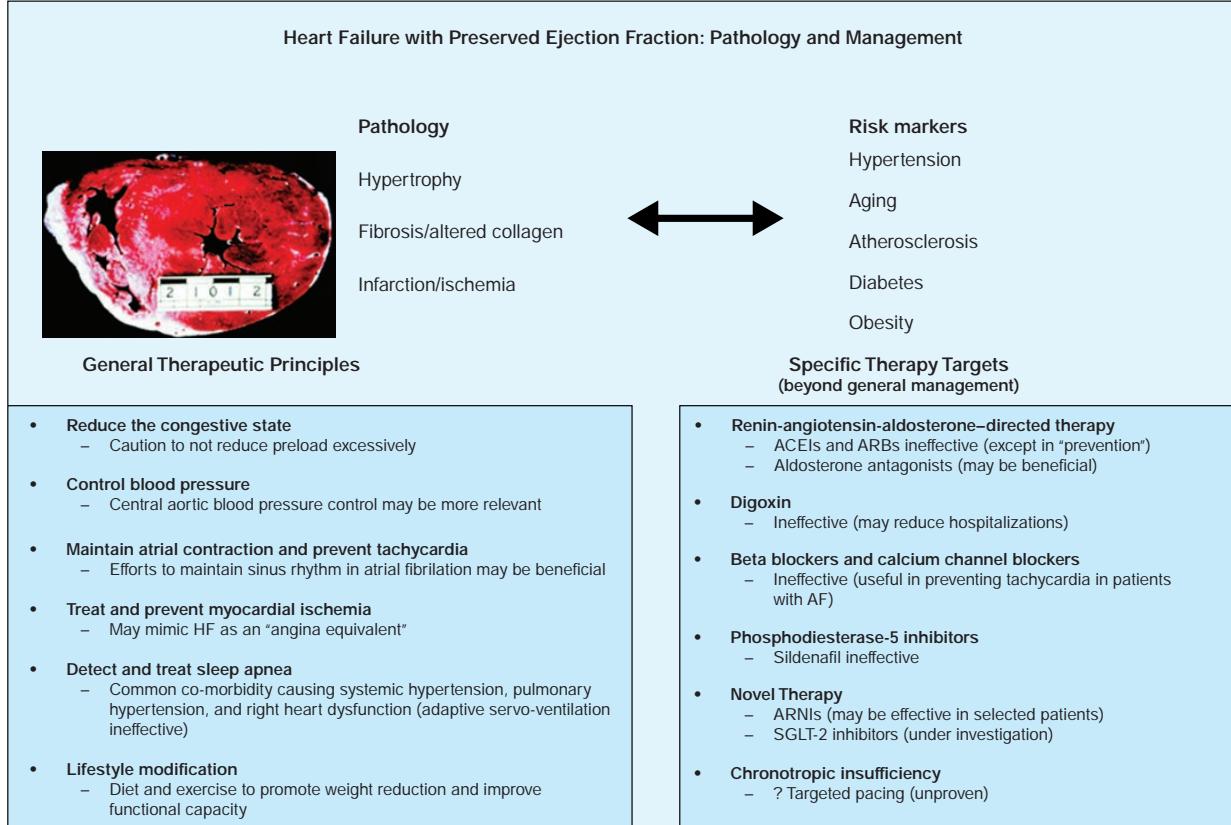
In contrast to the rather disappointing results of these studies of targeted drug therapy, small studies of exercise training in patients with HFpEF have suggested benefits on functional capacity and QOL, indicating a possible role for lifestyle interventions to improve cardiorespiratory fitness in this population.

### NOVEL TARGETS

A novel paradigm for understanding the pathophysiology of HFpEF has focused on the role of microvascular endothelial inflammation driven by comorbidities that results in impaired nitric oxide (NO) signaling and associated increases in myocardial stiffening. This paradigm has emphasized the potential for improving outcomes in HFpEF by enhancing NO bioavailability and improving downstream protein kinase G-based signaling. In this regard, a small trial demonstrated that the phosphodiesterase-5 inhibitor *sildenafil* improved filling pressures and right ventricular function in a cohort of HFpEF patients with pulmonary venous hypertension. This finding led to the phase 2 trial, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX), in HFpEF patients (left ventricular EF [LVEF] >50%) with New York Heart Association (NYHA) functional class II or III symptoms, who received sildenafil at 20 mg three times daily for 3 months, followed by 60 mg three times daily for another 3 months, compared with a placebo. There was no improvement in functional capacity, QOL, or other clinical and surrogate parameters in those allocated to sildenafil compared to placebo. On the premise that *nitrates*, which are NO donors, might improve preload, coronary perfusion, endothelial function, and exercise tolerance, the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) study was conducted. Isosorbide mononitrate did not improve QOL or submaximal exercise capacity and decreased overall activity levels in treated patients. *Inorganic nitrate* compounds have also been shown to enhance NO signaling but did not improve functional capacity compared to placebo among patients with HFpEF randomized in the Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure with Preserved Ejection Fraction (INDIE-HFpEF) trial.

Neprilysin inhibition is known to increase circulating levels of various vasoactive peptides, including the natriuretic peptides, which may facilitate cyclic guanosine 3',5'-monophosphate based signaling, enhance myocardial relaxation, and reduce ventricular hypertrophy. Composite *angiotensin receptor-neprilysin inhibition* (ARNI) with sacubitril-valsartan reduced cardiovascular mortality, overall mortality, and HF hospitalization compared with enalapril among patients with HFrEF randomized in the PARADIGM-HF trial. The PARAGON-HF trial randomized 4822 patients with symptomatic HFpEF (LVEF 45%), elevated natriuretic peptides, and structural heart disease to treatment with either sacubitril-valsartan or valsartan with the novel composite primary endpoint of cardiovascular death and total hospitalizations for HF. Although there was a 13% reduction in the rate of the primary composite endpoint in those allocated to sacubitril-valsartan, this result narrowly missed the margin for statistical significance in the primary statistical analysis ( $p = .06$ ). Directional benefits in secondary endpoints including QOL, NYHA class, and renal function favoring sacubitril-valsartan support a possible modest benefit of neprilysin inhibition in this population, particularly among patients with lower (i.e., mildly reduced or mid-range) EF and women, subgroups who appeared to derive greater benefit. On the basis of these data, sacubitril-valsartan has recently been approved in the United States

## Heart Failure with Preserved Ejection Fraction: Pathology and Management



**FIGURE 258-1** Pathophysiologic correlations, general therapeutic principles, and results of specific "directed" therapy in heart failure (HF) with preserved ejection fraction. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT-2, sodium-glucose cotransporter-2.

for treatment of symptomatic heart failure across the full spectrum of ejection fraction, with benefits acknowledged to be greatest in those with LVEF below normal. Further study may be required to define the optimal therapeutic role for neprilysin inhibition in HFpEF.

Treatment of diabetic patients with *inhibitors of the sodium-glucose cotransporter-2* (SGLT-2) has been shown to reduce the incidence of HF, raising the possibility that these agents may be effective in patients with established HF. Addition of the SGLT-2 inhibitor dapagliflozin to guideline-directed medical therapy of HFrEF was associated with reductions in cardiovascular mortality and HF hospitalization among patients with and without diabetes enrolled in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study. Ongoing clinical trials of dapagliflozin (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure [DELIVER]; clinicaltrials.gov identifier: NCT03619213) and empagliflozin (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction [EMPEROR-PRESERVED]; clinicaltrials.gov identifier: NCT03057951) will assess whether these benefits can be extended to the population of patients with HFpEF, both with and without diabetes.

### CLINICAL GUIDING PRINCIPLES

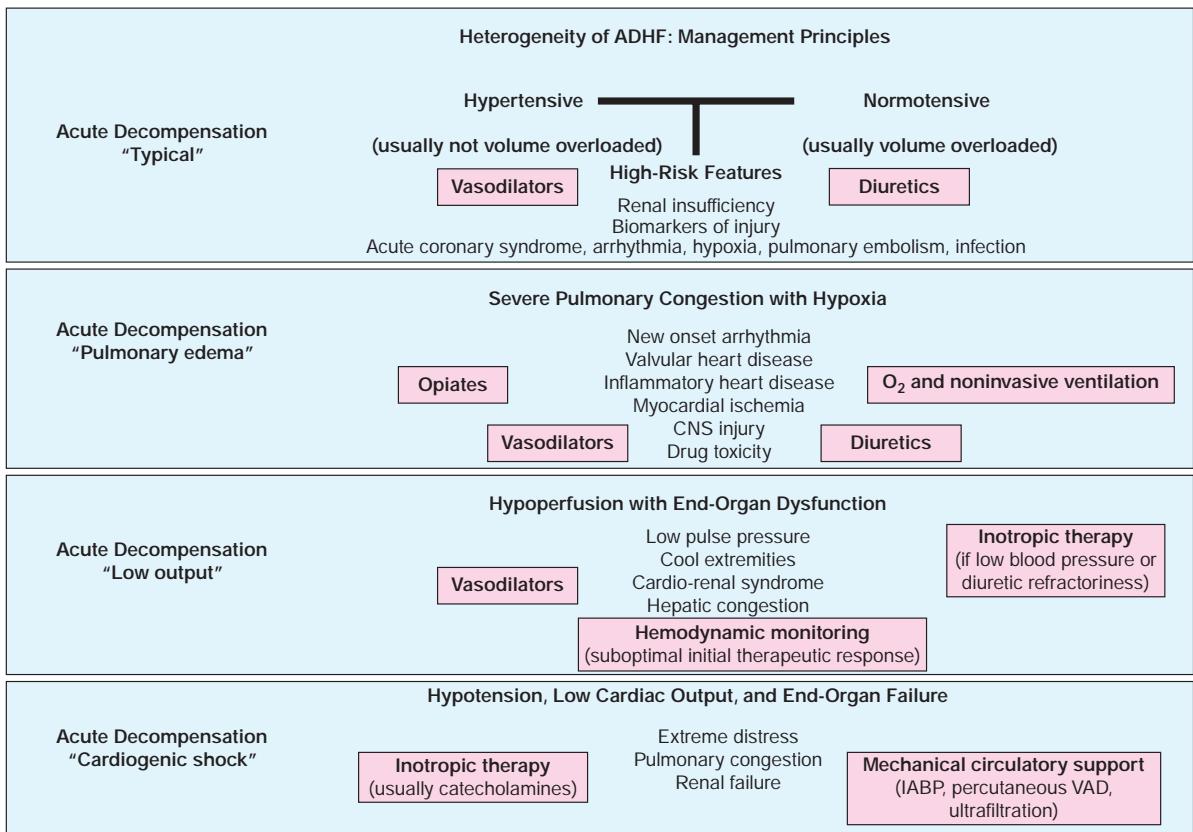
In the absence of evidence-based, targeted medical therapy, treatment of HFpEF should focus on decongestion, aggressive management of medical comorbidities, and relief of exacerbating factors. A careful diagnostic approach is critical, since patients with HF and a normal or near normal LVEF compose a heterogeneous group that includes patients with infiltrative heart disease (amyloidosis, hemochromatosis, sarcoidosis), storage disease (Fabry's disease, Gaucher's disease), hypertrophic cardiomyopathy, pericardial disease, pulmonary arterial hypertension, valvular heart disease, and primary right ventricular

failure who may require a different management approach. For those with true HFpEF, aggressive control of blood pressure to guideline-recommended targets and relief of volume overload with diuretics are critical to symptom relief. Excessive decrease in preload with diuretics and vasodilators may lead to underfilling of the ventricle and subsequent azotemia, hypotension, and syncope. For patients at risk for coronary heart disease, deliberate evaluation for ischemia and consideration of coronary revascularization is important. Since clinical outcomes in HFpEF are worse in the setting of atrial fibrillation, aggressive rate control, anticoagulation, and early consideration of sinus rhythm restoration are important. Comorbidities such as obesity, obstructive lung disease, sleep apnea, chronic kidney disease, and anemia/iron deficiency are increasingly recognized as important contributors to diminished functional capacity and QOL in patients with HFpEF and may be additional targets for therapy. Some investigators have suggested that the exercise intolerance in HFpEF is a manifestation of chronotropic insufficiency and that such aberrations could be corrected with use of rate responsive pacemakers, but this remains an inadequately investigated contention (Fig. 258-1).

## ACUTE DECOMPENSATED HEART FAILURE

### GENERAL PRINCIPLES

ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance. Admission with a diagnosis of ADHF is associated with excessive morbidity and mortality, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5% in-hospital) and long-term cardiovascular mortality (20% at 1 year). Importantly, long-term outcomes remain poor, with



**FIGURE 258-2** The distinctive phenotypes of acute decompensated heart failure (ADHF), their presentations, and suggested therapeutic routes. (Unique causes of ADHF, such as isolated right heart failure and pericardial disease, and rare causes, such as aortic and coronary dissection or ruptured valve structures or sinuses of Valsalva, are not delineated and are covered elsewhere.) CNS, central nervous system; IABP, intraaortic balloon pump; VAD, ventricular assist device.

a combined incidence of cardiovascular deaths, HF hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The management of these patients remains difficult and principally revolves around volume control and hemodynamic optimization to maximize end-organ perfusion.

The first principle of management in ADHF is to identify and address the factors that precipitated decompensation. Important historical factors to consider are nonadherence to medications, dietary salt indiscretion, and usage of medications (including over-the-counter preparations) that may exacerbate HF, including nonsteroidal anti-inflammatory drugs, thiazolidinediones, tumor necrosis factor inhibitors, selected antidepressants, selected cancer therapies, cold and flu preparations with cardiac stimulants, and some herbal preparations. Coronary ischemia frequently drives HF exacerbation in patients with atherosclerotic cardiovascular disease and should be systematically investigated (either invasively or noninvasively) in all patients at risk to identify candidates for revascularization. Atrial and ventricular arrhythmias are common contributors to HF exacerbation and may trigger the need for antiarrhythmic drug suppression, cardioversion, or catheter ablation. Valvular heart disease is increasingly recognized as a target for therapy in patients with recurrent HF exacerbations and can be readily identified through echocardiography. Systemic infection and pulmonary thromboembolism are additional triggers of HF decompensation and should be routinely considered.

Concurrent with the identification of HF precipitants, effective management of ADHF requires pharmacologic therapy directed at hemodynamic optimization, including relief of congestion, reduction in afterload, and maximization of vital organ perfusion. The routine use of a pulmonary artery catheter is not recommended and should be restricted to those who present with features typical of low-output

HF or cardiogenic shock who may require vasopressor or mechanical circulatory support, those who are resistant or refractory to diuretic therapy, those with combined cardiorenal dysfunction in whom therapeutic goals are difficult to define at the bedside, and those with known or suspected pulmonary arterial hypertension in whom vasodilator therapy may be appropriate. Analysis of in-hospital registries has identified several parameters associated with worse outcomes: a blood urea nitrogen level >43 mg/dL (to convert to mmol/L, multiply by 0.357), systolic blood pressure <115 mmHg, a serum creatinine level >2.75 mg/dL (to convert to  $\mu\text{mol}/\text{L}$ , multiply by 88.4), and elevated cardiac biomarkers including natriuretic peptides and cardiac troponins. A useful clinical schema to identify treatment targets for the various phenotypic presentations and management goals in ADHF is depicted in Fig. 258-2.

## VOLUME MANAGEMENT

**Intravenous Diuretic Agents** Intravenous loop diuretic agents rapidly and effectively relieve symptoms of congestion and are essential when oral drug absorption is impaired. When high doses of diuretic agents are required or when the effect of bolus dosing is suboptimal, a continuous infusion may be needed to reduce toxicity and maintain stable serum drug levels. Randomized clinical trials of high- versus low-dose and bolus versus continuous infusion diuresis have not provided clear justification for the best diuretic strategy in ADHF, and as such, the use of diuretic regimens remains an art rather than science. For those refractory to loop diuretic treatment alone, addition of a thiazide diuretic agent such as chlorothiazide or metolazone to provide sequential nephron blockade may enhance natriuresis and facilitate decongestion, but also increases the risk of significant hypokalemia.

Change in weight is often used as a surrogate for adequate diuresis, but this objective measure of volume status may be surprisingly difficult to interpret, and weight loss during hospitalization does not necessarily correlate closely with outcomes. Effective decongestion may also be confirmed by improvement in clinical symptoms as well as the bedside examination documenting normalization of the jugular venous pressure, clearance of pulmonary rales, suppression of cardiac gallops, and resolution of peripheral edema, hepatomegaly, and abdominal ascites. It is generally advisable to continue diuresis until euvolemia has been achieved, since residual congestion or volume overload is strongly associated with risk for recurrent decompensation. Predischarge measurement of natriuretic peptide levels, which are highly correlated with risk for postdischarge mortality and readmission, may also be useful in assessing the adequacy of therapy and stratifying risk.

**The Cardiorenal Syndrome** The cardiorenal syndrome is being recognized increasingly as a complication of ADHF. Multiple definitions have been proposed for the cardiorenal syndrome, but at its simplest, it can be thought to reflect the interplay between abnormalities of heart and kidney function, with deteriorating function of one organ while therapy is administered to preserve the other. Approximately 30% of patients hospitalized with ADHF exhibit abnormal renal function at baseline, and this is associated with longer hospitalizations and increased mortality. However, mechanistic studies have been largely unable to find correlation between deterioration in renal function, cardiac output, left-sided filling pressures, and reduced renal perfusion; most patients with cardiorenal syndrome demonstrate a preserved cardiac output. It is hypothesized that in patients with established HF, this syndrome represents a complex interplay of neurohormonal factors, potentially exacerbated by “backward failure” resulting from increased intraabdominal pressure and impairment in return of renal venous blood flow. Continued use of diuretic therapy may be associated with a reduction in glomerular filtration rate and a worsening of the cardiorenal syndrome when right-sided filling pressures remain elevated. In patients in the late stages of disease characterized by profound low cardiac output state, inotropic therapy or mechanical circulatory support has been shown to preserve or improve renal function in selected individuals in the short term until more definitive therapy such as assisted circulation or cardiac transplantation is implemented.

**Ultrafiltration** Ultrafiltration (UF) is an invasive fluid removal technique that may supplement the need for diuretic therapy. Proposed benefits of UF include controlled rates of fluid removal, neutral effects on serum electrolytes, and decreased neurohormonal activity. This technique has also been referred to as aquapheresis in recognition of its electrolyte depletion-sparing effects. In an initial study evaluating UF versus conventional therapy, fluid removal was improved and subsequent HF hospitalizations and urgent clinic visits were reduced with UF; however, no improvement in renal function and no subjective differences in dyspnea scores or adverse outcomes were noted. In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, 188 patients with ADHF and worsening renal failure were randomized to stepped pharmacologic care or UF. The primary endpoint was a change in serum creatinine and change in weight (reflecting fluid removal) at 96 h. Although similar weight loss occurred in both groups (~5.5 kg), there was a rise in serum creatinine among patients allocated to the UF group. Deaths and hospitalizations for HF were no different between groups, but there were more adverse events in the UF group, mainly due to kidney failure, bleeding complications, and intravenous catheter-related complications. This investigation argues against using UF as a primary strategy in patients with ADHF who are diuretic-responsive. Whether UF is useful as a rescue strategy in diuretic refractory patients with advanced renal disease remains an open question, and this strategy continues to be employed judiciously in such situations.

### VASOACTIVE THERAPY

Vasodilators including *intravenous nitroglycerin*, *sodium nitroprusside*, and *nesiritide* (a recombinant brain-type natriuretic peptide) are frequently used in ADHF to lower intracardiac filling pressures and

reduce systemic vascular tone. Rapid reduction in ventricular preload and afterload with these therapies may be effective in providing symptom relief in patients with pulmonary edema and in restoring end-organ perfusion for those with low cardiac output and high systemic vascular resistance. Nitroglycerine principally impacts venous tone and ventricular preload, whereas sodium nitroprusside is a potent arterial and venous vasodilator with more comprehensive effects on both preload and afterload. While intravenous nitroglycerine is commonly utilized as an adjunct to diuretics for acute management of symptomatic HF and pulmonary edema, nitroprusside is typically reserved for use in those with adequate arterial pressure or hemodynamic monitoring due to the risk for hypotension. The hemodynamic effects of nesiritide are intermediate between those of nitroglycerine and nitroprusside, with head-to-head comparisons with nitroglycerine suggesting more rapid reduction in pulmonary capillary wedge pressure and pulmonary vascular resistance. Clinical utilization of nesiritide has waned due to concerns raised regarding heightened risks of renal insufficiency and mortality identified in early trials. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) study randomizing 7141 patients with ADHF to nesiritide or placebo did not confirm this risk, but also identified no clear clinical benefit with regard to subsequent HF admissions, mortality, or symptom relief (reduction in dyspnea). Renal function did not worsen, but increased rates of hypotension were noted. A smaller study of low-dose nesiritide in acute HF (Renal Optimization Strategies Evaluation Acute Heart Failure Study [ROSE-AHF]) also showed no incremental benefit over intravenous diuretics for relief of congestion or preservation of renal function. Despite apparent safety in ADHF, the routine use of nesiritide is accordingly not recommended.

Other novel vasodilators have been explored for the management of ADHF. Recombinant human relaxin-2, or *serelaxin*, is a vasodilatory hormone known to contribute to cardiovascular and renal adaptations during pregnancy. In the Relaxin in Acute Heart Failure (RELAX-AHF) trial, 1161 patients hospitalized with ADHF, evidence of congestion, and systolic pressure >125 mmHg were randomized to treatment with serelaxin or placebo in addition to standard HF therapy. Serelaxin improved dyspnea, reduced signs and symptoms of congestion, and was associated with less early worsening of HF. A positive signal of reduced mortality identified in an exploratory analysis prompted a second study (RELAX-AHF2), which did not confirm an effect on cardiovascular death or worsening HF. Accordingly, this agent was not approved for use in clinical practice.

One hypothesis for the failure of vasodilator therapies to improve clinical outcomes in ADHF despite favorable hemodynamic effects is related to the acute injury hypothesis; in this model, acute HF is analogized to presentation with an acute coronary syndrome, with the initial hours of presentation representing a period of vulnerability to myocardial damage (reflected in a rise in markers of myocyte injury such as cardiac troponins) as a consequence of abrupt increases in ventricular wall stress related to acute plasma volume expansion. To test this hypothesis, the Trial of Ularitide Safety and Efficacy in Acute Heart Failure (TRUE-AHF) randomly allocated 2157 patients with acute HF to early treatment with the synthetic natriuretic peptide *ularitide* (at a dose sufficient to reduce ventricular wall stress) or placebo. Despite a very short duration between initial clinical presentation and pharmacologic intervention (<6 h) and early hemodynamic benefits, no improvement in clinical outcomes was observed in patients allocated to ularitide at 6 months. Ularitide was associated with a higher rate of hypotension and worsening serum creatinine. These data undermine the notion that acute myocardial damage related to ventricular distension associated with HF exacerbation drives subsequent clinical outcomes and argue against the clinical importance of early vasodilator therapy in ADHF.

### INOTROPIC THERAPY

Impairment of myocardial contractility often accompanies ADHF, and pharmacologic agents that increase intracellular concentration of cyclic adenosine monophosphate via direct or indirect pathways, such as sympathomimetic amines (*dopamine*, *dobutamine*) and

phosphodiesterase-3 inhibitors (*milrinone*), respectively, serve as positive inotropic agents. Their activity leads to an increase in cytoplasmic calcium. Inotropic therapy in those with a low-output state augments cardiac output, reduces systemic vascular resistance, improves perfusion, and relieves congestion acutely. Although systematic head-to-head comparisons are available to identify a “best” agent, slight variations in the hemodynamic effects of inotropic drugs may condition selection of the appropriate drug for a given clinical context. Dopamine exhibits dose-dependent effects on dopaminergic,  $\alpha$ , and  $\beta$ -adrenergic receptors, with vasodilatory effects predominating at lower doses ( $<2 \mu\text{g}/\text{kg}$  per min),  $\alpha$ -adrenergic (inotropic) effects at moderate doses, and  $\beta$ -adrenergic effects (vasoconstriction) at higher doses (typically  $>10 \mu\text{g}/\text{kg}$  per min). Low-dose (“renal dose”) dopamine has been explored as an adjunctive strategy for preservation of renal function and augmentation of diuresis in acute HF but does not appear to provide incremental advantage over routine therapy with intravenous diuretics (ROSE-AHF).

Milrinone is typically associated with a greater reduction in systemic and pulmonary vascular resistance than dobutamine and, accordingly, carries a higher risk of systemic hypotension. Moreover, because milrinone has a longer half-life and is renally excreted, it requires dose adjustments in the setting of kidney dysfunction. Because milrinone acts downstream from the  $\beta_1$ -adrenergic receptor, it may provide an advantage in patients receiving beta blockers when admitted to the hospital.

Long-term inotropic therapy is associated with a heightened risk of mortality in HF, perhaps due to the increased risk of arrhythmia and sudden death. Routine, short-term use of milrinone in patients hospitalized with ADHF in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial was associated with increased risk of atrial arrhythmias and prolonged hypotension, but no benefit with regard to subsequent mortality or HF hospitalization. Accordingly, routine use of inotropic support in ADHF is discouraged, and these agents are currently indicated principally for short-term use as bridge therapy (to either left ventricular assist device support or to transplant) in cardiogenic shock or as selectively applied palliation in end-stage HF.

Novel inotropic agents that leverage the concept of myofilament calcium sensitization rather than increasing intracellular calcium levels have been introduced. *Levosimendan* is a calcium sensitizer that provides inotropic activity but also possesses phosphodiesterase-3 inhibition properties that are vasodilatory. Two trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), have tested this agent in ADHF. SURVIVE compared levosimendan with dobutamine, and despite an initial reduction in circulating B-type natriuretic peptide levels in the levosimendan group compared with patients in the dobutamine group, this drug did not reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. The second trial compared levosimendan against traditional noninotropic therapy and found a modest improvement in symptoms with worsened short-term mortality and ventricular arrhythmias. Although levosimendan has been approved for use to support management of HF in several countries worldwide, it is not approved for use in the United States, largely owing to the lack of compelling data for incremental efficacy in comparison with conventional inotropic drugs or standard HF therapies.

(Table 258-1) depicts typical inotropic, vasodilator, and diuretic drugs used in ADHF.

### OTHER THERAPIES FOR ADHF

Other trials testing unique agents have yielded disappointing results in the situation of ADHF. Adenosine has been implicated as a mediator of worsening renal function and diuretic resistance, and accordingly, treatment with *adenosine receptor antagonists* was postulated to be potentially beneficial in relieving symptoms and preserving renal function in patients with acute HF. Among patients with acute HF and renal dysfunction enrolled in the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline

for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial, no cardiovascular or renal benefit was observed. Similarly, despite compelling theoretical benefit of vasoressin receptor antagonism in acute HF (based on the central role of vasopressin in mediating the fluid retention that contributes to worsening HF), no benefit of the oral selective vasopressin-2 antagonist *tolvaptan* was seen with regard to mortality or HF-associated morbidity in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial.

### CLINICAL GUIDING PRINCIPLES

In the absence of data to support specific pharmacologic interventions in ADHF, management is largely goal-directed and focused on decongestion to relieve symptoms, investigation and suppression of triggers for recurrent decompensation, and careful transition to longitudinal HF management. Patients who fail to respond adequately to medical therapy or who develop hemodynamic instability may benefit from pulmonary artery catheter placement to guide titration of vasoactive therapy or inotropic support; in those with hemodynamics suggestive of cardiogenic shock, mechanical assist devices may be required (Chap. 260). Following stabilization, all patients should receive education regarding HF self-management prior to discharge, including guidance regarding diet and lifestyle modification, identification of worsening HF symptoms, and whom to contact in the event of clinical deterioration. Early postdischarge follow-up of patients following hospitalization for management of worsening HF is associated with lower rates of hospital readmission. For patients with HFrEF hospitalized with ADHF, data suggest that institution of appropriate guideline-directed medical therapy prior to hospital discharge is associated with higher rates of adherence to appropriate pharmacologic treatment in longitudinal follow-up and may be associated with improved outcomes in the early postdischarge interval. Most recently, in the Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) study of patients with HFrEF stabilized after hospital admission for ADHF, pre-discharge initiation of sacubitril-valsartan compared with enalapril was associated with greater reductions in natriuretic peptides as well as lower rates of composite death and HF readmission at 8 weeks.

### HEART FAILURE WITH REDUCED EJECTION FRACTION

The past 50 years have witnessed great strides in the management of HFrEF. Treatment of symptomatic HF has evolved from a renocentric (diuretics) and hemodynamic therapy model (digoxin, inotropic therapy) to an era of disease-modifying therapy with neurohormonal antagonism. In this regard, RAAS blockers, beta-adrenergic receptor blockers, and most recently, SGLT2 inhibitors, form the pillars of pharmacotherapy and facilitate stabilization and even improvement in cardiac structure and function with consequent reduction in symptoms, improvement in QOL, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths (Fig. 258-3).

### NEUROHORMONAL ANTAGONISM

Meta-analyses suggest a 23% reduction in mortality and a 35% reduction in the combined endpoint of mortality and hospitalizations for HF in patients with symptomatic HFrEF treated with ACE inhibitors (ACEIs). Addition of  $\beta$ -adrenergic receptor blockers to background therapy with ACEIs provides a further 35% reduction in mortality. Although placebo-controlled studies are lacking, a number of noninferiority trials have demonstrated comparable efficacy of ARBs and ACEIs in patients with HFrEF, making ARBs a suitable alternative for patients who are intolerant to ACEIs due to cough or angioedema. Abundant data support the efficacy across the full spectrum of HF severity (including those with NYHA class III–IV functional capacity), as well as the safety data of these agents. These observations demonstrate the basis for the tolerability of these agents even in subgroups at higher risk for adverse effects such as those with mild-moderate

TABLE 258-1 Vasoactive Therapy in Acute Decompensated Heart Failure

DRUG CLASS	GENERIC DRUG	USUAL DOSING	SPECIAL CAUTION	COMMENTS
Inotropic therapy	Dobutamine	2–20 µg/kg per min	Increased myocardial oxygen demand, arrhythmia	Use in hypotension, end-organ hypoperfusion, or shock states Short acting, an advantage; variable efficacy in presence of beta blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare)
	Milrinone	0.375–0.75 µg/kg per min	Hypotension, arrhythmia	Decrease dose in renal insufficiency; avoid initial bolus; effectiveness retained in presence of beta blockers
	Levosimendan	0.1 µg/kg per min; range, 0.05–0.2 µg/kg per min	Hypotension, arrhythmia	Long acting; should not be used in presence of low blood pressure; similar effectiveness as dobutamine but effectiveness retained in presence of beta blockers
Vasodilators				Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved blood pressure
	Nitroglycerin	10–20 µg/min, increase up to 200 µg/min	Headache, flushing, tolerance	Most common vasodilator but often underdosed; effective in higher doses
	Nesiritide	Bolus 2 µg/kg and infusion at 0.01 µg/kg per min	Hypotension	Decrease in blood pressure may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection
	Nitroprusside	0.3 µg/kg per min titrated to 5 µg/kg per min	Thiocyanate toxicity in renal insufficiency (>72 h)	Requires arterial line placement for titration for precise blood pressure management and prevention of hypotension
	Serelaxin	N/A (tested at 30 µg/kg per d)	Baseline blood pressure should be >125 mmHg	Not widely commercially available; ineffective in confirmatory trials
	Ularitide	15 ng/kg per min (48 h)	Baseline blood pressure >116 mmHg	Excess hypotension and increased serum creatinine
Diuretics				First line of therapy in volume overload with congestion; may use bolus or continuous dosing; initial low dose (1 × home dose) or high dose (2.5 × home dose) equally effective with higher risk of renal worsening with higher dose
	Furosemide	20–240 mg daily	Monitor for electrolyte loss	In severe congestion, use intravenously and consider continuous infusion (not trial supported)
	Torsemide	10–100 mg daily	Monitor for electrolyte loss	High bioavailability, can be given orally; anecdotally more effective in advanced heart failure states if furosemide less bioavailable (due to gut congestion)
	Bumetanide	0.5–5 mg daily	Monitor for electrolyte loss	Can be used orally; intermediate bioavailability
	Adjuvant diuretics for augmentation	N/A	Metolazone, chlorthalidone, spironolactone, acetazolamide	Acetazolamide is useful in presence of alkalosis; metolazone given in 2.5- to 10-mg doses; concomitant use of loop diuretics and thiazides associated with risk for severe hypokalemia, careful laboratory monitoring advised; spironolactone is useful in presence of severe hypokalemia and normal renal function

Abbreviation: N/A, not applicable.

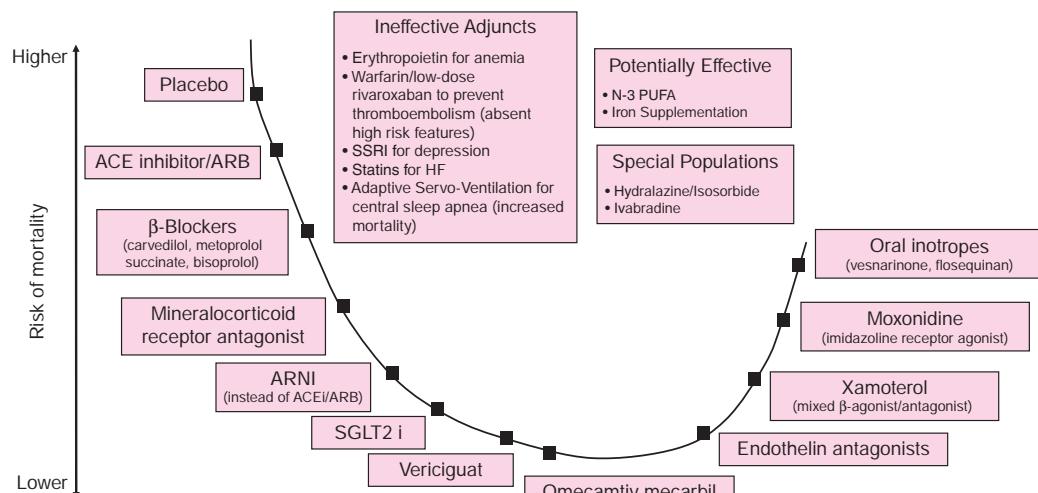


FIGURE 258-3 Progressive decline in mortality with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitors (ARNIs), beta blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and balanced vasodilators (\*selected populations such as African Americans); addition of selected therapies (ivabradine, vericiguat) may further reduce heart failure (HF) hospitalization but does not substantially impact mortality; further stack-on neurohormonal therapy is ineffective or results in worse outcome; management of comorbidity (e.g., iron deficiency, sleep apnea) is of unproven efficacy. HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitor.

chronic kidney disease. In diabetes mellitus and chronic obstructive lung disease, these agents have been established as foundational therapy for HFrEF as directed by consensus guidelines. Both agents are generally recommended for all patients with HFrEF, independent of symptom burden, and should be titrated to the doses proven to provide clinical benefit or to the maximally tolerated dose. The inability to tolerate initiation or dose titration of neurohumoral antagonists due to hypotension, worsening HF, or progressive renal insufficiency is a poor prognostic marker and may be a cardinal manifestation of transition to an advanced HF phenotype.

**Class Effect and Sequence of Administration** ACEIs and ARBs exert their beneficial effects in HFrEF as a class; however, the beneficial effects of beta blockers are thought to be limited to specific drugs. Beta blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not demonstrated a survival benefit. On the basis of the available data, beta blocker use in HFrEF should ideally be restricted to carvedilol, bisoprolol, and metoprolol succinate—agents tested and proven to improve survival in clinical trials. Whether beta blockers or ACEIs should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary based on the sequence of drug initiation. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACEIs and beta blockers be established in a timely manner.

**Dose and Outcome** In general, the benefits of neurohumoral antagonists in HFrEF are closely related to the dose achieved, girding the rationale for aggressive titration to target doses as defined by clinical trials. Prospective trials of high- versus low-dose ACEIs (ATLAS), ARBs (HEAAL), and beta blockers (MOCHA) consistently favor the higher dose, with lower rates of death and HF hospitalization seen in the higher-dose group. Clinical experience suggests that, in the absence of symptoms to suggest hypotension (fatigue and dizziness), pharmacotherapy may be uptitrated every 2 weeks in stable ambulatory patients as tolerated. Notably, data from large registries in the United States and Europe suggest that guideline-directed medical therapy for patients with HFrEF is frequently underutilized and underdosed, leaving considerable room for quality improvement.

### MINERALOCORTICOID RECEPTOR ANTAGONISTS

Addition of mineralocorticoid receptor antagonists to treatment with ACEI/ARBs and beta blockers in patients with symptomatic HFrEF (NYHA class II–IV) is associated with further reductions in morbidity and mortality. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, and endothelial dysfunction and may directly contribute to myocardial fibrosis. Hyperkalemia and worsening renal function are concerns, especially in patients with underlying chronic kidney disease, and renal function and serum potassium levels must be closely monitored. Spironolactone is the most commonly utilized agent in this class based on efficacy demonstrated in the Randomized Aldactone Evaluation Study (RALES) in patients with HFrEF and NYHA class III–IV symptoms. Eplerenone (studied principally in patients with milder NYHA class II symptoms and those with HF or left ventricular dysfunction complication myocardial infarction) lacks the antiandrogen effects of spironolactone and may be a suitable alternative for patients who experience sexual side effects (gynecomastia, erectile dysfunction, diminished libido).

### RAAS THERAPY AND NEUROHORMONAL “ESCAPE”

Since angiotensin II can be generated by non-ACE pathways, levels of angiotensin II may recover to pretreatment levels during long-term ACEI therapy. This phenomenon of neurohormonal “escape” has fueled interest in dual blockade of the RAAS using ACEI and ARBs in combination. In both the Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM-Added) trial, addition of an ARB to an ACEI and other HF therapy was associated with a lower risk of HF hospitalizations. Since neither trial mandated an evidence-based

dose of an ACEI, however, it remained unclear whether combination therapy was clearly superior to a strategy of maximizing a single agent through dose titration. Subsequent data from the Valsartan in Acute Myocardial Infarction (VALIANT) trial suggested that the addition of the ARB valsartan to an evidence-based dose of the ACEI captopril in patients with HF complicating myocardial infarction was associated with an increase in adverse events without any added benefit compared with monotherapy for either group. The findings of the VALIANT trial are buttressed by more recent data from the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE), which randomly allocated 7016 patients with HFrEF to treatment with enalapril (targeted dose 10 mg twice daily as recommended by guidelines), the plasma renin inhibitor aliskiren, or the combination on top of standard HF therapy. In that study, combination treatment with aliskiren and enalapril was associated with higher rates of hyperkalemia, hypotension, and worsening renal function, but no incremental benefit with regard to HF hospitalization or cardiovascular mortality. Together, these data argue for a ceiling of benefit of angiotensin inhibition in HFrEF, beyond which further inhibition brings more adverse effects without additional efficacy. Guidelines discourage the combination of an ACEI, ARB, and spironolactone in HFrEF due to the risks of hyperkalemia and renal dysfunction, and for most patients, treatment with either an ACEI or ARB and spironolactone is appropriate.

### ALTERNATIVE VASODILATORS

The combination of hydralazine and nitrates has been demonstrated to improve survival in HFrEF. Hydralazine reduces systemic vascular resistance and induces arterial vasodilation by affecting intracellular calcium kinetics; nitrates are transformed in smooth muscle cells into NO, which stimulates cyclic guanosine monophosphate production and consequent arterial-venous vasodilation. This combination improves survival but to a lesser extent than ACEIs. However, in individuals with HFrEF unable to tolerate RAAS-based therapy for reasons such as renal insufficiency or hyperkalemia, this combination is preferred as a disease-modifying approach. A trial conducted in self-identified African Americans, the African-American Heart Failure Trial (A-HeFT), studied a fixed dose of isosorbide dinitrate with hydralazine in patients with advanced symptoms of HFrEF who were receiving standard background therapy including an ACEI and beta blocker. The study demonstrated improvements in survival and hospital admission for HF in the treatment group. Adherence to this regimen is limited by the thrice-daily dosing schedule.

### NOVEL NEUROHORMONAL ANTAGONISTS

Despite an abundance of animal and clinical data demonstrating deleterious effects of activated neurohormonal pathways beyond the RAAS and sympathetic nervous system, targeting such pathways with incremental blockade has been largely unsuccessful. As an example, the endothelin antagonist bosentan is associated with worsening HF in HFrEF despite demonstrating benefits in right-sided HF due to pulmonary arterial hypertension. Similarly, the centrally acting sympatholytic agent moxonidine worsens outcomes in left HF. The combined drug omapatrilat hybridizes an ACEI with a neutral endopeptidase (neprilysin) inhibitor, and this agent was tested in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial. This drug did not favorably influence the primary outcome measure of the combined risk of death or hospitalization for HF requiring intravenous treatment compared with enalapril alone, and notably, the risk of angioedema was increased in patients assigned to omapatrilat.

The risk of angioedema with composite ACE/neprilysin inhibition appears to be related to excessive blockade of bradykinin breakdown by this combination. Blockade of angiotensin at the receptor level with an ARB leaves intact the ACE pathway for bradykinin breakdown and is associated with lower angioedema risk. Recently, a composite ARNI, sacubitril-valsartan (formerly LCZ696), was developed and applied to the treatment of patients with HFrEF. In the PARADIGM-HF trial, 8399 patients with HFrEF treated with guideline-directed medical therapy were randomly allocated to treatment with either enalapril or sacubitril-valsartan after a run-in period designed to ensure tolerability

TABLE 258-2 Guideline-Directed Pharmacologic Therapy and Target Doses in Heart Failure with Reduced Ejection Fraction

DRUG CLASS	GENERIC DRUG	MEAN DAILY DOSE IN CLINICAL TRIALS (mg)	INITIATION (mg)	TARGET DOSE (mg)
<b>Angiotensin-Converting Enzyme Inhibitors</b>				
	Lisinopril	4.5–33	2.5–5 qd	20–35 qd
	Enalapril	17	2.5 bid	10–20 bid
	Captopril	123	6.25 tid	50 tid
	Trandolapril	N/A	0.5–1 qd	4 qd
<b>Angiotensin Receptor Blockers</b>				
	Losartan	129	50 qd	150 qd
	Valsartan	254	40 bid	160 bid
	Candesartan	24	4–8 qd	32 qd
<b>Aldosterone Antagonists</b>				
	Eplerenone	42.6	25 qd	50 qd
	Spironolactone	26	12.5–25 qd	25–50 qd
<b>Beta Blockers</b>				
	Metoprolol succinate CR/XL	159	12.5–25 qd	200 qd
	Carvedilol	37	3.125 bid	25–50 bid
	Bisoprolol	8.6	1.25 qd	10 qd
<b>Arteriovenous Vasodilators</b>				
	Hydralazine isosorbide dinitrate	270/136	37.5/20 tid	75/40 tid
	Fixed-dose hydralazine/isosorbide dinitrate	143/76	37.5/20 qid	75/40 qid
<b>Angiotensin Receptor-Neprilisyn Inhibitor</b>				
	Sacubitril-valsartan	375	100 bid	200 bid
<b>Novel Therapies (Under Investigation)</b>				
	Vericiguat (sGC stimulator)	9.2	2.5 qd	10 qd
	Dapagliflozin, Empagliflozin (SGLT-2 inhibitors)	10	10 qd	10 qd
	Omeceantiv mecarbil (myosin activator)	Not reported	25 bid	Up to 50 mg bid (based on plasma concentrations)

Abbreviations: sGC, soluble guanylyl cyclase; SGLT-2, sodium-glucose cotransporter-2.

of both drugs at target doses. Compared to those assigned to enalapril, patients assigned to sacubitril-valsartan experienced a dramatic 20% reduction in the composite primary endpoint of cardiovascular death or HF hospitalization and a 16% reduction in all-cause mortality, as well as clinically important improvements in QOL measures. Sacubitril-valsartan was well tolerated and associated with lower rates of hyperkalemia and worsening renal function, but greater rates of symptomatic hypotension, than enalapril. Guidelines now advocate a switch to ARNI for patients with symptomatic HFrEF who tolerate ACEIs and ARBs, and emerging data suggest that up-front utilization of ARNI in patients with de novo HF naïve to ACEIs/ARBs may also be appropriate for those with adequate blood pressure to tolerate it. Given ongoing concern for angioedema, use of ARNI is contraindicated in patients with prior history of angioedema, and those being transitioned from ACEIs should receive ARNI only after a 36-hour gap to limit the risk of overlap. Table 258-2 lists the common neurohormonal and vasodilator regimens for HFrEF.

### HEART RATE MODIFICATION

Distinct from -adrenergic receptor blockers, ivabradine, an inhibitor of the  $I_f$  current in the sinoatrial node, selectively reduces heart rate without affecting cardiac contractility or vascular tone. The Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial (SHIFT) was conducted in patients with NYHA class II or III HFrEF prior HF hospitalization, sinus rhythm, and heart rate >70 beats/min. Ivabradine reduced the combined endpoint of cardiovascular-related death and HF hospitalization in proportion to the degree of heart rate reduction, which supports the notion that heart rate may be a therapeutic target in patients with HFrEF in sinus rhythm. Importantly, despite

a protocol requirement for patients to be treated with a maximally tolerated dose of a beta blocker prior to study entry, 10% of patients randomized were not treated with a beta blocker, and 75% were treated at subtarget doses. Accordingly, it remains unclear whether this agent would have been effective in patients receiving robust, guideline-recommended therapy for HF; however, these data do support the potential value of ivabradine as an adjunct or alternative in those who are intolerant to initiation or dose titration of beta blockers. Clinical guidelines have been adapted to encourage consideration of ivabradine in patients with HFrEF who remain symptomatic after treatment with guideline-based ACEi/ARB/ARNI, beta blockers, and mineralocorticoid receptor antagonists; are in sinus rhythm; and have a residual heart rate >70 beats/min.

### SGLT-2 INHIBITION

Inhibitors of SGLT-2 have been shown to reduce cardiovascular events and mortality among patients with type 2 diabetes mellitus at high cardiovascular risk or with established atherosclerotic cardiovascular disease. A particular signal of benefit has been seen with regard to the incidence of HF hospitalization, which was reduced by 35% in comparison to placebo in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOMES) study. Because the cardiovascular benefits of SGLT-2 inhibition appear to be unrelated to the degree of reduction in hemoglobin A<sub>1c</sub>, it has been postulated that the HF benefits of this therapy might be extended to patients without diabetes mellitus. Recently, the Dapagliflozin in Heart Failure (DAPA-HF) study randomized 4744 patients with symptomatic HFrEF treated with guideline-directed medical therapy (including a beta blocker, ACEI/ARB/ARNI, and spironolactone in >70% of patients) to

treatment with either the SGLT-2 inhibitor dapagliflozin (dosage 10 mg daily) or placebo over a median duration of follow-up of 18.2 months. Patients allocated to dapagliflozin experienced a highly significant 26% reduction in the primary composite endpoint of worsening HF or death from cardiovascular causes, an effect that was consistent in both patients with (42%) and without diabetes mellitus at baseline. These results have been reinforced by the results of the EMPEROR-Reduced trial, in which 3730 patients with symptomatic HF and ejection fraction of 40% or less were randomized to treatment with empagliflozin (dosage 10 mg once daily) or placebo in addition to recommended therapy. Over median 16 month follow up, patients allocated to empagliflozin experienced a 25% reduction in the primary composite endpoint of cardiovascular death or hospitalization for HF, an effect that was again consistent regardless of the presence or absence of diabetes mellitus. Together, these studies have driven consensus guidelines to consider use of SGLT2 inhibitors as foundational therapy for HF alongside ARNI, beta-blockers, and mineralocorticoid receptor antagonists.

### SOLUBLE GUANYLYL CYCLASE STIMULATION

Soluble guanylyl cyclase (sGC) is a key enzyme of the NO signaling pathway that catalyzes synthesis of cyclic guanosine monophosphate (cGMP), producing vasodilation. Vericiguat is a novel oral sGC stimulator that enhances cGMP and NO signaling by directly stimulating sGC and sensitizing sGC to endogenous NO. The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) randomly assigned 5050 patients with chronic HF, NYHA class II–IV symptoms, LVEF <45%, elevated natriuretic peptide levels, and evidence of worsening HF (requiring recent hospitalization or intravenous diuretic therapy) despite guideline-directed medical therapy to treatment with vericiguat (target dose 10 mg) or matching placebo over a median follow-up of 11 months. The primary study results were notable for a modest 10% relative risk reduction in the primary composite outcome of cardiovascular death or HF hospitalization among those assigned to vericiguat, an effect driven principally by effects on HF hospitalization, rather than cardiovascular death. As vericiguat was generally well tolerated with a low rate of serious adverse events, these data suggest a potential role for sGC stimulation as an adjunct to guideline-directed medical therapy in the high-risk group of HFrEF patients with recent congestive exacerbations requiring treatment, although these data await further review by regulatory agencies and guidelines committees.

### MYOSIN ACTIVATION

A novel approach to augmentation of cardiac output is to prolong ventricular systole without increasing myocardial contractility. As a selective myosin activator, *omecamtiv mecarbil* prolongs the ejection period and increases fractional shortening without altering the force of contraction as a consequence. This agent, distinct from inotropic agents, is not associated with an increase in myocardial oxygen demand. Importantly, the drug is available for oral, rather than intravenous, administration, enabling chronic use in the ambulatory setting. In the COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial of 448 patients with chronic HF and left ventricular systolic dysfunction, treatment with *omecamtiv mecarbil* for 20 weeks was associated with significant improvements in cardiac function and indices of left ventricular remodeling, as well as reductions in natriuretic peptide levels. Notably, the safety profile was comparable to placebo, with no increase in cardiac adverse events despite a modest increase in cardiac troponins in patients allocated to *omecamtiv mecarbil*. These promising preliminary data fueled a larger clinical outcomes trial (GALACTIC-HF, in which 8256 patients with symptomatic chronic heart failure and ejection fraction of 35% or less were randomized to treatment with *omecamtiv mecarbil* (dosage 25–50 mg twice daily based on plasma levels) or placebo in addition to standard HF therapy. Over median follow up of 21.8 months, patients allocated to *omecamtiv mecarbil* experienced a 14% reduction in the primary composite endpoint of death from cardiovascular causes or first heart failure event (hospitalization or urgent visit for heart failure), an outcome driven principally by reduction in heart failure events (no measureable effect on CV death alone). A possible signal of greater

benefit in patients with features of advanced HF (lower EF, higher natriuretic peptide levels, more severe symptoms) combined with a favorable safety and tolerability profile suggests a possible role for this agent in patients with late-stage disease, though additional study is needed.

### DIGOXIN

Digitalis glycosides exert a mild inotropic effect, attenuate carotid sinus baroreceptor activity, and are sympatho-inhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels. The Digitalis Investigation Group (DIG) trial demonstrated a reduction in HF hospitalizations in the treatment group (patients with HF and sinus rhythm) but no reduction in mortality or improvement in QOL. Importantly, treatment with digoxin resulted in a higher mortality rate and hospitalizations in women than men. It should be noted that low doses of digoxin are sufficient to achieve any potentially beneficial outcomes, and higher doses breach the therapeutic safety index. Although digoxin levels should be checked to minimize toxicity and although dose reductions are indicated for higher levels, no adjustment is made for low levels. Generally, digoxin is now relegated as late-line therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control.

### ORAL DIURETICS

Neurohormonal activation results in avid salt and water retention. Diuretic therapy is typically required in patients with symptomatic HF to remedy congestive symptoms as a prelude to initiation and titration of neurohormonal therapy. Because of their potent effect on renal sodium excretion, loop diuretic agents are the preferred agents, with thiazide diuretics reserved for use in combination with loop diuretics for those with refractory volume overload. Frequent dose adjustments of loop diuretics may be necessary during longitudinal follow-up of patients with HF because of variable oral absorption and fluctuations in renal function. Patients who fail to respond to furosemide at high doses may benefit from transition to torsemide or bumetanide, which have greater oral bioavailability. Importantly, clinical trial data confirming efficacy are limited, and no data suggest that these agents improve survival. Since loop diuretics do enhance neurohumoral activation, dosing should be minimized as possible to maximize the balance of risk and benefit.

### CALCIUM CHANNEL ANTAGONISTS

*Amlodipine* and *felodipine*, second-generation calcium channel-blocking agents, safely and effectively reduce blood pressure in HFrEF but do not affect morbidity, mortality, or QOL. The first-generation agents, including *verapamil* and *diltiazem*, may exert negative inotropic effects and destabilize previously asymptomatic patients. Accordingly, their use should be discouraged in patients with HFrEF.

### ANTI-INFLAMMATORY THERAPY

Targeting inflammatory cytokines such as tumor necrosis factor (TNF- $\alpha$ ) for the management of HF by using anticytokine agents such as *infliximab* and *etanercept* has been unsuccessful and associated with worsening HF. Use of intravenous immunoglobulin therapy in nonischemic etiology of HF has not been shown to result in beneficial outcomes. Nonspecific immunomodulation has been tested in the Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy (ACCLAIM-HF) trial where ex vivo exposure of a blood sample from systolic HF patients to controlled oxidative stress was hypothesized to initiate apoptosis of leukocytes soon after intramuscular gluteal injection of the treated sample. The physiologic response to apoptotic cells results in a reduction in inflammatory cytokine production and upregulation of anti-inflammatory cytokines. This promising hypothesis was not proven, although certain subgroups (those with no history of previous myocardial infarction and those with mild HF) showed signals in favor of immunomodulation. Most recently, in the *Canakinumab Anti-inflammatory Thrombosis Outcomes Study* (CANTOS), treatment of post-myocardial infarction patients with elevated high-sensitivity C-reactive protein using a

monoclonal antibody targeted at interleukin 1 was associated with a dose-dependent reduction in hospitalization for HF and HF-associated mortality. Whether this approach might have relevance for patients with established HF remains unclear.

### HMG-CoA REDUCTASE INHIBITORS (STATINS)

Potent lipid-altering and pleiotropic effects of statins reduce major cardiovascular events and improve survival in non-HF populations. Once HF is well established, this therapy may not be as beneficial and theoretically could even be detrimental by depleting ubiquinone in the electron transport chain. Two trials, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF), have tested low-dose rosuvastatin in patients with HFrEF and demonstrated no improvement in aggregate clinical outcomes. If statins are required to treat progressive atherosclerotic vascular disease or significant dyslipidemia in the background setting of HF, then they should be employed. However, no rationale appears to exist for routine statin therapy in nonischemic HF.

### ANTICOAGULATION AND ANTIPLATELET THERAPY

HFrEF is accompanied by a hypercoagulable state and therefore a high risk of thromboembolic events, including stroke, pulmonary embolism, and peripheral arterial embolism. Although the value of long-term oral anticoagulation is established in certain groups, including patients with atrial fibrillation, the data are insufficient to support the use of warfarin in patients in normal sinus rhythm without a history of thromboembolic events or echocardiographic evidence of left ventricular thrombus. In the large Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, full-dose aspirin or international normalized ratio-controlled warfarin was tested with follow-up for 6 years. Among patients with reduced LVEF in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. A recent trial of the direct oral anticoagulant rivaroxaban at low dose (2.5 mg daily) for patients with ischemic heart disease, HFrEF, and sinus rhythm also indicated no reduction in stroke or ischemic events compared with placebo. Aspirin blunts ACEI-mediated prostaglandin synthesis, but the clinical importance of this finding remains unclear. Current guidelines support the use of aspirin in patients with ischemic cardiomyopathy who do not have a contraindication.

### FISH OIL

Treatment with long-chain omega-3 polyunsaturated fatty acids ( $\omega$ -3 PUFAs) has been shown to be associated with modestly improved clinical outcomes in patients with HFrEF. This observation from the GISSI-HF trial was extended to measurements of  $\omega$ -3 PUFAs in plasma phospholipids at baseline and after 3 months. Three-month treatment with  $\omega$ -3 PUFAs enriched circulating eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Low EPA levels are inversely related to total mortality in patients with HFrEF.

### MICRONUTRIENTS

A growing body of evidence suggests an association between HF and micronutrient status. Reversible HF has been described as a consequence of severe thiamine and selenium deficiency. Thiamine deficiency has received attention in HF due to the fact that malnutrition and diuretics are prime risk factors for thiamine loss. Small exploratory randomized studies have suggested benefit of supplementation with thiamine in HFrEF with evidence of improved cardiac function. This finding is restricted to chronic HF states and does not appear to be beneficial in the ADHF phenotype. Due to the exploratory nature of the evidence, no recommendations for routine supplementation or testing for thiamine deficiency can be made.

### ENHANCED EXTERNAL COUNTERPULSATION

Peripheral lower extremity therapy using graded external pneumatic compression at high pressure is administered in 1-h sessions for 35

treatments (7 weeks) and has been proposed to reduce angina symptoms and extend time to exercise-induced ischemia in patients with coronary artery disease. The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) study assessed the benefits of enhanced external counterpulsation in the treatment of patients with mild-to-moderate HF. This randomized trial improved exercise tolerance, QOL, and NYHA functional classification but without an accompanying increase in peak oxygen consumption. A placebo effect due to the nature of the intervention simply cannot be excluded.

### EXERCISE

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study investigated short-term (3-month) and long-term (12-month) effects of a supervised exercise training program in patients with moderate HFrEF. Exercise was safe, improved patients' sense of well-being, and correlated with a trend toward mortality reduction. Maximal changes in 6-min walk distance were evident at 3 months with significant improvements in cardiopulmonary exercise time and peak oxygen consumption persisting at 12 months. Therefore, exercise training is recommended as an adjunctive treatment in patients with HF.

### MANAGEMENT OF SELECTED COMORBIDITY

**Sleep-disordered breathing** is common in HF and particularly in HFrEF. A range of presentations exemplified by obstructive sleep apnea, central sleep apnea, and its extreme form of Cheyne-Stokes breathing are noted. Frequent periods of hypoxia and repeated micro- and macro-arousals trigger adrenergic surges, which can worsen hypertension and impair systolic and diastolic function. A high index of suspicion is required, especially in patients with difficult-to-control hypertension or with predominant symptoms of fatigue despite reverse remodeling in response to optimal medical therapy. Worsening of right heart function with improvement of left ventricular function noted on medical therapy should immediately trigger a search for underlying sleep-disordered breathing or pulmonary complications such as occult embolism or pulmonary hypertension. Treatment with nocturnal positive airway pressure improves oxygenation, LVEF, and 6-min walk distance. However, no conclusive data exist to support this therapy as a disease-modifying approach with reduction in mortality. A recent trial using adaptive servo-ventilation in patients who had HFrEF and predominantly central sleep apnea increased all-cause and cardiovascular mortality, so this approach should be avoided.

**Anemia** is common in HF patients, reduces functional status and QOL, and is associated with increased proclivity for hospital admissions and mortality. Anemia in HF is more common in the elderly, in those with advanced stages of HFrEF, in the presence of renal insufficiency, and in women and African Americans. The mechanisms include iron deficiency, dysregulation of iron metabolism, and occult gastrointestinal bleeding. Intravenous iron using either iron sucrose or carboxymaltose (Ferric Carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure [FAIR-HF] trial) has been shown to correct anemia and improve functional capacity. Another trial, CONFIRM-HF, enrolled similar patients with iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%) and demonstrated that use of ferric carboxymaltose in a simplified high-dose schedule resulted in improvement in functional capacity, symptoms, and QOL. Oral iron supplementation does not appear to be effective in treating iron deficiency in HF. Erythropoiesis-regulating agents such as erythropoietin analogues have been studied with disappointing results. The Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial demonstrated that treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic HF and may increase risk of stroke.

**Depression** is common in HFrEF, with a reported prevalence of one in five patients, and is associated with a poor QOL, limited functional status, and increased risk of morbidity and mortality in this population. However, the largest randomized study of depression in HFrEF, the Sertraline Against Depression and Heart Disease in Chronic Heart

Failure (SADHART-CHF) trial, showed that although sertraline was safe, it did not provide greater reduction in depression or improve cardiovascular status among patients with HF and depression compared with nurse-driven multidisciplinary management.

**Atrial arrhythmias**, especially atrial fibrillation, are common and serve as a harbinger of worse prognosis in patients with HF. When rate control is inadequate or symptoms persist, pursuing a rhythm control strategy is reasonable. Rhythm control may be achieved via pharmacotherapy or by percutaneous or surgical techniques, and referral to practitioners or centers experienced in these modalities is recommended. Antiarrhythmic drug therapy should be restricted to amiodarone and dofetilide, both of which have been shown to be safe and effective but do not alter the natural history of the underlying disease. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) studied the effects of the novel antiarrhythmic agent dronedarone and found an increased mortality due to worsening HF. Catheter ablation and pulmonary vein isolation appear to be safe and effective in this high-risk cohort and compare favorably with the more established practice of atrioventricular node ablation and biventricular pacing.

**Diabetes mellitus** is a frequent comorbidity in HF. Prior studies using thiazolidinediones (activators of peroxisome proliferator-activated receptors) have been associated with worsening HF. Glucagon-like peptide 1 (GLP-1) agonists such as liraglutide have also been tested and do not lead to greater post-hospitalization, clinical stability, or worsening in HF. The role of SGLT-2 inhibitors in HF has been previously discussed.

### NEUROMODULATION USING DEVICE THERAPY

Autonomic dysfunction is common in HF, and attempts at using devices to modulate the sympathetic and parasympathetic systems have been undertaken. Broadly, devices that achieve vagal nerve stimulation, baroreflex activation, renal sympathetic denervation, spinal cord stimulation, or left cardiac sympathetic denervation have been employed. While small preclinical and clinical studies have demonstrated benefits, large randomized trials, when conducted, have failed. The INOVATE-HF study tested vagal nerve stimulation versus optimal medical therapy among individuals with stable HF. Vagus nerve stimulation did not reduce the rate of death or hospitalization for HF. However, functional capacity and QOL were favorably affected by vagus nerve stimulation.

### CARDIAC CONTRACTILITY MODULATION

Cardiac contractility modulation (CCM) is a device-based therapy for HF that involves nonexcitatory electrical stimulation to the right ventricular septal wall during the absolute myocardial refractory period to augment the strength of subsequent myocardial contraction. A series of small, randomized, prospective clinical trials, as well as a number of real-world observational registries, have suggested that application of CCM to selected patients with HF may improve symptoms, functional capacity, and QOL, although no effect on hard clinical outcomes such as HF hospitalization or mortality has been established. The predominant benefits of CCM appear to accrue to those with symptomatic HFrEF (EF 25–45%) and narrow QRS duration (for whom cardiac resynchronization therapy is not an option), and the approach can be combined with an implantable defibrillator. The device is currently available for use in selected patients with HFrEF outside the United States but is not currently endorsed by clinical treatment guidelines in the United States or Europe as part of the routine HF treatment armamentarium.

### CARDIAC RESYNCHRONIZATION THERAPY

Nonsynchronous contraction between the walls of the left ventricle (intraventricular) or between the ventricular chambers (interventricular) impairs systolic function, decreases mechanical efficiency of contraction, and adversely affects ventricular filling. Mechanical dysynchrony results in an increase in wall stress and worsens functional mitral regurgitation. The single most important association of extent of

dysynchrony is a widened QRS interval on the surface electrocardiogram, particularly in the presence of a left bundle branch block pattern. With placement of a pacing lead via the coronary sinus to the lateral wall of the ventricle, cardiac resynchronization therapy (CRT) enables a more synchronous ventricular contraction by aligning the timing of activation of the opposing walls. Early studies showed improved exercise capacity, reduction in symptoms, and evidence of reverse remodeling. The Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial was the first study to demonstrate a reduction in all-cause mortality with CRT placement in patients with HFrEF on optimal therapy with continued moderate-to-severe residual symptoms of NYHA class III or IV HF. More recent clinical trials have demonstrated disease-modifying properties of CRT in even minimally symptomatic patients with HFrEF, including the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), both of which sought to use CRT in combination with an implantable defibrillator. Most benefit in mildly symptomatic HFrEF patients accrues from applying this therapy in those with a QRS width of >149 ms and a left bundle branch block pattern. Attempts to further optimize risk stratification and expand indications for CRT using modalities other than electrocardiography have proven disappointing. In particular, echocardiographically derived measures of dysynchrony vary tremendously, and narrow QRS dysynchrony has not proven to be a good target for treatment. Uncertainty surrounds the benefits of CRT in those with ADHF, a predominant right bundle branch block pattern, atrial fibrillation, and evidence of scar in the lateral wall, which is the precise location where the CRT lead is positioned.

### SUDDEN CARDIAC DEATH PREVENTION IN HEART FAILURE

Sudden cardiac death (SCD) due to ventricular arrhythmias is the mode of death in approximately half of patients with HF and is particularly proportionately prevalent in HFrEF patients with early stages of the disease. Patients who survive an episode of SCD are considered to be at very high risk and qualify for placement of an implantable cardioverter-defibrillator (ICD). Although primary prevention is challenging, the degree of residual left ventricular dysfunction despite optimal medical therapy (35%) to allow for adequate remodeling and the underlying etiology (post-myocardial infarction or ischemic cardiomyopathy) are the two single most important risk markers for stratification of need and benefit. Currently, patients with NYHA class II or III symptoms of HF and an LVEF <35%, irrespective of etiology of HF, are appropriate candidates for ICD prophylactic therapy. In patients with a myocardial infarction and optimal medical therapy with residual LVEF 30% (even when asymptomatic), placement of an ICD is appropriate. A recent Danish trial suggested that prophylactic ICD implantation in patients with symptomatic systolic HF not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. In this trial, benefits were noted in those aged <60 years. In patients with a terminal illness and a predicted life span of <6 months or in those with NYHA class IV symptoms who are refractory to medications and who are not candidates for transplant, the risks of multiple ICD shocks must be carefully weighed against the survival benefits. If a patient meets the QRS criteria for CRT, combined CRT with ICD is often employed (Table 258-3).

### SURGICAL THERAPY IN HEART FAILURE

**Coronary artery bypass grafting (CABG)** is considered in patients with ischemic cardiomyopathy with multivessel coronary artery disease. The recognition that hibernating myocardium, defined as myocardial tissue with abnormal function but maintained cellular function, could recover after revascularization led to the notion that revascularization with CABG would be useful in those with living myocardium. Revascularization is most robustly supported in individuals with ongoing angina and left ventricular failure.

**TABLE 258-3 Principles of ICD Implantation for Primary Prevention of Sudden Death**

PRINCIPLE	COMMENT
Arrhythmia-sudden death mismatch	Sudden death in heart failure patients is generally due to progressive LVD, not a focal arrhythmia substrate (except in patients with post-MI HF)
Diminishing returns with advanced disease	Intervention at early stages of HF most successful since sudden death diminishes as cause of death with advanced HF
Timing of benefits	LVEF should be evaluated on optimal medical therapy or after revascularization before ICD therapy is employed; no benefit to ICD implant within 40 days of an MI (unless for secondary prevention)
Estimation of benefits and prognosis	Patients and clinicians often overestimate benefits of ICDs; an ICD discharge is not equivalent to an episode of sudden death (some ventricular arrhythmias terminate spontaneously); appropriate ICD discharges are associated with a worse near-term prognosis

Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; LVD, left ventricular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Revascularizing those with left ventricular failure in the absence of angina remains controversial. The Surgical Treatment for Ischemic Heart Failure (STICH) trial in patients with an EF of 35% and coronary artery disease amenable to CABG demonstrated no significant initial benefit compared to medical therapy. However, patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes over 10 years than among those who received medical therapy alone. An ancillary study of this trial also determined that the detection of hibernation (viability) pre-revascularization did not materially influence the efficacy of this approach, nor did it help to define a population unlikely to benefit if hibernation was not detected.

**Surgical ventricular restoration (SVR)**, a technique characterized by infarct exclusion to remodel the left ventricle by reshaping it surgically in patients with ischemic cardiomyopathy and dominant anterior left ventricular dysfunction, has been proposed. However, in a 1000-patient trial in patients with HFrEF who underwent CABG alone or CABG plus SVR, the addition of SVR to CABG had no disease-modifying effect. However, left ventricular aneurysm surgery is still advocated in those with refractory HF, ventricular arrhythmias, or thromboembolism arising from an akinetic aneurysmal segment of the ventricle. Other remodeling procedures, such as use of an external mesh-like net attached around the heart to limit further enlargement, have not been shown to provide hard clinical benefits, although favorable cardiac remodeling was noted.

**Functional (or secondary) mitral regurgitation (MR)** occurs with varying degrees in patients with HFrEF and dilated ventricles, and its severity is correlated inversely with prognosis. Annular dilatation and leaflet noncoaptation related to distorted papillary muscle geometry in the context of ventricular remodeling is typically responsible, although in patients with ischemic heart disease and prior myocardial infarction, leaflet tethering and displacement may contribute. The primary approach to management of functional MR is optimization of guideline-directed medical therapy, followed by CRT in eligible patients, but relief may be incomplete for many patients with advanced HF. In these patients with HF and severe left ventricular dysfunction who are not candidates for surgical coronary revascularization, surgical mitral valve repair (MVR) to remedy functional MR carries significant risk and remains controversial. The development of percutaneous approaches to edge-to-edge MVR has provided a less invasive approach that enables reduction in functional MR at lower risk than conventional surgery. Recently, two large randomized trials of transcatheter MVR using this approach have been conducted in patients with symptomatic HFrEF and moderate-severe functional MR. In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous

Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) study, patients allocated to MVR versus standard HF therapy experienced a marked reduction in both HF hospitalizations and mortality at 2 years, supporting the efficacy of this approach. In the second trial, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR), which employed a similar design, the rates of death or HF hospitalization did not differ between the percutaneous MVR and medical therapy groups. The precise reason for discrepant results between these studies remains unclear but may be related to differences in background utilization of guideline-directed medical therapy, procedural success rates, and patient selection (particularly whether or not the severity of MR is proportionate or disproportionate to the degree of left ventricular cavity dilation). Because mortality rates at 2 years remain high even with percutaneous MVR, patients with advanced symptoms of HF in whom MR severity is driven principally by end-stage left ventricular remodeling should also be considered for advanced therapies such as mechanical circulatory support.

## CELLULAR AND GENE-BASED THERAPY

The cardiomyocyte possesses regenerative capacity, and such renewal is accelerated under conditions of stress and injury, such as an ischemic event or HF. Investigations that use either bone marrow-derived precursor cells or autologous cardiac-derived cells have gained traction but have not generally improved clinical outcomes in a convincing manner. More promising, however, are cardiac-derived stem cells. Two preliminary pilot trials delivering cells via an intracoronary approach have been reported. In one, autologous c-kit-positive cells isolated from the atria obtained from patients undergoing CABG were cultured and reinfused. In another, cardiosphere-derived cells grown from endomyocardial biopsy specimens were used. These small trials demonstrated improvements in left ventricular function but require far more work to usher in a clinical therapeutic success. Efforts to utilize mesenchymal stem cells to facilitate left ventricular recovery and weaning from mechanical circulatory support in patients with left ventricular assist devices have also been disappointing. The appropriate route of administration, the quantity of cells to achieve a minimal therapeutic threshold, the constitution of these cells (single source or mixed), the mechanism by which benefit accrues, and short- and long-term safety remain to be elucidated.

Targeting molecular aberrations using gene transfer therapy, mostly with an adenoviral vector, has been tested in HFrEF. A cellular target includes calcium cycling proteins such as inhibitors of phospholamban such as SERCA2a, which is deficient in patients with HFrEF. Primarily responsible for reincorporating calcium into the sarcoplasmic reticulum during diastole, this target was tested in the CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) trial. This study used coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a and initially demonstrated that natriuretic peptides were decreased, reverse remodeling was noted, and symptomatic improvements were forthcoming. However, a confirmatory trial failed to meet its primary efficacy endpoint.

**More advanced therapies for late-stage HF such as left ventricular assist devices and cardiac transplantation are covered in detail in Chap. 260.**

## DISEASE MANAGEMENT AND SUPPORTIVE CARE

Despite stellar outcomes with medical therapy, admission rates following HF hospitalization remain high, with nearly half of all patients readmitted to hospital within 6 months of discharge. Recurrent HF and related cardiovascular conditions account for only half of readmissions in patients with HF, whereas other comorbidity-related conditions account for the rest. The key to achieving enhanced outcomes must begin with the attention to transitional care at the index hospitalization with facilitated discharge through comprehensive discharge planning,

patient and caregiver education, appropriate use of visiting nurses, and planned follow-up. Early postdischarge follow-up, whether by telephone or clinic-based, may be critical to ensuring stability because most HF-related readmissions tend to occur within the first 2 weeks after discharge. Although routinely advocated, intensive surveillance of weight and vital signs with use of telemonitoring has not decreased hospitalizations. Serial measurement of intrathoracic impedance has been utilized to identify early signals of worsening congestion to guide preemptive management to obviate the need for hospitalization. However, when systematically studied in randomized trials, this approach has not been proven to improve outcomes in comparison with routine HF care and may even enhance the rate of hospitalization due to the high frequency of impedance threshold crossings and device alerts. Implantable hemodynamic monitoring systems that directly measure pulmonary artery pressure tend to provide signals for early decompensation, and in patients with HF and moderately advanced symptoms across the full spectrum of EF, such systems have been shown to provide information that can allow implementation of therapy to avoid hospitalizations by as much as 39% (in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION] trial). Whether this reduction in hospital admissions translates into a long-term reduction in mortality remains to be determined by ongoing trials (Hemodynamic Guided Management of Heart Failure [GUIDE-HF]; clinicaltrials.gov identifier: NCT03387813). Alternate approaches to longitudinal HF monitoring that leverage multiparameter signals derived from implantable cardiac rhythm devices such as pacemakers and defibrillators to provide a global index of congestion are also being explored as adjuncts to longitudinal HF management (Multiple Cardiac Sensors for the Management of Heart Failure [MANAGE-HF]; clinicaltrials.gov identifier: NCT03237858).

Once HF becomes advanced, regularly scheduled review of the disease course and options with the patient and family is recommended, including discussions surrounding end-of-life preferences when patients are comfortable in an outpatient setting. As the disease state advances further, integrating care with social workers, pharmacists, and community-based nursing may be critical in improving patient satisfaction with the therapy, enhancing QOL, and avoiding HF hospitalizations. Equally important is attention to seasonal influenza vaccinations and periodic pneumococcal vaccines that may obviate non-HF hospitalizations in these ill patients. When nearing end of life, facilitating a shift in priorities to outpatient and hospice palliation is key, as are discussions around advanced therapeutics and continued use of ICD prophylaxis, which may worsen QOL and prolong death. Small randomized trials have suggested that systematic integration of palliative care considerations in high-risk HF patients by a specialized team has been demonstrated to improve QOL, anxiety, depression, and spiritual well-being and to facilitate goal-concordant care.

## GLOBAL CONSIDERATIONS

Substantial differences exist in the practice of HF therapeutics and outcomes by geographic location. The penetrance of CRT and ICD is higher in the United States than in Europe. Conversely, therapy unavailable in the United States, such as levosimendan, is designated as useful in Europe. Variation in the benefits of beta blockers based on world region remains an area of controversy. In oral pharmacologic therapy trials of HFrEF, patients from southwest Europe have a lower incidence of ischemic cardiomyopathy and those in North America tend to have more diabetes and prior coronary revascularization. There is also regional variation in medication use even after accounting for indication. In trials of HF, disparate effects are noted across populations. As a recent example, in TOPCAT, the drug spironolactone was effective when used in the U.S. population, whereas patients recruited from Russia and contiguous territories showed no difference.

Whether this represents population differences or trial conduct disparity remains to be investigated. ADHF patients in Eastern Europe tend to be younger, with higher EFs and lower natriuretic peptide levels. Patients from South America tend to have the lowest rates of comorbidities, revascularization, and device use. In contrast, patients from North America have the highest comorbidity burden with high revascularization and device use rates. Given geographic differences in baseline characteristics and clinical outcomes, the generalizability of therapeutic outcomes in patients in the United States and Western Europe may require verification.

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## 259

# Cardiomyopathy and Myocarditis



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## DEFINITION AND CLASSIFICATION

Cardiomyopathy is disease of the heart muscle. It is estimated that cardiomyopathy accounts for 5–10% of the heart failure in the 5–6 million patients carrying that diagnosis in the United States. This term is intended to exclude cardiac dysfunction that results from other structural heart disease, such as coronary artery disease, primary valve disease, or severe hypertension; however, in general usage, the phrase *ischemic cardiomyopathy* is sometimes applied to describe diffuse dysfunction attributed to multivessel coronary artery disease, and *nonischemic cardiomyopathy* is used to describe cardiomyopathy from other causes. As of 2013, cardiomyopathies are defined as “disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype.” *It was further specified that many cardiomyopathies will be attributable to genetic disease.*<sup>1</sup>

The traditional classification of cardiomyopathies into a triad of dilated, restrictive, and hypertrophic was based initially on autopsy specimens and later on echocardiographic findings. Dilated and hypertrophic cardiomyopathies can be distinguished on the basis of left ventricular wall thickness and cavity dimension; however, restrictive cardiomyopathy can have variably increased wall thickness and chamber dimensions that range from reduced to slightly increased, with prominent atrial enlargement. Restrictive cardiomyopathy is now defined more on the basis of abnormal diastolic function, which is also present but initially less prominent in dilated and hypertrophic cardiomyopathy. Restrictive cardiomyopathy can overlap in presentation, gross morphology, and etiology with both hypertrophic and dilated cardiomyopathies (**Table 259-1**).

Expanding information renders this classification triad based on phenotype increasingly inadequate to define disease or therapy. While dilated cardiomyopathy is associated with low left ventricular ejection fraction and hypertrophic cardiomyopathy with normal or high ejection fraction, efforts to define intermediate phenotypes based on arbitrary thresholds for mid-range ejection fraction are confounded by the increasing prevalence of patients whose low ejection has improved with contemporary therapies. Identification of more genetic determinants of cardiomyopathy has suggested a four-way classification scheme of etiology as primary (affecting primarily the heart) and secondary to other systemic disease. The primary causes are then divided into genetic, mixed genetic and acquired, and acquired. In practice, however, genetic information is rarely available at initial presentation, the phenotypic expression of a given mutation varies widely, and acquired cardiomyopathies may also be influenced by genetic predisposition, which can be monogenic or polygenic, to establish a “two-hit” etiology. Identification of genetic causes of cardiomyopathy will become increasingly relevant as classification moves beyond morphology to identify specific molecular targets for intervention.

## GENERAL PRESENTATION

The early symptoms of cardiomyopathy often reflect exertional intolerance with breathlessness or fatigue. As filling pressures become elevated at rest, shortness of breath may occur during routine activity or when lying down at night. Although often considered the hallmark of congestion, peripheral edema may be absent despite severe fluid retention, particularly in younger patients in whom abdominal discomfort from hepato-splanchnic congestion and ascites may dominate. Patients

may also present initially with atypical chest pain, with palpitations or syncope related to associated rhythm disorders, or with an embolism from an intracardiac thrombus. Acute cardiogenic shock is the primary presentation for fulminant myocarditis, which can occur in otherwise healthy young adults and require rapid diagnosis and aggressive support, after which cardiac function may improve to near-normal levels.

The nonspecific term *congestive heart failure* describes only the resulting syndrome of fluid retention, which is common to all three structural phenotypes of cardiomyopathy and also to other cardiac structural diseases, such as mitral valve disease, that are associated with elevated intracardiac filling pressures. Initial evaluation begins with a detailed clinical history and examination seeking clues to cardiac, extracardiac, and genetic causes of heart disease (**Tables 259-1** and **259-2**). Echocardiography remains the initial imaging modality, with increasing use of MRI to provide further information on myocardial tissue characterization and evidence of focal and diffuse inflammation and abnormal interstitium.

## GENETIC CAUSES OF CARDIOMYOPATHY

 Estimates for the prevalence of a genetic etiology for cardiomyopathy continue to rise, with increasing availability of genetic testing and attention to the family history. Well-recognized in hypertrophic cardiomyopathy, heritability is also present in at least 30% of dilated cardiomyopathy (DCM) without other clear etiology. Careful family history should elicit information about not only known cardiomyopathy and heart failure, but also family members who have had sudden death, often incorrectly attributed to “a massive heart attack,” who have had atrial fibrillation or pacemaker implantation by middle age, or who have muscular dystrophy.

Most familial cardiomyopathies are inherited in an autosomal dominant pattern, with occasional autosomal recessive, matrilineal (mitochondrial), and X-linked inheritance (**Table 259-3**). Missense mutations with amino acid substitutions and truncating variants are the most common genetic abnormalities in cardiomyopathy. Expressed mutant proteins may interfere with function of the normal allele through a dominant negative mechanism. Mutations introducing a premature stop codon (nonsense) or shift in the reading frame (frame-shift) may create a truncated or unstable protein, the lack of which causes cardiomyopathy (haploinsufficiency). Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies.

Many different genes have been implicated in human cardiomyopathy (locus heterogeneity), and many mutations within those genes have been associated with disease (allelic heterogeneity). Although most identified mutations are “private” to individual families, several specific mutations are found repeatedly, either due to a founder effect or recurrent mutations at a common residue.

Genetic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of cardiomyopathy is rarely present at birth and, in some individuals, may never manifest. Related individuals who carry the same mutation may differ in the severity and rate of progression of cardiac dysfunction and associated rhythm disorders, indicating the important role of other genetic, epigenetic, and environmental modifiers in disease expression. Sex appears to play a role, as penetrance and clinical severity may be greater in men for most cardiomyopathies. Clinical disease expression is generally more severe in the ~1% of individuals who harbor two or more mutations linked to cardiomyopathy. However, the clinical course of a patient usually cannot be predicted based on which mutation is present; thus, current therapy is based on the phenotype rather than the genetic defect. Currently, the greatest utility of genetic testing for cardiomyopathy is to inform family evaluations. However, genetic testing occasionally enables the detection of a disease for which specific therapy is indicated, such as the replacements for defective metabolic enzymes in Fabry’s disease and Gaucher’s disease.

## GENES AND PATHWAYS IN CARDIOMYOPATHY

Mutations in sarcomeric genes, encoding the thick and thin myofilament proteins, are the best characterized. While the majority are

<sup>1</sup>From E Arbustini et al: J Am Coll Cardiol 62:2046, 2013.

**TABLE 259-1 Typical Presentation with Symptomatic Cardiomyopathy**

	DILATED	RESTRICTIVE	HYPERTROPHIC
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	Usually >40–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	60 mm if chronic	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Normal or decreased	Normal or increased	Markedly increased
Atrial size	Increased, left before right	Increased: may be massive and involve both atria equally	Increased: related to elevated filling pressures
Valvular regurgitation	Related to annular and ventricular dilation; mitral appears earlier during decompensation; tricuspid regurgitation with right ventricular dysfunction	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early, may have dominant right-sided symptoms	Exertional intolerance; may have chest pain
Congestive symptoms <sup>a</sup>	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion at rest may develop late
Arrhythmias	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some genetic etiologies. Atrial fibrillation	Conduction disease is common in amyloidosis, in which ventricular arrhythmias are uncommon. Atrial fibrillation is very common	Ventricular tachyarrhythmias; atrial fibrillation

<sup>a</sup>Left-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic venous congestion: hepatic and abdominal distention, discomfort on bending, peripheral edema. It should be noted that overlaps exist between these phenotypes, such that nondilated cardiomyopathy may have aspects of both dilated and restrictive cardiomyopathy, while restrictive cardiomyopathy with small internal ventricular dimensions may be difficult to distinguish from hypertrophic cardiomyopathy.

**TABLE 259-2 Initial Evaluation of Cardiomyopathy****Clinical Evaluation**

Thorough history and physical examination to identify cardiac and noncardiac disorders<sup>a</sup>  
Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders, tachyarrhythmias, and sudden death  
History of alcohol, illicit drugs, chemotherapy, or radiation therapy<sup>a</sup>  
Assessment of ability to perform routine and desired activities<sup>a</sup>  
Assessment of volume status, orthostatic blood pressure, body mass index<sup>a</sup>

**Laboratory Evaluation**

Electrocardiogram<sup>a</sup>  
Chest radiograph<sup>a</sup>  
Two-dimensional and Doppler echocardiogram<sup>a</sup>  
Magnetic resonance imaging for evidence of myocardial inflammation and fibrosis  
Chemistry:  
Serum sodium,<sup>a</sup> potassium,<sup>a</sup> calcium,<sup>a</sup> magnesium<sup>a</sup>  
Fasting glucose (glycohemoglobin in diabetes mellitus)  
Creatinine,<sup>a</sup> blood urea nitrogen<sup>a</sup>  
Albumin,<sup>a</sup> total protein,<sup>a</sup> liver function tests<sup>a</sup>  
Lipid profile  
Thyroid-stimulating hormone<sup>a</sup>  
Serum iron, transferrin saturation  
Urinalysis  
Creatine kinase isoforms  
Cardiac troponin levels  
Hematology:  
Hemoglobin/hematocrit<sup>a</sup>  
White blood cell count with differential,<sup>a</sup> including eosinophils  
Erythrocyte sedimentation rate

**Initial Evaluation When Specific Diagnoses Are Suspected**

DNA sequencing for genetic disease, panel selection based on phenotype  
Titers for infection in the setting of clinical suspicion:  
Acute viral (coxsackie, echovirus, influenza)  
Human immunodeficiency virus  
Chagas' (*Trypanosoma cruzi*), Lyme (*Borrelia burgdorferi*), toxoplasmosis  
Catheterization with coronary angiography in patients with angina who are candidates for intervention<sup>a</sup>  
Serologies for active rheumatologic disease  
Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications

<sup>a</sup>Level I recommendations from American College of Cardiology/American Heart Association Practice Guidelines for Chronic Heart Failure in the Adult.

associated with hypertrophic cardiomyopathy, sarcomeric mutations are also implicated in DCM, and some in left ventricular noncompaction. The most commonly recognized genetic causes of DCM are truncating mutations of the giant protein titin, encoded by *TTN*, which maintains sarcomere structure and acts as a key signaling molecule.

As cytoskeletal proteins play crucial roles in the structure, connection, and stability of the myocyte, multiple defects in these proteins can lead to cardiomyopathy, usually with a dilated phenotype (Fig. 259-1). For example, desmin forms intermediate filaments that connect the nuclear and plasma membranes, Z-lines, and the intercalated disks between muscle cells. Desmin mutations impair the transmission of force and signaling for both cardiac and skeletal muscle and may cause combined cardiac (restrictive > dilated) and skeletal myopathy.

Defects in the sarcolemmal membrane proteins are associated with DCM. The best known is dystrophin, encoded by the X chromosome gene *DMD*, abnormalities of which cause Duchenne's and Becker's muscle dystrophy. (Interestingly, abnormal dystrophin can be acquired when the coxsackie virus cleaves dystrophin during viral myocarditis.) This protein provides a network that supports the sarcolemma and also connects to the sarcomere. The progressive functional defect in both cardiac and skeletal muscle reflects vulnerability to mechanical stress. Dystrophin is associated at the membrane with a complex of other proteins, such as metavinculin, abnormalities of which also cause DCM. Defects in the sarcolemmal channel proteins (*channelopathies*) are generally associated with primary arrhythmias, but mutations in *SCN5A*, the  $\alpha$  subunit of the Nav 1.5 ion channel protein, distinct from those that cause the Brugada or long QT syndromes, have been implicated in DCM with conduction disease.

Nuclear membrane protein defects in cardiac and skeletal muscle occur in either autosomal (lamin A/C) or X-linked (emerin) patterns. These defects are associated with a high prevalence of atrial and ventricular arrhythmias and conduction system disease, which can occur in some family members without or before detectable cardiomyopathy.

Intercalated disks contribute to intracellular connections, allowing mechanical and electrical coupling between cells and also connections to desmin filaments within the cell. Mutations in proteins of the desmosomal complex compromise attachment of the myocytes, which can become disconnected and die via activation of Wnt/β-catenin and proinflammatory signaling pathways, to be replaced by fat and fibrous tissue. These areas are highly arrhythmogenic and may dilate to form aneurysms. Although more often noted in the right ventricle (arrhythmogenic right ventricular cardiomyopathy), this condition can affect both ventricles and has also been termed "arrhythmogenic cardiomyopathy."

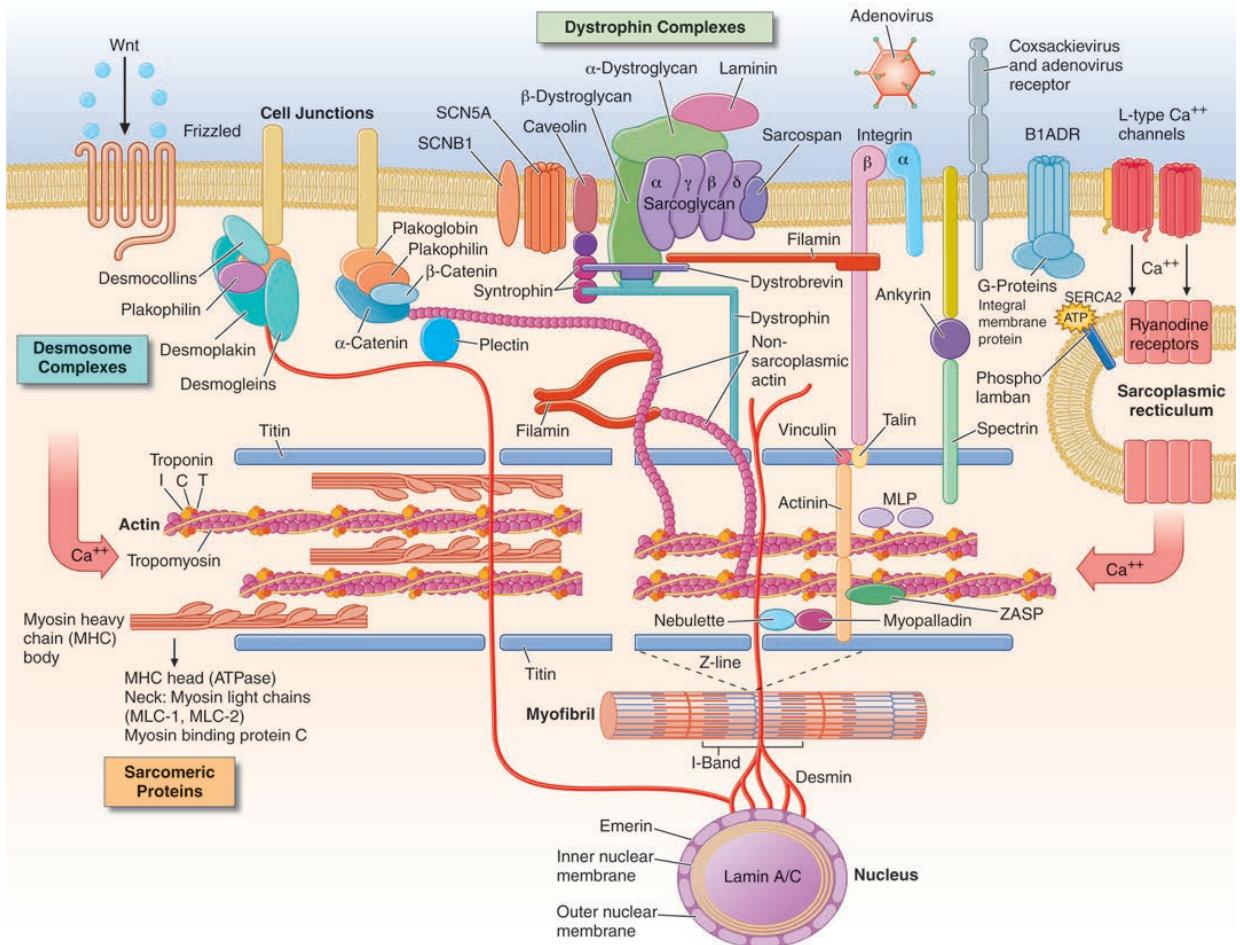
As many signaling pathways are conserved over multiple systems, we anticipate discovering extracardiac manifestations of abnormal

TABLE 259-3 Selected Genetic Defects Associated with Cardiomyopathy

	GENE PRODUCT	INHERITANCE	CARDIAC PHENOTYPE	ISOLATED CARDIAC PHENOTYPE <sup>a</sup>	EXTRACARDIAC MANIFESTATIONS
Sarcomere	<i>ACTC1</i> (cardiac actin)	AD	HCM, DCM	Yes	
	<i>MYH7</i> ( $\beta$ myosin heavy chain)	AD	HCM, DCM, LVNC	Yes	Skeletal myopathy
	<i>MYBPC3</i> (myosin binding protein C)	AD	HCM	Yes	
	<i>TNNT2</i> (cardiac troponin T)	AD	HCM, DCM, LVNC	Yes	
	<i>TNNI3</i> (cardiac troponin I)	AD, AR	HCM, DCM, RCM	Yes	
	<i>TTN</i> (Titin)	AD	DCM	Yes	
	<i>TPM1</i> ( $\alpha$ -tropomyosin)	AD	HCM, DCM	Yes	
	<i>TNNC1</i> (cardiac troponin C)	AD	DCM	Yes	
	<i>MYL2</i> (myosin regulatory light chain)	AD	HCM	Yes	Skeletal myopathy
	<i>MYL3</i> (myosin essential light chain)	AD	HCM	Yes	
Z-Disk and Cytoskeleton	<i>DES</i> (desmin)	AD	RCM, DCM	Yes	Skeletal myopathy
	<i>FLNC</i> (filamin C)	AD	DCM	Yes	Skeletal myopathy
	<i>NEXN</i> (nexilin)	AD	DCM	Yes	
	<i>VCL</i> (vinculin)	AD	DCM	Yes	
Nuclear Membrane	<i>LMNA</i> (lamin A/C)	AD, AR	CDDC	Yes	Skeletal myopathy
	<i>EMD</i> (emerin)	X-linked	CDDC	No	Skeletal myopathy, contractures
Excitation-Contraction Coupling	<i>PLN</i> (phospholamban)	AD	DCM, ARVC	Yes	
	<i>SCN5A</i> (NAV 1.5)	AD	CDDC	Yes	Note other mutations associated with Brugada syndrome
	<i>RYR2</i> (cardiac ryanodine receptor)	AD	ARVC	Yes	
	<i>CASQ2</i> (calsequestrin 2)	AR	ARVC	Yes	
Cellular Metabolism	<i>PRKAG2</i> ( $\gamma$ -subunit of AMP kinase)	AD	HCM+	Yes	
	<i>LAMP2</i> (lysosomal associated membrane protein)	X-linked	HCM+	No <sup>b</sup>	Danon's disease: skeletal myopathy, cognitive impairment
	<i>TAZ</i> (tafazzin)	X-linked	DCM, LVNC	No	Barth's syndrome: skeletal myopathy, cognitive impairment, neutropenia
	<i>FXN</i> (frataxin)	AR	HCM	No	Friedreich's ataxia: ataxia, diabetes mellitus type 2
	<i>TMEM43</i> (transmembrane protein 43)	AD	ARVC	Yes	
	<i>GLA</i> ( $\alpha$ -galactosidase-A)	X-linked	HCM+	No	Fabry's disease: renal failure, angiokeratomas and painful neuropathy
Mitochondria	Mitochondrial DNA	Maternal transmission	DCM, HCM	No	MELAS, MERRF, Kearns-Sayre syndrome, ocular myopathy
Sarcolemmal Membrane	<i>DMD</i> (dystrophin)	X-linked	DCM	No <sup>b</sup>	Duchenne's and Becker's muscular dystrophy
	<i>DMPK</i> (dystrophica myotonica protein kinase)	AD	DCM	No	Myotonic dystrophy type 1
Desmosome	<i>DSP</i> (desmoplakin) <i>JUP</i> (Plakoglobin)	AD, AR	ARVC, DCM	Yes	Carvajal syndrome (AR), Naxos syndrome (AR), "woolly hair" and hyperkeratosis of palms and soles
	<i>DSG2</i> (desmoglein 2), <i>DSC2</i> (desmocollin 2), <i>PKP2</i> (plakophilin 2)	AD	ARVC	Yes	
Other Examples	<i>RBM20</i> (RNA binding motif 20)	AD	DCM	Yes	
	<i>PSEN1</i> (presenilin-1,2)	AD	DCM	Yes	Dementia
	<i>BAG3</i> (BCL2-associated athanogene 3)	AD	DCM	Yes	
	<i>ALPK3</i> ( $\alpha$ -kinase 3)	AR	HCM	Yes	

<sup>a</sup>Indicates that the usual clinical presentation is of isolated cardiomyopathy; however, occasionally present extracardiac manifestations are also provided. <sup>b</sup>Indicates that isolated cardiac phenotype can occur in women with the X-linked defects.

**Abbreviations:** AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; CDDC, conduction disease with dilated cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCM+, HCM with preexcitation; LVNC, left ventricular noncompaction; MELAS, (mitochondrial) myopathy, encephalopathy, lactic acidosis, and strokelike episodes syndrome; MERRF, myoclonic epilepsy with ragged red fibers; RCM, restrictive cardiomyopathy.



**FIGURE 259-1** Drawing of myocyte indicating multiple sites of abnormal gene products associated with cardiomyopathy. Major functional groups include the sarcomeric proteins (actin, myosin, tropomyosin, and the associated regulatory proteins), the dystrophin complex stabilizing and connecting the cell membrane to intracellular structures, the desmosome complexes associated with cell-cell connections and stability, and multiple cytoskeletal proteins that integrate and stabilize the myocyte. ATP, adenosine triphosphate. (Figure adapted from Jeffrey A. Towbin, MD, University of Tennessee Health Science Center.)

proteins initially considered restricted to the heart. In contrast, the monogenic disorders of metabolism that affect the heart are already clearly recognized to affect multiple organ systems. Currently, it is most important to diagnose defective enzymes for which specific therapy can now ameliorate the course of disease, such as with alpha-galactosidase A deficiency (Fabry's disease). Abnormalities of mitochondrial DNA (maternally transmitted) impair energy production with multiple clinical manifestations, including impaired cognitive function and skeletal myopathy. The phenotypic expression is highly variable depending on the distribution of the maternal mitochondria during embryonic development. Heritable systemic diseases, such as familial amyloidosis and hemochromatosis, can affect the heart without mutation of genes expressed in the heart.

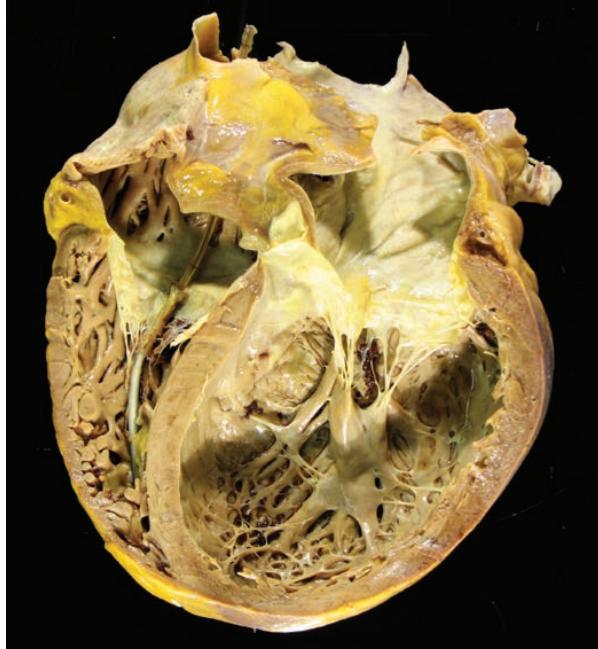
For any patient with suspected or proven genetic disease, family members should be considered and evaluated in a longitudinal fashion. Screening generally includes both an echocardiogram and electrocardiogram (ECG). The indications and implications for confirmatory specific genetic testing vary depending on the specific mutation. The profound questions raised by families about diseases shared and passed down merit serious and sensitive discussion, ideally provided by a trained genetic counselor.

## DILATED CARDIOMYOPATHY

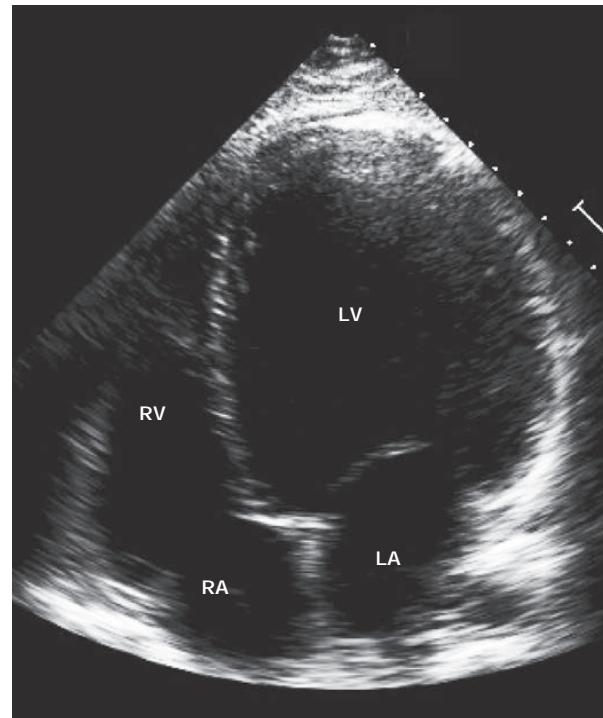
An enlarged left ventricle with reduced systolic function as measured by left ventricular ejection fraction characterizes DCM (**Figs. 259-2, 259-3, and 259-4**). *Systolic failure* is more prominent than diastolic

dysfunction. Although the syndrome of DCM has many disparate etiologies (**Table 259-4**), these often evolve to common pathways of secondary response and disease progression (convergent phenotype). When myocardial injury is acquired, some myocytes may die initially, whereas others survive only to have later programmed cell death (apoptosis), and remaining myocytes hypertrophy in response to increased wall stress. Local and circulating factors stimulate deleterious secondary responses that contribute to progression of disease. Dynamic remodeling of the interstitial scaffolding affects diastolic function and the amount of ventricular dilation. Mitral regurgitation commonly develops as the valvular apparatus is distorted and is usually substantial by the time heart failure is severe. Many cases that present "acutely" have progressed silently through these stages over months to years. Dilatation and decreased function of the right ventricle may result directly from the initial injury, but more often develops later in response to elevated afterload presented by secondary pulmonary hypertension and in relation to mechanical interactions with the failing left ventricle.

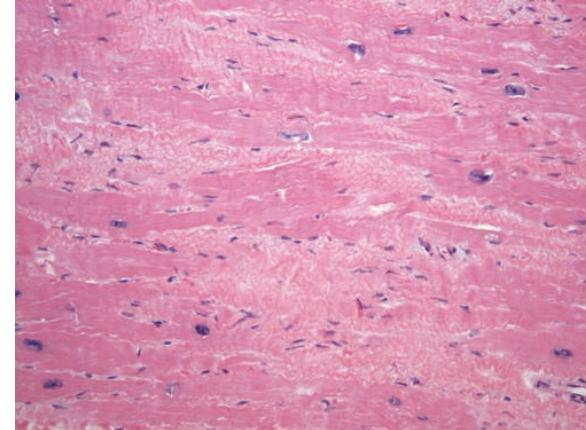
Regardless of the nature and degree of direct cell injury and loss, the resulting impairment often reflects secondary responses that may be modifiable or reversible. About a third of patients with new-onset cardiomyopathy demonstrate substantial spontaneous recovery. Chronic DCM may also improve in some patients without underlying structural heart disease to near-normal ejection fractions during recommended therapy with neurohormonal modulation, cardiac resynchronization therapy for left bundle branch block, and diuretics as needed to



**FIGURE 259-2 Dilated cardiomyopathy.** This gross specimen of a heart removed at the time of transplantation shows massive left ventricular dilation and moderate right ventricular dilation. Although the left ventricular wall in particular appears thinned, there is significant hypertrophy of this heart, which weighs >800 g (upper limit of normal = 360 g). A defibrillator lead is seen traversing the tricuspid valve into the right ventricular apex. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)



**FIGURE 259-3 Dilated cardiomyopathy.** This echocardiogram of a young man with dilated cardiomyopathy shows massive global dilation and thinning of the walls of the left ventricle (LV). The left atrium (LA) is also enlarged compared to normal. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. RA, right atrium; RV, right ventricle. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)



**FIGURE 259-4 Dilated cardiomyopathy.** Microscopic specimen of a dilated cardiomyopathy heart showing nonspecific changes of interstitial fibrosis and myocyte hypertrophy characterized by increased myocyte size and enlarged, irregular nuclei. Hematoxylin and eosin-stained section, 100x original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

maintain fluid balance. In many patients, these therapies can stabilize cardiac and clinical function and extend survival ([Chap. 252](#)). Further aspects of diagnosis and therapy specific to etiologies of DCM are discussed below.

### MYOCARDITIS

Myocarditis (inflammation of the heart) is most often attributable to infective agents but can also arise from other causes of inflammation. Infectious myocarditis cannot be assumed from a presentation of decreased systolic function in the setting of an acute infection, as any severe condition causing systemic cytokine release can depress cardiac function transiently, as seen frequently in medical intensive care units. Myocardial inflammation without obvious infection is seen in sarcoidosis and giant cell myocarditis, with checkpoint inhibitor therapy, in eosinophilic myocarditis, or in association with autoimmune diseases such as polymyositis and systemic lupus erythematosus. Fulminant myocarditis can result from viral infection, checkpoint inhibitor therapy, giant cell myocarditis, or necrotizing eosinophilic myocarditis, and is often complicated by recurrent arrhythmias. Early recognition of fulminant myocarditis is crucial as recovery to near-normal cardiac function can occur during aggressive circulatory support.

### INFECTIVE MYOCARDITIS

Infections can injure the myocardium through direct invasion, disruption of normal cellular processes, production of cardiotoxic substances, or stimulation of chronic inflammation with or without persistent infection. Myocarditis has been reported with almost all types of infective agents but is most commonly associated with viruses and the protozoan *Trypanosoma cruzi*. The pathogenesis of viral myocarditis has been extensively studied in murine models as divided into three phases. For the direct viral invasion phase, viruses gain entry through the respiratory or gastrointestinal tract and infect organs possessing specific receptors, such as the coxsackie-adenovirus receptors on the heart, which are prominent around intercalated disks and the atrioventricular (AV) node. Viral infection and replication can cause myocardial injury and lysis. For example, the enteroviral protease 2A degrades the myocyte structural protein dystrophin and interacts with other host proteins to induce apoptosis, inhibit the host serum response factor, and interfere with autophagy of protein aggregates.

The second phase is the nonspecific (innate) host response to infection, which is heavily dependent on Toll-like receptors that recognize common antigenic patterns. Cytokine release is rapid, followed by triggered activation and expansion of specific T- and B-cell populations. This initial response appears to be crucial, as early immunosuppression in animal models can increase viral replication and worsen cardiac

**TABLE 259-4 Major Causes of Dilated Cardiomyopathy (with Common Examples)****Inflammatory Myocarditis****Infective**

- Viral (coxsackie,<sup>a</sup> adenovirus,<sup>a</sup> HIV, hepatitis C)
- Parasitic (*T. cruzi*—Chagas' disease, trypanosomiasis, toxoplasmosis)
- Bacterial (diphtheria)
- Spirochetal (*Borrelia burgdorferi*—Lyme disease)
- Rickettsial (Q fever)
- Fungal (with systemic infection)

**Noninfective**

- Granulomatous inflammatory disease
  - Sarcoidosis
  - Giant cell myocarditis
  - Eosinophilic myocarditis
- Polymyositis, dermatomyositis
- Collagen vascular disease
- Checkpoint inhibitor chemotherapy
- Transplant rejection

**Toxic**

- Alcohol
- Catecholamines: amphetamines, cocaine
- Chemotherapeutic agents (anthracyclines, trastuzumab)
- Interferon
- Other therapeutic agents (hydroxychloroquine, chloroquine)
- Drugs of misuse (emetine, anabolic steroids)
- Heavy metals: lead, mercury
- Occupational exposure: hydrocarbons, arsenicals

**Metabolic<sup>a</sup>**

- Nutritional deficiencies: thiamine, selenium, carnitine
- Electrolyte deficiencies: calcium, phosphate, magnesium
- Endocrinopathy
  - Thyroid disease
  - Pheochromocytoma
  - Diabetes
- Obesity
- Hemochromatosis

**Inherited Metabolic Pathway Defects<sup>a</sup>****Familial<sup>a</sup> (See Table 259-3)**

- Skeletal and cardiac myopathy
- Dystrophin-related dystrophy (Duchenne's, Becker's)
- Mitochondrial myopathies (e.g., Kearns-Sayre syndrome)
- Hemochromatosis
- Associated with other systemic diseases
- Susceptibility to immune-mediated myocarditis

**Overlap with Nondilated Cardiomyopathy**

- "Minimally dilated cardiomyopathy"
- Hemochromatosis<sup>a</sup>
- Amyloidosis<sup>a</sup>
- Hypertrophic cardiomyopathy<sup>a</sup> ("burned-out")

**"Idiopathic"<sup>a</sup>****Miscellaneous (Shared Elements of Above Etiologies)**

- Arrhythmogenic ventricular cardiomyopathy
- Peripartum cardiomyopathy
- Left ventricular noncompaction<sup>a</sup>
- Tachycardia-related cardiomyopathy
  - Supraventricular arrhythmias with uncontrolled rate
  - Very frequent nonsustained ventricular tachycardia or high premature ventricular complex burden

<sup>a</sup>Some specific cases can be linked now to specific genetic mutation in a familial cardiomyopathy; others with similar phenotypes that appear to be acquired or idiopathic may represent genetic factors not yet identified.

injury. However, successful recovery from viral infection depends not only on the efficacy of the immune response to limit viral infection, but also on timely downregulation to prevent ongoing autoimmune injury to the host.

The secondary acquired (adaptive) immune response is specifically addressed against the viral proteins and can include both T-cell infiltration and antibodies to viral proteins. If unchecked, the acquired immune response can perpetuate secondary cardiac damage. Ongoing cytokine release activates matrix metalloproteinases that can disrupt the collagen and elastin scaffolding of the heart, potentiating ventricular dilation. Stimulation of profibrotic factors leads to pathologic interstitial fibrosis. Some antibodies triggered through co-stimulation or molecular mimicry also recognize targets within the host myocyte, such as the  $\alpha$ -adrenergic receptor,  $\alpha$ -myosin, and troponin, but it remains unclear as to whether or not these antibodies contribute to cardiac dysfunction in humans or merely serve as markers of cardiac injury.

It is not known how long the viruses persist in the human heart, whether late persistence of the viral genome continues to be deleterious, or how often a dormant virus can be reactivated. Genomes of common viruses are often present in patients with clinical diagnoses of myocarditis or DCM, but there is little information on how often these are present in patients without cardiac disease (see below). Further information is needed to understand the relative timing and contribution of infection, immune responses, and secondary adaptations in the progression of heart failure after viral myocarditis (Fig. 259-5).

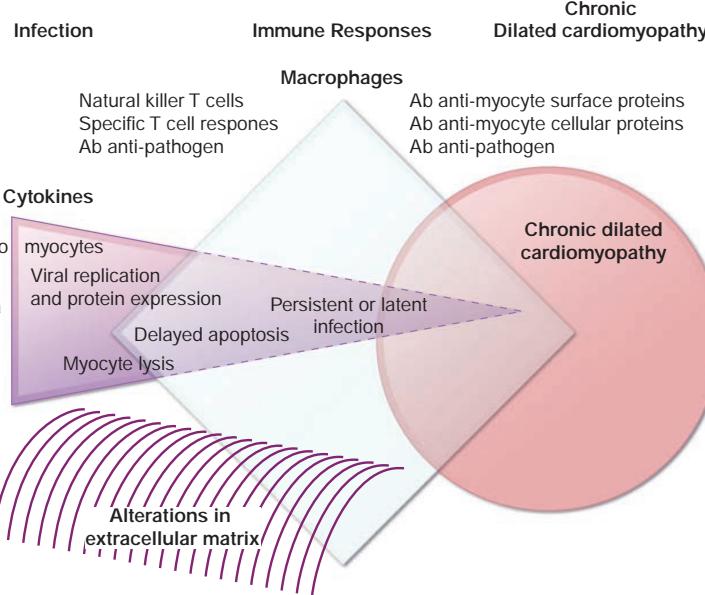
**Clinical Presentation of Viral Myocarditis** *Acute viral myocarditis* often presents with symptoms and signs of heart failure, but may present with chest pain and ECG changes suggestive of pericarditis or acute myocardial infarction, and occasionally with atrial or ventricular tachyarrhythmias. The typical patient with presumed viral myocarditis is a young to middle-aged adult who develops progressive dyspnea and weakness within a few days to weeks after a viral syndrome that was accompanied by fever and myalgias. Subacute presentation may occur within a few weeks or months of a viral infection. As viral infections are common and the resulting cytokine activation can depress cardiac function, it is often difficult to determine whether viral infection caused myocarditis or unmasked a previously unrecognized cardiomyopathy.

A small number of patients present with fulminant myocarditis, with rapid progression within hours from a severe febrile respiratory syndrome to cardiogenic shock that may involve multiple organ systems, leading to renal failure, hepatic failure, and coagulopathy. These patients are typically young adults who have recently been dismissed from urgent care settings with antibiotics for bronchitis, only to return within a few days in rapidly progressive cardiogenic shock. Recognition of patients with this fulminant presentation is potentially life-saving as more than half can survive with aggressive support, which may include high-dose intravenous catecholamine therapy and sometimes temporary mechanical circulatory support. The ejection fraction function of these patients often recovers to near-normal, although residual diastolic dysfunction may limit vigorous exercise for some survivors.

*Chronic viral myocarditis* is often invoked, but rarely proven, as a diagnosis when no other cause of DCM can be identified. Many cases attributed to previous viral infection will later be recognized as due to genetic causes or consumption of excess alcohol or illicit stimulant drugs. The proportion of chronic DCM due to viral infection remains a subject of controversy.

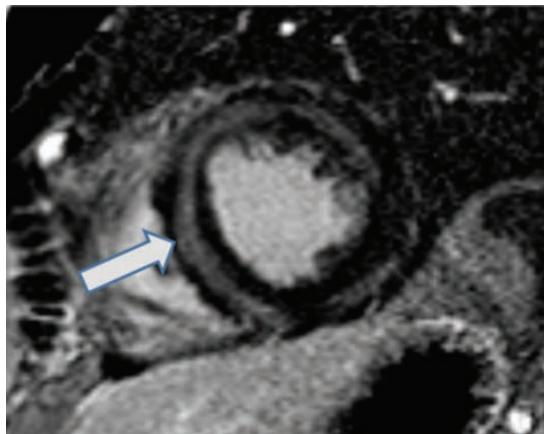
**Laboratory Evaluation for Myocarditis** The initial evaluation for suspected myocarditis includes an ECG, an echocardiogram, and serum levels of troponin and creatine phosphokinase, of which both cardiac and skeletal muscle fractions may be elevated. Magnetic resonance imaging is increasingly used for the diagnosis of myocarditis, which is supported but not proven by evidence of increased tissue edema and gadolinium enhancement (Fig. 259-6), particularly in the mid-wall (as distinct from usual coronary artery territories).

*Endomyocardial biopsy* is indicated when a new presentation of heart failure is accompanied by conduction blocks or ventricular tachyarrhythmias, which suggest possible etiologies of noninfectious



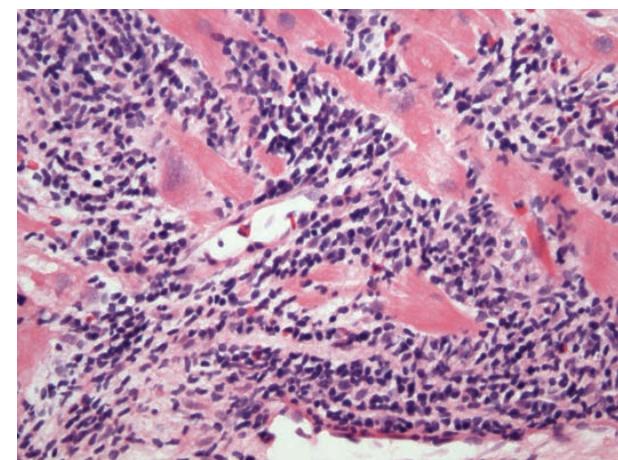
**FIGURE 259-5** Schematic diagram demonstrating the possible progression from infection through direct, secondary, and autoimmune responses to dilated cardiomyopathy. Most of the supporting evidence for this sequence is derived from animal models. It is not known to what degree persistent infection and/or ongoing immune responses contribute to ongoing myocardial injury in the chronic phase.

inflammatory causes that warrant aggressive immunosuppression, such as sarcoidosis or giant cell myocarditis. The indications, yield, and benefit of endomyocardial biopsy for evaluation of myocarditis or new-onset cardiomyopathy are not well established. When biopsy is performed, the key Dallas criteria for myocarditis include lymphocytic infiltrate with evidence of myocyte necrosis (Fig. 259-7) and are negative in 80–90% of patients with clinical myocarditis. Negative Dallas criteria can reflect sampling error or early resolution of lymphocytic infiltrates, but may also be influenced by the insensitivity of the test when inflammation results from cytokines and antibody-mediated injury. Routine histologic examination of endomyocardial biopsy rarely reveals a specific infective etiology, such as toxoplasmosis or cytomegalovirus subsets. Immunohistochemistry of myocardial biopsy samples is commonly used to identify active lymphocyte subtypes and may also detect upregulation of HLA antigens and the presence of complement components attributed to inflammation, but the specificity and significance of these findings are uncertain.



**FIGURE 259-6** Magnetic resonance image of myocarditis showing the typical mid-wall location (arrow) for late gadolinium enhancement from cardiac inflammation and scarring. (Image courtesy of Ron Blankstein, MD, and Marcelo Di Carli, MD, Division of Nuclear Medicine, Brigham and Women's Hospital, Boston.)

is diagnosed when there is histologic or immunohistologic evidence of inflammation on endomyocardial biopsy (see below) and does not require any other laboratory or clinical criteria. Magnetic resonance imaging is increasingly employed early in the evaluation for possible myocarditis. With the original 2009 Lake Louise criteria for myocarditis, a positive study required any two of three findings: abnormal T2-weighted imaging or early or late gadolinium enhancement. Revised criteria for specificity require both a T2-weighted criterion indicating edema and one T1-based criterion consistent with inflammatory injury, although more liberal diagnostic criteria allowing for the presence of either one yields higher sensitivity. The presence of pericardial effusion supports the diagnosis of inflammation, although it is not specific.



**FIGURE 259-7** Acute myocarditis. Microscopic image of an endomyocardial biopsy showing massive infiltration with mononuclear cells and occasional eosinophils associated with clear myocyte damage. The myocyte nuclei are enlarged and reactive. Such extensive involvement of the myocardium would lead to extensive replacement fibrosis even if the inflammatory response could be suppressed. Hematoxylin and eosin-stained section, 200 $\times$  original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

An increase in circulating viral titers between acute and convalescent blood samples supports a diagnosis of acute viral myocarditis with potential spontaneous improvement. Respiratory virus panels can detect adenovirus, influenza, and coronavirus. There is no established role for measuring circulating anti-heart antibodies, which may be the result, rather than a cause, of myocardial injury and have also been found in patients with coronary artery disease and genetic cardiomyopathy.

Patients with recent or ongoing viral syndromes have been classified into three levels of myocarditis diagnosis. (1) *Possible subclinical acute myocarditis* is diagnosed when a typical viral syndrome occurs without cardiac symptoms, but with elevated biomarkers of cardiac injury, ECG suggestive of acute injury, and/or reduced left ventricular ejection fraction or regional wall motion abnormality. (2) *Probable acute myocarditis* is diagnosed when the above criteria are met and accompanied by cardiac symptoms, such as shortness of breath or chest pain, which can result from pericarditis or myocarditis. When clinical findings of pericarditis are accompanied by elevated troponin or CK-MB or abnormal cardiac wall motion, the terms perimyocarditis or myopericarditis are sometimes used. (3) *Definite myocarditis*

## SPECIFIC VIRUSES IMPLICATED IN MYOCARDITIS

In humans, viruses are rarely proven to be the direct cause of clinical myocarditis. First implicated was the picornavirus family of RNA viruses, principally the enteroviruses, coxsackie virus, echovirus, and poliovirus. Influenza, another RNA virus, is implicated with varying frequency every winter and spring as epitopes change. Of the DNA viruses, adenovirus, vaccinia, and the herpesviruses (varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 [HHV6]) are well recognized to cause myocarditis but also occur commonly in the healthy population. Polymerase chain reaction (PCR) detects viral genomes in the majority of patients with DCM, but also in normal "control" hearts. Most often detected are parvovirus B19 and HHV6, which may affect the cardiovascular system, in part, through infection of vascular endothelial cells. However, their contribution to chronic cardiomyopathy is uncertain, as serologic evidence of exposure is present in many children and most adults.

*Human immunodeficiency virus* (HIV) was associated with an incidence of DCM of 1–2%. However, with the advent of highly active antiretroviral therapy (HAART), HIV has been associated with a significantly lower incidence of cardiac disease. Cardiomyopathy in HIV may also result from cardiac involvement with other associated viruses, such as cytomegalovirus and hepatitis C. Antiviral drugs to treat chronic HIV can cause cardiomyopathy, both directly and through drug hypersensitivity. The clinical picture may be complicated by pericardial effusions and pulmonary hypertension. There is a high frequency of lymphocytic myocarditis found at autopsy, and viral particles have been demonstrated in the myocardium in some cases, consistent with direct causation.

*Hepatitis C* has been repeatedly implicated in cardiomyopathy, particularly in Germany and Asia. Cardiac dysfunction may improve after interferon therapy. As this cytokine itself often depresses cardiac function transiently, careful coordination of its administration and ongoing clinical evaluation are critical. The cardiac effects of curative treatments for hepatitis C on cardiac function have not yet been well studied but do not appear to have limited the successful transplantation of hepatitis C-positive donors. Involvement of the heart with hepatitis B is uncommon but can be seen when associated with systemic vasculitis (polyarteritis nodosa).

Additional viruses implicated specifically in myocarditis include mumps, *respiratory syncytial virus*, the arboviruses (*dengue fever* and *yellow fever*), and arenaviruses (*Lassa fever*). For any serious infection, the systemic inflammatory response can cause nonspecific depression of cardiac function, which is generally reversible if the patient survives. This nonspecific inflammatory response is likely responsible for most of the cardiac findings with SARS-CoV-2, for which clinical information is accumulating rapidly. There is some evidence for direct cardiomyocyte invasion by the virus, consistent with an early model of acute myocarditis in rabbits caused by rabbit coronavirus. Some patients do present with ECG changes mimicking acute myocardial infarction. The endothelium is also a distinct cellular target of SARS-CoV-2, and the resulting vasoconstrictive and prothrombotic endotheliopathy may contribute to myocardial ischemia (and stroke). The dominant injury is to the lungs, where adult respiratory distress syndrome can develop, particularly in older patients and those with underlying comorbidities. When heart failure develops later in the course, it is usually in the setting of refractory respiratory failure and other organ failure from which survival is unlikely.

## THERAPY OF VIRAL MYOCARDITIS

There is currently no specific therapy recommended during any stage of viral myocarditis. During acute infection, therapy with anti-inflammatory or immunosuppressive medications is avoided, as their use has been shown to increase viral replication and myocardial injury in animal models. Therapy with specific antiviral agents (such as oseltamivir) has not been studied in specific relation to cardiac involvement. There is ongoing investigation into the impact of antiviral therapy to treat chronic viral persistence identified from endomyocardial biopsy. Large trials of immunosuppressive therapy for Dallas criteria-positive myocarditis have been negative. There are some initial

encouraging results and ongoing investigations with immunosuppressive therapy for immune-mediated myocarditis defined by immunohistologic criteria on biopsy or circulating antimyocardial antibodies in the absence of myocardial viral genomes. However, neither antiviral nor anti-inflammatory therapies are currently recommended. Until we have a better understanding of the phases of viral myocarditis and the effects of targeted therapies, treatment will continue to be guided by general recommendations for DCM.

## OTHER INFECTIOUS CAUSES

**Parasitic Myocarditis** *Chagas' disease* is the third most common parasitic infection in the world and the most common infective cause of cardiomyopathy. The protozoan *T. cruzi* is transmitted by the bite of the reduviid bug, endemic in the rural areas of South and Central America. Transmission can also occur through blood transfusion, organ donation, from mother to fetus, and occasionally orally. While programs to eradicate the insect vector have decreased the prevalence from about 16 million to <10 million in South America, cases are increasingly recognized in Western developed countries (see Global Perspectives below).

Multiple pathogenic mechanisms are implicated. The parasite itself can cause myocyte lysis and primary neuronal damage. Specific immune responses may recognize the parasites or related antigens and lead to chronic immune activation in the absence of detectable parasites. Molecular techniques have revealed persistent parasite DNA fragments in infected individuals. Further evidence for persistent infection is the eruption of parasitic skin lesions during immunosuppression after cardiac transplantation. As with viral myocarditis, the relative roles of persistent infection and of secondary autoimmune injury have not been resolved (Fig. 259-5). An additional factor in the progression of Chagas' disease is the autonomic dysfunction and microvascular damage that may contribute to cardiac and gastrointestinal disease.

The acute phase of Chagas' disease with parasitemia is usually unrecognized, but in fewer than 5% of cases, it presents clinically within a few weeks of infection with nonspecific symptoms or occasionally with acute myocarditis and meningoencephalitis. In the absence of antiparasitic therapy, the silent stage progresses slowly for >10–30 years in almost half of patients to manifest chronically in the cardiac and gastrointestinal systems. Features typical of Chagas' disease are conduction system abnormalities, particularly sinus node and AV node dysfunction and right bundle branch block. Atrial fibrillation and ventricular tachyarrhythmias also occur. Small ventricular aneurysms are common, particularly at the ventricular apex. These dilated ventricles are particularly thrombogenic, giving rise to pulmonary and systemic emboli. Xenodiagnosis, detection of the parasite itself, is rarely performed. The serologic tests for specific IgG antibodies against the trypanosome lack sufficient specificity and sensitivity, requiring two separate positive tests to make a diagnosis.

Treatment of the advanced stages focuses on clinical manifestations of the disease and includes heart failure medications, pacemaker-defibrillators, and anticoagulation. The most common antiparasitic therapies are benznidazole and nifurtimox, which have been effective in children with chronic *T. cruzi* infection. Both drugs are associated with multiple severe reactions, including dermatitis, gastrointestinal distress, and neuropathy. Moreover, in a large trial of adults with established Chagas' cardiomyopathy, benznidazole did not prevent disease progression, leaving the role of antiparasitic therapy unclear. Survival is <30% at 5 years after the onset of overt clinical heart failure. Patients without major extracardiac disease have occasionally undergone transplantation, after which they require surveillance testing and recurrent antiparasitic therapy to suppress reactivation of infection.

*African trypanosomiasis* infection results from the tsetse fly bite and can occur in travelers exposed during trips to Africa. The West African form is caused by *Trypanosoma brucei gambiense* and progresses silently over years. The East African form caused by *T. brucei rhodesiense* can progress rapidly through perivascular infiltration to myocarditis and heart failure, with frequent arrhythmias. The diagnosis is made by identification of trypanosomes in blood, lymph nodes,

or other affected sites. Antiparasitic therapy has limited efficacy and is determined by the specific type and the stage of infection. *Toxoplasmosis* is contracted through ingestion of undercooked infected beef or pork, transmission from feline feces, organ transplantation, transfusion, or maternal-fetal transmission. Immunocompromised hosts are most likely to experience reactivation of latent infection from cysts, found in up to 40% of autopsies of patients dying from HIV infection. Toxoplasmosis may present with encephalitis or chorioretinitis and, in the heart, can cause myocarditis, pericardial effusion, constrictive pericarditis, and heart failure. The diagnosis in an immunocompetent patient is made when the IgM is positive and the IgG becomes positive later. Active toxoplasmosis may be suspected in an immunocompromised patient with myocarditis and a positive IgG titer for toxoplasmosis, particularly when avidity testing identifies high specificity of the antibody. Fortuitous sampling occasionally reveals the cysts in the myocardium. Combination therapy can include pyrimethamine and sulfadiazine or clindamycin.

*Trichinellosis* is caused by *Trichinella spiralis* larva ingested with undercooked meat. Larvae migrating into skeletal muscles cause myalgias, weakness, and fever. Periorbital and facial edema, and conjunctival and retinal hemorrhage may also be seen. Although the larva may occasionally invade the myocardium, clinical heart failure is rare and, when observed, attributed to the eosinophilic inflammatory response. The diagnosis is made from the specific serum antibody and is further supported by the presence of eosinophilia. Treatment includes antihelminthic drugs (albendazole, mebendazole) and glucocorticoids if inflammation is severe.

Cardiac involvement with echinococcus is rare, but cysts can form and rupture in the myocardium and pericardium.

**Bacterial Infections** Most bacterial infections can involve the heart occasionally through direct invasion and abscess formation, but do so rarely. More commonly, systemic inflammatory responses depress contractility in severe infection and sepsis. Diphtheria specifically affects the heart in almost one-half of cases, and cardiac involvement is the most common cause of death in patients with this infection. The prevalence of vaccines has shifted the incidence of diphtheria from children worldwide to countries without routine immunization and to older populations who have lost their immunity. The bacillus releases a toxin that impairs protein synthesis and may particularly affect the conduction system. The specific antitoxin should be administered as soon as possible, with higher priority than antibiotic therapy. Clostridial toxin causes myocardial damage, and gas bubbles can be detected in the myocardium, with occasional abscess formation in the myocardium and pericardium. Streptococcal infection with -hemolytic streptococci is most commonly associated with acute rheumatic fever and is characterized by inflammation and fibrosis of cardiac valves and systemic connective tissue, but it can also lead to a myocarditis with focal or diffuse infiltrates of mononuclear cells. Other systemic bacterial infections that can involve the heart include brucellosis, legionella, meningococcus, mycoplasma, psittacosis, and salmonellosis, for which specific treatment is directed at the systemic infection.

Tuberculosis can involve the myocardium directly as well as through tuberculous pericarditis, but rarely does so when the disease is treated with antibiotics. Whipple's disease is caused by *Tropheryma whipplei*. The usual manifestations are in the gastrointestinal tract, but pericarditis, coronary arteritis, valvular lesions, and occasionally clinical heart failure may also occur. Multidrug antituberculous regimens are effective, but the disease tends to relapse even with appropriate treatment.

**Tick-Borne Infections** Spirochetal myocarditis has been diagnosed from myocardial biopsies containing *Borrelia burgdorferi*, which causes Lyme disease. Lyme carditis most often presents with arthritis and conduction system disease that resolves within 1–2 weeks of antibiotic treatment and is only rarely implicated in chronic heart failure. Other tick-borne illnesses associated with febrile illnesses and myocarditis include Rocky Mountain spotted fever, Q fever, and ehrlichiosis, all of which are treated with doxycycline alone or in combination with other agents.

## NONINFECTIVE MYOCARDITIS

Myocardial inflammation can occur in the absence of infectious causes. The paradigm of noninfective inflammatory myocarditis is cardiac transplant rejection, from which we have learned that myocardial depression can develop and reverse quickly, that noncellular mediators such as antibodies and cytokines play a major role in addition to lymphocytes, and that myocardial antigens are exposed by prior physical injury and viral infection.

The most commonly diagnosed noninfective inflammatory process affecting the myocardium is granulomatous myocarditis, including both sarcoidosis and giant cell myocarditis. Sarcoidosis, as discussed in Chap. 367, is a multisystem disease most commonly affecting the lungs. Although classically presenting with higher prevalence in young African-American men, the epidemiology appears to be changing, with increasing recognition of sarcoidosis in Caucasian patients in nonurban areas. Patients with pulmonary sarcoid are at high risk for cardiac involvement, but cardiac sarcoidosis also occurs without clinical lung disease. Regional clustering of the disease supports the suspicion that the granulomatous reaction is triggered by infectious or environmental allergens not yet identified.

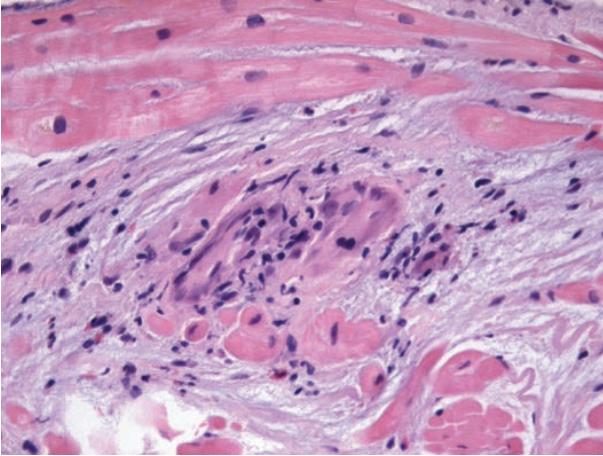
The sites and density of cardiac granulomata, the time course, and the degree of extracardiac involvement are remarkably variable. Patients may present with rapid-onset heart failure and ventricular tachyarrhythmias, conduction block, chest pain syndromes, or minor cardiac findings in the setting of ocular involvement, an infiltrative skin rash, or a nonspecific febrile illness. They may also present less acutely after months to years of fluctuating cardiac symptoms. When ventricular tachycardia or conduction block dominates the initial presentation of heart failure without coronary artery disease, suspicion should be high for these granulomatous myocarditides.

Depending on the time course, the ventricles may appear restrictive or dilated. There may be a right ventricular predominance of both dilation and ventricular arrhythmias, sometimes initially attributed to arrhythmogenic right ventricular cardiomyopathy, with which sarcoidosis shares multiple features.

Small ventricular aneurysms are common in the heart with sarcoid. Computed tomography of the chest often reveals pulmonary lymphadenopathy even in the absence of clinical lung disease. Metabolic imaging (positron emission tomography [PET]) of the whole chest can highlight active sarcoid lesions that are avid for glucose. Magnetic resonance imaging (MRI) of the heart can identify myocardial scar in a pattern not compatible with myocardial infarction, and this distinctive type of late gadolinium enhancement is associated, as in other cardiac disease, with increased risk of ventricular arrhythmias. To rule out chronic infections, such as tuberculosis or histoplasmosis, as the cause of adenopathy, the diagnosis often requires pathologic confirmation. Biopsy of enlarged mediastinal nodes may provide the highest yield. The scattered granulomata of sarcoidosis are commonly missed on cardiac biopsy (Fig. 259-8).

Immunosuppressive treatment for sarcoidosis is initiated with high-dose glucocorticoids, often supplemented with methotrexate, and is generally more effective in suppressing arrhythmias than improving severely impaired systolic function. Patients with sarcoid lesions that persist or recur during tapering of corticosteroids are considered candidates for other immunosuppressive therapies. Pacemakers and implantable defibrillators are generally indicated to prevent life-threatening heart block or ventricular tachycardia, respectively. Because the inflammation often resolves into extensive fibrosis that impairs cardiac function and provides pathways for reentrant arrhythmias, the prognosis for improvement is best when the density of granulomata is limited and the ejection fraction is not severely reduced.

Giant cell myocarditis is less common than sarcoidosis, but accounts for 10–20% of biopsy-positive cases of myocarditis. Giant cell myocarditis typically presents with rapidly progressive heart failure and tachyarrhythmias in patients generally older than those with acute viral myocarditis. Diffuse granulomatous lesions are surrounded by extensive inflammatory infiltrate unlikely to be missed on endomyocardial biopsy, often with eosinophilic infiltration. Associated conditions are thymomas, thyroiditis, pernicious anemia, other autoimmune diseases,



**FIGURE 259-8 Sarcoidosis.** Microscopic image of an endomyocardial biopsy showing a noncaseating granuloma and associated interstitial fibrosis typical of sarcoidosis. No microorganisms were present on special stains, and no foreign material was identified. Hematoxylin and eosin-stained section, 200 $\times$  original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

and occasionally recent infections. Glucocorticoid therapy alone is rarely effective, but in combination with other immunosuppression therapies similar to those used for severe transplant rejection, it may improve short-term outcomes in patients who are hemodynamically stable at presentation. Most patients in cardiogenic shock from giant cell myocarditis progress to urgent mechanical support or transplantation, which may be precluded by systemic infection from intensive immunosuppression. Although the severity of presentation and myocardial histology are more fulminant than with sarcoidosis, the occasional finding of giant cell myocarditis after a previous diagnosis of sarcoidosis suggests that they may share the same disease spectrum.

*Eosinophilic myocarditis* can be an important manifestation of the hypereosinophilic syndrome, which in Western countries is often considered idiopathic, although in Mediterranean and African countries, it is associated with antecedent infection. It may also be seen with systemic eosinophilic syndromes such as Churg-Strauss syndrome or malignancies. *Hypersensitivity myocarditis* is often an unexpected diagnosis, made when the biopsy reveals infiltration with lymphocytes and mononuclear cells with a high proportion of eosinophils. Most commonly, the reaction is attributed to antibiotics, particularly those taken chronically, but thiazides, anticonvulsants, indomethacin, and methyldopa have also been implicated. Occasional associations with the smallpox vaccine (vaccinia) have been reported. Although the circulating eosinophil count may be slightly elevated in hypersensitivity myocarditis, it is lower than in the hypereosinophilic syndrome. High-dose glucocorticoids and discontinuation of the trigger agent can be curative for hypersensitivity myocarditis.

Myocarditis is often associated with systemic inflammatory diseases, such as *polymyositis* and *dermatomyositis*, which affect skeletal and cardiac muscle. Although noninfective inflammatory myocarditis is sometimes included in the differential diagnosis, cardiac involvement with connective tissue disease such as systemic lupus erythematosus more often presents as pericarditis, vasculitis, pulmonary hypertension, and accelerated coronary artery disease.

The most dramatic form of noninfective inflammatory myocarditis is that seen with combined immune checkpoint inhibitors. Targeted monoclonal antibody therapy to unblock the host immune response has produced remarkable remission of melanoma, renal cell carcinoma, refractory Hodgkin's lymphoma, and other advanced tumors. Inhibitory receptors on T lymphocytes (such as CTLA4 and PD-1) and the "programmed death" ligands, such as PD-L1, on target tissues interact to turn off immune activation as part of normal autoregulation. Tumor cells can upregulate these ligands to hide from immune recognition. Antibodies to the inhibitory receptors or ligands can reawaken host

response, but also unleash immune attack against host tissues expressing PD-L1, which include myocytes and endothelial cells and multiple organs, such as liver, pancreas, thyroid, skin, and skeletal muscle. The frequency of myocarditis as reported is <0.5%, is higher with monoclonal therapy against PD-1 than against CTLA4, and is over tenfold higher with combined use of two checkpoint inhibitors. Patients can present with acute heart failure, often with bizarre electrocardiographic arrhythmias or conduction block and with evidence of skeletal myositis. Echocardiography may suggest myocardial edema without ventricular dilation, and initial ejection fraction may not be markedly reduced. Troponin is often positive, B-type natriuretic peptide may be elevated, and creatine phosphokinase may be high, particularly with skeletal involvement. If performed, MRI shows widespread inflammation, and biopsy shows extensive lymphocytic infiltration with CD4+ and CD8+ T cells and CD68+ macrophages. The diagnosis should be suspected immediately with acute cardiac presentation in patients treated with checkpoint inhibitors, who may also present initially with other acute organ system involvement, which warrants urgent multidisciplinary management usually in an intensive care unit. Initial therapy involves high-dose glucocorticoids, which may be followed by other immunosuppressive agents. Reported fatality in fulminant checkpoint inhibition myocarditis has been ~50% and is higher after combined checkpoint inhibition. Less commonly, cardiovascular involvement can cause pericarditis or arteritis, particularly temporal arteritis.

### PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy (PPCM) develops during the last trimester or within the first 6 months after pregnancy, affecting between 1:2000 and 1:4000 deliveries in the United States. Risk factors are increased maternal age, increased parity, twin pregnancy, malnutrition, use of tocolytic therapy for premature labor, and preeclampsia or toxemia of pregnancy. Several of these risk factors contribute to antiangiogenic signaling through secreted vascular endothelial growth factor (VEGF) inhibitors, such as soluble FLT1 (sFLT1). Recent animal and human studies have confirmed the role of decreased angiogenic reserve in the pathogenesis of PPCM, which may be rescued by correcting the angiogenic imbalance. Another recently proposed mechanism invokes an abnormal prolactin cleavage fragment, which is induced by oxidative stress and also affects angiogenesis; this observation has led to preliminary investigation of bromocriptine as possible therapy.

However, other processes also contribute to PPCM. Heart failure early after delivery was previously common in Nigeria, when the custom for new mothers included salt ingestion while reclining on a warm bed, which likely impaired mobilization of the excess circulating volume after delivery. In the Western world, lymphocytic myocarditis has sometimes been found on myocardial biopsy. This inflammation has been hypothesized to reflect increased susceptibility to viral myocarditis or an autoimmune myocarditis due to cross-reactivity of anti-uterine antibodies against cardiac muscle.

As the increased circulatory demand of pregnancy can aggravate other cardiac disease that was clinically unrecognized, it is crucial to the diagnosis of PPCM that there be no evidence for a preexisting cardiac disorder. By contrast, heart failure presenting earlier in pregnancy has been termed pregnancy-associated cardiomyopathy (PACM). Both PPCM and PACM have been found in some families with other presentations of DCM. As in familial and sporadic DCM, truncating mutations, predominantly in *TTN*, are present in 15% of patients with PPCM and are associated with systolic dysfunction that persists. Pregnancy may represent another example of environmental triggers for accelerated phenotypic expression of genetic cardiomyopathies.

### TOXIC CARDIOMYOPATHY

Cardiotoxicity has been reported with multiple environmental and pharmacologic agents. Often these associations are seen only with very high levels of exposure or acute overdoses, in which acute electrocardiographic and hemodynamic abnormalities may reflect both direct drug effect and systemic toxicity.

**Alcohol** is the most common toxin implicated in chronic DCM. Excess consumption may contribute to >10% of cases of heart failure,

including exacerbation of heart failure with structural heart disease. Alcoholic cardiomyopathy causes many more hospital admissions in men than women, but prevalence is similar between men and women with alcoholism, with left ventricular dysfunction detected in about a third of asymptomatic patients. Estimates of the alcohol intake necessary to cause cardiomyopathy have been 4–5 ounces or 80–100 g of pure ethanol daily for 5–10 years, about 1 L of wine, 8 beers, or  $\frac{1}{2}$  pint of hard liquor. Frequent binge drinking may also be sufficient. Toxicity is attributed both to alcohol and to its primary metabolite, acetaldehyde. Chronic heavy exposure may alter metabolism, protein synthesis, substrate utilization, and oxidative stress. Polymorphisms of the genes encoding alcohol dehydrogenase and the angiotensin-converting enzyme may influence the likelihood of alcoholic cardiomyopathy. Superimposed vitamin deficiencies and toxic alcohol additives are rarely implicated currently. Mutations in *TTN* and other DCM disease genes can be identified in ~10% of patients with presumed alcohol cardiomyopathy.

Many patients with alcoholic cardiomyopathy are fully functional in their daily lives without apparent stigmata of alcoholism. The cardiac impairment in severe alcoholic cardiomyopathy is the sum of both permanent damage and a substantial component that is reversible after cessation of alcohol consumption. Atrial fibrillation occurs commonly both early in the disease ("holiday heart") and in advanced stages. Medical therapy includes neurohormonal antagonists and diuretics as needed for fluid management. Withdrawal should be supervised to avoid exacerbations of heart failure or arrhythmias, and ongoing support arranged. Even with severe disease, marked improvement can occur within 3–6 months of abstinence, but the prognosis is grim if alcohol consumption continues.

*Cocaine, amphetamines*, and related catecholaminergic stimulants can produce chronic cardiomyopathy as well as acute ischemia, tachyarrhythmias, malignant hypertension, aortic dissection, and stroke. Cardiac pathology reveals microinfarcts consistent with small vessel ischemia, similar to those seen with pheochromocytoma, and thrombosis secondary to endothelial dysfunction in the case of cocaine.

**Chemotherapy agents** are the most common drugs implicated in toxic cardiomyopathy. Judicious use balances risks of the malignancy and the risks of cardiotoxicity presented not only by the drug regimens but also by the patient's cardiovascular profile and possibly genetic factors influencing myocyte response to injury. Receipt of cardiotoxic drugs or radiation may warrant designation as "stage B" heart failure, with asymptomatic changes in cardiac structure and biomarkers. Once symptoms are apparent, the prognosis with heart failure is worse than for many types of cancer.

*Anthracyclines* (e.g., doxorubicin) cause characteristic histologic changes of vacuolar degeneration and myofibrillar loss. Multiple mechanisms have been implicated, involving reactive oxygen species and iron compounds, mitochondrial damage, transcription factors such as hypoxia-induced factor, and, most recently, inhibition of topoisomerase II involved in DNA repair. Risk for cardiotoxicity increases with older age, preexisting cardiac disease, higher doses or combination therapies, or left chest irradiation. Systolic dysfunction can occur acutely with symptoms of heart failure noted soon after drug administration, but more often is detected by surveillance echocardiography during the first year after exposure. Doxorubicin cardiotoxicity generally does not result in marked left ventricular dilation, such that stroke volume and systemic perfusion can be severely reduced with only a modest reduction of ejection fraction. Therapy for reduced ejection fraction includes

-adrenergic receptor blockade and inhibition of the renin-angiotensin system, with conflicting data on whether these agents decrease toxicity when given in parallel with chemotherapy. Once thought to have an inexorable downward course, many patients with symptomatic heart failure can improve to near-normal function with careful management, including prevention of "second-hit" insults such as atrial fibrillation or hypertension. The course differs for some children treated with these agents before puberty, in whom inadequate growth of the heart may lead to refractory heart failure as they reach their twenties.

*Trastuzumab* (Herceptin) is one of the humanized monoclonal antibodies that interfere with human epidermal growth receptor 2 (HER2),

which is crucial for growth of some tumors, such as breast cancer, and for cardiac adaptation. Cardiotoxicity is highest when anthracyclines are administered in conjunction with trastuzumab; however, less toxicity is seen now when these agents are combined compared with the toxicity observed previously with paclitaxel for breast cancer. Although more often reversible than anthracycline cardiotoxicity, trastuzumab cardiomyopathy may persist in about a third of affected patients and can progress to clinical heart failure and death. For cardiotoxicity with anthracyclines or trastuzumab, therapy is recommended as for other causes of reduced ejection fraction, but it is not clear whether treatment enhances the spontaneous rate of improvement or whether it decreases progression.

Cardiotoxicity with *cyclophosphamide* and *ifosfamide* generally occurs acutely and with very high doses. 5-Fluorouracil, cisplatin, and some other alkylating agents can cause recurrent coronary spasm that occasionally leads to depressed contractility. Acute administration of *interferon*-, interleukin 2, and other cytokine-based therapies can cause hypotension and arrhythmias. Clinical heart failure occurring during their chronic administration usually resolves after discontinuation.

VEGF, produced endogenously or by tumors, enhances angiogenesis by activating the VEGF signaling pathways. Inhibitors of this pathway and its receptors are potent against multiple cancers. Many small-molecule *tyrosine kinase inhibitors* that affect VEGF are in use for different malignancies. Although these agents are "targeted" at specific tumor receptors or pathways, the biologic conservation of signaling pathways means that some of these drugs also find targets in the cardiovascular and other organ systems. Blood pressures increase in most patients during therapy, attributed to an imbalance between endogenous vasodilators and vasoconstrictors and alteration of glomerular function. Hypertension and proteinuria can develop with these agents, similar to preeclampsia, and presentation is associated with increased risk of future cardiac disease. Recognition of cardiotoxicity during therapy with these agents is complicated because they occasionally cause peripheral fluid accumulation (ankle edema, periorbital swelling, pleural effusions) due to local factors rather than elevated central venous pressures. Therapeutic approaches include withdrawal of the tyrosine kinase inhibitor (when possible) and conventional treatment for heart failure. Newer tyrosine kinase inhibitors effective against multiple kinases may have more complex off-target effects.

The most dramatic toxicity of contemporary cancer therapy results from combined immune checkpoint inhibitors, which block the natural counterregulatory T-cell suppression and unleash potentially fatal inflammation directed toward multiple organs that can include the heart and vessels. These are discussed in the previous section on non-infectious myocarditis (above).

*Proteasome inhibitors* used to treat multiple myeloma are associated with an increased risk of hypertension, ischemic events, thromboembolism, and heart failure. The more potent agent, carfilzomib, appears more cardiotoxic than bortezomib.

**Other therapeutic drugs** that can cause cardiotoxicity during chronic use include tumor necrosis factor antagonists for rheumatologic conditions, and carbamazepine, clozapine, and lithium for neurologic and psychiatric diagnoses. Antiretroviral therapies for HIV have been implicated in cardiomyopathy. Chloroquine and hydroxychloroquine are widely used for systemic lupus erythematosus and rheumatoid arthritis and can decrease ejection fraction with either restrictive or dilated phenotype, often in association with conduction block. The presumed mechanism of toxicity is impaired lysosomal function, with accumulation of inclusion bodies that can be seen on cardiac biopsy.

**Toxic exposures** can cause arrhythmias or respiratory injury acutely during accidents. Chronic exposures implicated in cumulative cardiotoxicity include hydrocarbons, fluorocarbons, arsenicals, lead, and mercury.

## METABOLIC CAUSES OF CARDIOMYOPATHY

**Endocrine disorders** affect multiple organ systems, including the heart. *Hyperthyroidism* and *hypothyroidism* do not often cause clinical heart failure in an otherwise normal heart but commonly exacerbate

heart failure. Clinical signs of thyroid disease may be masked, so tests of thyroid function are part of the routine evaluation of cardiomyopathy. Hyperthyroidism should always be considered with new-onset atrial fibrillation or ventricular tachycardia or atrial fibrillation in which the rapid ventricular response is difficult to control. The most common current reason for thyroid abnormalities in the cardiac population is the treatment of tachyarrhythmias with amiodarone, a drug with substantial iodine content. Hypothyroidism should be treated with very slow escalation of thyroid supplements to avoid exacerbating tachyarrhythmias and heart failure. Hyperthyroidism and heart failure create a dangerous combination that merits very close supervision, often hospitalization, during titration of antithyroid medications, during which decompensation of heart failure may occur precipitously and fatally.

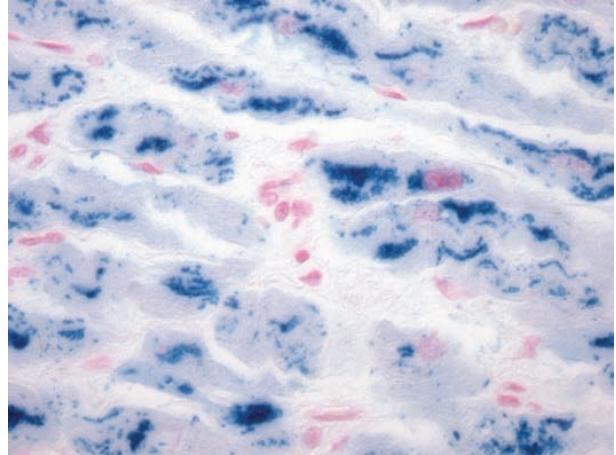
**Pheochromocytoma** is rare but should be considered when a patient has heart failure and very labile blood pressure and heart rate, sometimes with episodic palpitations (Chap. 387). Patients with pheochromocytoma often have postural hypotension. In addition to  $\alpha$ -adrenergic receptor antagonists, definitive therapy requires surgical extirpation. Very high renin states, such as those caused by renal artery stenosis, can lead to modest depression in ejection fraction with little or no ventricular dilation and markedly labile symptoms with flash pulmonary edema, related to sudden shifts in vascular tone and intravascular volume.

Controversies remain regarding whether *diabetes* and *obesity* are sufficient to cause cardiomyopathy. Most heart failure in diabetes results from epicardial coronary disease, with further increase in coronary artery risk due to accompanying hypertension and renal dysfunction. Cardiomyopathy may result in part from insulin resistance and increased advanced-glycosylation end products, which impair both systolic and diastolic function. However, much of the dysfunction can be attributed to scattered focal ischemia resulting from distal coronary artery tapering and limited microvascular perfusion even without proximal focal stenoses. Diabetes is a typical factor in heart failure with “preserved” ejection fraction, along with hypertension, advanced age, and female gender.

The existence of a cardiomyopathy due to *obesity* is generally accepted. In addition to cardiac involvement from associated diabetes, hypertension, and vascular inflammation of the metabolic syndrome, obesity alone is associated with impaired excretion of excess volume load, which, over time, can lead to increased wall stress and secondary adaptive neurohumoral responses. Fluid retention may be aggravated by large fluid intake and the rapid clearance of natriuretic peptides by adipose tissue. In the absence of another obvious cause of cardiomyopathy in an obese patient with systolic dysfunction without marked ventricular dilation, effective weight reduction is often associated with major improvement in ejection fraction and clinical function. Improvement in cardiac function has been described after successful bariatric surgery, although all major surgical therapy poses increased risk for patients with heart failure. Postoperative malabsorption and nutritional deficiencies, such as calcium and phosphate deficiencies, may be particularly deleterious for patients with cardiomyopathy.

**Nutritional deficiencies** can occasionally cause DCM but are not commonly implicated in developed countries. *Beri-beri heart disease* due to thiamine deficiency can result from poor nutrition in undernourished populations and in patients deriving most of their calories from alcohol and has been reported in teenagers subsisting only on highly processed foods. This disease is initially a vasodilated state with very-high-output heart failure that can later progress to a low-output state; thiamine repletion can lead to prompt recovery of cardiovascular function. Abnormalities in *carnitine* metabolism can cause dilated or restrictive cardiomyopathies, usually in children. Deficiency of trace elements such as *selenium* can cause cardiomyopathy (Keshan's disease).

**Calcium** is essential for excitation-contraction coupling. Chronic deficiencies of calcium, such as can occur with hypoparathyroidism (particularly postsurgical) or intestinal dysfunction (from diarrheal syndromes and following extensive resection), can cause severe chronic heart failure that responds over days or weeks to vigorous calcium



**FIGURE 259-9 Hemochromatosis.** Microscopic image of an endomyocardial biopsy showing extensive iron deposition within the cardiac myocytes with the Prussian blue stain (400 $\times$  original magnification). (Image courtesy of Robert Padra, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

repletion. *Phosphate* is a component of high-energy compounds needed for efficient energy transfer and multiple signaling pathways. *Hypophosphatemia* can develop during starvation and early refeeding following a prolonged fast and occasionally during hyperalimentation.

**Hemochromatosis** is variably classified as a metabolic or storage disease (Chap. 414). It is included among the causes of restrictive cardiomyopathy, but the clinical presentation is often that of a DCM. The autosomal recessive form is related to the *HFE* gene. With up to 10% of the population heterozygous for one mutation, the clinical prevalence might be as high as 1 in 500. The lower observed rates highlight the limited penetrance of the disease, suggesting the role of additional genetic and environmental factors such as alcoholism affecting clinical expression. Cardiac siderosis can also be acquired from iron overload due to hemoglobinopathies in patients treated with recurrent transfusions. Excess iron is deposited in the perinuclear compartment of cardiomyocytes, with resulting disruption of intracellular architecture and mitochondrial function. Diagnosis is easily made from measurement of serum iron and transferrin saturation, with a threshold of >60% for men and >45–50% for women. MRI can help to quantitate iron stores in the liver and heart, and endomyocardial biopsy tissue can be stained for iron (Fig. 259-9), which is particularly important if the patient has another cause for cardiomyopathy. If diagnosed early, hemochromatosis can often be managed by repeated phlebotomy to remove iron. For more severe iron overload, iron chelation therapy with desferrioxamine (deferoxamine) or deferasirox can help to improve cardiac function if myocyte loss and replacement fibrosis are not too severe.

Inborn disorders of metabolism occasionally present with DCM, although they are most often associated with restrictive cardiomyopathy (Table 259-4).

### FAMILIAL DILATED CARDIOMYOPATHY

The genetic basis for cardiomyopathy is discussed above in the section, “Genetic Etiologies of Cardiomyopathy.” The recognized frequency of familial involvement in DCM has increased to >30%. Mutations in *TTN*, encoding the giant sarcomeric protein titin, are the most common cause of DCM, accounting for up to 25% of familial disease. On average, men with *TTN* mutations develop cardiomyopathy a decade before women, without distinctive clinical features. Mutations in thick and thin filament genes account for ~8% of DCM and may manifest in early childhood.

The most recognizable familial cardiomyopathy syndromes with extracardiac manifestations are the *muscular dystrophies*. Both Duchenne's and the milder Becker's dystrophies result from abnormalities in the X-linked dystrophin gene of the sarcolemmal membrane. Skeletal myopathy is present in multiple other genetic cardiomyopathies (Table 259-3), some of which are associated with creatine kinase elevations.

Patients and families with a history of arrhythmias and/or conduction system disease that precede or supersede cardiomyopathy may have abnormalities of the nuclear membrane lamin proteins, which are present in ~5% of patients with DCM. While all DCMs carry a risk of sudden death, a family history of cardiomyopathy with sudden death raises suspicion for a particularly arrhythmogenic mutation; affected family members may be considered for implantable defibrillators to prevent sudden death even without meeting the reduced ejection fraction threshold.

A prominent family history of sudden death or ventricular tachycardia before clinical cardiomyopathy suggests genetic defects in the desmosomal proteins (Fig. 259-10). Originally described as affecting the right ventricle (arrhythmogenic right ventricular cardiomyopathy [ARVC]), this disorder (arrhythmogenic cardiomyopathy) can affect either or both ventricles. Patients often present first with ventricular tachycardia. Genetic defects in proteins of the desmosomal complex disrupt myocyte junctions and adhesions, leading to replacement of myocardium by deposits of fat. Thin ventricular walls may be recognized on echocardiography but are better visualized on MRI. Because desmosomes are also important for elasticity of hair and skin, some of the defective desmosomal proteins are associated with striking "woolly hair" and thickened skin on the palms and soles. Implantable defibrillators are usually indicated to prevent sudden death. There is variable progression to right, left, or biventricular failure.

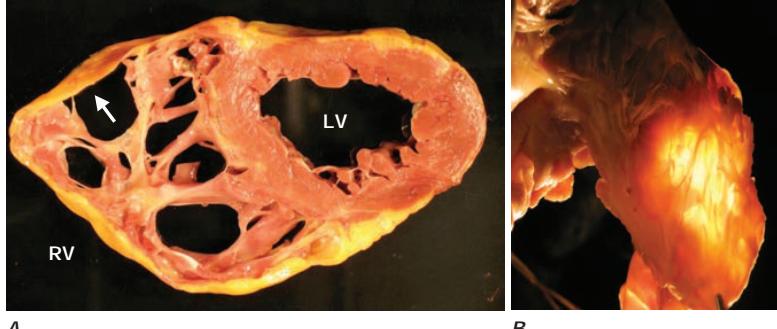
**Left ventricular noncompaction** is a condition of unknown prevalence that is increasingly suspected with the refinement of imaging techniques. The diagnostic criteria include the presence of multiple trabeculations in the left ventricle distal to the papillary muscles, creating a "spongy" appearance of the apex, but are increasingly recognized as nonspecific findings in other cardiac diseases. Noncompaction has been associated with multiple genetic variants in the sarcomeric and other genes, such as *TAZ* (encoding tafazzin). The diagnosis may be made incidentally or in patients previously diagnosed with cardiomyopathy, in whom the criteria for noncompaction may appear and disappear with changing left ventricular size and function. The three cardinal clinical features of ventricular arrhythmias, embolic events, and heart failure are largely restricted to noncompaction with concomitant systolic dysfunction. Treatment generally includes anticoagulation and early consideration for an implantable defibrillator, in addition to neurohormonal antagonists as indicated by stage of disease.

Some families inherit a susceptibility to viral-induced myocarditis. This propensity may relate to abnormalities in cell surface receptors, such as the coxsackie-adenovirus receptor, that bind viral proteins. Some may have partial homology with viral proteins such that an autoimmune response is triggered against the myocardium.

Prognosis and therapy of familial DCM are dictated primarily by the stage of clinical disease and the risk for sudden death. In some cases, the familial etiology facilitates prognostic decisions, particularly regarding the likelihood of recovery after a new diagnosis, which is unlikely for familial disease. The rate of progression of disease is to some extent heritable, although marked variation can be seen. However, there have been cases of remarkable clinical remission after acute presentation, likely after a reversible "second hit," such as prolonged tachycardia or viral myocarditis.

### TAKOTSUBO CARDIOMYOPATHY

The apical ballooning syndrome, or acute stress-induced cardiomyopathy, occurs typically in older women after sudden intense emotional or physical stress. The ventricle shows global ventricular dilation with basal contraction, forming the shape of the narrow-necked jar (*takotsubo*) used in Japan to trap octopuses. Originally described in Japan, it is well recognized elsewhere during emergency cardiac catheterization and intensive care unit admissions for noncardiac conditions. Presentations include pulmonary edema, hypotension, and chest pain with ECG changes mimicking an acute infarction. The left ventricular dysfunction



**FIGURE 259-10** Arrhythmogenic right ventricular cardiomyopathy. **A.** Cross-sectional slice of a pathology specimen removed at transplantation, showing severe dilation and thinning of the right ventricle (RV) with extensive fatty replacement of right ventricular myocardium. **B.** The remarkably thin right ventricular free wall is revealed by transillumination. LV, left ventricle. (Images courtesy of Gayle Winters, MD, and Richard Mitchell, MD, PhD, Division of Pathology, Brigham and Women's Hospital, Boston.)

extends beyond a specific coronary artery distribution and generally resolves within days to weeks. Animal models and ventricular biopsies suggest that this acute cardiomyopathy may result from intense sympathetic activation with heterogeneity of myocardial autonomic innervation, diffuse microvascular spasm, and/or direct catecholamine toxicity. Cardiac MRI demonstrates diffuse myocardial edema without necrosis. Coronary angiography may be required to rule out acute coronary occlusion. No therapies have been proven beneficial, but reasonable strategies include nitrates for pulmonary edema; intraaortic balloon pump if needed for low output, provided transient left ventricular outflow tract obstruction is absent; combined alpha and beta blockers rather than selective beta blockade if hemodynamically stable; and magnesium for arrhythmias related to QT prolongation. The long-term prognosis is generally good, with the lowest mortality associated with episodes triggered by emotional rather than physical triggers. In-hospital complications and mortality are similar to acute myocardial infarction. Recurrences have been described in up to 10% of patients.

### IDIOPATHIC DCM

**Idiopathic** DCM is a diagnosis of exclusion, when all other known factors have been excluded. Approximately two-thirds of DCMs are still labeled as idiopathic; however, a substantial proportion of these may reflect unrecognized genetic disease. Continued reconsideration of etiology during chronic heart failure management often reveals specific causes later in a patient's course.

### OVERLAPPING TYPES OF CARDIOMYOPATHY

The limitations of our phenotypic classification are revealed through the multiple overlaps between the etiologies and presentations of the three types. Cardiomyopathy with reduced systolic function but without severe dilation can represent early DCM, "minimally dilated cardiomyopathy," or restrictive diseases without marked increases in ventricular wall thickness. For example, sarcoidosis and hemochromatosis can present as dilated or restrictive disease. Early stages of amyloidosis are often mistaken for hypertrophic cardiomyopathy. Progression of hypertrophic cardiomyopathy into a "burned-out" phase occurs occasionally, with decreased contractility and modest ventricular dilation. Overlaps are particularly common with the inherited metabolic disorders, which can present as any of the three major phenotypes (Fig. 259-4).

### DISORDERS OF METABOLIC PATHWAYS

Multiple genetic disorders of metabolic pathways can cause myocardial disease, due to infiltration of abnormal products or cells containing them between the myocytes, and storage disease, due to their accumulation within cells (Tables 259-3 and 259-4). Hypertrophic cardiomyopathy may be mimicked by the myocardium thickened with these abnormal products causing "pseudohypertrophy," usually with an abnormally short PR interval. The pseudohypertrophic phenotype



**FIGURE 259-11** Fabry's disease. Transmission electron micrograph of a right ventricular endomyocardial biopsy specimen at high magnification showing the characteristic concentric lamellar inclusions of glycosphingolipids accumulating as a result of deficiency of the lysosomal enzyme alpha-galactosidase A. Image taken at 15,000 $\times$  original magnification. (Image courtesy of Robert Paderia, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

is most common, but restrictive cardiomyopathy and DCM may occur. Most of these diseases are diagnosed during childhood.

*Fabry's disease* results from a deficiency of the lysosomal enzyme alpha-galactosidase A caused by one of more than 160 mutations in *GLA*. This disorder of glycosphingolipid metabolism is an X-linked disorder that may also cause clinical disease in female carriers. Glycolipid accumulation may be limited to the cardiac tissues but usually also involves the skin, peripheral nerve, and kidney. Electron microscopy of endomyocardial biopsy tissue shows diagnostic vesicles containing concentric lamellar figures (Fig. 259-11). Diagnosis can be made through assessment of enzyme activity and/or *GLA* sequencing and is crucial because enzyme replacement can reduce abnormal deposits and improve cardiac and clinical function. The magnitude of clinical impact has not been well established for this therapy, which requires frequent infusions of the enzyme at a cost of >\$100,000 a year. The oral chaperone therapy, migalastat, stabilizes mutant forms of alpha-galactosidase, increases enzymatic activity, and was approved for use in a subset of patients with Fabry's disease bearing mutations amenable to this therapy. Enzyme replacement can also improve the course of Gaucher's disease, in which cerebroside-rich cells accumulate in multiple organs due to a deficiency of beta-glucuronidase. Cerebroside-rich cells infiltrate the heart, which can also lead to a hemorrhagic pericardial effusion and valvular disease.

Glycogen storage diseases lead to accumulation of lysosomal storage products and intracellular glycogen accumulation, particularly with *glycogen storage disease type III*, due to a defective debranching enzyme. There are >10 types of *mucopolysaccharidoses*, in which autosomal recessive or X-linked deficiencies of lysosomal enzymes lead to the accumulation of glycosaminoglycans in the skeleton, nervous system, and occasionally the heart. With characteristic facies, short stature, and frequent cognitive impairment, most individuals are diagnosed early in childhood and die before adulthood.

Carnitine is an essential cofactor in long-chain fatty acid metabolism. Multiple defects have been described that lead to carnitine deficiency, causing intracellular lipid inclusions and restrictive cardiomyopathy or DCM, often presenting in children. Fatty acid oxidation requires many metabolic steps with specific enzymes that can be deficient, with complex interactions with carnitine. Depending on the defect, cardiac and skeletal myopathy can be ameliorated with replacement of fatty acid intermediates and carnitine.

Two monogenic metabolic cardiomyopathies cause markedly increased ventricular wall thickness without an increase in muscle subunits or an increase in contractility. Mutations in the gamma-2 regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase important for glucose metabolism (*PRKAG2*) have

been associated with a high prevalence of conduction abnormalities, such as AV block and ventricular preexcitation. Several defects have been reported in an X-linked lysosome-associated membrane protein (*LAMP2*). This defect can be maternally transmitted or sporadic and has occasionally been isolated to the heart, although it often leads to a syndrome of skeletal myopathy, mental retardation, and hepatic dysfunction referred to as *Danon's disease*. Extreme left ventricular hypertrophy appears early, often in childhood, and can progress rapidly to end-stage heart failure with low ejection fraction. Electron microscopy of these metabolic disorders shows that the myocytes are enlarged by multiple intracellular vacuoles of metabolic by-products.

## RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy is dominated by abnormal diastolic function, often with mildly decreased contractility and ejection fraction (usually 30–50%). Both atria are enlarged, sometimes massively. Modest left ventricular dilation can be present, usually with an end-diastolic dimension <6 cm. End-diastolic pressures are elevated in both ventricles, with preservation of cardiac output until late in the disease. Subtle exercise intolerance is usually the first symptom but is often not recognized until after clinical presentation with congestive symptoms. The restrictive diseases often present with relatively more right-sided symptoms, such as edema, abdominal discomfort, and ascites, although filling pressures are elevated in both ventricles. The cardiac impulse is less displaced than in DCM and less dynamic than in hypertrophic cardiomyopathy. A fourth heart sound is more common than a third heart sound in sinus rhythm, but atrial fibrillation is common. Jugular venous pressures often show rapid Y descents and may increase during inspiration (positive Kussmaul's sign). Most restrictive cardiomyopathies are due to infiltration of abnormal substances between myocytes, storage of abnormal metabolic products within myocytes, or fibrotic injury (Table 259-5). The differential diagnosis should include constrictive pericardial disease, which may also be dominated by right-sided heart failure.

## INFILTRATIVE DISEASE

The most common restrictive cardiomyopathy is amyloidosis, in which a common protein assembles into -pleated sheets of amyloid fibrils that infiltrate between cells of target organs (Figs. 259-12, 259-13, and 259-14). Almost all amyloid that affects the heart is caused by assembly either of immunoglobulin light chains from clonal plasma cells (AL or "primary" amyloid) or of transthyretin (ATTR), which is made in the liver and can either be an inherited mutant protein (ATTRm) or the normal protein (ATTRwt [wild-type]), which accumulates with age, leading to cardiac amyloid in half of people >90 years old, but clinically much more common in men than women). There are multiple mutations in the transthyretin molecule, of which the most common is V122I, which confers a 50% increased risk of heart failure in the 3–4% of African Americans who are heterozygous, but it is often clinically silent.

Right heart failure often dominates the clinical presentation of cardiac amyloidosis, although both ventricles are affected. Conduction system disease and atrial fibrillation are common. Nephrotic syndrome is common in AL amyloid, which may also cause angina as the amyloid encircles the coronary arteries. Because the ventricular cavity is diminished by amyloid infiltration, cardiac output may be very low with a modest ejection fraction reduction. Peripheral and autonomic neuropathy are common in both AL amyloidosis and ATTRm amyloidosis. A history of carpal tunnel syndrome is common in ATTRm and ATTRwt, often preceding cardiac symptoms by many years. ATTRwt is also associated with spinal stenosis.

Amyloidosis should be suspected when ventricular myocardium appears thick on imaging with low ECG voltage, but this mismatch is more common with AL than TTR amyloidosis. Atrial enlargement is prominent and diastolic dysfunction more severe than that of other causes of hypertrophy. Longitudinal strain is frequently more preserved at the apex, creating a "bull's-eye" pattern. MRI shows diffuse late gadolinium enhancement. Technetium-pyrophosphate scanning reliably highlights TTR amyloidosis but does not detect AL amyloid.

**TABLE 259-5 Causes of Restrictive Cardiomyopathies****Infiltrative (Between Myocytes)****Amyloidosis**

- Primary (light chain amyloid)
- Familial (abnormal transthyretin)<sup>a</sup>
- Senile (normal transthyretin or atrial peptides)

**Inherited metabolic defects<sup>a</sup>****Storage (Within Myocytes)**

- Hemochromatosis (iron)<sup>a</sup>
- Inherited metabolic defects<sup>a</sup>
- Fabry's disease
- Glycogen storage disease (II, III)

**Fibrotic**

- Radiation
- Scleroderma

**Endomyocardial**

- Possibly related fibrotic diseases
- Tropical endomyocardial fibrosis
- Hypereosinophilic syndrome (Löffler's endocarditis)
- Carcinoid syndrome
- Radiation

**Overlap with Other Cardiomyopathies**

- Hypertrophic cardiomyopathy/"pseudohypertrophic"<sup>a</sup>
- "Minimally dilated" cardiomyopathy
- Early-stage dilated cardiomyopathy
- Partial recovery from dilated cardiomyopathy

**Sarcoidosis****Idiopathic<sup>a</sup>**

<sup>a</sup>Can be familial.

Endomyocardial biopsy is virtually 100% reliable for the diagnosis of all amyloid due to the characteristic birefringence pattern of Congo red staining of the amyloid fibrils under polarized light, but immunohistochemistry may be necessary to confirm the amyloid type, as serum or urine electrophoresis may be misleading. Until recently, the therapy of amyloidosis was limited to the treatment of congestion and arrhythmias. There is no evidence for benefit from neurohormonal antagonists, which may complicate the postural hypotension and fixed low stroke volume of amyloid disease. However, specific therapies for amyloidosis are changing the prognosis. Median survival with AL amyloidosis was previously 6–12 months but has markedly improved with the use of the proteasome inhibitor bortezomib. If present, multiple myeloma may be treated with conventional chemotherapy, if not limited by cardiac dysfunction. AL amyloid can sometimes be treated with heart transplantation followed by delayed stem cell transplantation, with some risk of recurrence of amyloid in the transplanted heart. The course of TTR amyloidosis is measured in years even after the typical delay in diagnosis and may be affected by new therapies. Stabilizers of the normal transthyretin structure, tafamidis and diflusinal, have been approved for therapy of the associated neuropathy and are now being studied for effect on cardiac outcomes. Expression of transthyretin can be decreased by patisiran, a small interfering RNA that decreases message production, or inotersen, an antisense mRNA that enhances mRNA degradation. Both have been approved as treatment for the polyneuropathy of TTR amyloid, with possible benefit on long-term outcomes. These therapies have not yet been approved for a cardiac indication.

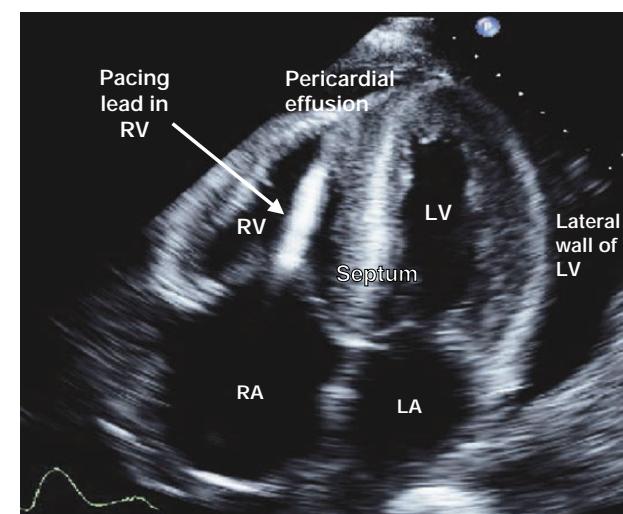
**FIBROTIC RESTRICTIVE CARDIOMYOPATHY**

Progressive fibrosis can cause restrictive myocardial disease without ventricular dilation. Thoracic radiation, common for breast and lung cancer or mediastinal lymphoma, can produce early or late restrictive

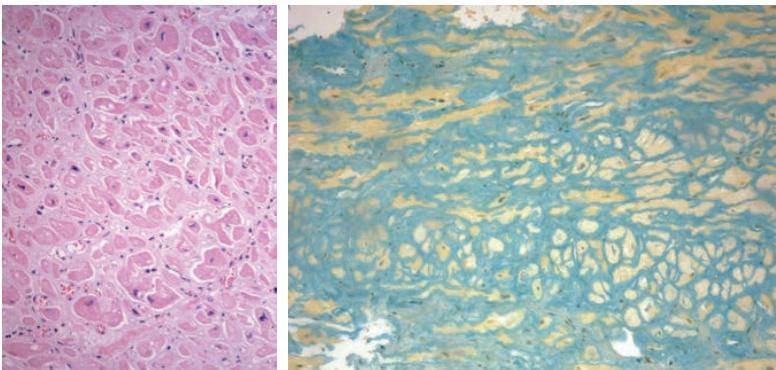


**FIGURE 259-12** **Restrictive cardiomyopathy—amyloidosis.** Gross specimen of a heart with amyloidosis. The heart is firm and rubbery with a waxy cut surface. The atria are markedly dilated, and the left atrial endocardium, normally smooth, has yellow-brown amyloid deposits that give texture to the surface. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

cardiomyopathy. Patients with *radiation cardiomyopathy* may present with a possible diagnosis of constrictive pericarditis, as the two conditions often coexist. Careful hemodynamic evaluation and, often, endomyocardial biopsy should be performed if considering pericardial



**FIGURE 259-13** **Restrictive cardiomyopathy—amyloidosis.** Echocardiogram showing thickened walls of both ventricles without major chamber dilation. The atria are markedly dilated, consistent with chronically elevated ventricular filling pressures. In this example, there is a characteristic hyperrefractile "glittering" of the myocardium typical of amyloid infiltration, which is a nonspecific finding with contemporary echocardiography. The mitral and tricuspid valves are thickened. A pacing lead is visible in the right ventricle (RV), and a pericardial effusion is evident. Note that the echocardiographic and pathologic images are vertically opposite, such that the left ventricle (LV) is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. LA, left atrium; RA, right atrium. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)



**FIGURE 259-14 Amyloidosis—microscopic images of amyloid involving the myocardium.** The left panel (hematoxylin and eosin stain) shows glassy, gray-pink amorphous material infiltrating between cardiomyocytes, which stain a darker pink. The right panel shows a sulfated blue stain that highlights the amyloid green and stains the cardiac myocytes yellow. (The Congo red stain can also be used to highlight amyloid; under polarized light, amyloid will have an apple-green birefringence when stained with Congo red.) Images at 100 $\times$  original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

stripping surgery, which is unlikely to be successful in the presence of underlying restrictive cardiomyopathy. *Scleroderma* causes small vessel spasm and ischemia that can lead to a small, stiff heart with reduced ejection fraction without dilation. The pulmonary hypertension associated with scleroderma may lead to more clinical right heart failure because of concomitant fibrotic disease of the right ventricle.

### ENDOMYOCARDIAL DISEASE

The physiologic picture of elevated filling pressures with atrial enlargement and preserved ventricular contractility with normal or reduced ventricular volumes can result from extensive fibrosis of the endocardium, without transmural myocardial disease. For patients who have not lived in the equatorial regions, this picture is rare, and when seen is often associated with a history of chronic hypereosinophilic syndrome (*Löffler's endocarditis*), which is more common in men than women. In this disease, persistent hypereosinophilia of >1500 eosinophils/ $\mu$ L for at least 6 months can cause an acute phase of eosinophilic injury in the endocardium (see earlier discussion of eosinophilic myocarditis), with systemic illness and injury to other organs. Hypereosinophilic syndromes can occasionally be explained by allergic or parasitic disease, but are increasingly being recognized as due to myeloproliferative variants. It is postulated to be followed by a period in which cardiac inflammation is replaced by evidence of fibrosis with superimposed thrombosis. In severe disease, the dense fibrotic layer can obliterate the ventricular apices and extend to thicken and tether the AV valve leaflets. The clinical disease may present with heart failure, embolic events, and atrial arrhythmias. While plausible, the sequence of transition from eosinophilic myocarditis or Löffler's endocarditis to endomyocardial fibrosis has not been clearly demonstrated.

In tropical countries, up to one-quarter of heart failure may be due to *endomyocardial fibrosis*, affecting either or both ventricles. This condition shares with the previous condition the partial obliteration of the ventricular apex with fibrosis extending into the valvular inflow tract and leaflets; however, it is not clear that the etiologies are the same for all cases. Pericardial effusions frequently accompany endomyocardial fibrosis but are not common in Löffler's endocarditis. For endomyocardial fibrosis, there is no gender difference, but there is a higher prevalence in African-American populations. While tropical endomyocardial fibrosis could represent the end-stage of previous hypereosinophilic disease triggered by endemic parasites, neither prior parasitic infection nor hypereosinophilia is usually documented. Geographic nutritional deficiencies have also been proposed as an etiology.

Clonal proliferation with specific mutations may respond to monoclonal antibody therapy. Other treatment includes glucocorticoids to suppress hypereosinophilia when present. Fluid retention may become increasingly resistant to diuretic therapy. Anticoagulation is

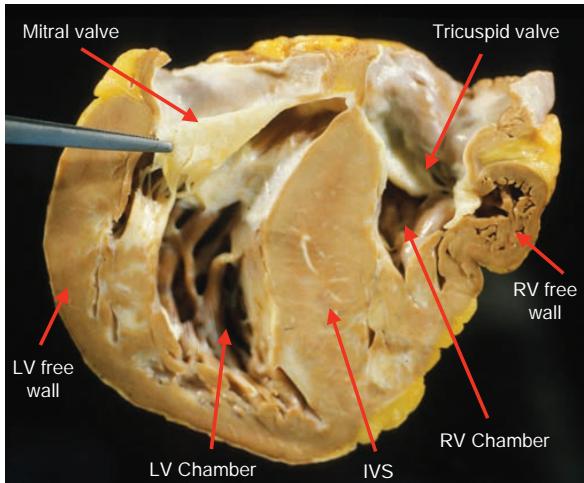
recommended. Atrial fibrillation is associated with worse symptoms and prognosis but may be difficult to suppress. Surgical resection of the apices and replacement of the fibrotic valves can improve symptoms, but surgical morbidity and mortality and later recurrence rates are high.

The serotonin secreted by *carcinoïd* tumors can produce fibrous plaques in the endocardium and right-sided cardiac valves, occasionally affecting left-sided valves as well. Valvular lesions may be stenotic or regurgitant. Systemic symptoms include flushing and diarrhea. Liver disease from hepatic metastases may play a role by limiting hepatic function and thereby allowing more serotonin to reach the venous circulation.

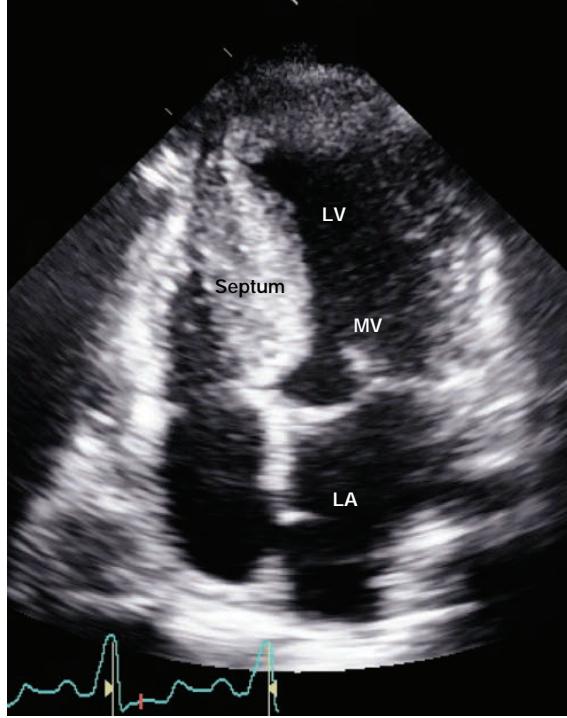
### HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is defined as left ventricular hypertrophy that develops in the absence of causative hemodynamic factors, such as hypertension, aortic valve disease, or systemic infiltrative or storage diseases (Figs. 259-15 and 259-16). It has previously been termed *hypertrophic obstructive cardiomyopathy* (HOCM), *asymmetric septal hypertrophy* (ASH), and *idiopathic hypertrophic subaortic stenosis* (IHSS). However, the accepted terminology is now hypertrophic cardiomyopathy with or without obstruction. Prevalence in North America, Africa, and Asia is about 1:500. It is a leading cause of sudden death in the young and is an important cause of heart failure. Although pediatric presentation is associated with increased early morbidity and mortality, the prognosis for patients diagnosed as adults is generally favorable, although worse than for age-matched individuals without hypertrophic cardiomyopathy.

A sarcomere mutation is present in ~50% of patients with hypertrophic cardiomyopathy and is more common in those with familial disease and characteristic asymmetric septal hypertrophy. More than nine different genes with >1500 mutations have been implicated, although ~80% of patients have a mutation in either *MYH7* or *MYBPC3* (Table 259-3).



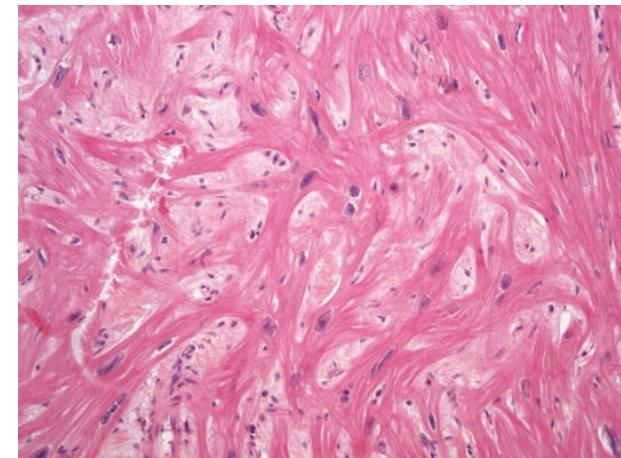
**FIGURE 259-15 Hypertrophic cardiomyopathy.** Gross specimen of a heart with hypertrophic cardiomyopathy removed at the time of transplantation, showing asymmetric septal hypertrophy (septum much thicker than left ventricular free wall) with the septum bulging into the left ventricular outflow tract causing obstruction. The forceps are retracting the anterior leaflet of the mitral valve, demonstrating the characteristic plaque of systolic anterior motion, manifest as endocardial fibrosis on the interventricular septum in a mirror-image pattern to the valve leaflet. There is patchy replacement fibrosis, and small thick-walled arterioles can be appreciated grossly, especially in the interventricular septum. IVS, interventricular septum; LV, left ventricle; RV, right ventricle. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)



**FIGURE 259-16 Hypertrophic cardiomyopathy.** This echocardiogram of hypertrophic cardiomyopathy shows asymmetric hypertrophy of the septum compared to the lateral wall of the left ventricle (LV). The mitral valve (MV) is moving anteriorly toward the hypertrophied septum in systole. The left atrium (LA) is enlarged. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

Hypertrophic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of left ventricular hypertrophy is rarely present at birth and usually develops later in life. Women appear to have lower penetrance of sarcomere mutations and an older age at hypertrophic cardiomyopathy diagnosis but subsequently increased rates of heart failure and mortality thereafter. Accordingly, screening of family members should begin in adolescence and extend through adulthood. In *MYBPC3* mutation carriers, the average age of disease development is ~40 years, while 30% remain free from hypertrophy after 70 years. Related individuals who carry the same mutation may have a different extent and pattern of hypertrophy (e.g., asymmetric vs concentric), occurrence of outflow tract obstruction, and associated clinical outcomes, although sudden death and progression to heart failure occur more commonly in families with that history.

At the level of the sarcomere, hypertrophic cardiomyopathy mutations lead to enhanced calcium sensitivity, maximal force generation, and ATPase activity. Calcium handling is affected through modification of regulatory proteins. Sarcomere mutations lead to abnormal energetics and impaired relaxation, both directly and as a result of hypertrophy. Hypertrophic cardiomyopathy is characterized by misalignment and disarray of the enlarged myofibrils and myocytes (Fig. 259-17), which can also occur to a lesser extent in other cardiac diseases. Although hypertrophy is the defining feature of hypertrophic cardiomyopathy, fibrosis and microvascular disease are also present. Interstitial fibrosis is detectable before overt hypertrophy develops and likely results from early activation of profibrotic pathways. In the majority of patients with overt cardiomyopathy, focal areas of replacement fibrosis can be readily detected with MRI. These areas of “scar” may represent substrate for the development of ventricular arrhythmias. Increased thickness and decreased luminal area of the intramural vessels in hypertrophied myocardium contribute to microvascular



**FIGURE 259-17 Hypertrophic cardiomyopathy.** Microscopic image of hypertrophic cardiomyopathy showing the characteristic disarrayed myocyte architecture with swirling and branching rather than the usual parallel arrangement of myocyte fibers. Myocyte nuclei vary markedly in size and interstitial fibrosis is present. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

ischemia and angina. Microinfarction of hypertrophied myocardium is a hypothesized mechanism for replacement scar formation.

Macroscopically, hypertrophy is typically manifest as nonuniform ventricular thickening (Fig. 259-15). The interventricular septum is the typical location of maximal hypertrophy, although other patterns of hypertrophic remodeling include concentric and midventricular. Hypertrophy confined to the ventricular apex (apical hypertrophic cardiomyopathy) is less often familial and has a different genetic substrate, with sarcomere mutations present in only ~15%. Left ventricular outflow tract obstruction represents the most common focus of diagnosis and intervention, although diastolic dysfunction, myocardial fibrosis, and microvascular ischemia also contribute to contractile dysfunction and elevated intracardiac pressures. Obstruction is present in ~30% of patients at rest and can be provoked by exercise in another ~30%. Systolic obstruction is initiated by drag forces, which push an anteriorly displaced and enlarged anterior mitral leaflet into contact with the hypertrophied ventricular septum. Mitral leaflet coaptation may ensue, leading to posteriorly directed mitral regurgitation. In order to maintain stroke volume across outflow tract obstruction, the ventricle generates higher pressures, leading to higher wall stress and myocardial oxygen demand. Smaller chamber size and increased contractility exacerbate the severity of obstruction. Conditions of low preload, such as dehydration, and low afterload, such as arterial vasodilation, may lead to transient hypotension and near-syncope. The systolic ejection murmur of left ventricular outflow tract obstruction is harsh and late peaking and can be enhanced by bedside maneuvers that diminish ventricular volume and transiently worsen obstruction, such as the Valsalva maneuver or standing from a squatting position.

## DIAGNOSIS

The substantial variability of hypertrophic cardiomyopathy pathology is reflected in the diversity of clinical presentations. Patients may be diagnosed after undergoing evaluations triggered by the abnormal physical findings (murmur) or by symptoms of exertional dyspnea, angina, or syncope. Alternatively, diagnosis may follow evaluations prompted by the detection of disease in family members. Cardiac imaging (Fig. 259-16) is central to diagnosis, for which the physical examination and ECG are insensitive. The identification of a disease-causing mutation in a proband can focus family evaluations on mutation carriers, but this strategy requires a high degree of certainty that the mutation is truly pathogenic and not a benign DNA variant. Biopsy is not needed to diagnose hypertrophic cardiomyopathy but can be used to exclude infiltrative and metabolic diseases. Rigorous athletic training (athlete's heart) may cause intermediate degrees of physiologic hypertrophy difficult to differentiate from mild hypertrophic

cardiomyopathy. Unlike hypertrophic cardiomyopathy, hypertrophy in the athlete's heart regresses with cessation of training and is accompanied by supernormal exercise capacity ( $\text{VO}_{\text{2max}} > 50 \text{ mL/kg per min}$ ), mild ventricular dilation, and normal diastolic function.

## TREATMENT

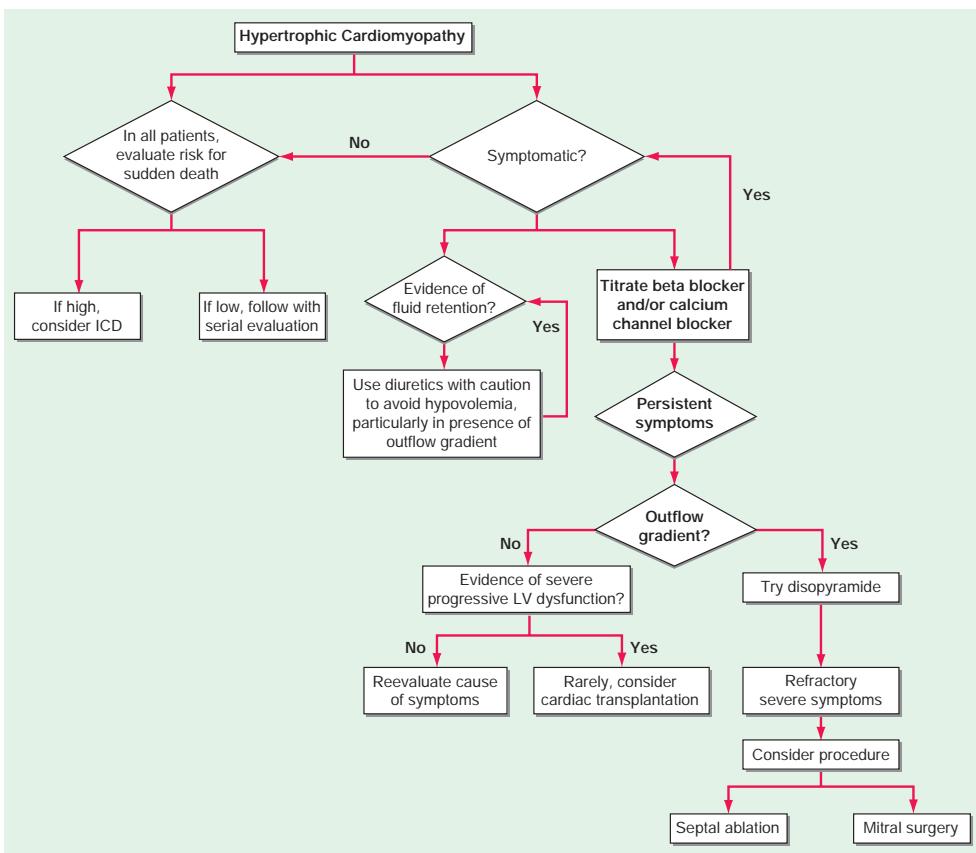
### Hypertrophic Cardiomyopathy

Management focuses on treatment of symptoms and prevention of sudden death and stroke (Fig. 259-18). Left ventricular outflow tract obstruction can be controlled medically in the majority of patients. -Adrenergic blocking agents and L-type calcium channel blockers (e.g., verapamil) are first-line agents that reduce the severity of obstruction by slowing heart rate, enhancing diastolic filling, and decreasing contractility. Persistent symptoms of exertional dyspnea or chest pain can sometimes be controlled with the addition of disopyramide, an antiarrhythmic agent with potent negative inotropic properties. Novel small-molecule inhibitors of actin-myosin interactions are being developed for obstructive and nonobstructive hypertrophic cardiomyopathy.

Patients with or without obstruction may develop heart failure symptoms due to fluid retention and require diuretic therapies for venous congestion. Severe medically refractory symptoms develop in ~5% of patients, for whom surgical myectomy or alcohol septal ablation may be effective. Developed over 60 years ago, surgical myectomy effectively relieves outflow tract obstruction by excising part of the septal myocardium involved in the dynamic obstruction. In selected patients, perioperative mortality is extremely low with excellent long-term survival free from recurrent obstruction and

symptoms. Mitral valve repair or replacement is usually unnecessary as associated eccentric mitral regurgitation resolves with myectomy alone. Alcohol septal ablation in patients with suitable coronary anatomy can relieve outflow tract obstruction via a controlled infarction of the proximal septum, which produces similar periprocedural outcomes and gradient reduction as surgical myectomy. Until long-term outcomes are demonstrated for septal ablation procedures, they are relegated primarily to patients who wish to avoid surgery or who have limiting comorbidities. Neither procedure has been shown to improve outcomes other than symptoms. With both procedures, the most common complication is the development of complete heart block necessitating permanent pacing. However, ventricular pacing as a primary therapy for outflow tract obstruction is ineffective and not generally advised.

Patients with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death from ventricular tachyarrhythmias. Vigorous physical activity and competitive sports have been historically prohibited; however, ongoing studies are reexamining the relationship between exertion and ventricular arrhythmias in hypertrophic cardiomyopathy. Factors that increase the risk of sudden death from a baseline of 0.5% per year are presented in Table 259-6. As sudden death has not been reduced by medical or procedural interventions, traditionally an implantable cardioverter-defibrillator has been advised for patients with two or more risk factors and advised on a selected basis for patient with one risk factor. Nevertheless, the positive predictive value of most risk factors is low, and many patients receiving a defibrillator never receive an appropriate device therapy. A complementary approach to sudden death risk stratification and discussion with patients is the application of an externally validated risk score using major criteria from Table 259-6 and



**FIGURE 259-18** Treatment algorithm for hypertrophic cardiomyopathy depending on the presence and severity of symptoms and the presence of an intraventricular gradient with obstruction to outflow. Note that all patients with hypertrophic cardiomyopathy should be evaluated for atrial fibrillation and risk of sudden death, whether or not they require treatment for symptoms. ICD, implantable cardioverter-defibrillator; LV, left ventricular.

**TABLE 259-6** Risk Stratification for Sudden Death in Hypertrophic Cardiomyopathy

RISK FACTOR		SCREENING TECHNIQUE
History of cardiac arrest or spontaneous sustained ventricular tachycardia <sup>a</sup>		History
Syncope	Nonvagal, often with or after exertion	History
Family history of sudden cardiac death		Family history
Spontaneous nonsustained ventricular tachycardia	>3 beats at rate >120	Exercise or 24- to 48-h ambulatory recording
LV thickness >30 mm	Present in <10% of patients	Echocardiography
Abnormal blood pressure response to exercise <sup>b</sup>	Systolic blood pressure fall or failure to increase at peak exercise	Maximal upright exercise testing
<b>Variables Utilized in the European Society of Cardiology Calculator for Estimated Risk of Sudden Death</b>		
LV outflow tract gradient	Peak gradient measured at rest or with the Valsalva maneuver, mmHg	Echocardiography
Left atrial diameter	Diameter measured in the parasternal long axis, mm	Echocardiography
LV thickness	Maximal wall thickness, mm	Echocardiography
Age		
Syncope, family history, nonsustained ventricular tachycardia	As above	As above
<b>Emerging Risk Factors</b>		
Late gadolinium enhancement	As a percentage of myocardial mass	Cardiac magnetic resonance imaging
Left ventricular apical aneurysm	Generally applicable to patients with apical hypertrophy	Echocardiography with contrast, cardiac magnetic resonance imaging

<sup>a</sup>Implantable cardioverter-defibrillator advised for patients with prior arrest or sustained ventricular tachycardia regardless of other risk factors if life expectancy is estimated to be >1 year. <sup>b</sup>Prognostic value most applicable to patients <40 years old. The European Society of Cardiology risk calculator can be found at <https://doc2do.com/hcm/webHCM.html> and provides an estimated 5-year risk of cardiac arrest. Patients with estimated risk of 6% are generally advised placement of an implantable cardioverter-defibrillator; those with risk between 4 and 6% can be considered for implant, and implant is not advised when risk is <4%. Emerging risk factors merit further clinical validation.

Abbreviation: LV, left ventricle.

continuous variables such as outflow tract gradient and left atrial size. Shared decision-making around implantable cardioverter-defibrillator implantation for primary prevention has emphasized discussions of estimated risk levels rather than dichotomous yes-no criteria. Long-term use of a defibrillator may be associated with serious device-related complications, particularly in young active patients. Refinement of sudden death risk through the application of contemporary technologies such as cardiac MRI is ongoing.

Atrial fibrillation is common in patients with hypertrophic cardiomyopathy and may lead to hemodynamic deterioration and embolic stroke. Rapid ventricular response is poorly tolerated and may worsen outflow tract obstruction. -Adrenergic blocking agents and L-type calcium channel blockers slow AV nodal conduction and improve symptoms; cardiac glycosides should be avoided, as they may increase contractility and worsen obstruction. Even with adequate rate control, symptoms exacerbated by atrial fibrillation may persist due to loss of AV synchrony and may require restoration of sinus rhythm. Disopyramide and amiodarone are the preferred antiarrhythmic agents, with radiofrequency ablation

considered for medically refractory cases. Anticoagulation to prevent embolic stroke in atrial fibrillation is recommended.

## PROGNOSIS

The general prognosis for hypertrophic cardiomyopathy is better than in early studies of referral populations, but mortality remains higher than in an age-matched population without cardiomyopathy. The sudden death risk is <1% per year; however, up to 1 in 20 patients will progress to overt systolic dysfunction with a reduced ejection fraction (<50%) with or without dilated remodeling (i.e., “burned out” or end-stage hypertrophic cardiomyopathy). These patients may suffer from low cardiac output and have an increased risk of death from progressive heart failure and sudden death unless they undergo timely cardiac transplantation.

## GLOBAL PERSPECTIVES

The worldwide prevalence of myocarditis and cardiomyopathy combined is estimated at 5.4 million people, compared to 26 million people with heart failure. The estimated prevalence of myocarditis cardiomyopathy has increased by >50% since 1990 due to the growing population, while the rate per 100,000 people has declined by >20% during the same period to 68, with an estimated mortality of 4.8 per 100,000. The highest age-standardized prevalence is reported in central Europe, whereas the highest attributed mortality is in Eastern Europe; however, comparison of myocardial diseases across eras and countries is complicated by differing ascertainment and techniques for cardiac diagnoses.

For comparison, the current mortality rates are similar to that of rheumatic heart disease, which has declined overall by 26.5% and by 55% after adjustment for age. Deaths from Chagas’ cardiomyopathy worldwide have declined from 12.7 thousand to 10.6 thousand, with a reduction of 51.7% in the age-adjusted rates per 100,000 population to 0.2, attributable, in major part, to improved health conditions in rural areas of South and Central America.

Health care for other diseases affects myocarditis and cardiomyopathy. Developed nations will see a higher prevalence of cardiomyopathy due to chemotherapy. However, vaccination has reduced deaths from diphtheria-associated myocarditis to <50 per 100 million population, currently most common in Russia. World regions providing HAART for HIV have decreased not only transmission but also the rate of associated cardiomyopathy by several-fold. Increasing global availability of genetic testing is expected to shift the apparent epidemiology of cardiomyopathy away from acquired causes toward causative and facilitating genetic factors. For example, heart failure with preserved ejection fraction attributed to hypertension and diabetes is increasingly recognized to represent amyloidosis from mutant transthyretin, with distinct, recognized mutations in Portugal, Japan, and the African-Caribbean population.

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Mandeep R. Mehra

Advanced heart failure, a distinct syndrome, is characterized by refractoriness to conventional therapy and represents a vexing clinical dilemma that is associated with an increased symptom burden, frequent hospitalization, a poor quality of life, and high risk of death. Such individuals do not tolerate neurohormonal antagonists at recommended doses, exhibit cardiorenal syndrome, maintain markedly poor cardiac reserve on cardiopulmonary stress testing, and typically display a low cardiac output state with elevated pulmonary pressures. In general, therapeutic targets shift away from disease-modifying neurohormonal therapy to surgical options that attend directly to supporting the dysfunctional heart and address myocardial stress and strain relationships. Most often, prolonged circulatory assistance using mechanical ventricular assist devices or cardiac transplantation is required to reliably improve quality of life and long-term survival.

## CARDIAC TRANSPLANTATION

A decade after Norman Shumway had accomplished the technique of a successful heart transplant in canines, Christian Barnard successfully performed the first human-to-human transplant on December 3, 1967. Now, >5 decades later, this surgery has become entrenched in the standard armamentarium for treating patients with advanced heart failure who are otherwise healthy enough to receive such a life-altering treatment. Globally, >150,000 patients have undergone cardiac transplantation with a 1-year survival >80% and median survival of 12.5 years and conditional survival of 14.8 years if the recipient survives the first year after transplant. These gains have been ushered by advances in immunosuppression, identification and management of allograft rejection, and a comprehensive appreciation for late complications including accelerated coronary artery disease, malignancy, and renal failure.

## CANDIDATES FOR CARDIAC TRANSPLANTATION

The demand for cardiac transplantation outstrips the availability of organ donors. Hence, attention to the optimal utility, equitable allocation, and patient autonomy must dominate the decisions to identify and list candidates for transplantation. Simultaneously, attempts at expanding the donor pool have surfaced. However, vigilance to evaluating candidates most likely to have a successful outcome from transplantation takes pre-eminence. In 2006, the International Society for Heart and Lung Transplantation identified a set of criteria to guide listing of patients. These criteria were updated in 2016 and include additional attention to the growing epidemiology of candidates suffering from congenital heart disease, restrictive and infiltrative cardiomyopathy (such as amyloidosis), and chronic infections in recipients (such as Chagas' disease, tuberculosis and viral hepatitis). Selected general principles for listing candidates for cardiac transplantation are enumerated in **Table 260-1**.

## PRINCIPLES OF DONOR RECOVERY AND ALLOCATION

Although listing criteria for candidates are typically adjudicated at a center level, organ allocation is handled by national regulatory processes in most countries. The allocation of donor hearts is based on (1) the urgency of the clinical situation, (2) the time spent on the waiting list, and (3) the distance from the recipient center. Candidates who are hospitalized in critical status and require extracorporeal membrane oxygenation or temporary mechanical circulatory support devices to support both ventricles are given the highest urgency status, followed by those requiring daily invasive hemodynamic evaluation and intravenous inotropic therapy to maintain stability, or those with

**TABLE 260-1 Principles for Listing Candidates for Cardiac Transplantation**

PRINCIPLE	COMMENT
Advanced Disease Severity	Refractory heart failure with a $\dot{V}O_2$ of <14 mL/kg per min (<12, if on beta blockers) or percent predicted $\dot{V}O_2$ <50%; combination of intolerance to disease-modifying therapy, cardiorenal syndrome, use of inotropic therapy to maintain stability, or need for a left ventricular assist system.
Comorbidity	Age is not an absolute contraindication, but frailty should be considered a relative contraindication; a BMI >35 kg/m <sup>2</sup> should require weight loss; cancer should be dealt with on an individual basis (e.g., low-grade prostate cancer may not be a contraindication); poorly controlled diabetes mellitus or end-organ damage may be a contraindication; eGFR <30 mL/min/1.73 m <sup>2</sup> is a relative contraindication, if persistent; severe cerebrovascular disease or peripheral vascular disease (which will limit rehabilitation or function) is also a relative contraindication.
Donor-Recipient Matching	Sensitized individuals with circulating antibodies should have a prospective or virtual cross match; pulmonary vascular resistance with a transpulmonary gradient >15, PVR >3 Wood units, and absolute PA systolic pressure >50 mmHg provided the systolic blood pressure is >85 mmHg is a relative contraindication unless reactive to therapy.
Psychosocial Issues	Tobacco use in any form limits posttransplant survival and should be stopped for at least 6 months; substance abuse, including marijuana, should be a contraindication if the individual cannot demonstrate control and cessation; patients with severe cognitive-behavioral disabilities or dementia (inability to ever understand and cooperate with medical care) have the potential for self-harm and should not receive a transplant.

*Abbreviations:* BMI, body mass index; eGFR, estimated glomerular filtration rate; PA, pulmonary artery; PVR, pulmonary vascular resistance;  $\dot{V}O_2$ , peak oxygen consumption.

complications of a durable left ventricular assist device. Others stable at home while supported by a left ventricular assist device or those able to ambulate and live at home receive a lower urgency status. The geographical regional reach for allocation is based not only on territorial considerations but also on the time that a donor heart would be in transit and therefore in out of body "ischemia time," which is typically limited to 4 h. The final key feature that is included in the allocation offer relates to the ABO blood group. Donor organs are offered based on these initial characteristics and then a more detailed donor assessment ensues, resulting in acceptance or decline for any given donor heart. It is important to note that the time constraints imposed on the retrieval process make it difficult to invoke HLA matching of the donor and recipient. In cases where there is a high likelihood of sensitization in the recipient (preformed circulating antibodies against donor antigens), a prospective or virtual cross match is entertained prior to acceptance. Other clinical criteria that are employed in the decision on accepting an offered donor include the donor-recipient size match, the age of the donor (typically restricted to <55 years, but is often exceeded due to organ shortages), and presence or absence of concomitant pathology such as coronary artery disease, left ventricular hypertrophy, or severe injury to the allograft manifest by excess leak of injury markers (troponins) or poor contractile performance. In many cases, the prospective cardiac allograft can be reconditioned by use of hormonal therapy (including thyroid hormone supplementation) and used for transplantation even if the initial evaluation suggests poor function. In efforts to enhance the donor pool, systems that allow ex vivo normothermic perfusion to evaluate and reanimate organs with a prolonged out of body time are being developed. The classic heart donor is derived from a donor with brain death; however, donors with circulatory death are being increasingly evaluated as candidates for cardiac reanimation using a variety of techniques including ex vivo reanimation and subsequent transplantation. Such donor organs obtained after circulatory death are gaining more widespread acceptance, and early outcomes suggest that their outcomes after transplantation are no different from those of organs retrieved from brain death donors. In order to increase

1974 the number of viable donors, organs from those infected with hepatitis C virus are increasingly being utilized since curative antiviral therapy can be used in the recipient shortly after transplantation.

## SURGERY FOR CARDIAC TRANSPLANTATION

The most common contemporary operation is referred to as a “bi-caval” orthotopic cardiac transplant that mimics the natural anatomic position. In this operation, the donor and recipient superior and inferior venae cavae are connected as are the aortic and pulmonary great vessels. The left atrium of the recipient retains its roof including the draining pulmonary veins, and the donor left atrium is then sutured to the retained atrial tissue. This technique maintains function of the donor right atrium, important for governing early postoperative right heart output, and may prevent atrial arrhythmias. The recipient is left with a surgical denervation, and the allograft is not responsive to any physiologic sympathetic or parasympathetic stimuli. Therefore, early in the adaptive postoperative phase, high-dose catecholamines are required to maintain adequate function. Due to denervation, bradycardia in a cardiac allograft cannot be treated with atropine and the drug of choice is isoproterenol, or temporary electrical pacing is used. Once the cardiac allograft adapts to its host circulation, the function is usually adequate at rest and with exercise to provide normal physical activity and quality of life.

## CARDIAC ALLOGRAFT REJECTION AND IMMUNOSUPPRESSION

The ability to perform endomyocardial biopsies and evaluate rejection pathologically and the introduction of the immunosuppression agent cyclosporine heralded cardiac transplantation as a viable clinical therapy. Triple-drug immunosuppression, which includes a calcineurin inhibitor (cyclosporine or tacrolimus), corticosteroids, and antiproliferative immunosuppression (azathioprine, mycophenolate mofetil, sirolimus, or everolimus), is now the standard combination used. The combination immunosuppression strategy that is most commonly used and that achieves the best standard outcomes includes tacrolimus, mycophenolate mofetil, and prednisone. In those at high risk for rejection (multiparous women, sensitized individuals) or in situations where use of calcineurin inhibitors needs to be delayed (renal dysfunction), induction therapy using monoclonal (basiliximab) or polyclonal antibodies (antithymocyte globulin) to provide augmented immunosuppression is used. Over several months, as surveillance endomyocardial biopsies are regularly performed and clinical as well as subclinical pathologic quiescence is established, gradual weaning of steroids is undertaken. **Table 260-2** describes the immunosuppression drugs in common use.

Acute cellular rejection (ACR) and antibody-mediated rejection (AMR) are two separate forms of cardiac allograft rejection that are

recognized and can sometimes coexist. ACR occurs early after transplantation and then tends to decline in incidence after 6 months. This occurs due to a T cell-mediated assault on the donor allograft tissue and histologically is characterized by lymphocytic infiltrates in the myocardium. In mild cases, these infiltrates are localized to the perivenular regions, and in severe cases, they progress diffusely into the cardiac interstitium. In late stages of severe ACR, most often associated with hemodynamic compromise, multiclonal cells such as macrophages, neutrophils, and eosinophils are observed with intramyocardial hemorrhage, myocyte injury, and myocyte necrosis. Subclinical ACR is typically treated with high doses of corticosteroid pulses, although some centers choose to simply observe mild forms of infiltration since it is known that many of these patients may recover spontaneously over time. If hemodynamic compromise occurs, rescue polyclonal antibodies are used in tandem with corticosteroids. Conversely, AMR is immunologically described as a noncellular antibody-driven phenomenon associated with a pattern of immunopathologic findings of immunoglobulin deposition and complement fixation on immunofluorescence, along with histopathologic findings of endothelial swelling and interstitial edema and cardiac allograft arteriolar vasculitis. AMR is characterized by the emergence of circulating donor-specific antibodies that are thought to fix complement and bind to the allograft. Commonly, AMR leads to allograft dysfunction, increases the risk for development of cardiac allograft vasculopathy, and is associated with worsened cardiac allograft survival compared with ACR. In this form of rejection, therapy is directed toward suppression and removal of circulating antibodies using plasmapheresis and drugs such as rituximab (chimeric monoclonal antibody directed against the CD20 antigen) or, in refractory cases, bortezomib (a proteasome inhibitor) or eculizumab (a terminal complement inhibitor). The treatment with immunosuppression requires prophylaxis for opportunistic infections and ongoing surveillance and expertise in recognizing the more common clinical presentations of infections caused by cytomegalovirus (CMV), *Aspergillus*, and other opportunistic agents such as *Nocardia* and toxoplasmosis.

## LATE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

The long-term consequences of exposure to chronic immunosuppression result in a variety of nonimmunologic cardiometabolic effects such as hypertension, hyperlipidemia, and hyperglycemia, as well as systemic disorders of bone loss and renal dysfunction. One aggressive complication that limits late survival of cardiac allografts includes the development of an accelerated form of coronary artery disease, referred to as cardiac allograft vasculopathy (CAV). This is characterized by a

**TABLE 260-2** Immunoprophylaxis Drugs in Cardiac Transplantation

DRUG CLASS	GENERIC DRUG	CELLULAR TARGET	MAJOR SIDE EFFECTS
Calcineurin inhibitors	Cyclosporine	Binds to cyclophilin, which then inhibits calcineurin	Hypertension, dyslipidemia, gum hypertrophy, hypertrichosis
	Tacrolimus	Binds to immunophilin FK506 binding protein, which inhibits calcineurin	Hypertension, dyslipidemia, alopecia, diabetes mellitus
Antithymocyte globulin (ATG)	Rabbit ATG	T-cell depletion in blood and peripheral lymphoid tissues through complement-dependent lysis and T-cell activation and apoptosis	Cytokine release syndrome, leukopenia, thrombocytopenia, serum sickness
	Horse ATG	Same as above	Same as above
Interleukin-2 receptor antagonists	Basiliximab	Inhibition of CD-25 of interleukin 2 receptor	Well tolerated; rare hypersensitivity; increased infection risk if used with calcineurin inhibitors
Antimetabolites	Azathioprine	Imidazolyl derivative and prodrug of 6-mercaptopurine (cell cycle inhibitor)	Bone marrow suppression, pancreatitis, hepatitis
	Mycophenolate Mofetil	Inhibits inosine monophosphate dehydrogenase, which controls guanine monophosphate in the de novo pathway of purine synthesis (inhibits T- and B-cell proliferation)	Leukopenia, gastrointestinal toxicity
Proliferation signal inhibitors	Sirolimus	Binds with FKBP12 and complex inhibits the mechanistic target of rapamycin (mTOR)	Delayed wound healing, nonspecific pneumonia, pericardial effusion, hyperlipidemia (hypertriglyceridemia)
	Everolimus	Binds to FKBP12, which inhibits mTORC1 (and not mTORC2)	Dyslipidemia, stomatitis, pericardial effusions, and pancytopenia

proliferative thickening of the vascular intima of the vasculature that is initiated as a diffuse endothelialitis in the setting of the confluence of the consequences of brain death, ischemia reperfusion injury during the transplant process, and early immunologic insults. Chronically, the metabolic consequences of hypertension, hyperlipidemia, and disordered glucose regulation result in worsening of vascular lesions that are diffuse and noted throughout the coronary tree. Early diagnosis and preventative therapy are critical since it is commonly silent in its development. Intravascular ultrasound is more sensitive than routine coronary angiography for the diagnosis of CAV. A standardized grading scheme for CAV was proposed by the International Society for Heart and Lung Transplantation in 2010. CAV is graded as absent (CAV0), mild (CAV1), moderate (CAV2), or severe (CAV3) based on extent of angiographic disease and presence of allograft dysfunction by echocardiography or restrictive cardiac physiology. The grade of CAV correlates with patient prognosis. Angiographic CAV is present in ~30% of patients by 5 years after transplant and ~50% of patients by 10 years after transplant. Use of statins may help prevent CAV development after heart transplantation. Antihypertensive agents and anti-CMV therapy have demonstrated some benefits in reducing CAV with varying degrees of supportive evidence. Antiproliferative immunosuppressive therapy such as mycophenolate mofetil and sirolimus or everolimus prevents vascular intimal thickening compared with azathioprine-based regimens. Options for medical treatment of established CAV remain limited. Revascularization using percutaneous coronary intervention or coronary artery bypass grafting may be employed in selected cases with focal lesions but does not improve survival in patients with CAV. However, retransplantation is the only definitive form of therapy for advanced CAV (Fig. 260-1).

Another concern in cardiac transplantation is the development of malignancy with a greater frequency than in the normal population, suggesting that immunosuppression plays a sentinel role in its generation. Posttransplant lymphoproliferative disorders, typically driven by Epstein-Barr virus, occur most frequently and require a reduction in immunosuppression, administration of antiviral agents, and traditional chemo- and radiotherapy. Specific antilymphocyte (targeted against CD20) therapy has also shown promise. Solid cancers most often manifest as skin malignancies (both basal cell and squamous cell

carcinomas), and regular use of sunscreen is advised. Future research is required to define strategies for immune modulation, immune suppression, and malignancy prevention; however, the impact of decreasing immunosuppression in the treatment of these cancers is unclear.

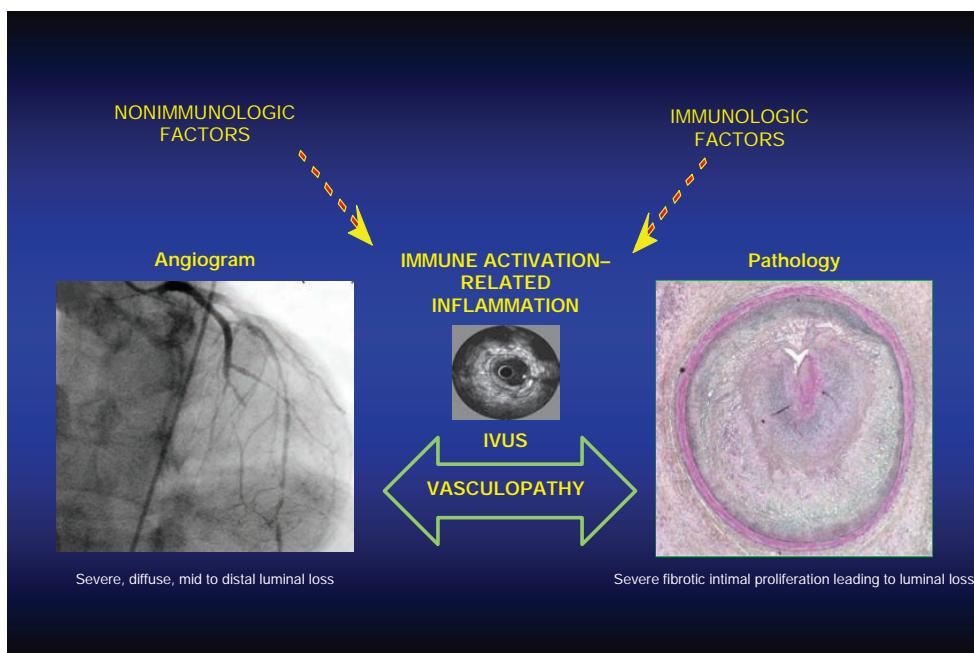
## PROLONGED ASSISTED CIRCULATION

The quest for a prolonged and durable implantable mechanical circulatory support device has led to the development of continuous flow left ventricular assist systems (LVAS). Initially designed for short-term support as a bridge to recovery or to cardiac transplantation, the most frequent use today entails permanent support for lifetime therapy ("destination therapy"). The decision to implant LVAS dichotomously as either a bridge to transplantation or for destination therapy is not always clear, and in several instances, these devices are used as a "bridge to decision" (in those with potentially reversible underlying relative contraindications such as renal insufficiency or pulmonary hypertension, who may become future candidates for transplantation).

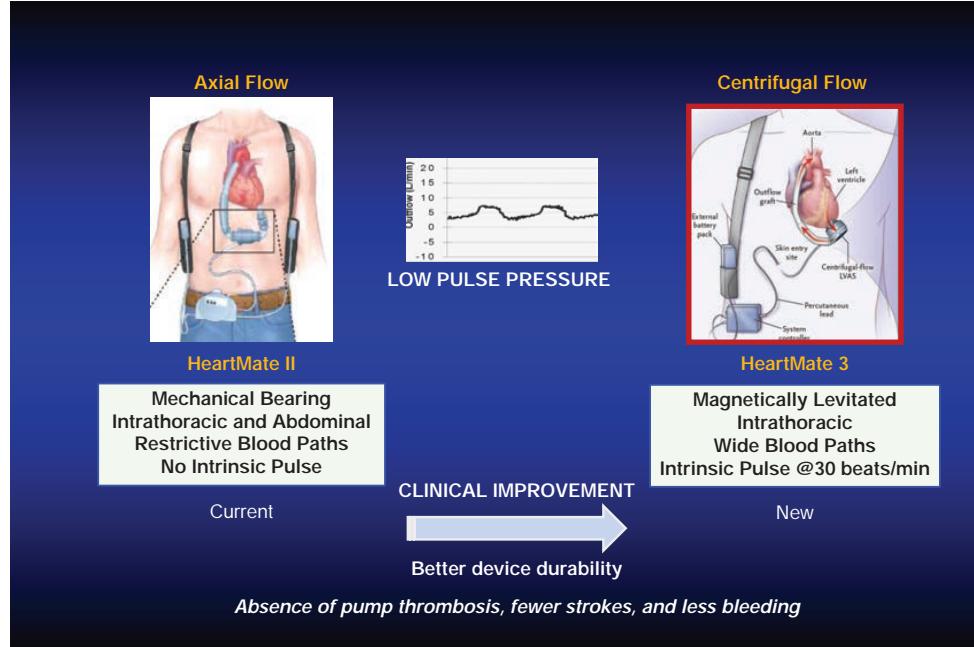
## LEFT VENTRICULAR ASSIST SYSTEMS AND CLINICAL TRIALS

A pivotal trial, REMATCH, published in 2001, was the first study to reliably demonstrate that survival of patients with transplant-ineligible, refractory, predominantly inotropic therapy-supported heart failure is improved by implantation of an LVAS. This study used an early generation pulsatile flow device and demonstrated a 48% reduction in risk of death. However, the LVAS used was of limited durability, and meaningful "out of hospital" survival was prolonged by a median of only 5 months. Furthermore, complications of strokes, multisystem organ failure, and infections reduced enthusiasm for widespread adoption. Over time, continuous flow systems that had small turbo-pumps with minimal moving parts and no valves were introduced, leading to greater durability and more generalized worldwide adoption.

A landmark trial compared the older bulky pulsatile LVAS studied in the REMATCH trial with a newer generation axial continuous flow LVAS, the HeartMate II, and demonstrated a marked improvement in short- and long-term survival, along with an improvement in functional capacity and meaningful quality-of-life enhancement. A centrifugal continuous flow LVAS, the HeartWare HVAD, was also



**FIGURE 260-1** Cardiac allograft vasculopathy is initiated and propagated by the combined influence of immunologic and nonimmunologic insults on the allograft vasculature. An inflammatory milieu determines the development of diffuse, aggressive luminal blockages that in early forms exhibit intimal thickening and fibrosis. IVUS, intravascular ultrasound (can be used to diagnose early forms of intimal thickening).



**FIGURE 260-2** Continuous flow left ventricular assist systems (LVAS) and their types and mechanisms. The mechanical bearing, axial flow HeartMate II pump is prone to thrombosis, while the frictionless, magnetically levitated, centrifugal flow HeartMate 3 does not induce hemolysis or pump thrombosis.

introduced and demonstrated noninferiority to the HeartMate II pump. A newer centrifugal device with a fully magnetically levitated system, the HeartMate 3 LVAS, is now the most commonly used pump. Unlike the HeartMate II LVAS, which requires an abdominal pump pocket, this smaller device is fully implanted in the thoracic cavity (Fig. 260-2). This LVAS has been shown to nearly eliminate the complication of pump thrombosis and markedly reduce stroke rates, as well as decrease bleeding complications. Real-world experience from registry analyses has pointed to a median survival of >50% at 4 years with currently available LVAS; however, long-term durability beyond 5–10 years remains a question. The patients for whom LVAS should ideally be employed include those with severe persistent systolic heart failure symptoms who have failed to respond to optimal medical management. Commonly, these patients have marked functional limitation indicated by a peak oxygen consumption of <12 mL/kg per min, or the patient is bound to continuous intravenous inotropic therapy owing to symptomatic hypotension or demonstrates worsening renal function or persistent refractory congestion. Currently, the role of LVAS in “less sick” patients (those with moderate symptoms) is less well supported since sufficient equipoise does not exist due to the adverse risk-benefit ratio from device-related complications and because it needs to be tethered to an external driveline that connects to a power source.

## MANAGEMENT OF LVAS AND THEIR COMPLICATIONS

Continuous flow LVAS rely on pressure gradients between the left ventricular cavity and the aorta. As such, forward flow is critically dependent on management of systemic blood pressure. Due to the low pulsatile nature of the blood flow, blood pressure is measured by using a Doppler ultrasound (which measures mean or opening blood pressure, which is less than the systolic blood pressure) since a peripheral pulse is usually not detectable. The ideal mean arterial blood pressure should be kept to ~90 mmHg and antihypertensive drug therapy prescribed using renin-angiotensin-aldosterone system drugs or other vasodilators. The blood flow path through current devices results in increased shear stress which may manifest in the form of low-grade hemolysis and the development of an acquired von Willebrand disease due to loss of high-molecular-weight multimers of von Willebrand Factor. This hematologic aberration has been associated with a risk of gastrointestinal

bleeding, particularly resulting from arteriovenous malformations in the intestines. Therefore, a common complication encountered in patients is that of an anemia, often due to iron deficiency.

The unsupported right ventricle often demonstrates worsening function and results in congestion requiring diuretic therapy. While unloading of the left ventricle decreases right-sided afterload, increased device flow results in a greater right heart preload, and effects of the LVAS on the septum reduce right ventricular contractile efficiency, leading to development of right ventricular dilatation and maladaptation between the right ventricle and pulmonary circuit. Cardiac arrhythmias are common in patients supported with LVAS and often require antiarrhythmic therapy since such events can trigger low flow through the device.

Hemocompatibility-related adverse outcomes include neurologic events (ischemic and hemorrhagic strokes), device-related thrombosis leading to pump malfunction, and nonsurgical bleeding complications (Fig. 260-3). Antiplatelet therapy using aspirin in doses of 81–325 mg daily along with warfarin targeted to an international normalized ratio of 2–3 is used with current LVAS to avoid the morbidity of hemocompatibility-related adverse events. On one hand, this therapy protects against thrombotic complications, whereas on the other hand, it predisposes the patient to bleeding complications. Strokes occur with a frequency ranging from 10% with the HeartMate 3 LVAS to as high as 29% with the HeartWare HVAD device by 2 years of treatment. Optimal control of blood pressure is associated with improved rates of strokes with some devices such as the HeartWare HVAD pump; however, this complication is an important reason for lack of adoption of device therapy in the less sick population. Another cause of morbidity is pump thrombosis requiring reoperation for device malfunction. This complication with the older devices was noted in 6–12% of LVAS implants, occurs early (in the first 6 months), and is more commonly encountered with the HeartMate II device than with the HeartWare HVAD pump. The subclinical phase of LVAS thrombosis is characterized by increasing hemolysis and elevation in the device power. Progressively, inability to “unload” the left ventricle is manifest leading to decompensated heart failure and possibly hemodynamic compromise. Lactate dehydrogenase is an excellent (although nonspecific) biomarker of hemolysis and hence impending or established pump thrombosis. Patients who have suspected left ventricular assist device



**FIGURE 260-3** Hemocompatibility-related adverse events with left ventricular assist systems (LVAS) are often interrelated and typically result in cerebrovascular, gastrointestinal, or pump malfunction events. AV, atrioventricular; TIA, transient ischemic attack.

(LVAD) thrombosis and do not undergo LVAD exchange or cardiac transplantation have a 6-month mortality rate of 48%, inferring that medical therapy for ventricular assist device thrombosis may be inadequate (or cause harm in the case of thrombolytic use). Reoperation (pump exchange) carries a modest 6.5% perioperative mortality risk and a 65% 2-year survival following exchange.

Infection is common, most often involving the driveline (the conduit connecting the device to the external controller and batteries) and occurs in 1 in 5 patients following LVAS implant. Such an infection is treated with local internal exploration and requires long-term suppressive antibiotics unless the patient undergoes cardiac transplantation or the device is exchanged. Infection and its inflammatory sequelae predispose to thrombosis and heighten the risk of neurologic complications, leading to a worsening milieu in hemocompatibility.

### NOVEL DEVICES

The HeartMate 3 is a centrifugal, continuous flow pump that is placed in the thorax and is engineered to be a more hemocompatible LVAS. This device is constructed with a fully magnetically levitated motor, offers wider blood flow paths, and exhibits a fixed intrinsic pulse (by the motor ramping its speed up and down at 2-s intervals). These features have been shown to reduce rates of hemolysis and decrease the shearing of high-molecular-weight multimers of von Willebrand factor. This pump has been tested in the MOMENTUM 3 trial, which reported its final results in 1028 patients randomly allocated to either the HeartMate 3 pump or the HeartMate II LVAS. The fully magnetically levitated HeartMate 3 pump was associated with less frequent need for pump replacement than the HeartMate II device and was superior with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device. The need for pump replacement and occurrence of stroke of any severity, major bleeding, or gastrointestinal hemorrhage were lower in the centrifugal-flow pump group than in the axial-flow pump group. Experience beyond 5 years with this LVAS will be important in discerning whether these findings result in improved long-term survival.

### TOTAL ARTIFICIAL HEART

Not all patients are candidates for an LVAS, particularly those with severe right-sided heart failure or conditions that do not allow placement of an LVAS (restrictive cardiomyopathy, massive anterior myocardial infarction, complex congenital heart disease). In such patients, either a biventricular assist device approach or a total artificial heart pump can be considered. The SynCardia total artificial heart is a

pulsatile, implantable pump that consists of two polyurethane ventricles with pneumatically driven diaphragms and four tilting disc valves. This requires excision of the native ventricles and thus cannot be employed as a myocardial recovery strategy. There are specific clinical issues that are unique to the total artificial heart management. This device operates on a steep physiologic curve and has little adaptability to tolerate either systemic blood pressure changes or large shifts in blood volume. As the ventricles are excised, most patients exhibit a sharp decline in renal function due to the loss of natriuretic peptide expression by the myocardium. Severe hemolysis is common due to the presence of four mechanical valves, and aberrant erythropoiesis is noted, leading to a severe anemia. Newer artificial hearts using biocompatible surfaces are under development, as well as those that use continuous flow technology.

### GLOBAL CONSIDERATIONS

While LVAS are available worldwide, their use and indications vary from country to country. In the United States, payers used to require discrete discrimination of indication into either a bridge to transplant or destination therapy, whereas in most European countries, this artificial segregation was not used. Cost-effectiveness studies suggest improvement with the newer devices, yet some countries only allow use of this technology as a bridge to transplantation (United Kingdom) while awaiting more definitive long-term studies for lifetime use. The use of LVAS in moderately symptomatic ambulatory patients with chronic systolic heart failure is still discouraged throughout the world, awaiting the availability of hemocompatible devices that can be fully internalized without the need for an external driveline. Globally, the rates of myocardial recovery allowing for decommissioning or removal of devices remain low.

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## 261 Aortic Stenosis

Patrick T. O'Gara, Joseph Loscalzo

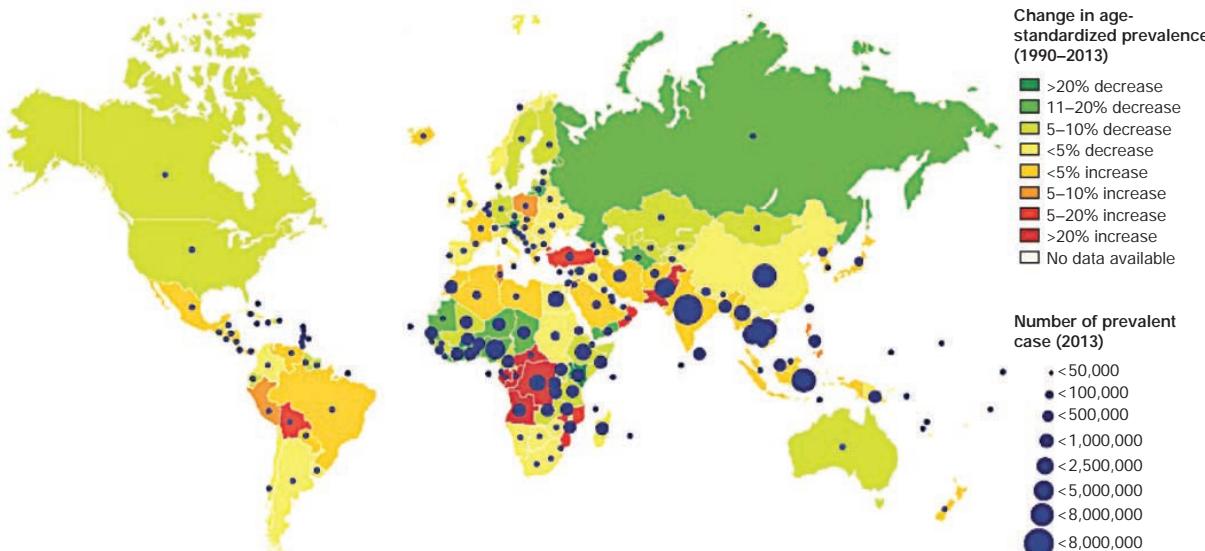
### GLOBAL BURDEN OF VALVULAR HEART DISEASE

Primary valvular heart disease ranks well below coronary heart disease, stroke, hypertension, obesity, and diabetes as a major threat to the public health. Nevertheless, it can cause significant morbidity and lead to premature death. Rheumatic fever (Chap. 359) is the dominant cause of valvular heart disease in low- and middle-income countries. Its prevalence has been estimated to range from as low as 1 per 100,000 school-age children in Costa Rica to as high as 150 per 100,000 in China (Fig. 261-1). Rheumatic heart disease accounts for 12–65% of hospital admissions related to cardiovascular disease and 2–10% of hospital discharges in some endemic countries. Prevalence and mortality rates vary among communities even within the same country as a function of overcrowding and the availability of medical resources and population-wide programs for detection and treatment of group A streptococcal pharyngitis. In economically deprived areas, tropical and subtropical climates (particularly on the Indian subcontinent and in

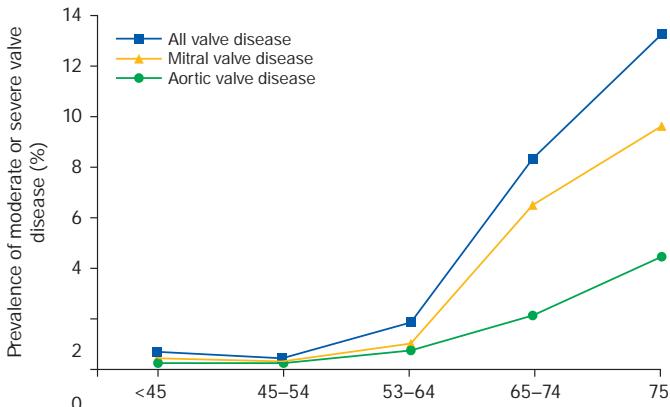
Southeast Asia), Central America, and the Middle East, rheumatic valvular disease progresses more rapidly than in more developed nations and frequently causes serious symptoms in patients aged <20 years. This accelerated natural history may be due to repeated infections with more virulent strains of rheumatogenic streptococci. Approximately 30–35 million people live with rheumatic heart disease worldwide, an estimated prevalence characterized by 300,000 new cases and 233,000 case fatalities per year, with the highest prevalence and age-adjusted mortality rates in sub-Saharan Africa, South Asia, and Oceania. The major drivers of untreated streptococcal pharyngitis in these endemic areas include reduced access to high-quality health care and social determinants of health. In the United States, rheumatic heart disease accounted for 3320 deaths in 2017. Although globally the age standardized mortality rate from rheumatic heart disease declined by nearly 50% between 1990 and 2015, the prevalence of heart failure attributable to rheumatic heart disease increased by nearly 90% over the same time interval.

Although there have been recent reports of isolated outbreaks of streptococcal infection in North America, valve disease in high-income countries is dominated by degenerative or inflammatory processes that lead to valve thickening, fibrosis, calcification, and dysfunction. The prevalence of valvular heart disease increases significantly with age. The prevalence of undiagnosed moderate or severe valvular heart disease is ~6% in individuals aged >65 years. Significant left-sided valve disease may affect as many as 12–13% of adults aged >75 years (Fig. 261-2). Severe aortic stenosis (AS) is estimated to affect 3.5% of the population aged >75 years. A Swedish epidemiologic study estimated the incidence of newly diagnosed valvular heart disease at 64 per 100,000 person-years. AS and mitral regurgitation contributed approximately one-half and one-quarter, respectively, of the valvular heart disease diagnoses in this study.

The incidence of infective endocarditis (Chap. 128) has increased with the aging of the population, the more widespread prevalence of vascular grafts and intracardiac devices, the emergence of more virulent multidrug-resistant microorganisms, the growing epidemic of diabetes mellitus, and the opioid crisis. The more restricted use of antibiotic prophylaxis since 2007 has not been convincingly associated with an increase in incidence rates for infective endocarditis cases attributable to oropharyngeal pathogens. Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation. Valve surgery during the acute phase of infective endocarditis is performed in ~50% of hospitalized patients. Duration of intravenous antibiotic use may be shortened in selective cases.



**FIGURE 261-1** The global burden of rheumatic heart disease. This world map provides a snapshot of both the change in prevalence of rheumatic heart disease cases between 1990 and 2013 (upper right legend) and the estimated number of rheumatic heart disease cases per country (lower right legend). Regions in which the disease is highly prevalent include sub-Saharan Africa, India, China, and Southeast Asia. (Reproduced with permission from JR Carapetis et al: Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers* 2:15084, 2016.)



**FIGURE 261-2** The burden of moderate or severe mitral and aortic valve disease in the United States. Prevalence estimates are derived from three population-based studies comprising a total of 11,911 individuals: The Coronary Artery Risk Development in Young Adults (CARDIA), the Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study (CHS). (Reproduced with permission from VT Nkomo et al: Burden of valvular heart diseases: A population-based study. *Lancet* 368:1005, 2006.)

Bicuspid aortic valve (BAV) disease affects as many as 0.5–1.4% of the general population and is accompanied by an associated aortopathy in ~30–40% of individuals, a disease process expressed as root or ascending aortic aneurysm formation or descending thoracic aortic coarctation. An increasing number of childhood survivors of congenital heart disease present later in life with valvular dysfunction. The global burden of valvular heart disease will continue to progress.

As is true for many other chronic health conditions, disparities in access to and quality of care for patients with valvular heart disease have been well documented, especially for those patients with rheumatic heart disease in low- and middle-income countries. In the Society for Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) registry, blacks comprise <5% of patients in the United States who have received a transcatheter valve for AS. Management decisions and outcome differences based on age, sex, race, and geography require intensification of educational efforts and prioritization of resources.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in Chaps. 42 and 239; of electrocardiography (ECG) in Chap. 240; of echocardiography and other noninvasive imaging techniques in Chap. 241; and of cardiac catheterization and angiography in Chap. 242.

## AORTIC STENOSIS

Aortic stenosis (AS) is the most common valve lesion among adult patients with chronic valvular heart disease; the majority of adult patients with symptomatic, valvular AS are male.

### Etiology and Pathogenesis

(**Table 261-1**) AS in adults is due to degenerative calcification of the aortic cusps and occurs most commonly on a substrate of congenital disease (BAV), chronic (trileaflet) deterioration, or previous rheumatic inflammation. A pathologic study of specimens removed at the time of aortic valve replacement (AVR) for AS in adults showed that 53% were bicuspid and 4% were unicuspido. The process of aortic valve deterioration and calcification is not a passive one, but rather one that shares many features with vascular atherosclerosis, including endothelial dysfunction, lipid accumulation, inflammatory cell activation,

cytokine release, and upregulation of several signaling pathways (**Fig. 261-3**). Eventually, a fibrocalcific response is established wherein collagen is deposited and valvular myofibroblasts differentiate phenotypically into osteoblasts and actively produce bone matrix proteins that allow for the deposition of calcium hydroxyapatite crystals. Genetic polymorphisms involving the vitamin D receptor, the estrogen receptor in postmenopausal women, interleukin 10, and apolipoprotein E4 have been linked to the development of calcific AS, and a strong familial clustering of cases with trileaflet valves has been reported from western France. Several traditional atherosclerotic risk factors have also been associated with the development and progression of calcific AS, including hypertension, low-density lipoprotein (LDL) cholesterol, lipoprotein a (Lp[a]), diabetes mellitus, smoking, chronic kidney disease, and the metabolic syndrome. In a Canadian observational cohort study, the incidence of severe AS was 144 per 100,000 person-years. Hypertension, diabetes mellitus, and dyslipidemia accounted for approximately one-third of the population-attributable risk for severe AS. The presence of aortic valve sclerosis (focal thickening and calcification of the leaflets not severe enough to cause obstruction) is associated with an excess risk of cardiovascular death and myocardial infarction (MI) among persons aged >65. Approximately 30% of persons aged >65 years exhibit some degree of aortic valve sclerosis. Rate and extent of progression to valve obstruction (stenosis) vary among individual patients.

Rheumatic disease of the aortic leaflets produces commissural fusion, sometimes resulting in a bicuspid-appearing valve. This condition, in turn, makes the leaflets more susceptible to trauma and ultimately leads to fibrosis, calcification, and further narrowing. By the time obstruction to left ventricular (LV) outflow causes serious clinical disability, the valve is usually a rigid calcified mass, and careful examination may make it difficult or even impossible to determine the etiology of the underlying process. Rheumatic AS is almost always associated with involvement of the mitral valve and with aortic regurgitation (AR). Mediastinal radiation can also result in late scarring, fibrosis, and calcification of the aortic leaflets.

### BICUSPID AORTIC VALVE DISEASE

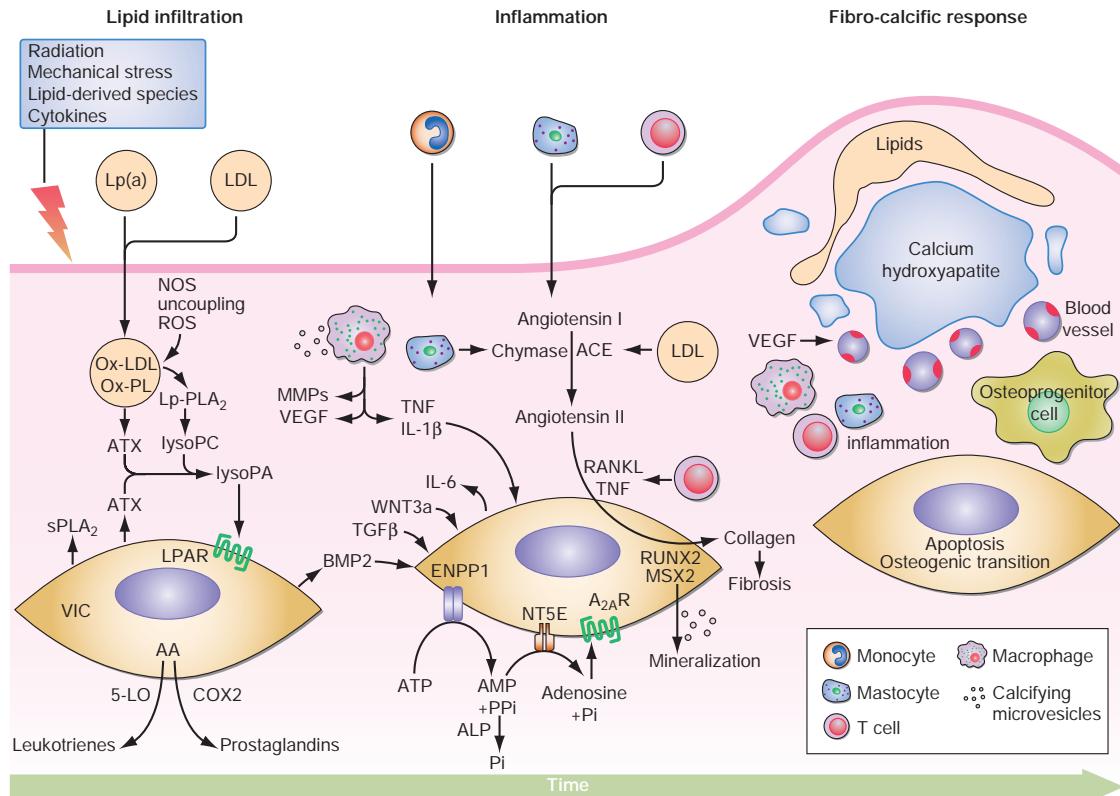
A bicuspid aortic valve (BAV) is the most common congenital heart valve defect and occurs in 0.5–1.4% of the population with a 2–4:1 male-to-female predominance. The inheritance pattern appears to be autosomal dominant with incomplete penetrance, although some have questioned an X-linked component as suggested by the prevalence of BAV disease among patients with Turner's syndrome. The prevalence of BAV disease among first-degree relatives of an affected individual is ~10%. A single gene defect to explain the majority of cases has not been identified, although mutations in the *NOTCH1*, *GATA5*, and *GATA4* genes have been described in some families. Abnormalities in endothelial nitric oxide synthase and *NKX2.5* have been implicated as well. Medial degeneration with ascending aortic aneurysm formation occurs commonly among patients with BAV disease; aortic coarctation is less frequently encountered. Patients with BAV disease have larger aortas than patients with comparable tricuspid aortic valve disease. The aortopathy develops independently of the hemodynamic severity of the valve lesion, but directional shear forces dictated by the anatomic configuration of the valve appear to influence its expression. For example, enlargement of the ascending aorta along its greater curvature is most often associated with right-left cusp fusion, the most common bicuspid variant. Patients with BAV disease are at risk for aneurysm formation and/or dissection. A BAV can be a component of more complex congenital heart disease with or without other left heart obstructing lesions, as seen in Shone's complex.

### OTHER FORMS OF OBSTRUCTION TO LEFT VENTRICULAR OUTFLOW

In addition to valvular AS, three other lesions may be responsible for obstruction to LV outflow: *hypertrophic obstructive cardiomyopathy* (Chap. 259), *discrete fibromuscular/membranous subaortic stenosis*,

**TABLE 261-1** Major Causes of Aortic Stenosis

VALVE LESION	ETIOLOGIES
Aortic stenosis	Congenital (bicuspid, unicuspido) Degenerative calcific disease Rheumatic fever Radiation



**FIGURE 261-3 Pathogenesis of calcific aortic stenosis.** Lipid and inflammatory cell infiltration occurs across damaged endothelium. A cascade of events follows that leads eventually to formation of disorganized collagen (fibrosis) and calcium hydroxyapatite (bone) deposition. Valvular interstitial cells (VIC) are critical participants in this active process. AA, arachidonic acid; ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase; ApoB, apolipoprotein B; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ATX, autotaxin; A<sub>2</sub>AR, adenosine A<sub>2</sub>A receptor; BMP, bone morphogenetic protein; COX2, cyclo-oxygenase 2; ENPP, ectonucleotide pyrophosphatase/phosphodiesterase; IL, interleukin; 5-LO, 5-lipoxygenase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPAR, lysophosphatidic acid receptor; Lp-PLA<sub>2</sub>, lipoprotein-associated phospholipase A2; lysoPA, lysophosphatidic acid; lysoPC, lysophosphatidylcholine; MMP, matrix metalloproteinase; NOS, nitric oxide synthase; Ox-PL, oxidized phospholipid; Ox-LDL, oxidized LDL; RANKL, receptor activator of nuclear factor- $\kappa$ B ligand; ROS, reactive oxygen species; RUNX2, runt-related transcription factor 2; sPLA<sub>2</sub>, secreted PLA<sub>2</sub>; TGF $\beta$ , transforming growth factor- $\beta$ ; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VIC, valvular interstitial cell. (Reproduced with permission from B Lindman et al: Calcific aortic stenosis. *Nat Rev Dis Primers* 2:16006, 2016.)

and *supravalvular AS* (Chap. 269). The causes of LV outflow obstruction can be differentiated on the basis of the cardiac examination and Doppler echocardiographic findings.

### PATHOPHYSIOLOGY

The obstruction to LV outflow produces a systolic pressure gradient between the LV and aorta. When severe obstruction is suddenly produced experimentally, the LV responds by dilation and reduction of stroke volume. However, in some patients, the obstruction may be present at birth and/or increase gradually over the course of many years, and LV contractile performance is maintained by the presence of concentric LV hypertrophy. Initially, this serves as an adaptive mechanism because it reduces toward normal the systolic stress developed by the myocardium, as predicted by the Laplace relation ( $S = Pr/h$ , where  $S$  = systolic wall stress,  $P$  = pressure,  $r$  = radius, and  $h$  = wall thickness). A large transaortic valve pressure gradient may exist for many years without a reduction in cardiac output (CO) or the development of LV dilation. Ultimately, however, excessive hypertrophy becomes maladaptive, LV systolic function declines because of afterload mismatch, abnormalities of diastolic function progress, and irreversible myocardial fibrosis develops.

A mean systolic pressure gradient  $>40$  mmHg with a normal CO or an effective aortic orifice area of  $\sim 1$  cm<sup>2</sup> (or  $\sim 0.6$  cm<sup>2</sup>/m<sup>2</sup> body surface area in a normal-sized adult)—i.e., less than approximately one-third of the normal orifice area—is generally considered to represent severe obstruction to LV outflow. The elevated LV end-diastolic pressure observed in many patients with severe AS and preserved ejection fraction (EF) signifies the presence of diminished compliance of the hypertrophied LV. Although the CO at rest is within normal limits

in most patients with severe AS, it usually fails to rise normally during exercise. Loss of an appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation (AF) or atrioventricular dissociation, may cause rapid progression of symptoms. Late in the course, contractile function deteriorates because of afterload excess, the CO and LV-aortic pressure gradient decline, and the mean left atrial (LA), pulmonary artery (PA), and right ventricular (RV) pressures rise. LV performance can be further compromised by superimposed epicardial coronary artery disease (CAD). Stroke volume (and thus CO) can also be reduced in patients with significant hypertrophy and a small LV cavity despite a normal EF. Low-flow (defined as a stroke volume index  $<35$  mL/m<sup>2</sup>), low-gradient (defined as a mean pressure gradient  $<40$  mmHg) AS (with either reduced or normal LV systolic function) is both a diagnostic and therapeutic challenge.

The hypertrophied LV causes an increase in myocardial oxygen requirements. In addition, even in the absence of obstructive CAD, coronary blood flow is impaired to the extent that ischemia can be precipitated under conditions of excess demand. Capillary density is reduced relative to wall thickness, compressive forces are increased, and the elevated LV end-diastolic pressure reduces the coronary driving pressure. The subendocardium is especially vulnerable to ischemia by this mechanism.

### SYMPTOMS

AS is rarely of clinical importance until the valve orifice has narrowed to  $\sim 1$  cm<sup>2</sup>. Even severe AS may exist for many years without producing any symptoms because of the ability of the hypertrophied LV to generate the elevated intraventricular pressures required to maintain a

normal stroke volume. Once symptoms occur, or the LV ejection fraction falls below normal, valve replacement is indicated.

Most patients with pure or predominant AS have gradually increasing obstruction over years but do not become symptomatic until the sixth to eighth decades. Adult patients with BAV disease, however, develop significant valve dysfunction and symptoms one to two decades sooner. Exertional dyspnea, angina pectoris, and syncope are the three cardinal symptoms. Often, there is a history of insidious progression of fatigue and dyspnea associated with gradual curtailment of activities and reduced effort tolerance. *Dyspnea* results primarily from elevation of the pulmonary capillary pressure caused by elevations of LV diastolic pressures secondary to impaired relaxation and reduced LV compliance. *Angina pectoris* usually develops somewhat later and reflects an imbalance between the increased myocardial oxygen requirements and reduced oxygen availability. CAD may or may not be present, although its coexistence is common among AS patients age >65. *Exertional syncope* may result from a decline in arterial pressure caused by vasodilation in exercising muscles and inadequate vasoconstriction in nonexercising muscles in the face of a fixed CO, or from a sudden fall in CO produced by an arrhythmia.

Because the CO at rest is usually well maintained until late in the course, marked fatigability, weakness, peripheral cyanosis, cachexia, and other clinical manifestations of a low CO are usually not prominent until this stage is reached. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, i.e., symptoms of LV failure, also occur only in the advanced stages of the disease. Severe pulmonary hypertension leading to RV failure and systemic venous hypertension, hepatomegaly, AF, and tricuspid regurgitation (TR) are usually late findings in patients with isolated severe AS.

When AS and mitral stenosis (MS) coexist, the reduction in flow (CO) caused by MS lowers the pressure gradient across the aortic valve and, thereby, masks many of the clinical findings produced by AS. The transaortic pressure gradient can be increased in patients with concomitant AR due to higher aortic valve flow rates.

## PHYSICAL FINDINGS

The heart rhythm is generally regular until late in the course; at other times, AF should suggest the possibility of associated mitral valve disease. Hypertension occurs commonly among older adults with AS. In the late stages, however, when stroke volume declines, the systolic pressure may fall and the pulse pressure narrow. The carotid arterial pulse rises slowly to a delayed peak (*pulsus parvus et tardus*). A thrill or anacrotic "shudder" may be palpable over the carotid arteries, more commonly the left. In the elderly, the stiffening of the arterial wall may mask this important physical sign. In many patients, the *a* wave in the jugular venous pulse is accentuated. This results from the diminished distensibility of the RV cavity caused by the bulging, hypertrophied interventricular septum.

The LV impulse is sometimes displaced laterally in the later stages of the disease. A double apical impulse (with a palpable *S<sub>1</sub>*) may be appreciated, particularly with the patient in the left lateral recumbent position. A systolic thrill may be present at the base of the heart to the right of the sternum when leaning forward or in the suprasternal notch.

**Auscultation** An early systolic ejection sound is frequently audible in children, adolescents, and young adults with congenital BAV disease. This sound usually disappears when the valve becomes calcified and rigid. As AS increases in severity, LV systole may become prolonged so that the aortic valve closure sound no longer precedes the pulmonic valve closure sound, and the two components may become synchronous, or aortic valve closure may even follow pulmonic valve closure, causing paradoxical splitting of *S<sub>1</sub>* (Chap. 239). The sound of aortic valve closure can be heard most frequently in patients with AS who have pliable valves, and calcification diminishes the intensity of this sound. Frequently, an *S<sub>4</sub>* is audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure; an *S<sub>3</sub>* generally occurs late in the course, when the LV dilates and its systolic function becomes severely compromised.

The murmur of AS is described as an ejection (mid) systolic murmur that commences shortly after the *S<sub>1</sub>*, increases in intensity to reach a peak toward the middle of ejection, and ends just before aortic valve closure. It is

characteristically low-pitched, rough, and rasping in character, and loudest at the base of the heart, most commonly in the second right intercostal space. It is transmitted upward along the carotid arteries. Occasionally it is transmitted downward and to the apex, where it may be confused with the systolic murmur of mitral regurgitation (MR) (Gallavardin effect). In almost all patients with severe obstruction and preserved CO, the murmur is at least grade III/VI. In patients with mild degrees of obstruction or in those with severe stenosis with heart failure and low CO in whom the stroke volume and, therefore, the transvalvular flow rate are reduced, the murmur may be relatively soft and brief.

## LABORATORY EXAMINATION

**ECG** In most patients with severe AS, there is LV hypertrophy. In advanced cases, ST-segment depression and T-wave inversion (LV "strain") in standard leads I and aVL and in the left precordial leads are evident. However, there is no close correlation between the ECG and the hemodynamic severity of obstruction, and the absence of ECG signs of LV hypertrophy does not exclude severe obstruction. Systemic hypertension can coexist and also contribute to the development of hypertrophy.

**Echocardiogram** The key findings on transthoracic echocardiogram are thickening, calcification, and reduced systolic opening of the valve leaflets and LV hypertrophy. Eccentric closure of the aortic valve cusps is characteristic of congenitally bicuspid valves. Transesophageal echocardiography imaging can display the obstructed orifice extremely well, but it is not routinely required for accurate characterization of AS. The valve gradient and aortic valve area can be estimated by Doppler measurement of the transaortic velocity. Severe AS is defined by a valve area <1 cm<sup>2</sup>, whereas moderate AS is defined by a valve area of 1–1.5 cm<sup>2</sup> and mild AS by a valve area of 1.5–2 cm<sup>2</sup>. Aortic valve sclerosis, conversely, is accompanied by a jet velocity of <2.5 m/s (peak gradient <25 mmHg). LV dilation and reduced systolic shortening reflect impairment of LV function. There is a robust experience with the use of longitudinal strain to characterize earlier changes in LV systolic function, before a decline in EF can be appreciated. Doppler indices of impaired diastolic function are frequently seen.

Echocardiography is useful for identifying coexisting valvular abnormalities, differentiating valvular AS from other forms of LV outflow obstruction, and measuring the aortic root and proximal ascending aortic dimensions. These aortic measurements are particularly important for patients with BAV disease. Dobutamine stress echocardiography is useful for the evaluation of patients with AS and severe LV systolic dysfunction (low-flow, low-gradient, severe AS with reduced EF), in whom the severity of the AS can often be difficult to judge. Patients with severe AS (i.e., valve area <1 cm<sup>2</sup>) with a relatively low mean gradient (<40 mmHg) despite a normal EF (low-flow, low-gradient, severe AS with normal EF) are often hypertensive, and efforts to control their systemic blood pressure should be optimized before Doppler echocardiography is repeated. The use of dobutamine stress echocardiography in this setting is generally not advised. When there is continued uncertainty regarding the severity of AS in patients with reduced CO, quantitative analysis of the amount of aortic valve calcium with chest computed tomography (CT) can be helpful. There is increasing use of chest CT angiography to assess aortic valve morphology and function. It has become the imaging method of choice to plan for transcatheter aortic valve implantation (TAVI). Finally, the use of cardiac magnetic resonance (CMR) imaging to screen for the presence of myocardial fibrosis with late gadolinium enhancement in patients with severe AS is an area of active investigation.

**Chest X-Ray** The chest x-ray may show no or little overall cardiac enlargement for many years. Hypertrophy without dilation may produce some rounding of the cardiac apex in the frontal projection and slight backward displacement in the lateral view. A dilated proximal ascending aorta may be seen along the upper right heart border in the frontal view. Aortic valve calcification may be discernible in the lateral view, but it is usually readily apparent on fluoroscopic examination or by echocardiography; the absence of valvular calcification on fluoroscopy in an adult suggests that severe valvular AS is *not* present. In later stages of the disease, as the LV dilates, there is increasing

**Catheterization** Right- and left-sided heart catheterization for invasive assessment of AS is performed infrequently but can be useful when there is a discrepancy between the clinical and noninvasive findings. Concern has been raised that attempts to cross the aortic valve for measurement of LV pressures are associated with a risk of cerebral embolization. Catheterization can also be useful in three distinct categories of patients: (1) *patients with multivalvular disease*, in whom the role played by each valvular deformity should be defined to aid in the planning of operative treatment; (2) *young, asymptomatic patients with noncalcific congenital AS*, to define the severity of obstruction to LV outflow, because operation or percutaneous aortic balloon valvuloplasty (PABV) may be indicated in these patients if severe AS is present, even in the absence of symptoms; and (3) *patients in whom it is suspected that the obstruction to LV outflow may not be at the level of the aortic valve* but rather at the sub- or supravalvular level.

Coronary angiography is indicated to screen for CAD in appropriate patients with severe AS who are being considered for surgical or transcatheter valve intervention. Angiography can be performed invasively at the time of catheterization for hemodynamic assessment or with noninvasive CT techniques. Decision-making regarding the need for coronary artery revascularization at the time of aortic valve intervention is individualized.

### NATURAL HISTORY

Death in patients with severe AS occurs most commonly in the seventh and eighth decades. Based on data obtained at postmortem examination in patients before surgical treatment became widely available, the average time to death after the onset of various symptoms was as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; heart failure, 1.5–2 years. Moreover, in >80% of patients who died with AS, symptoms had existed for <4 years. Among adults dying with valvular AS, sudden death, which presumably resulted from an arrhythmia, occurred in 10–20%; however, most sudden deaths occurred in patients who had previously been symptomatic. Sudden death as the first manifestation of severe AS is very uncommon (~1% per year) in asymptomatic adult patients. Calcific AS is a progressive disease, with an annual reduction in valve area averaging  $0.1 \text{ cm}^2$  and annual increases in peak jet velocity and mean valve gradient averaging  $0.3 \text{ m/s}$  and  $7 \text{ mmHg}$ , respectively.

## TREATMENT

### Aortic Stenosis (Fig. 261-4)

#### MEDICAL TREATMENT

In patients with severe AS (valve area  $<1 \text{ cm}^2$ ), strenuous physical activity and competitive sports should be avoided, even in the asymptomatic stage. Care must be taken to avoid dehydration and hypovolemia to protect against a significant reduction in CO. Medications used for the treatment of hypertension or CAD, including beta blockers and angiotensin-converting enzyme (ACE) inhibitors, are generally safe for asymptomatic patients with preserved LV systolic function. Nitroglycerin is helpful in relieving angina pectoris in patients with CAD. Neither HMG-CoA reductase inhibitors ("statins") nor inhibitors of the renin-angiotensin-aldosterone system slow the rate of progression of AS. The use of statin medications should be driven by considerations regarding primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events. The need for endocarditis prophylaxis is restricted to AS patients with a prior history of endocarditis.

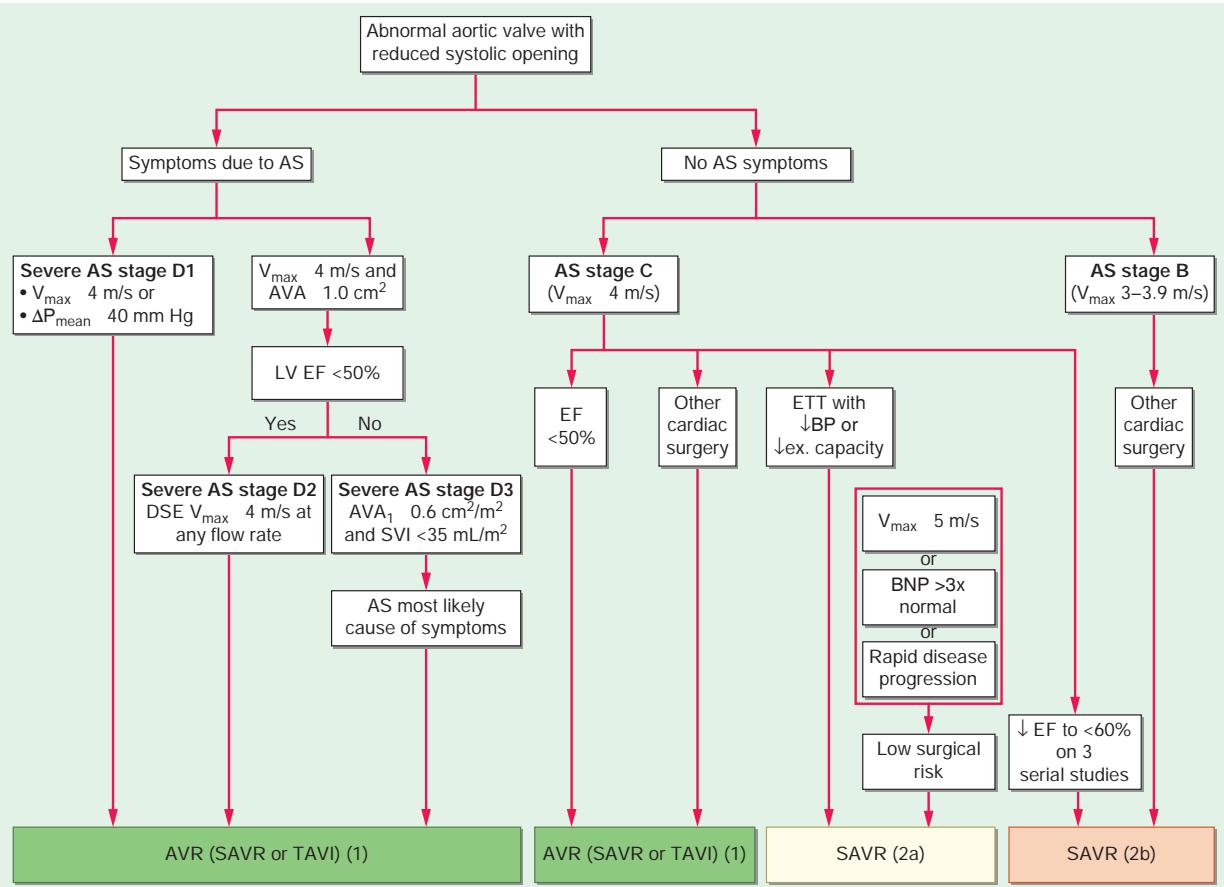
#### SURGICAL TREATMENT

Asymptomatic patients with calcific AS and severe obstruction should be followed carefully for the development of symptoms and by serial echocardiograms for evidence of deteriorating LV function. Operation is indicated in patients with severe AS (valve area  $<1 \text{ cm}^2$  or  $0.6 \text{ cm}^2/\text{m}^2$  body surface area) who are symptomatic, those who exhibit LV systolic dysfunction (EF  $<50\%$ ), and those

with AS due to BAV disease and an aneurysmal root or ascending aorta (maximal dimension  $>5.5 \text{ cm}$ ). Operation for aneurysm disease is recommended at smaller aortic diameters (4.5–5.0 cm) for patients with a family history of an aortic catastrophe and for patients who exhibit rapid aneurysm growth ( $>0.5 \text{ cm/year}$ ). Patients with asymptomatic moderate or severe AS who are referred for coronary artery bypass grafting surgery should also have AVR. In patients without heart failure, the operative risk of surgical AVR (SAVR) (including patients with AS or AR) is ~2% (Table 261-2) but increases as a function of age and the need for concomitant aortic or other heart valve surgery or coronary bypass grafting. The indications for SAVR in the asymptomatic patient have been the subject of intense debate, as surgical outcomes in selected patients have continued to improve. Relative indications for which surgery can be considered include an abnormal response to treadmill exercise; rapid progression of AS, especially when urgent access to medical care might be compromised; very severe AS, defined by an aortic valve jet velocity  $>5 \text{ m/s}$  or mean gradient  $>60 \text{ mmHg}$  and low operative risk; and excessive LV hypertrophy in the absence of systemic hypertension. Exercise testing can be safely performed in asymptomatic patients, as many as one-third of whom will show signs of functional impairment. In a small randomized controlled trial (RCT) of early surgery versus conservative care for asymptomatic patients with very severe AS (defined by a transaortic valve jet velocity  $4.5 \text{ m/s}$ , mean gradient  $50 \text{ mmHg}$ , or aortic valve area  $0.75 \text{ cm}^2$ ), the rate of operative death or death from cardiovascular causes during follow-up was reduced with early surgery. In the conservative care group, the cumulative incidence of sudden death was 4% at 4 years and 14% at 8 years.

Operation should be carried out promptly (1–3 months) after symptom onset. Clinical decision-making is straightforward for patients with normal flow ( $>35 \text{ mL/m}^2$ ), high gradient ( $>40 \text{ mmHg}$ ) severe AS. In patients with low-flow, low-gradient severe AS with reduced LVEF, perioperative mortality rates are high (15–20%), and evidence of LV dysfunction usually persists even after a technically successful operation. Long-term postoperative survival correlates with preoperative LV function. Nonetheless, in view of the even worse prognosis of such patients when they are treated medically, there is usually little choice but to advise valve replacement, especially in patients in whom flow reserve can be demonstrated by dobutamine stress echocardiography (defined by a 20% increase in stroke volume after dobutamine challenge). Patients in this high surgical risk group are usually treated with TAVI (see below), but robust data from RCTs in this subpopulation of severe AS patients are lacking. The management of patients with low-flow, low-gradient severe AS with normal LVEF is also challenging. Outcomes are improved with surgery or TAVI compared with conservative medical care for symptomatic patients with this type of "paradoxical" low-flow AS, but more research is needed to guide therapeutic decision making for individual patients. In patients in whom severe AS and CAD coexist, relief of the AS and revascularization may sometimes result in striking clinical and hemodynamic improvement.

Because many patients with calcific AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function before AVR is recommended. Age alone is not a contraindication to SAVR for AS. The perioperative mortality rate depends to a substantial extent on the patient's preoperative clinical and hemodynamic state. Assessment of frailty is a critical component of preprocedural evaluation. Treatment decisions for AS patients who are not at low operative risk are made by a multidisciplinary heart team with representation from general cardiology, interventional cardiology, multimodality imaging, cardiac surgery, and other subspecialties as needed, including geriatrics. The 10-year survival rate of older adult patients with SAVR is ~60%. Recommendations regarding the type of valve prosthesis (biological or mechanical) must weigh the trade-offs between limited bioprosthetic valve durability and the risks of thromboembolism and bleeding with a mechanical valve and are heavily influenced by patient age and preferences. Bioprostheses are generally favored for patients



**FIGURE 261-4 Management strategy for patients with aortic stenosis.** Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored with clinical and echocardiographic follow-up. The class designations refer to the American Heart Association/American College of Cardiology methodology for treatment recommendations. Class I recommendations should be performed or are indicated; Class IIa recommendations are considered reasonable to perform; Class IIb recommendations may be considered. The stages refer to the stages of progression of the disease. At disease stage A, risk factors are present for the development of valve dysfunction; stage B refers to progressive, mild-moderate, asymptomatic valve disease; stage C disease is severe in nature but clinically asymptomatic; stage C1 characterizes asymptomatic patients with severe valve disease but compensated ventricular function; stage C2 refers to asymptomatic, severe disease with ventricular decompensation; stage D refers to severe, symptomatic valve disease. With aortic stenosis, stage D1 refers to symptomatic patients with severe aortic stenosis and a high valve gradient ( $>40$  mmHg mean gradient); stage D2 comprises patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and low left ventricular ejection fraction (LVEF); and stage D3 characterizes patients with symptomatic, severe, low-flow, low-gradient severe aortic stenosis and preserved left ventricular ejection fraction (paradoxical, low-flow, low-gradient severe aortic stenosis). Patients with symptomatic severe AS (left side of the diagram, jet velocity  $4\text{ m/s}$ ) should be referred for AVR (SAVR or TAVI). Asymptomatic patients with severe AS (jet velocity  $4\text{ m/s}$ ) should be referred for AVR (SAVR or TAVI) for LVEF  $<50\%$  or when other cardiac surgery is needed (e.g., aneurysm repair). There are several findings for which referral for AVR would be reasonable related to results of exercise testing, the presence of a jet velocity  $>5\text{ m/s}$  or elevated B-type natriuretic peptide (BNP), provided the patient is considered low risk for complications related to AVR. AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BP, blood pressure; DSE,dobutamine stress echocardiography; EF, ejection fraction; ETT, exercise treadmill test;  $\Delta P_{\text{mean}}$ , mean pressure gradient; SAVR, surgical AVR; TAVI, transcatheter aortic valve implantation;  $V_{\text{max}}$ , maximum velocity. (Reproduced with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 143:e72, 2021.)

age  $>65$  years. Shared decision-making with younger patients must be individualized, although increasing numbers of patients age  $<65$  now opt for a biological valve replacement. Approximately 30% of bioprosthetic valves evidence primary valve failure by 10 years,

requiring re-replacement (or valve-in-valve TAVI, see below), and an approximately equal percentage of patients with mechanical prostheses develop hemorrhagic complications as a consequence of treatment with vitamin K antagonists. In a large observational study of patients who underwent SAVR in California between 1996 and 2013, receipt of a biological versus a mechanical prosthesis in patients  $<55$  years old was associated with an excess hazard of death over 15 years of follow-up. Homograft AVR is usually reserved for patients with aortic valve endocarditis.

The Ross procedure involves replacement of the diseased aortic valve with the autologous pulmonic valve and implantation of a homograft in the native pulmonic position. It is a technically complex procedure that may be considered in young or middle-aged adult patients when surgical and institutional expertise are available. Late postoperative complications include aortic root dilation, AR, and pulmonary homograft stenosis.

**TABLE 261-2 Mortality Rates After Aortic Valve Surgery<sup>a</sup>**

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
AVR (isolated)	25,274	1.9
AVR + CAB	15,855	3.6

<sup>a</sup>Data are for calendar year 2018 during which 1088 participant groups reported a total of 287,872 procedures.

Abbreviations: AVR, aortic valve replacement; CAB, coronary artery bypass.

Source: Adapted from ME Bowdish et al: Ann Thorac Surg 109:1646, 2020.

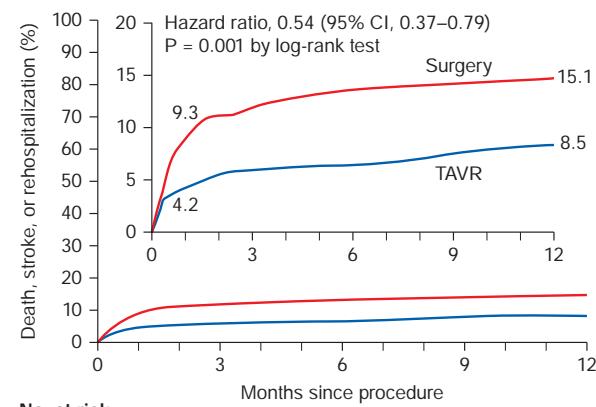
This procedure is preferable to operation in many children and young adults with congenital, noncalcific AS (**Chap. 269**). It is not recommended as definitive therapy in adults with severe calcific AS because of a very high restenosis rate (80% within 1 year) and the risk of procedural complications, but on occasion, it has been used successfully as a bridge to operation or TAVI in patients with severe LV dysfunction and shock. It is performed routinely as part of the TAVI procedure (see below).

#### TRANSCATHETER AORTIC VALVE IMPLANTATION

TAVI surpassed SAVR for treatment of AS in the United States in 2016 and is now available to symptomatic patients across the entire surgical risk spectrum (prohibitive, high, intermediate, and low) on the basis of the favorable results seen in a series of landmark RCTs reported over the past decade (**Fig. 261-5**). Application of TAVI in asymptomatic AS patients is under active investigation. It is most commonly performed using one of two systems, a balloon-expandable valve or a self-expanding valve, both of which incorporate a pericardial bioprosthetic (**Fig. 261-6**). TAVI is most frequently undertaken via the transfemoral route, although trans-LV apical, subclavian, carotid, and ascending aortic routes have been used. Aortic balloon valvuloplasty under rapid RV (or LV) pacing is performed as a first step to create an orifice of sufficient size for the prosthesis. Procedural success rates exceed 95% in appropriately selected patients. Valve performance characteristics are excellent over 5 years; longer-term durability assessment is ongoing. Outcomes achieved with this transformative technology have been very favorable and have allowed the extension of AVR to groups of patients previously considered at high or prohibitive risk for conventional surgery. Nevertheless, some prohibitive or high surgical risk patients are not candidates for this procedure because their comorbidity profile and frailty would make its undertaking inappropriate. The heart team is specifically charged with making challenging decisions of this nature. The use of these devices for treatment of patients with structural deterioration of bioprosthetic aortic valves (valve-in-valve TAVI), as an alternative to reoperative valve replacement, has increased sharply over the past 5 years. The technology has also been increasingly applied to BAV patients despite the fact that patients with this anatomy were excluded from the landmark RCTs.

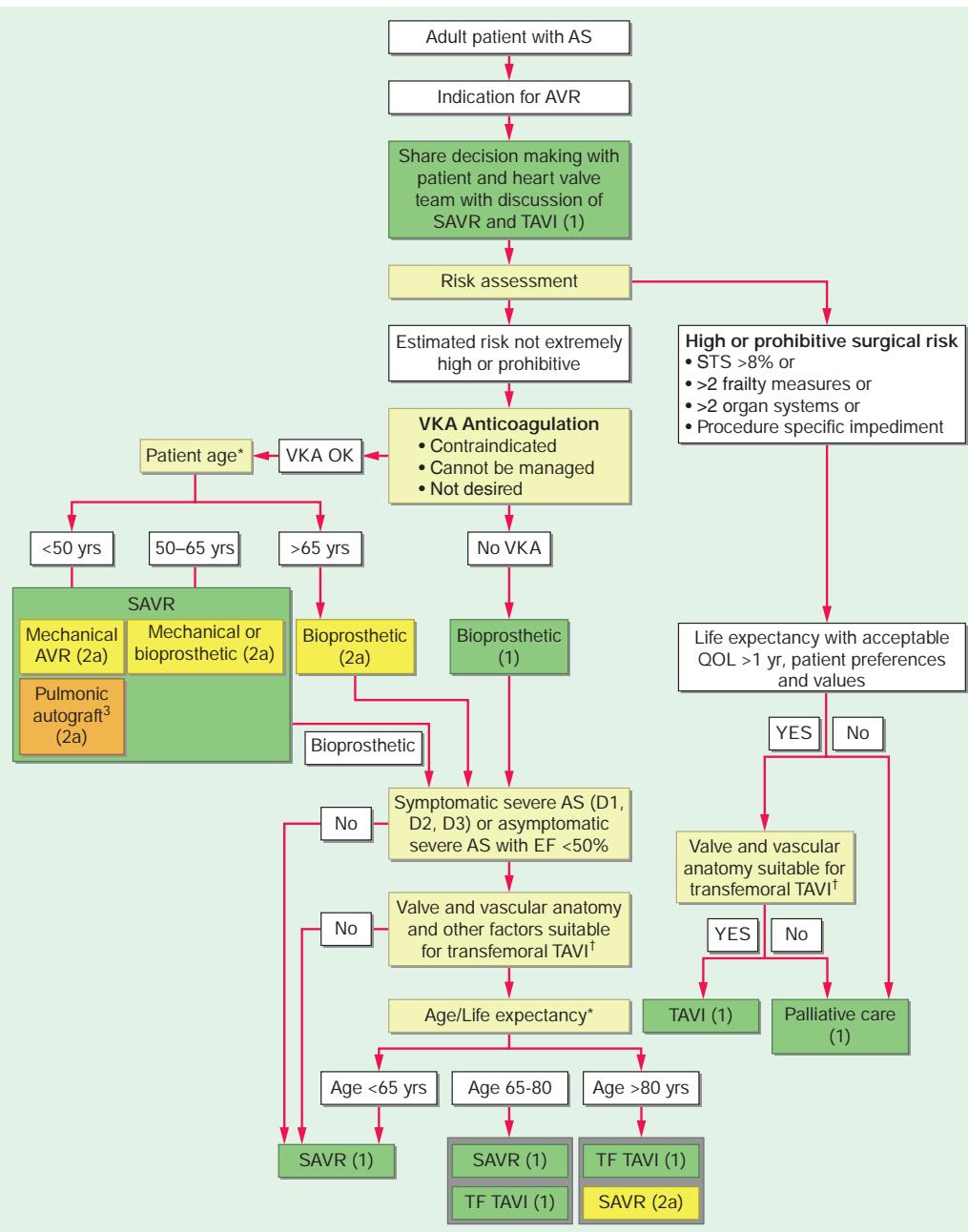


**FIGURE 261-5** Balloon-expandable (A) and self-expanding (B) valves for transcatheter aortic valve replacement (TAVR). B, inflated balloon; N, nose cone; V, valve. (Part A, courtesy of Edwards Lifesciences, Irvine, CA; with permission. NovaFlex+ is a trademark of Edwards Lifesciences Corporation. Part B, © Medtronic, Inc. 2015. Medtronic CoreValve Transcatheter Aortic Valve. CoreValve is a registered trademark of Medtronic, Inc.)



**FIGURE 261-6** Transcatheter aortic valve replacement (TAVR) with a balloon expandable valve versus surgical aortic valve replacement in low surgical risk patients. Shown are Kaplan-Meier estimates of the rate of the primary composite end point including death from any cause, stroke, or rehospitalization. In this randomized trial, transfemoral TAVR resulted in a marked reduction in the composite endpoint at 1 year, although the individual components did not differ significantly. (From MJ Mack et al: Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 380:1695, 2019. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

Compared with SAVR, transfemoral TAVI results in fewer perioperative deaths and confers lower risks of strokes, major bleeding, and AF. Hospital lengths of stay are shorter and return to normal activity more rapid with TAVI. Rates of permanent pacemaker use, perivalvular AR, and vascular complications are lower with SAVR. The choice between TAVI and SAVR for patients with trileaflet AS who prefer a biological prosthesis rests on several clinical, imaging, and technical considerations (**Fig. 261-7** and **Table 261-3**). Because there



**FIGURE 261-7** Choice of surgical aortic valve replacement (SAVR) versus transcatheter aortic valve implantation (TAVI) when indications for aortic valve replacement are met. For patients who are not prohibitive or high surgical risk candidates, TAVI is not recommended for patients age <65 years (left hand side of flow diagram). For prohibitive or high surgical risk patients, TAVI is preferred over SAVR but is recommended on an individual basis only after multidisciplinary heart team consensus decision-making in collaboration with the patient and family. Palliative care is recommended when TAVI is considered futile (right side of flow diagram). AS, aortic stenosis; AVR, aortic valve replacement; EF, ejection fraction; QOL, quality of life; STS, Society of Thoracic Surgeons; VKA, vitamin K antagonist. \*Approximate ages, based on US Actuarial Life Expectancy tables, are provided for guidance. The balance between expected patient longevity and valve durability varies continuously across the age range, with more durable valves preferred for patients with a longer life expectancy. Bioprosthetic valve durability is finite (with shorter durability for younger patients), whereas mechanical valves are very durable but require lifelong anticoagulation. Long-term (20-y) data on outcomes with surgical bioprosthetic valves are available; robust data on transcatheter bioprosthetic valves extend to only 5 years, leading to uncertainty about longer-term outcomes. The decision about valve type should be individualized on the basis of patient-specific factors that might affect longevity. <sup>†</sup>Placement of a transcatheter valve requires vascular anatomy that allows transfemoral delivery and the absence of aortic root dilation that would require surgical replacement. Valvular anatomy must be suitable for placement on the specific prosthetic valve, including annulus size and shape, leaflet number and calcification, and ostial height. (Reproduced with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 143:e72, 2021.)

are scant RCT data on TAVI outcomes in patients <65 years, SAVR is recommended in this age group. Aortic valve/root anatomy, as well as the extent, severity, and distribution of calcium, and the distance of the coronary arteries from the plane of the annulus, may dictate a surgical approach, as could the need to perform a concomitant

procedure such as ascending aortic replacement. Lastly, inability to achieve transfemoral access is a relative impediment to TAVI given the higher complication rates observed when this procedure is undertaken from other vascular access sites.

**TABLE 261-3 Factors Favoring SAVR, TAVI, or Palliative Care in Patients with Aortic Stenosis**

	FAVORS SAVR	FAVORS TAVI	FAVORS PALLIATION
Age/life expectancy <sup>a</sup>	<ul style="list-style-type: none"> <li>Younger age/longer life expectancy</li> </ul>	<ul style="list-style-type: none"> <li>Older age/fewer expected remaining years of life</li> </ul>	<ul style="list-style-type: none"> <li>Limited life expectancy</li> </ul>
Valve anatomy	<ul style="list-style-type: none"> <li>Bicuspid aortic valve</li> <li>Subaortic (LVOT) calcification</li> <li>Rheumatic valve disease</li> <li>Small or large aortic annulus<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Calcific trileaflet AS</li> </ul>	
Prosthetic valve preference	<ul style="list-style-type: none"> <li>Mechanical or surgical bioprosthetic valve preferred</li> <li>Concern for patient-prosthesis mismatch (annular enlargement might be considered)</li> </ul>	<ul style="list-style-type: none"> <li>Bioprosthetic valve preferred</li> <li>Favorable ratio of life expectancy to valve durability</li> <li>TAVI provides larger valve area than same-sized SAVR</li> </ul>	
Concurrent cardiac conditions	<ul style="list-style-type: none"> <li>Aortic dilation<sup>c</sup></li> <li>Severe primary MR</li> <li>Severe CAD requiring bypass grafting</li> <li>Septal hypertrophy requiring myectomy</li> <li>Atrial fibrillation</li> </ul>	<ul style="list-style-type: none"> <li>Severe calcification of the ascending aorta ("porcelain" aorta)</li> </ul>	<ul style="list-style-type: none"> <li>Irreversible severe LV systolic dysfunction</li> <li>Severe MR due to annular calcification</li> </ul>
Noncardiac conditions		<ul style="list-style-type: none"> <li>Severe lung, liver, or renal disease</li> <li>Mobility issues (high risk for sternotomy)</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms likely due to noncardiac conditions</li> <li>Severe dementia</li> <li>Moderate to severe involvement of 2 or more other organ systems</li> </ul>
Frailty	<ul style="list-style-type: none"> <li>Not frail or few frailty measures</li> </ul>	<ul style="list-style-type: none"> <li>Frailty likely to improve after TAVI</li> </ul>	<ul style="list-style-type: none"> <li>Severe frailty unlikely to improve after TAVI</li> </ul>
Estimated risk of SAVR or TAVI	<ul style="list-style-type: none"> <li>SAVR risk low</li> <li>TAVI risk high</li> </ul>	<ul style="list-style-type: none"> <li>TAVI risk low to medium</li> <li>SAVR risk high to prohibitive</li> </ul>	<ul style="list-style-type: none"> <li>Prohibitive SAVR risk (&gt;15%) or post-TAVI life expectancy &lt;1 year</li> </ul>
Procedure-specific impediments	<ul style="list-style-type: none"> <li>Valve anatomy, annular size, or low coronary ostial height precludes TAVI</li> <li>Vascular access does not allow transfemoral TAVI</li> </ul>	<ul style="list-style-type: none"> <li>Previous cardiac surgery with at-risk coronary grafts</li> <li>Previous chest irradiation</li> </ul>	<ul style="list-style-type: none"> <li>Valve anatomy, annular size, or coronary ostial height precludes TAVI</li> <li>Vascular access does not allow transfemoral TAVI</li> </ul>
Goals of care and patient preferences and values	<ul style="list-style-type: none"> <li>Less uncertainty about valve durability</li> <li>Avoid repeat intervention</li> <li>Lower risk of permanent pacer</li> <li>Life prolongation</li> <li>Symptom relief</li> <li>Improved long-term exercise capacity and QOL</li> <li>Avoid vascular complications</li> <li>Accepts longer hospital stay, pain in recovery period</li> </ul>	<ul style="list-style-type: none"> <li>Accepts uncertainty about valve durability and possible repeat intervention</li> <li>Higher risk of permanent pacer</li> <li>Life prolongation</li> <li>Symptom relief</li> <li>Improved exercise capacity and QOL</li> <li>Prefers shorter hospital stay, less postprocedure pain</li> </ul>	<ul style="list-style-type: none"> <li>Life prolongation not an important goal</li> <li>Avoid futile or unnecessary diagnostic or therapeutic procedures</li> <li>Avoid procedural stroke risk</li> <li>Avoid possibility of cardiac pacer</li> </ul>

<sup>a</sup>Data on bioprosthetic valve durability are more robust for SAVR valves than for TAVI valves. Mechanical valves are very durable but require lifelong anticoagulation. Choice of prosthesis is a shared decision-making process accounting for individual patient values and preferences. <sup>b</sup>Surgical root enlargement can be performed at time of SAVR to allow a use of a larger prosthesis and reduce the occurrence of prosthesis-patient mismatch. <sup>c</sup>Aortic root or ascending aortic enlargement may require surgical correction at time of SAVR.

**Abbreviations:** AS, aortic stenosis; CAD, coronary artery disease; LV, left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; QOL, quality of life; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

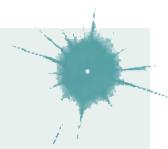
**Source:** Reproduced with permission from CR Burke et al. Goals of care in patients with severe aortic stenosis. Eur Heart J 41:929, 2020.

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## 262 Aortic Regurgitation

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### ETIOLOGY

**(Table 262-1)** Aortic regurgitation (AR) may be caused by primary valve disease, aortic root disease, or their combination.

**Primary Valve Disease** Rheumatic disease results in thickening, deformity, and shortening of the individual aortic valve cusps, changes that prevent their proper opening during systole and closure during diastole. A rheumatic origin is much less common in patients with isolated AR who do not have associated rheumatic mitral valve disease. Patients with congenital bicuspid aortic valve (BAV) disease may develop predominant AR, and ~20% of these patients will require aortic valve surgery between 10 and 40 years of age. Congenital

**TABLE 262-1 Major Causes of Aortic Regurgitation**

VALVE LESION	ETIOLOGIES
Aortic regurgitation	
	Valvular
	Congenital (bicuspid)
	Endocarditis
	Rheumatic fever
	Myxomatous (prolapse)
	Radiation
	Trauma
	Syphilis
	Ankylosing spondylitis
	Aortic root disease
	Aortic dissection
	Medial degeneration
	Marfan syndrome
	Bicuspid aortic valve
	Nonsyndromic familial aneurysm
	Aortitis
	Hypertension

fenestrations of the aortic valve occasionally produce mild AR. Membranous subaortic stenosis results in a high velocity systolic jet that often leads to thickening and scarring of the aortic valve leaflets and secondary AR. Prolapse of an aortic cusp, resulting in progressive chronic AR, occurs in ~15% of patients with ventricular septal defect (**Chap. 269**), but may also occur as an isolated phenomenon or as a consequence of myxomatous degeneration sometimes associated with mitral and/or tricuspid valve involvement.

AR may result from infective endocarditis (IE), which can develop on a valve previously affected by rheumatic disease, a congenitally deformed valve, or on a normal aortic valve, and may lead to perforation or erosion of one or more leaflets. The aortic valve leaflets may become scarred and retracted during the course of syphilis or ankylosing spondylitis and contribute further to the AR that derives primarily from the associated root dilation. Although traumatic rupture or avulsion of an aortic cusp is an uncommon cause of acute AR, it represents the most frequent serious lesion in patients surviving nonpenetrating cardiac injuries. The coexistence of hemodynamically significant aortic stenosis (AS) with AR usually excludes all the rarer forms of AR because it occurs almost exclusively in patients with rheumatic or congenital AR. In patients with AR due to primary valvular disease, dilation of the aortic annulus may occur secondarily and lead to worsening regurgitation.

**Primary Aortic Root Disease** AR also may be due entirely to marked aortic annular dilation, i.e., aortic root disease, without primary involvement of the valve leaflets; widening of the aortic annulus and lack of diastolic coaptation of the aortic leaflets are responsible for the AR (**Chap. 280**). Medial degeneration of the ascending aorta, which may or may not be associated with other manifestations of Marfan syndrome; idiopathic dilation of the aorta; annuloaortic ectasia; osteogenesis imperfecta; and severe, chronic hypertension may all widen the aortic annulus and lead to progressive AR. Occasionally AR is caused by retrograde dissection of the aorta involving the aortic annulus. Syphilis and ankylosing spondylitis, both of which may also affect the aortic leaflets, may be associated with cellular infiltration and scarring of the media of the thoracic aorta, leading to aortic dilation, aneurysm formation, and severe regurgitation. In syphilis of the aorta (**Chap. 182**), now a very rare condition, the involvement of the intima may narrow the coronary ostia, which in turn may be responsible for myocardial ischemia. Takayasu's arteritis and giant cell arteritis can also result in aneurysm formation and secondary AR.

## PATOPHYSIOLOGY

The total stroke volume ejected by the left ventricle (LV) (i.e., the sum of the effective forward stroke volume and the volume of blood that

regurgitates back into the LV) is increased in patients with AR. In patients with severe AR, the volume of regurgitant flow may equal the effective forward stroke volume. In contrast to MR, in which a portion of the LV stroke volume is delivered into the low-pressure left atrium (LA), in AR, the entire LV stroke volume is ejected into a high-pressure zone, the aorta. An increase in the LV end-diastolic volume (increased preload) constitutes the major hemodynamic compensation for AR. The dilation and eccentric hypertrophy of the LV allow this chamber to eject a larger stroke volume without requiring any increase in the relative shortening of each myofibril. Therefore, severe AR may occur with a normal effective forward stroke volume and a normal LV ejection fraction (LVEF, total [forward plus regurgitant] stroke volume/end-diastolic volume), together with an elevated LV end-diastolic pressure and volume. However, through the operation of Laplace's law, LV dilation increases the LV systolic tension required to develop any given level of systolic pressure. Chronic AR is, thus, a state in which LV preload and afterload are both increased. Ultimately, these adaptive measures fail. As LV function deteriorates, the end-diastolic volume rises further and the forward stroke volume and ejection fraction (EF) decline. Deterioration of LV function often precedes the development of symptoms. Considerable thickening of the LV wall also occurs with chronic AR, and at autopsy, the hearts of these patients may be among the largest encountered, sometimes weighing >1000 g.

The reverse diastolic pressure gradient from aorta to LV, which drives the AR flow, falls progressively during diastole, accounting for the typical decrescendo nature of the diastolic murmur. Equilibration between aortic and LV pressures may occur toward the end of diastole in patients with chronic severe AR, particularly when the heart rate is slow. In patients with acute severe AR, the LV is unprepared for the regurgitant volume load. LV compliance is normal or reduced, and LV diastolic pressures rise rapidly, occasionally to levels >40 mmHg. The LV pressure may exceed the LA pressure toward the end of diastole, and this reversed pressure gradient closes the mitral valve prematurely.

In patients with chronic severe AR, the effective forward cardiac output (CO) usually is normal or only slightly reduced at rest, but often it fails to rise normally during exercise. An early sign of LV dysfunction is a reduction in the EF. In advanced stages, there may be considerable elevation of the LA, pulmonary artery (PA) wedge, PA, and right ventricular (RV) pressures and lowering of the forward CO at rest.

*Myocardial ischemia* may occur in patients with AR because myocardial oxygen requirements are elevated by LV dilation, hypertrophy, and elevated LV systolic tension, and coronary blood flow may be compromised. A large fraction of coronary blood flow occurs during diastole, when aortic pressure is low, thereby reducing coronary perfusion or driving pressure. This combination of increased oxygen demand and reduced supply may cause myocardial ischemia, particularly of the subendocardium, even in the absence of epicardial coronary artery disease (CAD).

## HISTORY

Approximately three-fourths of patients with pure or predominant valvular AR are men; women predominate among patients with primary valvular AR who have associated rheumatic mitral valve disease. A history compatible with IE may sometimes be elicited from patients with rheumatic or congenital involvement of the aortic valve, and the infection often precipitates or seriously aggravates preexisting symptoms.

In patients with *acute severe AR*, as may occur in IE, aortic dissection, or trauma, the LV cannot dilate sufficiently to maintain stroke volume, and LV diastolic pressure rises rapidly with associated marked elevations of LA and PA wedge pressures. Pulmonary edema and/or cardiogenic shock may develop rapidly.

*Chronic severe AR* may have a long latent period, and patients may remain relatively asymptomatic for as long as 10–15 years. Uncomfortable awareness of the heartbeat, especially on lying down, may be an early complaint. Sinus tachycardia, during exertion or with emotion, or premature ventricular contractions may produce particularly uncomfortable palpitations as well as head pounding. These complaints may persist for many years before the development of exertional dyspnea, usually the first symptom of diminished cardiac reserve. The dyspnea is followed by orthopnea, paroxysmal nocturnal dyspnea, and excessive

diaphoresis. Anginal chest pain even in the absence of CAD may occur in patients with severe AR, even in younger patients. Anginal pain may develop at rest as well as during exertion. Nocturnal angina may be a particularly troublesome symptom, and it may be accompanied by marked diaphoresis. The anginal episodes can be prolonged and often do not respond satisfactorily to sublingual nitroglycerin. Systemic fluid accumulation, including congestive hepatomegaly and ankle edema, may develop late in the course of the disease.

## PHYSICAL FINDINGS

In chronic severe AR, the jarring of the entire body and the bobbing motion of the head with each systole can be appreciated, and the abrupt distention and collapse of the larger arteries are easily visible. The examination should be directed toward the detection of conditions predisposing to AR, such as bicuspid valve, IE, Marfan syndrome, or ankylosing spondylitis.

**Arterial Pulse** A rapidly rising “water-hammer” pulse, which collapses suddenly as arterial pressure falls rapidly during late systole and diastole (Corrigan’s pulse), and capillary pulsations, an alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke’s pulse), are characteristic of chronic severe AR. A booming “pistol-shot” sound can be heard over the femoral arteries (Traube’s sign), and a to-and-fro murmur (Duroziez’s sign) is audible if the femoral artery is lightly compressed with a stethoscope.

The arterial pulse pressure is widened as a result of both systolic hypertension and a lowering of the diastolic pressure. The measurement of arterial diastolic pressure with a sphygmomanometer may be complicated by the fact that systolic sounds are frequently heard with the cuff completely deflated. However, the level of cuff pressure at the time of muffling of the Korotkoff sounds (phase IV) generally corresponds fairly closely to the true intra-arterial diastolic pressure. As the disease progresses and the LV end-diastolic pressure rises, the arterial diastolic pressure may actually rise as well, because the aortic diastolic pressure cannot fall below the LV end-diastolic pressure. For the same reason, acute severe AR may also be accompanied by only a slight widening of the pulse pressure. Such patients are invariably tachycardic as the heart rate increases in an attempt to preserve the CO.

**Palpation** In patients with chronic severe AR, the LV impulse is heaving and displaced laterally and inferiorly. The systolic expansion and diastolic retraction of the apex are prominent. A diastolic thrill may be palpable along the left sternal border in thin-chested individuals, and a prominent systolic thrill may be palpable in the suprasternal notch and transmitted upward along the carotid arteries. This systolic thrill and the accompanying murmur do not necessarily signify the coexistence of AS. In some patients with AR or with combined AS and AR, the carotid arterial pulse may be bisferiens, i.e., with two systolic waves separated by a trough (see Fig. 239-2C).

**Auscultation** In patients with severe AR, the aortic valve closure sound ( $A_2$ ) is usually absent. A systolic ejection sound is audible in patients with BAV disease, and occasionally an  $S_4$  also may be heard. The murmur of chronic AR is typically a high-pitched, blowing, decrescendo diastolic murmur, heard best in the third intercostal space along the left sternal border (see Fig. 239-5B). In patients with mild AR, this murmur is brief, but as the severity increases, it generally becomes louder and longer, indeed holodiastolic. When the murmur is soft, it can be heard best with the diaphragm of the stethoscope and with the patient sitting up, leaning forward, and with the breath held in forced expiration. In patients in whom the AR is caused by primary valvular disease, the diastolic murmur is usually louder along the left than the right sternal border. However, when the murmur is louder along the right sternal border, it suggests that the AR is caused by aneurysmal dilation of the aortic root. “Cooing” or musical diastolic murmurs suggest eversion of an aortic cusp vibrating in the regurgitant stream.

A mid-systolic ejection murmur is frequently audible in isolated AR. It is generally heard best at the base of the heart and is transmitted along the carotid arteries. This murmur may be quite loud without signifying aortic valve obstruction. A third murmur sometimes heard in

patients with severe AR is the *Austin Flint murmur*, a soft, low-pitched, rumbling mid-to-late diastolic murmur. It is probably produced by the diastolic displacement of the anterior leaflet of the mitral valve by the AR stream and is not associated with hemodynamically significant mitral valve obstruction. The auscultatory features of AR are intensified by strenuous and sustained handgrip, which augments systemic vascular resistance and increases LV afterload.

In acute severe AR, the elevation of LV end-diastolic pressure may lead to early closure of the mitral valve, a soft  $S_1$ , a pulse pressure that is not particularly wide, and a soft, short, early diastolic murmur of AR.

## LABORATORY EXAMINATION

**ECG** In patients with chronic severe AR, ECG signs of LV hypertrophy are common (Chap. 240). In addition, these patients frequently exhibit ST-segment depression and T-wave inversion in leads I, aVL,  $V_5$ , and  $V_6$  (“LV strain”). Left axis deviation and/or QRS prolongation may also be present.

**Echocardiogram** LV size is increased in chronic AR, and systolic function is normal or even supernormal until myocardial contractility declines, as signaled by a decrease in EF or increase in the end-systolic dimension. A rapid, high-frequency diastolic fluttering of the anterior mitral leaflet produced by the impact of the regurgitant jet is a characteristic finding. The echocardiogram is also useful in determining the cause of AR, by detecting dilation of the aortic annulus and root, aortic dissection (see Fig. 241-5), or primary leaflet pathology. With severe AR, the central jet width assessed by color flow Doppler imaging exceeds 65% of the width of the LV outflow tract, the regurgitant volume is  $\geq 60$  mL/beat, the regurgitant fraction is  $\geq 50\%$ , and there is diastolic flow reversal in the proximal portion of the descending thoracic aorta. The continuous-wave Doppler profile of the AR jet shows a rapid deceleration time in patients with acute severe AR, due to the rapid increase in LV diastolic pressure. Surveillance transthoracic echocardiography (TTE) forms the cornerstone of longitudinal follow-up and allows for the early detection of changes in LV size and/or function. For patients in whom TTE is limited by poor acoustical windows or inadequate characterization of LV function or the cause or severity of the regurgitation, cardiac magnetic resonance (CMR) imaging can be performed. This modality also allows for accurate assessment of aortic size and contour. It can also be utilized to screen for LV fibrosis as assessed with late gadolinium enhancement. Both CMR imaging and cardiac computed tomography (CT) can provide detailed assessment of aortic valve and root anatomy. Transesophageal echocardiography (TEE) can also provide detailed anatomic assessment of the valve, root, and portions of the aorta. There is increasing experience with the use of three-dimensional echocardiography to measure LV volumes.

**Chest X-Ray** In chronic severe AR, the apex is displaced downward and to the left in the frontal projection. In the left anterior oblique and lateral projections, the LV is displaced posteriorly and encroaches on the spine. When AR is caused by primary disease of the aortic root, aneurysmal dilation of the aorta may be noted, and the aorta may fill the retrosternal space in the lateral view. Echocardiography, CMR imaging, and chest CT angiography are more sensitive than the chest x-ray for the detection of root and ascending aortic enlargement.

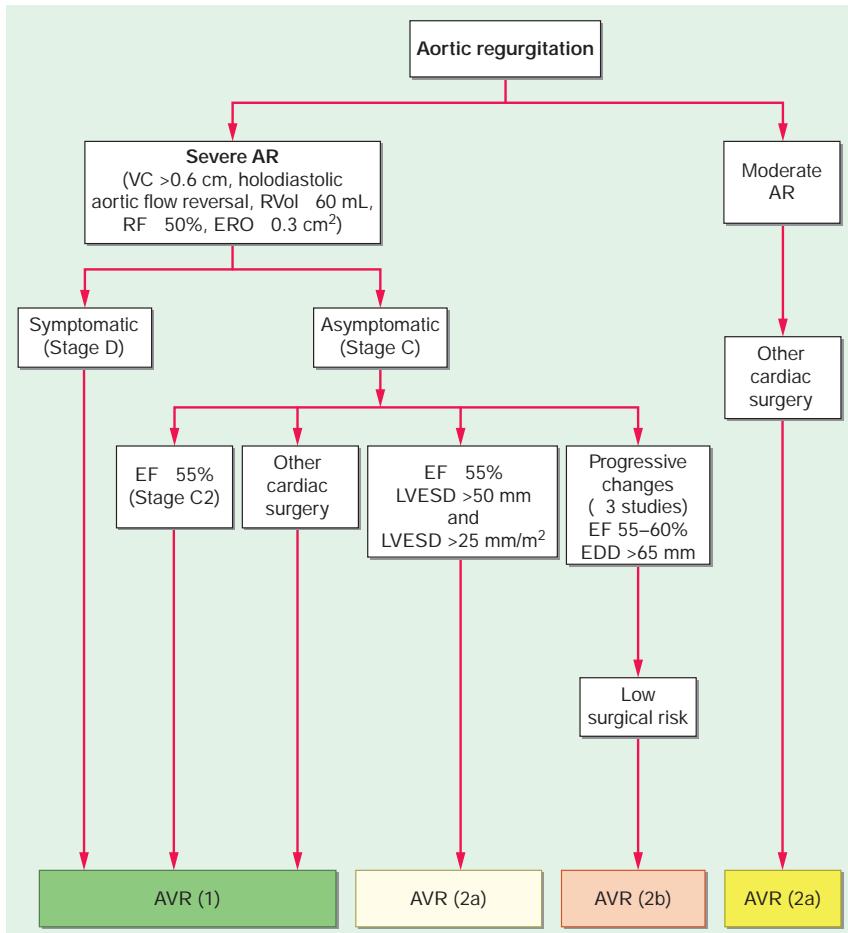
**Cardiac Catheterization and Angiography** When needed, right and left heart catheterization with contrast aortography can provide confirmation of the magnitude of regurgitation and the status of LV function. Coronary angiography is performed routinely in appropriate patients prior to surgery, although this anatomic information can also be gained with coronary CT angiographic techniques.

## TREATMENT

### Aortic Regurgitation

#### ACUTE AORTIC REGURGITATION (FIG. 262-1)

Patients with acute severe AR may respond to intravenous diuretics and vasodilators (such as sodium nitroprusside), but stabilization is



**FIGURE 262-1 Management of patients with aortic regurgitation.** See legend for Fig. 261-4 for explanation of treatment recommendations (Class I, IIa, and IIb) and disease stages (B, C1, C2, and D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Surgery is indicated for patients with severe AR and symptoms, LV dysfunction, or other indications for operation (e.g., aneurysm disease). Surgery is also reasonable once the LV indexed end-systolic dimension reaches or exceeds 25 mm/m<sup>2</sup>. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. AR, aortic regurgitation; AVR, aortic valve replacement (valve repair may be appropriate in selected patients); EDD, end-diastolic dimension; EF, ejection fraction; ERO, effective regurgitant orifice; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reproduced with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 143:e72, 2021.)

usually short-lived and operation is indicated urgently. Intra-aortic balloon counterpulsation is contraindicated. Beta blockers are best avoided so as not to reduce the CO further or slow the heart rate, thus allowing more time for diastolic filling of the LV. Surgery is the treatment of choice and is usually necessary within 24 h of diagnosis.

#### CHRONIC AORTIC REGURGITATION

The onset of symptoms, or LV systolic dysfunction, is an indication for surgery. Medical treatment with diuretics and vasodilators (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers [ARBs], dihydropyridine calcium channel blockers, or hydralazine) may be useful as a temporizing measure. Surgery can then be performed in a more controlled setting. The use of vasodilators to extend the compensated phase of chronic severe AR in asymptomatic patients before the onset of symptoms or the development of LV dysfunction is not useful, although these agents should be employed to treat hypertension (systolic blood pressure >140 mm Hg). It is often difficult to achieve adequate blood pressure control because of the increased stroke volume and enhanced LV ejection that accompany severe AR. Cardiac arrhythmias and systemic infections are poorly tolerated in patients with

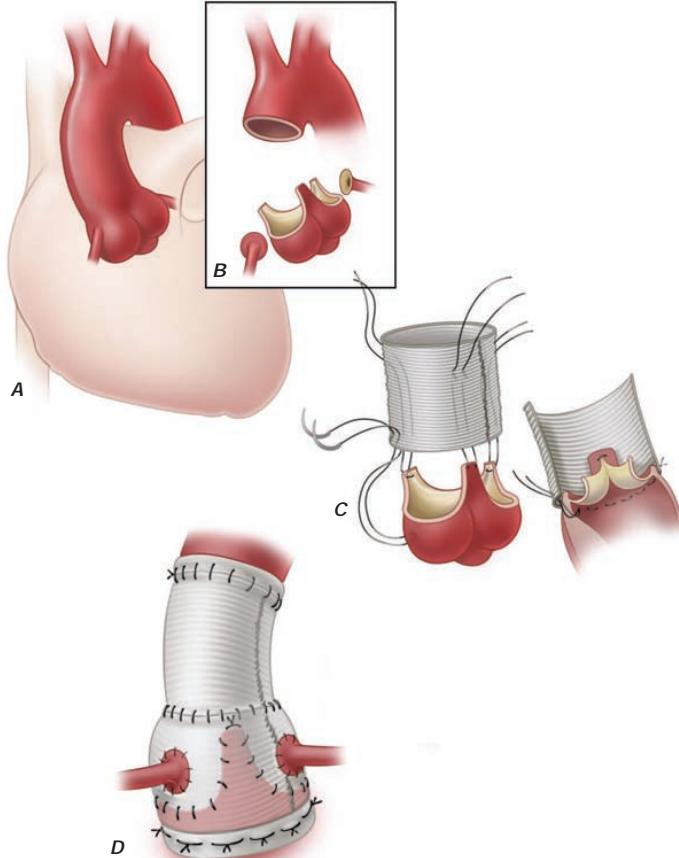
severe AR and must be treated promptly and vigorously. Although nitroglycerin and long-acting nitrates are not as helpful in relieving anginal pain as they are in patients with coronary heart disease, they are worth a trial. Patients with syphilitic aortitis should receive a full course of penicillin therapy (Chap. 182). Beta blockers and the ARB losartan may be useful to retard the rate of aortic root enlargement in young patients with Marfan's syndrome and aortic root dilation. A randomized controlled trial showed no difference in efficacy between atenolol and losartan for this indication. Whether beta blockers or ARBs are useful in retarding the rate of growth of aortic aneurysms in other patient subsets (e.g., BAV disease with aortopathy, Takayasu's disease) has not been demonstrated. Beta blockers in patients with valvular AR were previously considered relatively contraindicated due to concern that slowing of the heart rate would allow more time for diastolic regurgitation. Observational reports, however, have suggested that beta blockers may provide functional benefit in some patients with chronic AR. Beta blockers can sometimes provide incremental blood pressure lowering in patients with chronic AR and hypertension. They can also lessen the sense of forceful heart action that many patients find uncomfortable. Patients with severe AR, particularly those with an associated aortopathy, should avoid isometric exercises.

In deciding on the advisability and proper timing of surgical treatment, two points should be kept in mind: (1) patients with chronic severe AR usually do not become symptomatic until after the development of myocardial dysfunction; and (2) when delayed too long (defined as >1 year from onset of symptoms or LV dysfunction), surgical treatment often does not restore normal LV size and function. Therefore, in patients with chronic severe AR, careful clinical follow-up and noninvasive testing with echocardiography at ~6- to 12-month intervals are necessary if operation is to be undertaken at the optimal time, i.e., *after* the onset of LV dysfunction but *prior to* the development of severe symptoms. Exercise testing may be helpful to assess effort tolerance more objectively. Operation can be deferred as long as the patient both remains asymptomatic and retains normal LV function without severe or progressive chamber dilation.

Aortic valve replacement (AVR) is indicated for the treatment of severe AR in symptomatic patients irrespective of LV function. In general, the operation should be carried out in asymptomatic patients with severe AR and progressive LV dysfunction defined by an LVEF <55% on serial studies, an LV end-systolic dimension >50 mm (>25 mm/m<sup>2</sup>), or an LV diastolic dimension >65 mm. Smaller dimensions may be appropriate thresholds in individuals of smaller stature or when there is evidence of progressively decreasing LV function or increasing LV size on serial studies and the anticipated risks for surgical morbidity and mortality are low. Two case series from surgical referral centers have suggested that

surgery should be performed at an even lower threshold for LV end-systolic dimension index (< 20 mm/m<sup>2</sup>), but data from randomized controlled trials are lacking. Patients with severe AR without indications for operation should be followed by clinical and echocardiographic examination every 6-12 months. Transcatheter aortic valve implantation (TAVI) is not recommended for patients with severe AR who are surgical candidates. Technical success with TAVI in patients with chronic AR is limited by the degree of aortic annular dilation and the relative paucity of valvular and annular calcium.

Surgical options for management of aortic valve and root disease have expanded considerably over the past decade. AVR with a suitable mechanical or tissue (biological) prosthesis is generally necessary in patients with rheumatic AR and in many patients with other causes of valvular AR. Rarely, when a leaflet has been perforated during IE or torn from its attachments to the aortic annulus by thoracic trauma, primary surgical repair may be possible. When AR is due to aneurysmal dilation of the root or proximal ascending aorta rather than to primary valve involvement, it may be possible to reduce or eliminate the regurgitation by narrowing the annulus or by excising a portion of the aortic root without replacing the valve. Elective, valve-sparing aortic root reconstruction generally involves reimplantation of the valve in a contoured graft with reattachment of the coronary artery buttons into the side of the graft and is best undertaken in specialized surgical centers (Fig. 262-2). Resuspension of the native aortic valve leaflets is possible in ~50% of patients with acute AR in the setting of type A aortic dissection.



**FIGURE 262-2** Valve-sparing aortic root reconstruction (David procedure). Aortic root and proximal ascending aorta (**A**) are resected (**B**) with sinuses of Valsalva and mobilized coronary artery buttons remaining. Subannular sutures (**C**) are placed, commissural posts are drawn up inside the valve, and the annular sutures are passed through the proximal end of the graft. The annular sutures are tied (**D**), the valve is reimplanted inside the graft, aortic continuity is reestablished with another graft of appropriate size, and the coronary buttons are attached to the side of the graft. (From P Steltzer et al [eds]: *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*, 3rd ed, Fig. 12-27, p. 200.)

**TABLE 262-2 Mortality Rates After Aortic Valve Surgery<sup>a</sup>**

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
AVR (isolated)	25,274	1.9
AVR + CAB	15,855	3.6

<sup>a</sup>Data are for calendar year 2018 during which 1088 participant groups reported a total of 287,872 procedures.

Abbreviations: AVR, aortic valve replacement; CAB, coronary artery bypass.

Source: Adapted from ME Bowdish et al: Ann Thorac Surg 109:1646, 2020.

In other conditions, however, AR can be effectively eliminated only by replacing the aortic valve, as well as the dilated or aneurysmal ascending aorta responsible for the regurgitation, and implanting a composite valve-graft conduit. This formidable procedure entails a higher risk than isolated AVR.

As is true in patients with other valvular heart disease, both operative and late mortality risks are largely dependent on the stage of the disease and myocardial function at the time of operation. The overall operative mortality rate for isolated AVR (performed for either or both AS or AR) is ~2% (**Table 262-2**). However, patients with AR, marked cardiac enlargement, and established LV dysfunction experience an operative mortality rate of ~10% and a late mortality rate of ~5% per year due to LV failure despite a technically satisfactory operation. Nonetheless, because of the very poor prognosis with medical management, even patients with advanced LV systolic dysfunction should be considered for operation.

Patients with acute severe AR require prompt (24–48 h) surgical treatment, which may be lifesaving.

## FURTHER READING

- Lacro RV et al: Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med* 371:2061, 2014.  
 Malaisrie SC, McCarthy PM: Surgical approach to disease of the aortic valve and the aortic root, in *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*, 5th ed. CM Otto, RO Bonow (eds). Philadelphia, Elsevier Saunders, 2020, pp 267–288.  
 Otto CM et al: 2020 ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 143:e72, 2021.

**TABLE 263-1 Major Causes of Mitral Stenosis**

Etiologies
Rheumatic fever
Congenital (parachute valve, cor triatriatum)
Severe mitral annular calcification with leaflet involvement
SLE, RA
Myxoma
IE with large vegetations

Abbreviations: IE, infective endocarditis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Pure or predominant MS occurs in ~40% of all patients with rheumatic heart disease and a history of rheumatic fever (**Chap. 359**). In other patients with rheumatic heart disease, lesser degrees of MS may accompany mitral regurgitation (MR) and aortic valve disease. With reductions in the incidence of acute rheumatic fever, particularly in temperate climates and middle- to high-income countries, the incidence of MS has declined considerably over the past several decades. However, it remains a major problem in low-income countries, especially in sub-Saharan Africa, India, Southeast Asia, and Oceania (**Chap. 261**).

In rheumatic MS, chronic inflammation leads to diffuse thickening of the valve leaflets with formation of fibrous tissue often with calcific deposits. The mitral commissures fuse, the chordae tendineae fuse and shorten, the valvular cusps become rigid, and the pathologic process eventually leads to narrowing at the apex of the funnel-shaped ("fish-mouth") valve. Although the initial insult to the mitral valve is rheumatic, later changes may be exacerbated by inflammation, fibrosis, and trauma to the valve due to altered flow patterns. Calcification of the stenotic mitral valve immobilizes the leaflets and narrows the orifice further. Thrombus formation and arterial embolization may arise from the calcific valve itself, but in patients with atrial fibrillation (AF), thrombi arise more frequently from the dilated left atrium (LA), particularly from within the LA appendage.

## PATHOPHYSIOLOGY

In normal adults, the area of the mitral valve orifice is 4–6 cm<sup>2</sup>. In the presence of significant obstruction, i.e., when the orifice area is reduced to <~2 cm<sup>2</sup>, blood can flow from the LA to the left ventricle (LV) only if propelled by an abnormally elevated left atrioventricular pressure gradient, the hemodynamic hallmark of MS. When the mitral valve opening is reduced to <1.5 cm<sup>2</sup>, referred to as "severe" MS, an LA pressure of ~25 mmHg is required to maintain a normal cardiac output (CO). The elevated pulmonary venous and pulmonary arterial (PA) wedge pressures reduce pulmonary compliance, contributing to exertional dyspnea. The first bouts of dyspnea are usually precipitated by clinical events that increase the rate of blood flow across the mitral orifice, resulting in further elevation of the LA pressure (see below).

To assess the severity of obstruction hemodynamically, both the transvalvular pressure gradient and the flow rate must be measured (**Chap. 242**). The latter depends not only on the CO but on the heart rate, as well. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore, at any given level of CO, tachycardia, including that associated with rapid AF, augments the transvalvular pressure gradient and elevates further the LA pressure. Similar considerations apply to the pathophysiology of tricuspid stenosis (TS).

The LV diastolic pressure and ejection fraction (EF) are normal in isolated MS. In MS and sinus rhythm, the elevated LA and PA wedge pressures exhibit a prominent atrial contraction pattern (a wave) and a gradual pressure decline after the v wave and mitral valve opening (y descent). In severe MS and whenever pulmonary vascular resistance is significantly increased, the PA pressure (PAP) is elevated at rest and rises further during exercise, often causing secondary elevations of right ventricular (RV) end-diastolic pressure and volume.

**Cardiac Output** In patients with severe MS (mitral valve orifice 1–1.5 cm<sup>2</sup>), the CO is normal or almost so at rest, but rises subnormally

# 263

## Mitral Stenosis

Patrick T. O'Gara, Joseph Loscalzo

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 42 and 239**; of electrocardiography (ECG) in **Chap. 240**; of echocardiography and other noninvasive imaging techniques in **Chap. 241**; and of cardiac catheterization and angiography in **Chap. 242**.

## MITRAL STENOSIS

### ETIOLOGY AND PATHOLOGY

Rheumatic fever is the leading cause of mitral stenosis (MS) (**Table 263-1**; see also **Chap. 359**). Other less common etiologies of obstruction to left ventricular inflow include congenital mitral valve stenosis, cor triatriatum, mitral annular calcification with extension onto the leaflets, systemic lupus erythematosus, rheumatoid arthritis, left atrial myxoma, and infective endocarditis with large vegetations.

during exertion. In patients with very severe MS (valve area <1 cm<sup>2</sup>), particularly those in whom pulmonary vascular resistance is markedly elevated, the CO is subnormal at rest and may fail to rise or may even decline during activity.

**Pulmonary Hypertension** The clinical and hemodynamic features of MS are influenced importantly by the level of the PAP. Pulmonary hypertension results from (1) passive backward transmission of the elevated LA pressure; (2) pulmonary arteriolar constriction (the so-called "second stenosis"), which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); (3) interstitial edema in the walls of the small pulmonary vessels; and (4) at end stage, organic obliterative changes in the pulmonary vascular bed. Severe pulmonary hypertension results in RV enlargement, secondary tricuspid regurgitation (TR), and pulmonic regurgitation (PR), as well as right-sided heart failure.

### SYMPTOMS

In temperate climates, the latent period between the initial attack of rheumatic carditis (in the increasingly rare circumstances in which a history of one can be elicited) and the development of symptoms due to MS is generally about two decades; most patients begin to experience disability in the fourth decade of life. Studies carried out before the development of surgical mitral valvotomy revealed that once a patient with MS became seriously symptomatic, the disease progressed inexorably to death within 2–5 years.

In patients whose mitral orifices are large enough to accommodate a normal blood flow with only mild elevations of LA pressure, marked elevations of this pressure leading to dyspnea and cough may be precipitated by sudden changes in the heart rate, volume status, or CO, as, for example, with severe exertion, excitement, fever, severe anemia, paroxysmal AF and other tachycardias, sexual intercourse, pregnancy, and thyrotoxicosis. As MS progresses, lesser degrees of stress precipitate dyspnea, the patient becomes limited in daily activities, and orthopnea and paroxysmal nocturnal dyspnea develop. The development of persistent AF often marks a turning point in the patient's course and is generally associated with acceleration of the rate at which symptoms progress. *Hemoptysis* (Chap. 39) results from rupture of pulmonary-bronchial venous connections secondary to pulmonary venous hypertension. It occurs most frequently in patients who have elevated LA pressures without markedly elevated pulmonary vascular resistances and is rarely fatal. *Recurrent pulmonary emboli* (Chap. 279), sometimes with infarction, are an important cause of morbidity and mortality late in the course of MS. *Pulmonary infections*, i.e., bronchitis, bronchopneumonia, and lobar pneumonia, commonly complicate untreated MS, especially during the winter months.

**Pulmonary Changes** In addition to the aforementioned changes in the pulmonary vascular bed, fibrous thickening of the walls of the alveoli and pulmonary capillaries occurs commonly in MS. The vital capacity, total lung capacity, maximal breathing capacity, and oxygen uptake per unit of ventilation are reduced (Chap. 285). Pulmonary compliance falls further as pulmonary capillary pressure rises during exercise.

**Thrombi and Emboli** *Thrombi* may form in the left atria, particularly within the enlarged atrial appendages of patients with MS. Systemic embolization, the incidence of which is 10–20%, occurs more frequently in patients with AF, in patients >65 years of age, and in those with a reduced CO. However, systemic embolization may be the presenting feature in otherwise asymptomatic patients with only mild MS.

### PHYSICAL FINDINGS

(See also Chaps. 42 and 239)

**Inspection and Palpation** In patients with severe MS, there may be a malar flush with pinched and blue facies. In patients with sinus rhythm and severe pulmonary hypertension or associated TS, the jugular venous pulse reveals prominent a waves due to vigorous right atrial systole. The systemic arterial pressure is usually normal or slightly low. A parasternal lift signifies an enlarged RV. A diastolic thrill may

rarely be present at the cardiac apex, with the patient in the left lateral recumbent position.

**Auscultation** The first heart sound (S<sub>1</sub>) is usually accentuated in the early stages of the disease and slightly delayed. The pulmonic component of the second heart sound (P<sub>2</sub>) also is often accentuated with elevated PAPs, and the two components of the second heart sound (S<sub>2</sub>) are closely split. The opening snap (OS) of the mitral valve is most readily audible in expiration at, or just medial to, the cardiac apex. This sound generally follows the sound of aortic valve closure (A<sub>2</sub>) by 0.05–0.12 s. The time interval between A<sub>2</sub> and OS varies inversely with the severity of the MS. The OS is followed by a low-pitched, rumbling, diastolic murmur, heard best at the apex with the patient in the left lateral recumbent position (see Fig. 239-5); it is accentuated by mild exercise (e.g., a few rapid sit-ups) carried out just before auscultation. In general, the duration of this murmur correlates with the severity of the stenosis in patients with preserved CO. In patients with sinus rhythm, the murmur often reappears or becomes louder during atrial systole (presystolic accentuation). Soft, grade I or II/VI systolic murmurs may be heard at or medial to the apex and may signify mixed mitral valve disease with regurgitation. Hepatomegaly, ankle edema, ascites, and pleural effusion, particularly in the right pleural cavity, may occur in patients with MS and RV failure.

**Associated Lesions** With severe pulmonary hypertension, a pansystolic murmur produced by functional TR may be audible along the left sternal border. This murmur is usually louder during inspiration and diminishes during forced expiration (Carvallo's sign). When the CO is markedly reduced in MS, the typical auscultatory findings, including the diastolic rumbling murmur, may not be detectable (silent MS), but they may reappear as compensation is restored. The *Graham Steell murmur* of PR, a high-pitched, diastolic, decrescendo blowing murmur along the left sternal border, results from dilation of the pulmonary valve ring and occurs in patients with mitral valve disease and severe pulmonary hypertension. This murmur may be indistinguishable from the more common murmur produced by aortic regurgitation (AR), although it may increase in intensity with inspiration and is accompanied by a loud and often palpable P<sub>2</sub>.

### LABORATORY EXAMINATION

**ECG** In MS and sinus rhythm, the P wave usually suggests LA enlargement (see Fig. 240-8). It may become tall and peaked in lead II and upright in lead V<sub>1</sub> when severe pulmonary hypertension or TS complicates MS and right atrial (RA) enlargement develops. The QRS complex is usually normal. However, with severe pulmonary hypertension, right axis deviation and RV hypertrophy are often present.

**Echocardiogram (See also Chap. 241)** Transthoracic echocardiography (TTE) with color flow and spectral Doppler imaging provides critical information, including measurements of mitral inflow velocity during early (E wave) and late (A wave in patients in sinus rhythm) diastolic filling, estimates of the transvalvular peak and mean gradients and mitral orifice area, the presence and severity of any associated MR, the extent of leaflet calcification and restriction, the degree of distortion of the subvalvular apparatus, and the anatomic suitability for percutaneous mitral balloon commissurotomy (PMBC; see below). In addition, TTE provides an assessment of LV and RV function, chamber sizes, an estimation of the PA systolic pressure based on the tricuspid regurgitant jet velocity, and an indication of the presence and severity of any associated valvular lesions, such as aortic stenosis (AS) and/or regurgitation. Transesophageal echocardiography (TEE) provides superior images and should be used when TTE is inadequate for guiding management decisions. TEE is especially indicated to exclude the presence of LA thrombus prior to PMBC. The performance of TTE with exercise to evaluate the mean mitral diastolic gradient and PAPs can be very helpful in the evaluation of patients with MS when there is a discrepancy between the clinical findings and the resting hemodynamics.

**Chest X-Ray** The earliest changes are straightening of the upper left border of the cardiac silhouette, prominence of the main PAs, dilation

of the upper lobe pulmonary veins, and posterior displacement of the esophagus by an enlarged LA. Kerley B lines are fine, dense, opaque, horizontal lines that are most prominent in the lower and mid-lung fields that result from distention of interlobular septae and lymphatics with edema when the resting mean LA pressure exceeds ~20 mmHg.

## DIFFERENTIAL DIAGNOSIS

Like MS, significant MR may also be associated with a prominent diastolic murmur at the apex due to increased antegrade transmural flow, but in patients with isolated MR, this diastolic murmur commences slightly later than in patients with MS, and there is often clear-cut evidence of LV enlargement. An OS and increased P<sub>2</sub> are absent, and S<sub>1</sub> is soft or absent. An apical pansystolic murmur of at least grade III/VI intensity as well as an S<sub>3</sub> suggests significant MR. Similarly, the apical mid-diastolic murmur associated with severe AR (*Austin Flint murmur*) may be mistaken for MS but can be differentiated from it because it is not intensified in pre-systole and becomes softer with administration of amyl nitrite or other arterial vasodilators. TS, which occurs rarely in the absence of MS, may mask many of the clinical features of MS or be clinically silent; when present, the diastolic murmur of TS increases with inspiration and the y descent in the jugular venous pulse is delayed.

**Atrial septal defect** (Chap. 269) may be mistaken for MS; in both conditions, there is often clinical, ECG, and chest x-ray evidence of RV enlargement and accentuation of pulmonary vascularity. However, the absence of LA enlargement and of Kerley B lines and the demonstration of fixed splitting of S<sub>2</sub> with a grade II or III mid-systolic murmur at the mid to upper left sternal border all favor atrial septal defect over

MS. Atrial septal defects with large left-to-right shunts may result in functional TS because of the enhanced diastolic flow.

**Left atrial myxoma** (Chap. 271) may obstruct LA emptying, causing dyspnea, a diastolic murmur, and hemodynamic changes resembling those of MS. However, patients with an LA myxoma often have features suggestive of a systemic disease, such as weight loss, fever, anemia, systemic emboli, and elevated serum IgG and interleukin 6 (IL-6) concentrations. The auscultatory findings may change markedly with body position. The diagnosis can be established by the demonstration of a characteristic echo-producing mass in the LA with TTE.

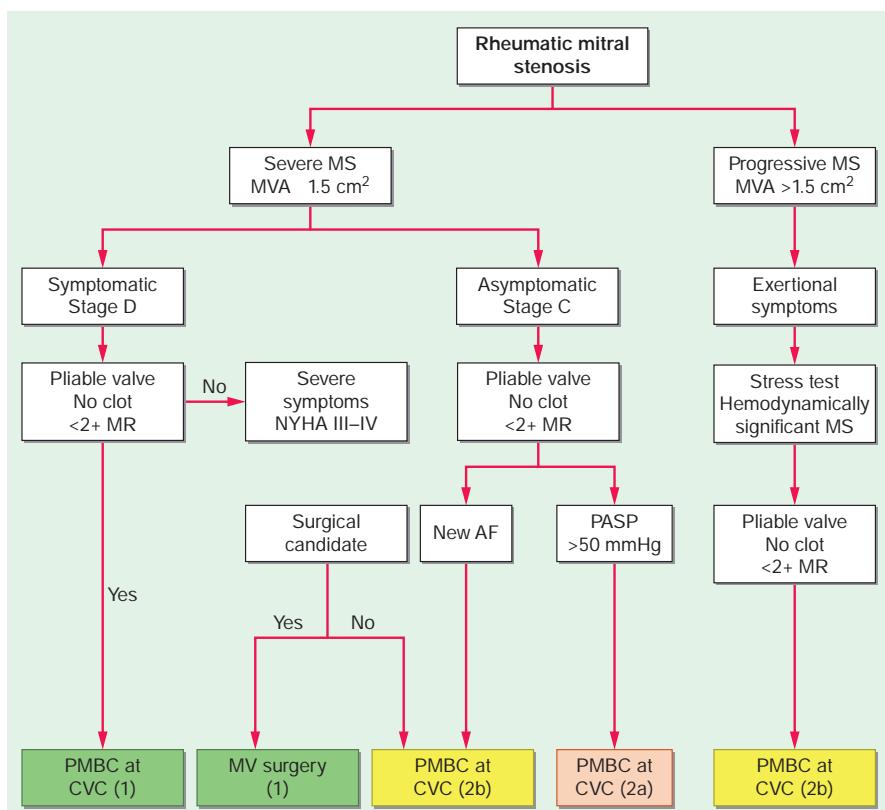
## CARDIAC CATHETERIZATION

Left and right heart catheterization can be useful when there is a discrepancy between the clinical and noninvasive findings, including those from TEE and exercise echocardiographic testing when appropriate. Catheterization can also be helpful in assessing associated lesions, such as AS and AR, and in patients with recurring or worsening symptoms later after mitral valve intervention. Computed tomographic coronary angiography is increasingly used to screen preoperatively for the presence of coronary artery disease in appropriate patients prior to heart valve surgery or transcatheter treatment.

## TREATMENT

### Mitral Stenosis (Fig. 263-1)

Penicillin prophylaxis of group A -hemolytic streptococcal infections (Chap. 359) for secondary prevention of rheumatic fever is



**FIGURE 263-1 Management of rheumatic mitral stenosis.** See legend for Fig. 261-4 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; CVC, comprehensive valve center; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; PMBC, percutaneous mitral balloon commissurotomy. (Reproduced with permission from CM Otto et al: ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 143:e72, 2021.)

important for at-risk patients with rheumatic MS. Recommendations for infective endocarditis prophylaxis are similar to those for other valve lesions and are restricted to patients at high risk for complications from infection, including patients with a history of endocarditis. In symptomatic patients, some improvement usually occurs with restriction of sodium intake and small doses of oral diuretics. Beta blockers, nondihydropyridine calcium channel blockers (e.g., verapamil or diltiazem), and digitalis glycosides are useful in slowing the ventricular rate of patients with AF. Vitamin K antagonist therapy (such as warfarin) targeted to an international normalized ratio (INR) of 2–3 should be administered indefinitely to patients with MS who have AF, a history of thromboembolism, or demonstrated LA thrombus. The routine use of a vitamin K antagonist in patients in sinus rhythm with LA enlargement (maximal dimension >5.5 cm) with or without spontaneous echo contrast is more controversial. As of this writing, non-vitamin K oral anti-coagulants (e.g., apixaban, rivaroxaban) have not been adequately studied in patients with moderate or severe rheumatic MS and, thus, are not recommended.

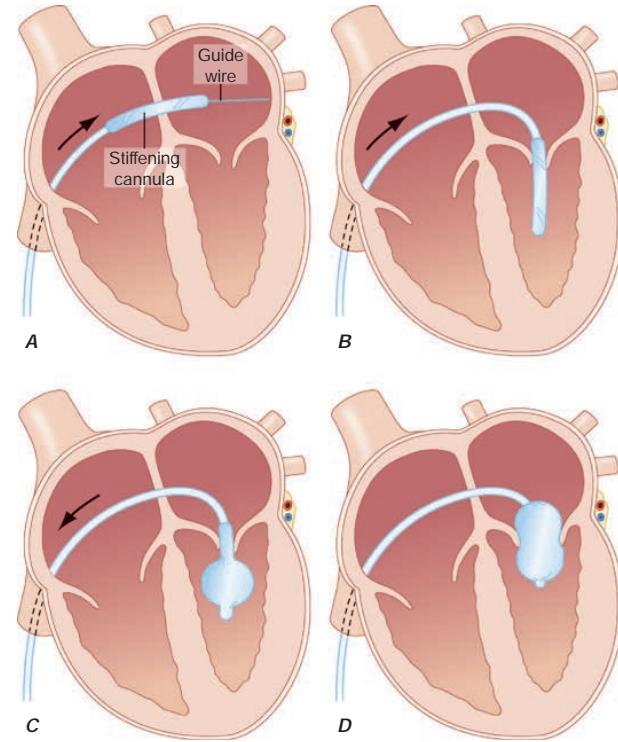
If AF is of relatively recent onset in a patient whose MS is not severe enough to warrant PMBC or surgical intervention, reversion to sinus rhythm pharmacologically or by means of electrical countershock is indicated. Usually, cardioversion should be undertaken after the patient has had at least 3 consecutive weeks of anticoagulant treatment to a therapeutic INR. If cardioversion is indicated more urgently, then intravenous heparin should be provided and TEE performed to exclude the presence of LA thrombus before the procedure. Conversion to sinus rhythm is rarely successful or sustained in patients with severe MS, particularly those in whom the LA is significantly enlarged or in whom AF has been present for >1 year, conditions that favor the development of an LA myopathy.

### MITRAL COMMISSUROTOMY

Unless there is a contraindication, mitral commissurotomy is indicated in symptomatic (New York Heart Association [NYHA] Functional Class II–IV) patients with isolated severe MS, whose effective orifice (valve area) is <~1 cm<sup>2</sup>/m<sup>2</sup> body surface area, or <1.5 cm<sup>2</sup> in normal-sized adults. Mitral commissurotomy can be carried out either percutaneously or surgically. In PMBC (Figs. 263-2 and 263-3), a catheter is directed into the LA after transseptal puncture, and a single balloon is directed across the valve and inflated in the valvular orifice. Ideal patients have relatively pliable leaflets with little or no commissural calcium. In addition, the subvalvular structures should not be significantly scarred or thickened, and there should be no LA thrombus. Any associated MR should be of 2+/4+ severity. The short- and long-term results of this procedure in appropriate patients are similar to those of surgical commissurotomy, but with less morbidity and a lower periprocedural mortality rate. Event-free survival in younger (<45 years) patients with pliable valves is excellent, with rates as high as 80–90% over 3–7 years. Therefore, PMBC is the procedure of choice for such patients when it can be performed by a skilled operator in a high-volume center.

TTE is helpful in identifying patients for the percutaneous procedure; TEE is performed routinely to exclude LA thrombus and to assess the degree of MR at the time of the scheduled procedure. An “echo score” has been developed to help guide decision-making. The score accounts for the degree of leaflet thickening, calcification, and mobility, and for the extent of subvalvular thickening. A lower score predicts a higher likelihood of successful PMBC.

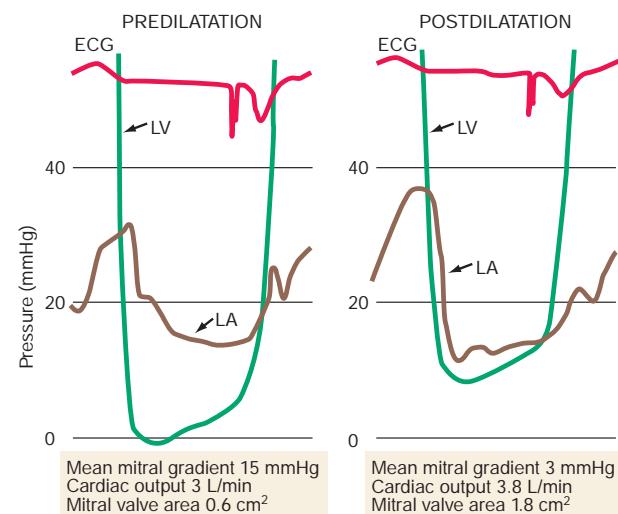
In patients in whom PMBC is not possible or unsuccessful, or in many patients with restenosis after previous surgery, an “open” surgical commissurotomy using cardiopulmonary bypass is necessary. In addition to opening the valve commissures, it is important to loosen any subvalvular fusion of papillary muscles and chordae tendineae; to remove large deposits of calcium, thereby improving



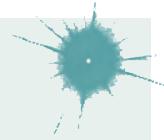
**FIGURE 263-2** Inoue balloon technique for percutaneous mitral balloon commissurotomy. **A.** After transseptal puncture, the deflated balloon catheter is advanced across the interatrial septum, then across the mitral valve and into the left ventricle. **B–D.** The balloon is inflated stepwise within the mitral orifice.

valvular function; and to remove atrial thrombi. The perioperative mortality rate for this type of mitral valve repair procedure is ~2%.

Successful commissurotomy is defined by a 50% reduction in the mean mitral valve gradient and a doubling of the mitral valve area. Successful commissurotomy, whether balloon or surgical, usually results in striking symptomatic and hemodynamic improvement



**FIGURE 263-3** Simultaneous left atrial (LA) and left ventricular (LV) pressure before and after percutaneous mitral balloon commissurotomy (PMBC) in a patient with severe mitral stenosis. ECG, electrocardiogram. (Courtesy of Raymond G. McKay, MD.)

**TABLE 263-2 Mortality Rates after Mitral Valve Surgery<sup>a</sup>**

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
MVR (isolated)	10,699	4.5
MVR + CAB	3509	9.6
MVRp	12,424	1.2
MVRp + CAB	4093	5.4

<sup>a</sup>Data are for calendar year 2018 during which 1088 participant groups reported a total of 287,872 procedures. Surgical mitral valve commissurotomy cases are included in the mitral valve repair procedures.

*Abbreviations:* CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

*Source:* Adapted from ME Bowdish et al: Ann Thorac Surg 109:1646, 2020.

and prolongs survival. However, there is no evidence that the procedure improves the prognosis of patients with slight or no functional impairment. Therefore, unless recurrent systemic embolization or severe pulmonary hypertension has occurred (PA systolic pressures >50 mmHg at rest or >60 mmHg with exercise), commissurotomy is *not* recommended for patients who are asymptomatic and/or who have mild or moderate stenosis (mitral valve area >1.5 cm<sup>2</sup>). When there is little symptomatic improvement after commissurotomy, it is likely that the procedure was ineffective, that it induced MR, or that associated valvular or myocardial disease was present. About half of all patients undergoing surgical mitral commissurotomy require reoperation by 10 years. In the pregnant patient with MS, commissurotomy should be carried out if pulmonary congestion occurs despite intensive medical treatment. PMBC is the preferred strategy in this setting and is performed with TEE and no or minimal x-ray exposure.

Mitral valve replacement (MVR) is necessary in patients with MS and significant associated MR, those in whom the valve has been severely distorted by previous transcatheter or operative manipulation, or those in whom the surgeon does not find it possible to improve valve function significantly with commissurotomy. MVR is now routinely performed with preservation of the chordal attachments to optimize LV functional recovery. Perioperative mortality rates with MVR vary with age, LV function, the presence of CAD, and associated comorbidities. They average 5% overall but are lower in young patients and may be twice as high in patients >65 years of age with significant comorbidities (Table 263-2). Because there are also long-term complications of valve replacement, patients in whom preoperative evaluation suggests the possibility that MVR may be required should be operated on only if they have severe MS—i.e., an orifice area 1.5 cm<sup>2</sup>—and are in NYHA Class III, i.e., symptomatic with ordinary activity despite optimal medical therapy. The overall 10-year survival of surgical survivors is ~70%. Long-term prognosis is worse in patients >65 years of age and those with marked disability and marked depression of the CO preoperatively. Pulmonary hypertension and RV dysfunction are additional risk factors for poor outcome.

## FURTHER READING

- Nishimura RA et al: Mitral valve disease: Current management and future challenges. Lancet 387:1324, 2016.  
 Otto CM et al: 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 143:e72, 2021.

## 264

# Mitral Regurgitation

Patrick T. O'Gara, Joseph Loscalzo

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in Chaps. 42 and 239; of electrocardiography (ECG) in Chap. 240; of echocardiography and other noninvasive imaging techniques in Chap. 241; and of cardiac catheterization and angiography in Chap. 242.

### ETIOLOGY

Mitral regurgitation (MR) may result from an abnormality or disease process that affects any one or more of the five functional components of the mitral valve apparatus (leaflets, annulus, chordae tendineae, papillary muscles, and subjacent myocardium) (Table 264-1). Acute MR can occur in the setting of acute myocardial infarction (MI) with papillary muscle rupture (Chap. 275), following blunt chest wall trauma, or during the course of infective endocarditis (IE) owing to leaflet perforation or destruction. With acute MI, the posteromedial papillary muscle is involved much more frequently than the anterolateral papillary muscle because of its singular blood supply. Transient, acute MR can occur during periods of active ischemia and bouts of angina pectoris. Rupture of chordae tendineae can result in “acute-on-chronic MR” in patients with myxomatous degeneration of the valve apparatus.

Chronic MR can result from several disease processes (Table 264-1). Distinction should be drawn between primary (degenerative) MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and secondary (functional) MR, in which the leaflets and chordae tendineae are usually normal but the regurgitation is caused by left ventricular (LV) remodeling, annular dilation, papillary muscle displacement, dyssynchrony, posterior leaflet tethering, or their combination. Patient assessment, treatment approach, and long-term prognosis differ significantly between primary and secondary MR. Mitral valve prolapse (MVP) is discussed more extensively

**TABLE 264-1 Major Causes of Mitral Regurgitation (MR)**

#### Etiologies

##### Acute

- IE
- Papillary muscle rupture (post-MI)
- Chordal rupture/leaflet flail (MVP, IE)
- Blunt trauma

##### Chronic

- Primary (affecting leaflets, chordae)**
  - Myxomatous (MVP, Barlow's, forme fruste)
  - Rheumatic fever
  - IE (healed)
  - Congenital (cleft, AV canal)
  - Radiation

##### Secondary (leaflets, chordae are “innocent bystanders”)

- Ischemic cardiomyopathy
- Dilated cardiomyopathy
- HOCM (with SAM)
- AF with LA enlargement and annular dilation (atrial functional MR)

##### Mitral annular calcification<sup>a</sup>

<sup>a</sup>Mitral annular calcification may include elements of both primary and secondary MR (mixed) as the disease process may encroach on the leaflets, impair the normal sphincteric function of the annulus, or both. There are additional examples of “mixed” secondary MR such as the coexistence of MVP with an ischemic cardiomyopathy.

*Abbreviations:* AF, atrial fibrillation; AV, atrioventricular; HOCM, hypertrophic obstructive cardiomyopathy; IE, infective endocarditis; LA, left atrial; LV, left ventricular; MI, myocardial infarction; MVP, mitral valve prolapse; SAM, systolic anterior motion.

in [Chap. 265](#). The rheumatic process produces rigidity, deformity, and retraction of the valve cusps and commissural fusion, as well as shortening, contraction, and fusion of the chordae tendineae. MR can persist after resolution of the acute phase of infection and inflammation. MR may occur as a congenital anomaly ([Chap. 269](#)), most commonly as a defect of the endocardial cushions (atrioventricular cushion defects). A cleft anterior mitral valve leaflet accompanies ostium primum atrial septal defect. Radiation can result in leaflet thickening, retraction, and calcification, often in association with annular and chordal involvement and some degree of mitral stenosis. Chronic MR occurs frequently after prior MI(s) associated with changes in LV size, shape, and function. Similar mechanisms of annular dilation and ventricular remodeling contribute to the MR that occurs among patients with nonischemic forms of dilated cardiomyopathy once the LV end-diastolic dimension reaches 6 cm. The MR associated with hypertrophic obstructive cardiomyopathy (HOCM) is usually dynamic in nature and dependent on systolic anterior motion of the anterior mitral valve leaflet into a narrowed LV outflow tract. Patients with chronic persistent atrial fibrillation (AF) may develop atrial remodeling and annular dilation with inadequate leaflet lengthening and MR (atrial functional MR). Secondary MR due to LV remodeling is more frequently encountered in the community than secondary MR that occurs in association with AF and annular dilation. Annular calcification can result in MR when it encroaches on the leaflets or results in decreased sphincteric function and is especially prevalent among patients with advanced renal disease and is commonly observed in women >65 years of age with hypertension and diabetes mellitus. Irrespective of cause, chronic severe MR is often progressive because enlargement of the left atrium (LA) places tension on the posterior mitral leaflet, pulling it further away from the mitral orifice and thereby aggravating the valvular dysfunction. Similarly, LV dilation increases the regurgitation, which, in turn, enlarges the LA and LV further, resulting in a vicious circle; hence the aphorism, "MR begets MR."

### PATOPHYSIOLOGY

The resistance to LV emptying (LV afterload) is reduced in patients with MR. As a consequence, the LV is decompressed into the LA during ejection, and with the reduction in LV size during systole, there is a rapid decline in LV tension. The initial compensation to MR is more complete LV emptying. However, LV volume increases progressively with time as the severity of the regurgitation increases and as LV contractile function deteriorates. This increase in LV volume is often accompanied by a reduced forward cardiac output (CO). LV compliance is often increased, and thus, LV diastolic pressure does not increase until late in the course. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced by the extent of LV and mitral annular dilation. Because ejection fraction (EF) rises in severe MR in the presence of normal LV function, even a modest reduction in this parameter (<60%) reflects significant contractile dysfunction.

During early diastole, as the distended LA empties, there is a particularly rapid y descent in the absence of accompanying MS. A brief, early diastolic LA-LV pressure gradient (often generating a rapid filling sound [ $S_3$ ] and mid-diastolic murmur masquerading as MS) may occur in patients with pure, severe MR as a result of the very rapid flow of blood across a normal-sized mitral orifice.

Measurements of LV ejection fraction (LVEF), CO, pulmonary arterial (PA) systolic pressure, regurgitant volume, regurgitant fraction (RF), and the effective regurgitant orifice area can be obtained during a careful Doppler echocardiographic examination. These measurements can also be obtained accurately with cardiac magnetic resonance (CMR) imaging, although this technology is not widely available. Left and right heart catheterization with contrast ventriculography is used less frequently. Chronic, severe MR is defined by a regurgitant volume  $\geq 60 \text{ mL/beat}$ , regurgitant fraction (RF)  $\geq 50\%$ , and effective regurgitant orifice area  $\geq 0.40 \text{ cm}^2$ .

In patients with secondary MR, in whom the severity of MR can be underappreciated using echocardiographic/Doppler techniques, lesser degrees of regurgitation may carry relatively greater prognostic weight. The adverse prognosis in secondary MR

related to adverse LV remodeling is intimately related to the degree of myocardial dysfunction.

**LA Compliance** In acute severe MR, the regurgitant volume is delivered into a normal-sized LA having normal or reduced compliance. As a result, LA pressures rise markedly for any increase in LA volume. The  $v$  wave in the LA pressure pulse is usually prominent, LA and pulmonary venous pressures are markedly elevated, and pulmonary edema is common. Because of the rapid rise in LA pressures during ventricular systole, the murmur of acute MR is early in timing and decrescendo in configuration ending well before  $S_2$ , as a reflection of the progressive diminution in the LV-LA pressure gradient. LV systolic function in acute MR may be normal, hyperdynamic, or reduced, depending on the clinical context.

Patients with chronic severe MR, on the other hand, develop marked LA enlargement and *increased* LA compliance with little if any increase in LA and pulmonary venous pressures for any increase in LA volume. The LA  $v$  wave is relatively less prominent. The murmur of chronic MR is classically holosystolic in timing and plateau in configuration, as a reflection of the near-constant LV-LA pressure gradient. These patients usually complain of severe fatigue and exhaustion secondary to a low forward CO, whereas symptoms resulting from pulmonary congestion are less prominent initially; AF is almost invariably present once the LA dilates significantly.

### SYMPTOMS

Patients with chronic mild-to-moderate, isolated MR are usually asymptomatic. This form of LV volume overload is well tolerated. Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR. Palpitations are common and may signify the onset of AF. Late-onset right-sided heart failure, with painful hepatic congestion, ankle edema, distended neck veins, ascites, and secondary tricuspid regurgitation (TR), occurs in patients with MR who have associated pulmonary vascular disease and pulmonary hypertension. Acute pulmonary edema is common in patients with acute severe MR.

### PHYSICAL FINDINGS

In patients with chronic severe MR, the arterial pressure is usually normal, although the carotid arterial pulse may show a sharp, low-volume upstroke owing to the reduced forward CO. A systolic thrill is often palpable at the cardiac apex, the LV is hyperdynamic with a brisk systolic impulse and a palpable rapid-filling wave ( $S_3$ ), and the apex beat is often displaced laterally.

In patients with acute severe MR, the arterial pressure may be reduced with a narrow pulse pressure, the jugular venous pressure and waveforms may be normal or increased and exaggerated, the apical impulse is not displaced, and signs of pulmonary congestion are prominent.

**Auscultation**  $S_1$  is generally absent, soft, or buried in the holosystolic murmur of chronic, severe MR. In patients with severe MR, the aortic valve may close prematurely (due to the reduced forward cardiac output), resulting in wide but physiologic splitting of  $S_2$ . A low-pitched  $S_3$  occurring 0.12–0.17 s after the aortic valve closure sound, i.e., at the completion of the rapid-filling phase of the LV, is believed to be caused by the sudden tensing of the papillary muscles, chordae tendineae, and valve leaflets. It may be followed by a short, rumbling, mid-diastolic murmur, even in the absence of structural MS. In patients with ischemic or dilated cardiomyopathy, however, a third sound ( $S_3$ ) may also signify ventricular dysfunction. A fourth heart sound is often audible in patients with acute severe MR who are in sinus rhythm. A presystolic murmur is not ordinarily heard with isolated MR.

A systolic murmur of at least grade III/VI intensity is the most characteristic auscultatory finding in chronic severe MR. It is usually holosystolic ([see Fig. 239-5A](#)), but as previously noted, it is decrescendo and ceases in mid-to-late systole in patients with acute severe MR. The systolic murmur of chronic MR is usually most prominent at the apex and radiates to the axilla. However, in patients with ruptured chordae tendineae or primary involvement of the posterior mitral leaflet with prolapse or flail, the regurgitant jet is eccentric, directed anteriorly, and

strikes the LA wall adjacent to the aortic root. In this situation, the systolic murmur is transmitted to the base of the heart and, therefore, may be confused with the murmur of AS. In patients with ruptured chordae tendineae, the systolic murmur may have a cooing or "seagull" quality, whereas a flail leaflet may produce a murmur with a musical quality. The systolic murmur of chronic MR not due to MVP is intensified by isometric exercise (handgrip) but is reduced during the strain phase of the Valsalva maneuver because of the associated decrease in LV preload.

## LABORATORY EXAMINATION

**ECG** In patients with sinus rhythm, there is evidence of LA enlargement, but right atrial (RA) enlargement also may be present when pulmonary hypertension is significant and affects RV function and size. Chronic severe MR is frequently associated with AF. In many patients, there is no clear-cut ECG evidence of enlargement of either ventricle. In others, the signs of eccentric LV hypertrophy are present.

**Echocardiogram** Transthoracic echocardiography (TTE) is indicated to assess the mechanism of the MR and its hemodynamic severity. LV function can be assessed from LV end-diastolic and end-systolic volumes and EF. Observations can be made regarding leaflet structure and function, chordal integrity, LA and LV size, annular calcification, and regional and global LV systolic function. Doppler imaging should demonstrate the width or area of the color flow MR jet within the LA, the duration and intensity of the continuous wave Doppler signal, the pulmonary venous flow contour, the early peak mitral inflow velocity, and quantitative measures of regurgitant volume, RF, and effective regurgitant orifice area. In addition, the PA pressures (PAPs) can be estimated from the TR jet velocity. TTE is also indicated to follow the

course of patients with chronic MR and to provide rapid assessment for any clinical change. Transesophageal echocardiography (TEE) provides greater anatomic detail than TTE (see Fig. 241-5). Exercise testing with TTE can be useful to assess exercise capacity as well as any dynamic change in MR severity, PA systolic pressures, and biventricular function, for patients in whom there is a discrepancy between clinical findings and the results of other noninvasive testing.

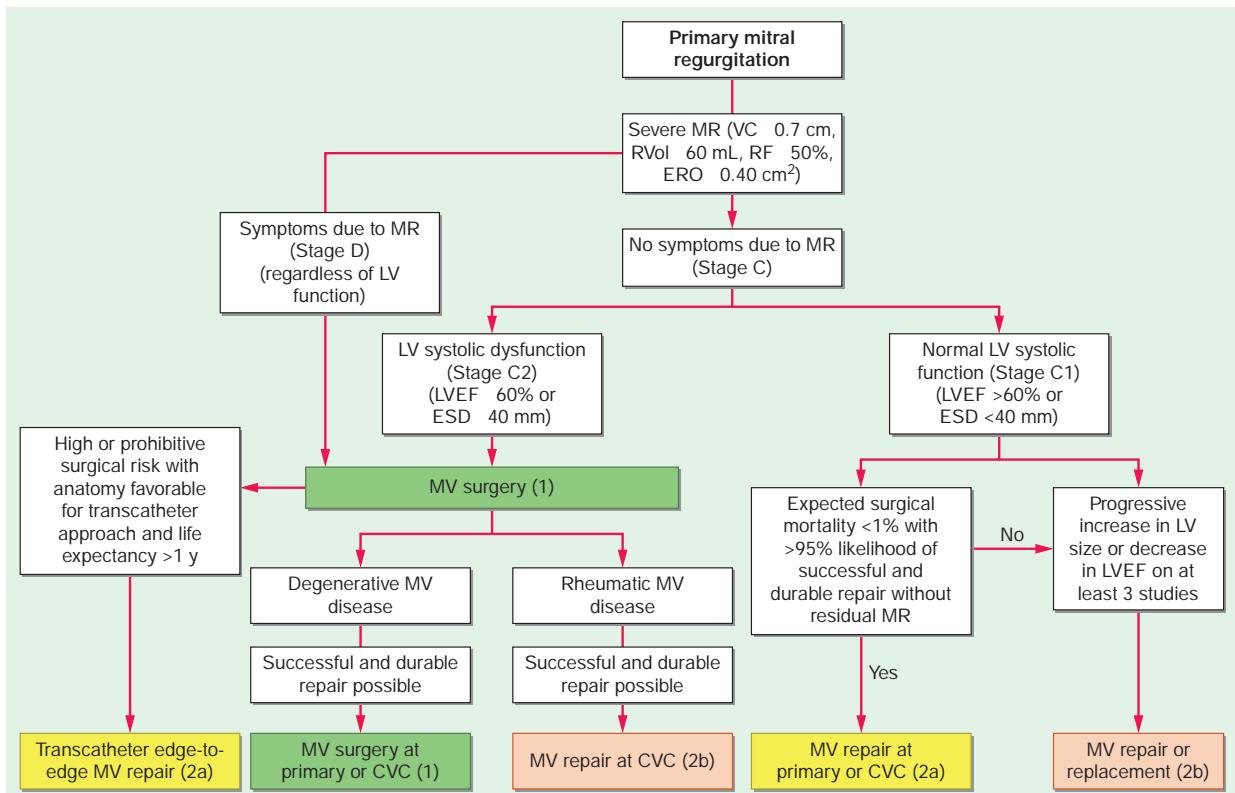
**Chest X-Ray** The LA and LV are the dominant chambers in chronic MR. Late in the course of the disease, the LA may be massively enlarged and forms the right border of the cardiac silhouette. Pulmonary venous congestion, interstitial edema, and Kerley B lines are sometimes noted. Marked calcification of the mitral leaflets occurs commonly in patients with long-standing, combined rheumatic MR and MS, as well as in patients with radiation-induced mitral valve disease. Calcification of the mitral annulus may be visualized, particularly on the lateral view of the chest. Patients with acute severe MR may have asymmetric pulmonary edema if the regurgitant jet is directed predominantly to the orifice of an upper lobe pulmonary vein.

## TREATMENT (FIGS. 264-1 AND 264-2)

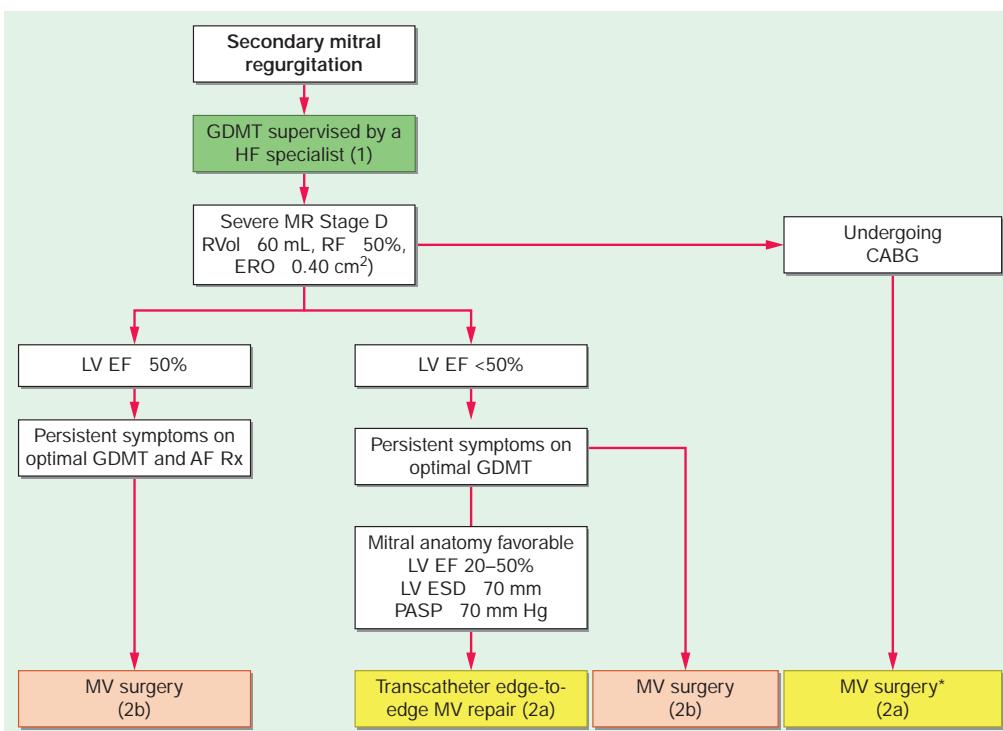
### Mitral Regurgitation

#### MEDICAL TREATMENT

The management of chronic severe MR depends to some degree on its cause. Anticoagulation with either warfarin or a direct oral agent (e.g., apixaban, rivaroxaban) should be provided if AF intervenes, as guided by the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score. The direct oral anticoagulants should not be used if moderate or severe rheumatic mitral



**FIGURE 264-1** Management of primary mitral regurgitation (MR). See legend for Fig. 261-4 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Mitral valve repair is strongly preferred over valve replacement whenever feasible for surgical treatment of primary MR. Transcatheter edge-to-edge repair (TEER) is reserved for high or prohibitive surgical risk patients with appropriate anatomy on transesophageal imaging. CVC, comprehensive valve center; EF, ejection fraction; ERO, effective regurgitant orifice; ESD, end-systolic dimension; LV, left ventricular; MV, mitral valve; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reproduced with permission from CM Otto et al: ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 143:e72, 2021.)



**FIGURE 264-2** Management of secondary mitral regurgitation. See legend for Fig. 261-4 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Surgery is recommended for patients with left ventricular ejection fraction (LVEF) >50%. Transcatheter edge-to-edge repair (TEER) is reasonable in selected patients after guideline-directed management and therapy (GDMT) has been optimized. \*MV replacement may be preferred over MV repair for ischemic MR; AF, atrial fibrillation; CABG, coronary artery bypass grafting; EF, ejection fraction; ERO, effective regurgitant orifice; ESD, end-systolic dimension; HF, heart failure; LV, left ventricular; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; Rx, treatment. (Reproduced with permission from CM Otto et al: ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 143:e72, 2021.)

stenosis is also present; they are also not approved for use in patients with mechanical prosthetic heart valves. Cardioversion should be considered depending on the clinical context, AF chronicity, and LA size. In contrast to the acute setting, there are no large, long-term prospective studies to substantiate the use of vasodilators for the treatment of chronic, isolated severe MR with preserved LV systolic function *in the absence of systemic hypertension*. The severity of secondary MR in the setting of an ischemic or dilated cardiomyopathy may diminish with aggressive guideline-directed therapy (GDMT) of heart failure including the use of diuretics for decongestion, beta blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers, angiotensin-neprilysin inhibitors, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 inhibitors and biventricular pacing (cardiac resynchronization therapy [CRT]) when indicated. Antibiotic prophylaxis for prevention of IE is indicated for MR patients with a prior history of IE. Asymptomatic patients with severe MR in sinus rhythm with normal LV size and systolic function should avoid isometric forms of exercise.

Patients with acute severe MR require urgent stabilization and preparation for surgery. Diuretics, intravenous vasodilators (particularly sodium nitroprusside), and even mechanical support may be needed for patients with post-MI papillary muscle rupture or other forms of acute severe MR.

#### SURGICAL TREATMENT

In the selection of patients with chronic, severe, primary MR for surgical treatment, the often slowly progressive nature of the condition must be balanced against the immediate and long-term risks associated with operation. These risks are significantly lower for primary valve repair than for valve replacement (Table 264-2). Repair usually consists of valve reconstruction using a variety of

valvuloplasty techniques and insertion of an annuloplasty ring. Repair spares the patient the long-term adverse consequences of valve replacement, including thromboembolic and hemorrhagic complications in the case of mechanical prostheses and late valve failure necessitating repeat valve replacement in the case of bioprostheses. In addition, by preserving the integrity of the papillary muscles, subvalvular apparatus, and chordae tendineae, mitral repair and valvuloplasty maintain LV function to a relatively greater degree than does valve replacement.

Surgery for chronic severe primary MR is indicated once symptoms occur, especially if valve repair is feasible (Fig. 264-1). Surgery should also be recommended for asymptomatic patients with LV dysfunction characterized by an EF ≤ 60% or an LV end-systolic dimension (LV ESD) ≥ 40 mm. Other indications for early consideration of mitral valve repair in asymptomatic patients include a progressive decrease in LVEF or increase in LV ESD on serial imaging

**TABLE 264-2** Mortality Rates after Mitral Valve Surgery<sup>a</sup>

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
MVR (isolated)	10,699	4.5
MVR + CAB	3509	9.6
MVRp	12,424	1.2
MVRp + CAB	4093	5.4

<sup>a</sup>Data are for calendar year 2018 during which 1088 participant groups reported a total of 287,872 procedures. Surgical mitral valve commissurotomy cases are included in the mitral valve repair procedures.

Abbreviations: CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

Source: Adapted from ME Bowdish et al: Ann Thorac Surg 109:1646, 2020.

as well as MV anatomy that would predict a >95% of a successful and durable repair in a low surgical risk patient. These aggressive recommendations for surgery are predicated on the adverse long-term consequences of waiting for LV function to decline further as well as the outstanding results achievable with mitral valve repair by reference surgeons at high-volume centers. Indeed, repair of myxomatous MR (e.g., prolapse, flail) in patients <75 years with normal LV systolic function and no coronary artery disease (CAD) can now be performed by experienced surgeons with <1% perioperative mortality risk. The risk of stroke, however, is also ~1%. Repair is feasible in up to 95% of patients with myxomatous disease operated on by a high-volume surgeon in a referral center of excellence. Repair techniques include chordal transfer, creation of neochords, limited leaflet resection, and insertion of an annuloplasty band. Long-term durability is excellent; the incidence of reoperative surgery for failed primary repair is ~1% per year for the first 10 years after surgery. For patients with AF, left or biatrial maze surgery, or radiofrequency isolation of the pulmonary veins, along with left atrial appendage amputation, is performed to reduce the risk of recurrent postoperative AF and associated thrombus formation.

The surgical management of patients with secondary MR is more complicated. Surgery for patients with ischemic MR most often involves simultaneous coronary artery revascularization. Current surgical practice includes either annuloplasty repair with an undersized, rigid ring or chord-sparing valve replacement for patients with moderate or greater degrees of MR. Valve repair for ischemic MR is associated with lower perioperative mortality rates than valve replacement but significantly higher rates of recurrent MR over time. Thus, replacement may be preferred over repair in this context. In patients with ischemic MR and significantly impaired LV systolic function (EF <30%), the risk of surgery is higher, recovery of LV performance is incomplete, and long-term survival is reduced. Referral for surgery must be individualized and made only after aggressive attempts to improve symptoms with GDMT and CRT, when indicated. The routine performance of surgical valve repair in patients with significant secondary MR due to a dilated cardiomyopathy has not been shown to improve long-term survival compared with optimal GDMT. Patients with acute severe MR can often be stabilized temporarily with appropriate medical therapy, but surgical correction will be necessary emergently in the case of papillary muscle rupture and within days to weeks in most other settings.

When surgical treatment is contemplated, left and right heart catheterization and left ventriculography may be helpful in confirming the presence of severe MR in patients in whom there is a discrepancy between the clinical and TTE findings that cannot be resolved with TEE or CMR. Coronary angiography identifies patients who require concomitant coronary revascularization.

### TRANSCATHETER MITRAL VALVE REPAIR AND REPLACEMENT

A transcatheter approach to the treatment of either primary or secondary MR may be feasible in selected patients with appropriate mitral valve anatomy. One approach involves the deployment of a clip delivered via transseptal puncture that grasps the leading edges of the mitral leaflets in their mid-portion (anterior scallop to posterior scallop or A2-P2; Fig. 264-3). The length and width of the gap between these leading edges, as well as other considerations such as leaflet thickening and calcification, dictate patient eligibility. The clip device for transcatheter edge-to-edge repair (TEER) is commercially available for treatment of both primary and secondary MR in appropriately selected patients (Figs. 264-1 and 264-2). The results of transthoracic and transesophageal echocardiographic imaging are critical to patient selection, along with a detailed assessment of surgical risk, comorbidities, and the adequacy of GDMT for heart failure. The use of TEER with a clip device in addition to medical therapy was shown to be superior to medical therapy alone in a trial involving symptomatic heart failure patients with reduced EF and at least moderately severe secondary MR. Patients treated with the clip device had fewer heart failure hospitalizations and longer survival than those treated



**FIGURE 264-3** Clip used to grasp the free edges of the anterior and posterior leaflets in their midsections during transcatheter repair of selected patients with mitral regurgitation. (*MitraClip* is a trademark of Abbott or its related companies. Reproduced with permission from Abbott © 2021. All rights reserved.)

medically. This was the first trial to show such benefit in patients with secondary MR and has impacted clinical practice. Other transcatheter approaches to mitral valve repair include the deployment of a device within the coronary sinus that can be adjusted to reduce mitral annular circumference and the effective orifice area of the valve much like a surgically implanted ring. Variations in the anatomic relationship of the coronary sinus to the mitral annulus and circumflex coronary artery have limited the applicability of this technique. Attempts to reduce the septal-lateral dimension of a dilated annulus using adjustable cords placed across the LV in a subvalvular location have also been investigated. Construction of neochords to the mitral leaflets under TEE guidance using a system delivered via the cardiac apex is also under study. Investigational experience to date with transcatheter mitral valve replacement systems is in early clinical stages, although the field is evolving rapidly.

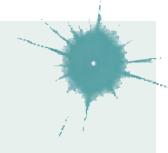
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## Mitral Valve Prolapse

Patrick T. O'Gara, Joseph Loscalzo



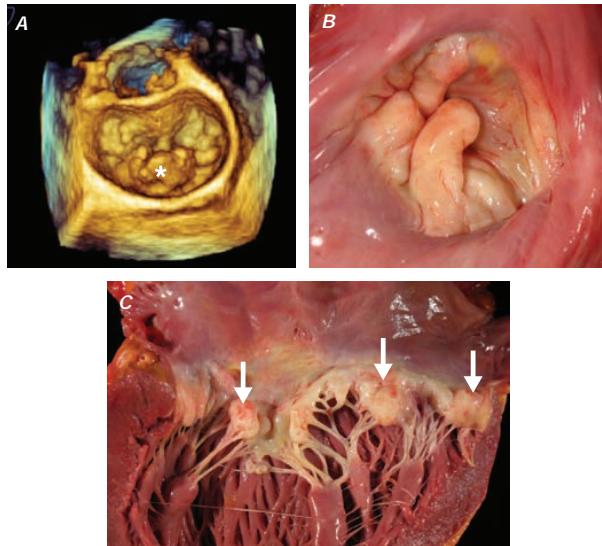
The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in Chaps. 42 and 239; of electrocardiography (ECG) in Chap. 240; of echocardiography and other noninvasive imaging techniques in Chap. 241; and of cardiac catheterization and angiography in Chap. 242.

Mitral valve prolapse (MVP), also variously termed the *systolic click-murmur syndrome*, *Barlow's syndrome* (Fig. 265-1), *floppy-valve syndrome*, and *billowing mitral leaflet syndrome*, is a relatively common but highly variable clinical syndrome resulting from diverse pathologic mechanisms affecting the mitral valve apparatus. Among these are excessive or redundant mitral leaflet tissue, which is commonly associated with myxomatous degeneration and greatly increased concentrations of certain glycosaminoglycans. MVP is the most common abnormality leading to primary mitral regurgitation (MR) (see Chap. 264).

In most patients with MVP, the cause is unknown, but in some, it appears to be genetically determined. A reduction in the production of type III collagen has been implicated, and electron microscopy has revealed fragmentation of collagen fibrils.

MVP is a frequent finding in patients with heritable disorders of connective tissue, including Marfan syndrome (Chap. 413), osteogenesis imperfecta, and Ehlers-Danlos syndrome. MVP may be associated with thoracic skeletal deformities similar to but not as severe as those in Marfan syndrome, such as a high-arched palate and alterations of the chest and thoracic spine, including the so-called straight back syndrome. Other associated features can include a history of inguinal hernias, joint dislocations, meniscal tears, and easy bruising.

In most patients with MVP, myxomatous degeneration is confined to the mitral valve, although the tricuspid and aortic valves may also be affected. The posterior mitral leaflet is usually more affected than the anterior, and the mitral valve annulus is often dilated. In many patients, elongated, redundant, or ruptured chordae tendineae cause or contribute to the regurgitation.



**FIGURE 265-1** Congenital or developmental mitral valve prolapse. Myxomatous thickening and prolapse of the mitral valve can occur in isolation in 2–3% of the general population or may be associated with heritable collagen-vascular disorders and aortic root dilation, such as in Marfan syndrome. Myxomatous degeneration of the valve predisposes to severe regurgitation and chordal rupture and is a frequent indication for mitral valve repair or replacement. Prolapse can affect one or both leaflets, to varying degrees. **A.** Three-dimensional transesophageal echocardiogram showing a myxomatous mitral valve from the left atrial *en face* aspect. There is billowing and prolapse of the entire middle scallop of the posterior leaflet (asterisk). (Figure courtesy of Douglas C. Shook, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital.) **B.** The posterior leaflet of the mitral valve demonstrates marked prolapse and hooding in all segments and severe redundancy in this photograph taken from the vantage point of the left atrium. **C.** Opening the left heart reveals prominent mitral leaflet hooding (arrows). The chordae are focally thickened but are not fused as would be the case in rheumatic valve disease. (Used with permission from JC Wu, RF Padera: Clinicopathologic correlates, in *Atlas of Echocardiography*, 2nd ed, SD Solomon [ed], E Braunwald [series ed]. Philadelphia, Current Medicine Group LLC, 2008, p 363.)

MVP also may occur rarely as a sequel to acute rheumatic fever, in ischemic heart disease, and in various cardiomyopathies, as well as in 20% of patients with ostium secundum atrial septal defect.

MVP may lead to excessive stress on the papillary muscles, which, in turn, leads to dysfunction and ischemia of the papillary muscles and the subjacent ventricular myocardium. Rupture of chordae tendineae and progressive annular dilation and calcification contribute to valvular regurgitation, which then places more stress on the diseased mitral valve apparatus, thereby creating a vicious cycle. ECG changes (see below) and ventricular arrhythmias described in some patients with MVP appear to result from regional ventricular dysfunction and fibrosis related to the increased stress placed on the papillary muscles.

### CLINICAL FEATURES

MVP is more common in women than men and occurs most frequently between the ages of 15 and 30 years; the clinical course is most often benign. MVP may also be observed in older (>50 years) patients, often men, in whom MR is often more severe because of chordal rupture and requires surgical treatment. There is an increased familial incidence for some patients, suggesting an autosomal dominant form of inheritance with incomplete penetrance. MVP varies in its clinical expression, ranging from only a systolic click and murmur with mild prolapse of the posterior leaflet to severe MR due to chordal rupture and leaflet flail. The degree of myxomatous change of the leaflets can also vary widely. In many patients, the condition progresses over years or decades; in others, it worsens rapidly as a result of chordal rupture or endocarditis.

Most patients are asymptomatic and remain so for their entire lives. However, in North America, MVP is now the most common cause of isolated severe MR requiring surgical treatment. Arrhythmias, most commonly ventricular premature contractions and paroxysmal supraventricular and ventricular tachycardia, as well as atrial fibrillation (AF), have been reported and may cause palpitations, lightheadedness, and syncope. Sudden death is a very rare complication and occurs most often in patients with severe MR and depressed left ventricle (LV) systolic function, although it can occur in individuals with normal LV size and function. A small subset of MVP patients with high-grade ventricular ectopy has been identified with phenotypic features including electrocardiographic inferior-apical T-wave abnormalities, high-density premature ventricular complexes at rest, mitral annular disjunction (defined as abnormal atrial displacement of the mitral valve leaflet hinge point), and papillary muscle fibrosis on cardiac magnetic resonance imaging with late gadolinium enhancement. In addition, there may be an excess risk of sudden death among patients with a flail leaflet. Many patients have chest pain that is difficult to evaluate; it is often substernal, prolonged, and not related to exertion, but may rarely resemble angina pectoris. Transient cerebral ischemic attacks secondary to emboli from the mitral valve due to endothelial disruption have been reported. Infective endocarditis may occur in patients with MR and/or leaflet thickening.

**Auscultation** A frequent finding is the mid- or late (nonejection) systolic click, which occurs 0.14 s or more after  $S_1$  and is thought to be generated by the sudden tensing of slack, elongated chordae tendineae or by the prolapsing mitral leaflet when it reaches its maximal excursion. Systolic clicks may be multiple and may be followed by a high-pitched, mid-late systolic crescendo-decrescendo murmur, which occasionally is "whooping" or "honking" and is heard best at the apex. Radiation of the murmur will depend on the involved leaflet. With posterior leaflet prolapse, the jet of MR is directed anteriorly and the murmur will radiate to the base of the heart. With anterior leaflet involvement, the jet of MR is directed posteriorly and the murmur will radiate to the axilla and back. The click and murmur occur earlier with standing, during the strain phase of the Valsalva maneuver and with any intervention that decreases LV volume (preload), exaggerating the propensity of the leaflet to prolapse. Conversely, squatting and isometric exercises, which increase LV volume, diminish MVP; the click-murmur complex is delayed, moves away from  $S_1$ , and may even disappear. Some patients have a mid-systolic click without a murmur; others have a murmur without a click. Still others have both sounds at different times.

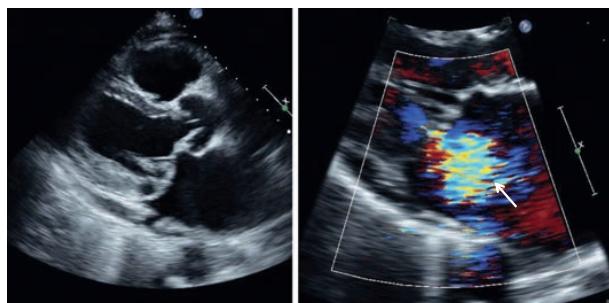
## LABORATORY EXAMINATION

The ECG most commonly is normal but may show biphasic or inverted T waves in leads II, III, and aVF and, occasionally, supraventricular or ventricular premature beats. Transthoracic echocardiography (TTE) is particularly effective in identifying the abnormal position and prolapse of the mitral valve leaflets. A useful echocardiographic definition of MVP is systolic displacement (in the parasternal long axis view) of the belly of the mitral valve leaflets by at least 2 mm into the left atrium (LA) superior to the plane of the mitral annulus. There can be prolapse of one or both leaflets (Fig. 265-2). Color flow and continuous wave Doppler imaging is helpful to evaluate the associated MR and provide estimates of severity. The jet lesion of MR due to MVP is most often eccentric, and assessment of the effective regurgitant orifice area and regurgitant volume can be difficult with standard techniques. Both three-dimensional echocardiography and cardiac magnetic resonance imaging can provide more precise determinations of LV volumes. Transesophageal echocardiography (TEE) is indicated when more accurate anatomic information is required and is performed routinely for intraoperative guidance during valve repair. Exercise testing can be performed when there is uncertainty regarding functional capacity. It is often combined with rest and immediate poststress TTE to assess LV and right ventricular (RV) function and the dynamic nature of MR and pulmonary artery pressures. Left ventriculography done at the time of right and left heart catheterization is rarely necessary but can also show prolapse of the posterior and sometimes of both mitral valve leaflets.

## TREATMENT

### Mitral Valve Prolapse

Infective endocarditis prophylaxis is indicated for patients with a prior history of endocarditis. Beta blockers sometimes relieve chest pain and control palpitations. Decisions regarding anticoagulation for stroke prevention in AF should be based on the CHA2DS2-VASc score and an assessment of bleeding risk. If the patient is symptomatic from severe MR, mitral valve repair is indicated (see Fig. 264-1). Other indications for surgery for MVP with severe primary MR include findings of established or progressive LV systolic dysfunction. Surgery can also be considered for low-risk asymptomatic patients in whom a successful and durable repair can be achieved with at least 95% likelihood by an expert surgeon. Mitral valve repair is preferred over replacement in patients with MVP or flail mitral leaflet (see Table 264-2); technical success is dependent not only on the anatomic findings but also on the skill and experience of the surgeon. Repair of isolated posterior leaflet prolapse is usually straightforward, but increasingly more complex pathologies (e.g., anterior leaflet prolapse, bileaflet prolapse, Barlow's deformity) require advanced skills. Careful pre- and intraoperative TEE imaging is an important component of patient evaluation and surgical planning. Transcatheter edge-to-edge repair (TEER) using a clip to grasp the anterior and posterior leaflets together can be



**FIGURE 265-2.** Barlow's valve with classic mitral valve prolapse, as seen on transthoracic echocardiogram in parasternal long-axis windows. Left: parasternal long-axis window, showing both myxomatous leaflets billowing into the left atrium in late systole. Right: same window with color Doppler showing significant mitral regurgitation (arrow) in systole. (Courtesy of Justina Wu, MD, PhD.)

considered for treatment of symptomatic patients at prohibitive or high surgical risk with severe primary MR due to MVP (see Fig. 264-3). Most often, the MR will be reduced in severity but not eliminated. Nevertheless, symptom status and indices of LV size and function can be improved with this approach, which is now offered at >475 specialized sites in the United States. Reported hospital mortality rates following the procedure are ~2%. Other transcatheter repair and replacement devices are not yet approved for clinical use in the United States (see Chap. 264).

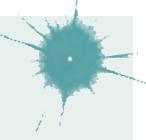
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## 266

### Tricuspid Valve Disease

Patrick T. O'Gara, Joseph Loscalzo



## TRICUSPID STENOSIS

Tricuspid stenosis (TS), which is much less prevalent than mitral stenosis (MS) in North America and Western Europe, is generally rheumatic in origin and is more common in women than men (Table 266-1). It does not occur as an isolated lesion and is usually associated with MS. Hemodynamically significant TS occurs in 5–10% of patients with severe MS; rheumatic TS is commonly associated with some degree of tricuspid regurgitation (TR). Nonrheumatic causes of TS are rare.

## PATHOPHYSIOLOGY

A diastolic pressure gradient between the right atrium (RA) and right ventricle (RV) defines TS. It is augmented when the transvalvular blood flow increases during inspiration and declines during expiration. A mean diastolic pressure gradient of 4 mmHg is usually sufficient to elevate the mean RA pressure to levels that result in systemic venous congestion. Unless sodium intake has been restricted and diuretics administered, this venous congestion is associated with hepatomegaly, ascites, and edema, sometimes severe. In patients with sinus rhythm, the RA wave may be extremely tall and may even approach the level of the RV systolic pressure. The y descent is prolonged. The cardiac output (CO) at rest is usually depressed, and it fails to rise during exercise. The low CO is responsible for the normal or only slightly elevated left atrial (LA), pulmonary artery (PA), and RV systolic pressures despite the presence of MS. Thus, the presence of TS can mask the hemodynamic and clinical features of any associated MS.

## SYMPTOMS

Because the development of MS generally precedes that of TS, many patients initially have symptoms of pulmonary congestion and fatigue. Characteristically, patients with severe TS complain of relatively little dyspnea for the degree of hepatomegaly, ascites, and edema that they have. However, fatigue secondary to a low CO and discomfort due to refractory edema, ascites, and marked hepatomegaly are common in patients with advanced TS and/or TR. In some patients, TS may be suspected for the first time when symptoms of right-sided failure persist after an adequate mitral commissurotomy.

**TABLE 266-1 Causes of Tricuspid Valve Diseases**

VALVE LESION	ETIOLOGIES
Tricuspid stenosis	Rheumatic Congenital
Tricuspid regurgitation	Primary (organic) Rheumatic Endocarditis Myxomatous (TVP) Carcinoid Radiation Congenital (Ebstein's) Trauma (including that due to intracardiac leads and RV endomyocardial biopsy) Papillary muscle injury (post-MI) Secondary (functional) RV and tricuspid annular dilation due to multiple causes (e.g., long-standing pulmonary HTN, remodeling post-RV MI, left-sided heart disease, cardiomyopathy, AF (atrial functional tricuspid regurgitation), chronic RV apical pacing (dyssynchrony)

Abbreviations: AF, atrial fibrillation; HTN, hypertension; MI, myocardial infarction; RV, right ventricular; TVP, tricuspid valve prolapse.

## PHYSICAL FINDINGS

Because TS usually occurs in the presence of other obvious valvular disease, the diagnosis may be missed unless it is considered. Severe TS is associated with marked hepatic congestion, often resulting in cirrhosis, jaundice, serious malnutrition, anasarca, and ascites. Congestive hepatomegaly and, in cases of severe tricuspid valve disease, splenomegaly are present. The jugular veins are distended, and in patients with sinus rhythm, there may be giant *a* waves. The *v* waves are less conspicuous, and because tricuspid obstruction impedes RA emptying during diastole, there is a slow *y* descent. In patients with sinus rhythm, there may be prominent presystolic pulsations of the enlarged liver as well.

On auscultation, an opening snap (OS) of the tricuspid valve may rarely be heard ~0.06 s after pulmonic valve closure. The diastolic murmur of TS has many of the qualities of the diastolic murmur of MS, and because TS almost always occurs in the presence of MS, it may be missed. However, the tricuspid murmur is generally heard best along the left lower sternal border and over the xiphoid process and is most prominent during presystole in patients with sinus rhythm. The murmur of TS is augmented during inspiration, and it is reduced during expiration and particularly during the strain phase of the Valsalva maneuver, when tricuspid transvalvular flow is reduced.

## LABORATORY EXAMINATION

The electrocardiogram (ECG) features of RA enlargement (see Fig. 240-8) include tall, peaked P waves in lead II, as well as prominent, upright P waves in lead V<sub>1</sub>. The absence of ECG evidence of RV hypertrophy (RVH) in a patient with right-sided heart failure who is believed to have MS should suggest associated tricuspid valve disease. The chest x-ray in patients with combined TS and MS shows particular prominence of the RA and superior vena cava without much enlargement of the PA and with less evidence of pulmonary vascular congestion than occurs in patients with isolated MS; engorgement of the azygos vein can often be appreciated. On transthoracic echocardiographic (TTE) examination, the tricuspid valve is usually thickened and domes in diastole; the transvalvular gradient can be estimated by continuous wave Doppler echocardiography. Severe TS is characterized by a valve area  $1 \text{ cm}^2$  or pressure half-time of  $190 \text{ ms}$ . The RA and inferior vena cava (IVC) are enlarged. TTE provides additional information regarding the severity of any associated TR, mitral valve structure and function, left ventricular (LV) and RV size and function, and PA pressure. Cardiac catheterization is not routinely necessary for assessment of TS.

## TREATMENT

### Tricuspid Stenosis

Patients with TS generally exhibit marked systemic venous congestion; salt restriction, bed rest, and diuretic therapy are required during the preoperative period. Such a preparatory period may diminish hepatic congestion and thereby improve hepatic function sufficiently so that the risks of operation, particularly bleeding, are diminished. Surgical relief of the TS should be carried out, preferably at the time of surgical mitral commissurotomy or mitral valve replacement (MVR) for mitral valve disease, in patients with moderate or severe TS who have mean diastolic pressure gradients exceeding  $\sim 4 \text{ mmHg}$  and tricuspid orifice areas  $<1.5\text{--}2 \text{ cm}^2$ . TS is almost always accompanied by significant TR. Operative repair may permit substantial improvement of tricuspid valve function. If repair cannot be accomplished, the tricuspid valve may have to be replaced. Meta-analysis has shown no difference in overall survival between mechanical and tissue valve replacement. Mechanical valves in the tricuspid position are more prone to thromboembolic complications than in other positions. Percutaneous tricuspid balloon commissurotomy for isolated severe TS without significant TR is very rarely performed.

## TRICUSPID REGURGITATION

More than 85% of TR cases encountered in clinical practice are secondary (functional) in nature and related to tricuspid annular dilation and leaflet tethering in the setting of RV remodeling caused by pressure or volume overload (or both), myocardial infarction (MI), or trauma (Table 266-1). Secondary TR is commonly seen in the late stages of heart failure due to rheumatic or congenital heart disease with severe PA hypertension (PA systolic pressure  $>55 \text{ mmHg}$ ), as well as in other types of left-sided valvular (e.g., mitral regurgitation) or myocardial diseases (e.g., ischemic and idiopathic dilated cardiomyopathies). Secondary TR can also develop from chronic RV apical pacing and dyssynchronous contraction; in some patients, the RV leads may also perforate or entrap the TV leaflets. TR can often emerge in the setting of new-onset atrial fibrillation (AF), particularly in older patients (atrial functional TR). Rheumatic fever may produce primary TR, often associated with TS. Tricuspid valve prolapse, carcinoid heart disease, endomyocardial fibrosis, radiation, infective endocarditis, and leaflet trauma can also produce primary TR. Less commonly, primary TR results from congenitally deformed tricuspid valves and can occur with defects of the atrioventricular canal, as well as with Ebstein's malformation of the tricuspid valve (Chap. 269).

## PATHOPHYSIOLOGY

The incompetent tricuspid valve allows blood to flow backward from the RV into the RA, the volume of which is dependent on the driving pressure (i.e., RV systolic pressure) and the size of the regurgitant orifice. The severity and physical signs of TR can vary as a function of PA systolic pressure (in the absence of RV outflow tract stenosis), the dimension of the tricuspid valve annulus, the respiratory cycle-dependent changes in RV preload, and RA compliance. RV filling is increased during inspiration. Forward CO is reduced and does not augment with exercise. Significant degrees of TR will lead to RA enlargement and elevation of the RA and jugular venous pressures with prominent *c-v* waves in the pulse tracings. Progressively severe TR can lead to "ventricularization" of the RA wave form (see Fig. 239-1B). Severe TR is also characterized by RV dilation (RV volume overload) and eventual systolic dysfunction, the progression of which can be accelerated by a concomitant pressure load from PA hypertension or by myocardial fibrosis from previous injury.

## SYMPTOMS

Mild or moderate degrees of TR are usually well tolerated in the absence of other hemodynamic disturbances. Because TR most often coexists with left-sided valve lesions, LV dysfunction, and/or PA hypertension, symptoms related to these lesions may dominate the clinical picture. Fatigue and exertional dyspnea owing to reduced forward CO are early symptoms of isolated, severe TR. As the disease progresses and RV

function declines, patients may report cervical pulsations, abdominal fullness/bloating, diminished appetite, and muscle wasting, although with progressive weight gain and painful swelling of the lower extremities.

## PHYSICAL FINDINGS

The neck veins in patients with severe TR are distended with prominent *c-v* waves and rapid *y* descents (in the absence of TS). TR is more often diagnosed by examination of the neck veins than by auscultation of the heart sounds. Other findings may include marked hepatomegaly with systolic pulsations, ascites, pleural effusions, edema, and a positive hepatojugular reflux sign. A prominent RV pulsation in the left parasternal region and a blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration (Carvallo's sign) and reduced during expiration or the strain phase of the Valsalva maneuver, are characteristic findings. The murmur of TR may sometimes be confused with that of mitral regurgitation (MR) unless attention is paid to its variation during the respiratory cycle and the extent of RV enlargement is appreciated. AF is usually present in the chronic phase of the disease.

## LABORATORY EXAMINATION

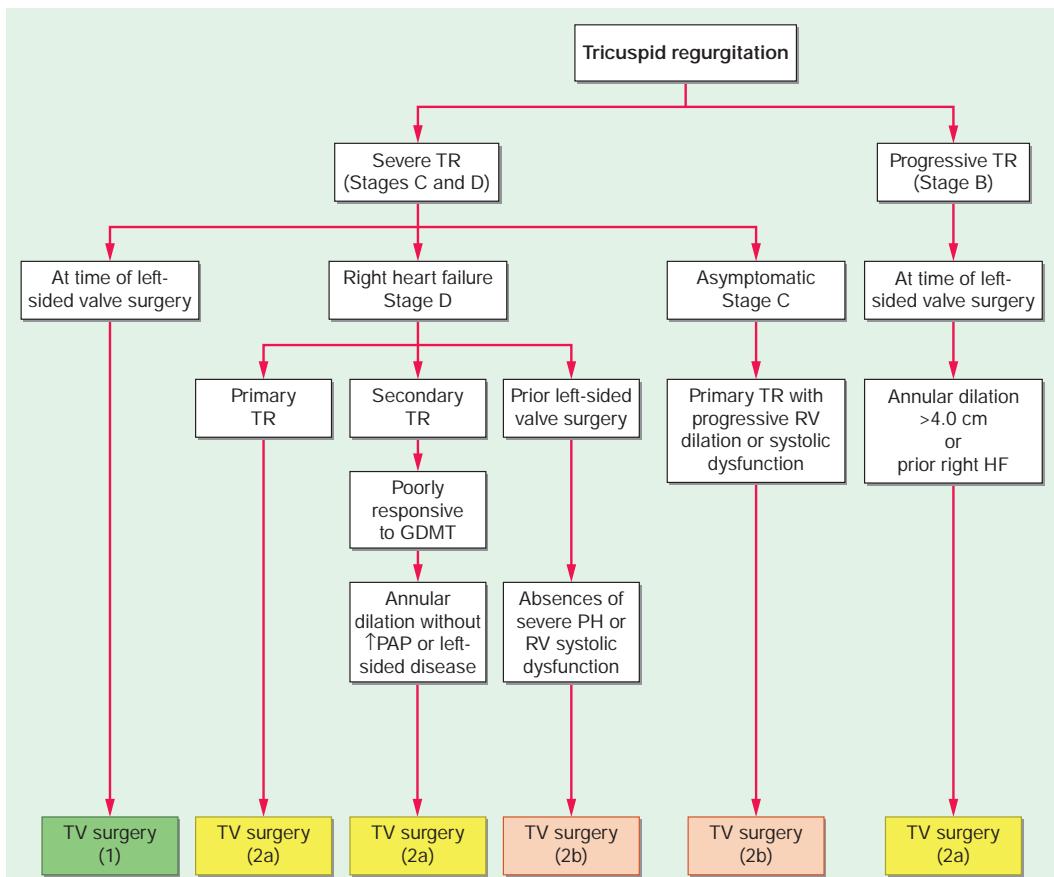
The ECG may show changes characteristic of the lesion responsible for the TR, e.g., an inferior Q-wave MI suggestive of a prior RV MI, RVH, or a bizarre right bundle branch block-type pattern with preexcitation in patients with Ebstein's anomaly. ECG signs of RA enlargement may be present in patients with sinus rhythm; AF is frequently noted. The chest x-ray may show RA and RV enlargement, depending on the chronicity

and severity of TR. TTE is usually definitive with demonstration of RA dilation and RV volume overload and prolapsing, flail, scarred, or displaced/tethered tricuspid leaflets with annular dilatation; the diagnosis and assessment of TR can be made by color flow Doppler imaging (see Fig. 241-8). Severe TR is accompanied by hepatic vein systolic flow reversal. Continuous wave Doppler of the TR velocity profile is useful in estimating PA systolic pressure, except when the TR is very severe and the jet velocity is blunted by rapidly increasing RA pressure. Accurate assessment of TR severity, PA pressures, and RV size and systolic function with TTE can be quite challenging in many patients. Real-time three-dimensional echocardiography and cardiac magnetic resonance (CMR) imaging provide alternative imaging modalities, although they are not widely available. In patients with severe TR, the CO is usually markedly reduced, and the RA pressure pulse may not exhibit an *x* descent during early systole but rather show a prominent *c-v* wave with a rapid *y* descent. The mean RA and RV end-diastolic pressures are often elevated. Exercise testing can be used to assess functional capacity in patients with asymptomatic severe TR. The prognostic significance of exercise-induced changes in TR severity and RV function has not been well studied.

## TREATMENT

### Tricuspid Regurgitation (Fig. 266-1)

Diuretics can be useful for patients with severe TR and signs of right heart failure. An aldosterone antagonist may be particularly



**FIGURE 266-1 Management of tricuspid regurgitation.** See legend for Fig. 261-4 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. GDMT, guideline-directed management and therapy; HF, heart failure; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RV, right ventricular; TR, tricuspid regurgitation; TV, tricuspid valve. Annular dilation is defined by >40 mm on transthoracic echocardiography ( $>21 \text{ mm/m}^2$ ) or >70 mm on direct intraoperative measurement. (Reproduced with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 143:e72, 2021.)

helpful because many patients have secondary hyperaldosteronism from marked hepatic congestion. Therapies to reduce elevated PA pressures and/or pulmonary vascular resistance, including those targeted at left-sided heart disease, can also be considered for patients with PA hypertension and severe secondary TR. Tricuspid valve surgery is recommended for patients with severe TR who are undergoing left-sided valve surgery and is also undertaken frequently for treatment of even moderate TR in patients undergoing left-sided valve surgery who have tricuspid annular dilation ( $>40$  mm), a history of right heart failure, or PA hypertension. Operation most often comprises repair rather than replacement in these settings and has become routine in most major surgical centers. Surgery may also infrequently be required for treatment of severe, primary TR with right heart failure not responsive to standard medical therapy or because of progressively declining RV systolic function. Reported perioperative mortality rates for isolated tricuspid valve surgery (repair and replacement) are high (~8–9%) and likely are influenced by the hazards encountered during reoperation on patients who have undergone previous left-sided valve surgery and have reduced RV function. Indwelling pacemaker or defibrillator leads can also pose technical challenges. Investigation of transcatheter tricuspid valve repair and replacement systems is ongoing.

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## Pulmonic Valve Disease

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### PULMONIC STENOSIS

Pulmonic valve stenosis (PS) is essentially a congenital disorder (**Table 267-1**). With isolated PS, the valve is typically domed. Dysplastic pulmonic valves are seen as part of the Noonan syndrome (**Chap. 281**), which maps to chromosome 12. Mutations in the *PTPN1* gene are associated with about half of all cases of Noonan syndrome. Much less common etiologies include carcinoid and obstructing tumors or bulky vegetations. The pulmonic valve is only very rarely affected by the rheumatic process.

#### PATOPHYSIOLOGY

PS is defined hemodynamically by a systolic pressure gradient between the right ventricle (RV) and the main pulmonary artery (PA). RV hypertrophy (RVH) develops as a consequence of sustained obstruction to RV outflow, and systolic ejection is prolonged. Compared with the ability of the LV to compensate for the pressure overload imposed by aortic stenosis (AS), RV dysfunction from afterload mismatch occurs earlier in the course of PS and at lower peak systolic pressures, because the RV adapts

**TABLE 267-1 Causes of Pulmonic Valve Disease**

VALVE LESION	ETIOLOGIES
Pulmonic stenosis	Congenital Carcinoid Tumor Endocarditis
Pulmonic regurgitation	Primary valve disease Congenital Post-valvotomy Endocarditis Carcinoid Annular enlargement Pulmonary hypertension Idiopathic dilation Marfan syndrome

less well to this type of hemodynamic burden. With normal systolic function and cardiac output (CO), severe PS is defined by a peak systolic gradient across the pulmonic valve of  $>64$  mmHg (mean gradient  $>35$  mm Hg, Doppler jet velocity  $>4$  m/s); moderate PS correlates with a peak gradient of 36–64 mmHg (Doppler jet velocity 3–4 m/s). Mild PS is characterized by a jet velocity  $<3$  m/s (peak gradient  $<36$  mmHg). PS rarely progresses in patients with mild PS mmHg but may worsen in those with moderate disease due to valve thickening and calcification with age. The right atrial (RA)  $\alpha$  wave elevates in relation to the higher pressures needed to fill a noncompliant, hypertrophied RV. A prominent RA  $v$  wave signifies functional tricuspid regurgitation (TR) from RV and annular dilation. The CO is maintained until late in the course of the disease.

#### SYMPTOMS

Patients with mild or even moderate PS are usually asymptomatic and first come to medical attention because of a heart murmur (or early systolic click) that leads to echocardiography. With severe PS, patients may report exertional dyspnea or early-onset fatigue. Anginal chest pain from RV oxygen supply-demand mismatch and syncope may occur with very severe forms of obstruction, particularly in the presence of a destabilizing trigger such as atrial fibrillation, fever, infection, anemia, or pregnancy.

#### PHYSICAL FINDINGS

The murmur of mild or moderate PS is mid-systolic in timing, crescendo–decrescendo in configuration, heard best in the left second interspace, and usually introduced by an ejection sound (click) in younger adults whose valves are still pliable. The ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. This phenomenon reflects premature opening of the pulmonic valve by the elevated RV end-diastolic (post-atrial  $a$  wave) pressure. The systolic murmur increases in intensity during inspiration. With progressively severe PS, the ejection sound moves closer to the first heart sound and eventually becomes inaudible. A right-sided fourth heart sound may emerge. The systolic murmur peaks later and may persist through the aortic component of the second heart sound ( $A_2$ ). Pulmonic valve closure is delayed, and the pulmonic component of the second heart sound ( $P_2$ ) is reduced or absent. A prominent  $a$  wave, indicative of the higher atrial pressure necessary to fill the noncompliant RV, may be seen in the jugular venous pulse. A parasternal or RV lift can be felt with significant pressure overload. Signs of right heart failure, such as hepatomegaly, ascites, and edema, are uncommon but may appear very late in the disease.

#### LABORATORY EXAMINATION

The electrocardiogram (ECG) will show right axis deviation, RVH, and RA enlargement in adult patients with severe PS. Chest x-ray findings include poststenotic dilation of the main PA in the frontal plane projection and filling of the retrosternal airspace due to RV enlargement on

the lateral film. In some patients with RVH, the cardiac apex appears to be lifted off the left hemidiaphragm. The RA may also be enlarged. Transthoracic echocardiography (TTE) allows definitive diagnosis and characterization in most cases, with depiction of the valve and assessment of the jet velocity, gradient, RV function, PA pressures (which should be low), and any associated cardiac lesions. Transesophageal echocardiography (TEE) may be useful in some patients for improved delineation of the RV outflow tract (RVOT) and assessment of infundibular hypertrophy. Cardiac catheterization is not usually necessary for diagnostic purposes, but if performed, pressures should be obtained from just below and above the pulmonic valve with attention to the possibility that a dynamic component to the gradient may exist. The correlation between Doppler assessment of peak instantaneous gradient and catheterization-measured peak-to-peak gradient is weak. The latter may correlate better with the Doppler mean gradient.

## TREATMENT

### Pulmonic Stenosis

Diuretics can be used to treat symptoms and signs of right heart failure. Provided there is less than moderate pulmonic regurgitation (PR), percutaneous pulmonic balloon valvuloplasty is recommended for symptomatic patients with moderate or severe PS and for asymptomatic patients with a peak gradient  $>64$  mmHg (or mean gradient  $>35$  mmHg). Surgery may be required when the valve is dysplastic (as seen in patients with Noonan's syndrome and other disorders). A multidisciplinary heart team is best positioned to make treatment decisions of this nature.

## PULMONIC REGURGITATION

PR may develop as a consequence of primary valve pathology, annular enlargement, or their combination; after surgical treatment of RVOT obstruction in children with such disorders as tetralogy of Fallot; or after percutaneous pulmonic balloon valvotomy (Table 267-1). Carcinoid usually causes mixed pulmonic valve disease with PR and PS. Long-standing severe PA hypertension from any cause can result in dilation of the pulmonic valve ring and PR.

### PATHOPHYSIOLOGY

Severe PR results in RV chamber enlargement and eccentric hypertrophy. As is the case for aortic regurgitation (AR), PR is a state of increased preload and afterload. The reverse pressure gradient from the PA to the RV, which drives the PR, progressively decreases throughout diastole and accounts for the decrescendo nature of the diastolic murmur. As RV diastolic pressure increases, the murmur becomes shorter in duration. The forward CO is preserved during the early stages of the disease but may not increase normally with exercise and declines over time. A reduction in RV ejection fraction may be an early indicator of hemodynamic compromise. In advanced stages, there is significant enlargement of the RV and RA with marked elevation of the jugular venous pressure.

### SYMPTOMS

Mild or moderate degrees of PR do not, by themselves, result in symptoms. Other issues, such as PA hypertension, may dominate the clinical picture. With progressively severe PR and RV dysfunction, fatigue, exertional dyspnea, abdominal fullness/bloating, and lower extremity swelling may be reported.

### PHYSICAL FINDINGS

The physical examination hallmark of PR is a high-pitched, decrescendo diastolic murmur (Graham Steell murmur) heard along the left sternal border that can be difficult to distinguish from the more frequently appreciated murmur of AR. The Graham Steell murmur may become louder with inspiration and is usually associated with a loud and sometimes palpable P<sub>2</sub> and an RV lift, as would be expected in patients with significant PA hypertension of any cause. Survivors of childhood surgery for tetralogy of Fallot or PS/pulmonary atresia may have an RV-PA conduit that is freely regurgitant because it does

not contain a valve. PA pressures in these individuals are not elevated, and the diastolic murmur can be misleadingly low pitched and of short duration despite significant degrees of PR and RV volume overload.

## LABORATORY EXAMINATION

Depending on both the etiology and severity of PR, the ECG may show findings of RVH and RA enlargement. On chest x-ray, the RV and RA may be enlarged. Pulmonic valve morphology and function can be assessed with transthoracic Doppler echocardiography. RV systolic pressure can be estimated from the tricuspid valve systolic jet velocity. Cardiac magnetic resonance (CMR) imaging can provide greater anatomic detail, particularly in patients with repaired congenital heart disease, and more precise assessment of RV volumes and function. Cardiac catheterization is not routinely necessary but would be performed as part of a planned transcatheter PV procedure.

## TREATMENT

### Pulmonic Regurgitation

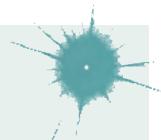
In patients with functional PR due to PA hypertension and annular dilation, efforts to reduce PA vascular resistance and pressure should be pursued. Such efforts may include pharmacologic/vasodilator and/or surgical/interventional strategies, depending on the cause of the PA hypertension (e.g., idiopathic PA hypertension, left-sided heart valve disease). Diuretics can be used to treat the manifestations of right heart failure. Surgical valve replacement for primary, severe, pulmonic valve disease, such as carcinoid or endocarditis, is rarely undertaken. Transcatheter pulmonic valve replacement has been successfully performed in many patients with severe PR after childhood repair of tetralogy of Fallot or pulmonic valve stenosis or atresia. This procedure was introduced clinically prior to transcatheter aortic valve replacement.

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## Multiple and Mixed Valvular Heart Disease



Patrick T. O'Gara, Joseph Loscalzo

Many acquired and congenital cardiac lesions may result in stenosis and/or regurgitation of one or more heart valves. For example, rheumatic heart disease can involve the mitral (mitral stenosis [MS], mitral regurgitation [MR], or MS and MR), aortic (aortic stenosis [AS], aortic regurgitation [AR], or AS and AR), and tricuspid (tricuspid stenosis [TS], tricuspid regurgitation [TR], or TS and TR) valve, alone or in combination. The common association of functional TR with significant mitral valve disease is discussed in [Chap. 266](#). Severe mitral annular calcification can result in regurgitation (due to decreased annular shortening during systole) and mild or moderate stenosis (caused by extension of the calcification onto the leaflets resulting in restricted valve opening). Patients with severe AS and LV remodeling may develop functional MR that may not improve after isolated aortic

valve replacement (AVR). Primary MR due to mitral valve prolapse or chordal rupture has been noted in patients with severe AS. Aortic valve infective endocarditis (IE) may secondarily involve the mitral apparatus either by abscess formation and contiguous spread via the intervalvular fibrosa or by “drop metastases” from the aortic leaflets onto the anterior leaflet of the mitral valve. Mediastinal radiation may result in aortic, mitral, and even tricuspid valve disease, most often with mixed stenosis and regurgitation. Carcinoid heart disease may cause mixed lesions of either or both the tricuspid and pulmonic valves. Ergotamines, and the previously used combination of fenfluramine and phenetermine, can rarely result in mixed lesions of the aortic and/or mitral valve. Patients with Marfan syndrome may have both AR from aortic root dilation and MR due to mitral valve prolapse (MVP). Myxomatous degeneration causing prolapse of multiple valves (mitral, aortic, tricuspid) can also occur in the absence of an identifiable connective tissue disorder. Bicuspid aortic or pulmonic valve disease can result in mixed stenosis and regurgitation. The former is also associated with aortic aneurysm disease and a predisposition to aortic dissection.

### PATOPHYSIOLOGY

In patients with multivalvular heart disease, the pathophysiologic derangements associated with the more proximal valve disease can mask the full expression of the attributes of the more distal valve lesion. For example, in patients with rheumatic mitral and aortic valve disease, the reduction in cardiac output (CO) imposed by the mitral valve disease will decrease the magnitude of the hemodynamic derangements related to the severity of the aortic valve lesion (stenotic, regurgitant, or both). Alternatively, the development of atrial fibrillation (AF) during the course of MS can lead to sudden worsening in a patient whose aortic valve disease was not previously felt to be significant. The development of reactive pulmonary vascular disease, sometimes referred to as a “secondary obstructive lesion in series,” can impose an additional challenge in these settings. As CO falls with progressive tricuspid valve disease, the severity of any associated mitral or aortic disease can be underestimated.

One of the most common examples of multivalve disease is that of functional TR in the setting of significant mitral valve disease. Functional TR occurs as a consequence of right ventricular and annular dilation; pulmonary artery (PA) hypertension may be present. The tricuspid leaflets are morphologically normal. Progressive degrees of TR lead to right ventricular volume overload and continued chamber and annular dilation. The TR is usually central in origin; reflux into the right atrium (RA) is expressed as large, systolic *c-v* waves in the RA pressure pulse. The height of the *c-v* wave is dependent on RA compliance and the volume of regurgitant flow. The RA waveform may become “ventricularized” in advanced stages of chronic, severe TR. CO falls and the severity of the associated mitral valve disease may become more difficult to appreciate. Findings related to advanced right heart failure (e.g., ascites, edema) predominate. Primary rheumatic tricuspid valve disease may occur with rheumatic mitral disease and cause hemodynamic changes reflective of TR, TS, or their combination. With TS, the *y* descent in the RA pressure pulse is prolonged. Typically, findings related to the mitral valve disease predominate over those related to the tricuspid valve disease.

Another example of rheumatic, multivalve disease involves the combination of mitral and aortic valve pathology, frequently characterized by MS and AR. In isolated MS, left ventricular (LV) preload and diastolic pressure are reduced as a function of the severity of inflow obstruction. With concomitant AR, however, LV filling is enhanced and diastolic pressure may rise depending on the compliance characteristics of the chamber. Because the CO falls with progressive degrees of MS, transaortic valve flows will decline, masking the potential severity of the aortic valve lesion (AR, AS, or its combination). As noted above, onset of AF in such patients can be especially deleterious. The loss of atrial systole with AF may result in a critical reduction in CO, a rise in LA and LV diastolic pressures, and a further deleterious increase in heart rate.

Secondary (functional) MR may complicate the course of some patients with severe AS. The mitral valve leaflets and chordae tendineae are usually normal. Incompetence is related to changes in LV geometry

(remodeling) and abnormal systolic tethering of the leaflets in the context of markedly elevated LV systolic pressures. Relief of the excess afterload with surgical or transcatheter AVR may result in reduction of the secondary MR. Persistence of significant, secondary MR following AVR is associated with impaired functional outcomes and reduced survival. Identification of patients who would benefit from concomitant treatment of their secondary MR at time of AVR is quite challenging. Most surgeons advocate for repair of moderate-to-severe or severe secondary MR at time of surgical AVR. Significant primary MR may also coexist with AS and is routinely managed with repair or replacement at the time of AVR. There is increasing experience with the combination of transcatheter aortic valve implantation (TAVI) and transcatheter edge-to-edge mitral valve repair (TEER) in high surgical risk patients with severe AS and moderate-severe primary or secondary MR.

In patients with mixed AS and AR, assessment of valve stenosis can be influenced by the magnitude of the regurgitant valve flow. Because transvalvular systolic flow velocities are augmented in patients with AR and preserved LV systolic function, the LV-aortic Doppler-derived pressure gradient and the intensity of the systolic murmur will be elevated to values higher than expected for the true systolic valve orifice size as measured by planimetry. Uncorrected, the Gorlin formula, which relies on forward CO (systolic transvalvular flow) and the mean pressure gradient for calculation of valve area, is not accurate in the setting of mixed aortic valve disease. Similar considerations apply to patients with mixed mitral valve disease. The peak mitral valve Doppler E wave velocity ( $v_e$ ) is increased in the setting of severe MR because of enhanced early diastolic flow and may not accurately reflect the contribution to left atrial (LA) hypertension from any associated MS. When either AR or MR is the dominant lesion in patients with mixed aortic or mitral valve disease, respectively, the LV is dilated. When AS or MS predominates, LV chamber size will be normal or small. It can sometimes be difficult to ascertain whether stenosis or regurgitation is the dominant lesion in patients with mixed valve disease, although an integrated clinical and noninvasive assessment can usually provide clarification for purposes of patient management. For patients with moderate, mixed AS and AR in whom stenosis is the dominant lesion, the natural history tends to parallel what might be expected for isolated severe AS, and the treatment approach should be accordingly aligned.

Patients with significant AS, a nondilated LV chamber, and concentric hypertrophy will poorly tolerate the abrupt development of aortic regurgitation, as may occur, for example, with IE or after surgical AVR or TAVI complicated by paravalvular leakage. The noncompliant LV is not prepared to accommodate the sudden volume load, and as a result, LV diastolic pressure rises rapidly and severe heart failure develops. Indeed, paravalvular regurgitation is a significant risk factor for short-to intermediate-term death following transcatheter AVR. Conditions in which the LV may not be able to dilate in response to chronic AR (or MR) include radiation heart disease and, in some patients, the cardiomyopathy associated with obesity and diabetes. Noncompliant ventricles of small chamber size predispose to earlier onset diastolic dysfunction and heart failure in response to any further perturbation in valve function.

### SYMPTOMS

Compared with patients with isolated, single-lesion valve disease, patients with multiple or mixed valve disease may develop symptoms at a relatively earlier stage in the natural history of their disease. Symptoms such as exertional dyspnea and fatigue are usually related to elevated filling pressures, reduced CO, or their combination. Palpitations may signify AF and identify mitral valve disease as an important component of the clinical presentation, even when not previously suspected. Chest pain compatible with angina could reflect left or right ventricular oxygen supply/demand mismatch on a substrate of hypertrophy and pressure/volume overload with or without superimposed coronary artery disease. Symptoms related to right heart failure (abdominal fullness/bloating, edema) are late manifestations of advanced disease.

### PHYSICAL FINDINGS

Mixed disease of a single valve is most often manifested by systolic and diastolic murmurs, each with the attributes expected for the valve in

question. Thus, patients with AS and AR will have characteristic mid-systolic, crescendo-decrescendo and blowing, decrescendo diastolic murmurs at the base of the heart in the second right interspace and along the left sternal edge, respectively. Many patients with significant AR have mid-systolic outflow murmurs even in the absence of valve sclerosis/stenosis, and other findings of AS must be sought. The separate murmurs of AS and AR can occasionally be difficult to distinguish from the continuous murmurs associated with either a patent ductus arteriosus (PDA) or ruptured sinus of Valsalva aneurysm. With mixed aortic valve disease, the systolic murmur should end before, and not envelope or extend through, the second heart sound ( $S_2$ ). The murmur associated with a PDA is heard best to the left of the upper sternum. The continuous murmur heard with a ruptured sinus of Valsalva aneurysm is often first appreciated after an episode of acute chest pain. An early ejection click, which usually defines bicuspid aortic valve disease in young adults, is often not present in patients with congenital mixed AS and AR. As noted above, both the intensity and duration of these separate murmurs can be influenced by a reduction in CO and transvalvular flow due to coexistent mitral valve disease. In patients with isolated MS and MR, expected findings would include a blowing, holosystolic murmur and a mid-diastolic rumble (with or without an opening snap) best heard at the cardiac apex. An irregularly irregular heart rhythm in such patients would likely signify AF. Findings with TS and TR would mimic those of left-sided MS and MR, save for the expected changes in the murmurs with respiration. The murmurs of pulmonic stenosis and regurgitation behave in a fashion directionally similar to AS and AR; dynamic changes during respiration should be noted. Specific attributes of these cardiac murmurs are reviewed in **Chaps. 42 and 266**.

## LABORATORY EXAMINATION

The electrocardiogram (ECG) may show evidence of ventricular hypertrophy and/or atrial enlargement. ECG signs indicative of right-sided cardiac abnormalities in patients with left-sided valve lesions should prompt additional assessment for PA hypertension and/or right-sided valve disease. The presence of AF in patients with aortic valve disease may be a clue to the presence of previously unsuspected mitral valve disease in the appropriate context. The chest x-ray can be reviewed for evidence of cardiac chamber enlargement, valve and/or annular calcification, and any abnormalities in the appearance of the pulmonary vasculature. The latter could include enlargement of the main and proximal pulmonary arteries with PA hypertension and pulmonary venous redistribution/engorgement or Kerley B lines with increasing degrees of LA hypertension. An enlarged azygos vein in the frontal projection indicates RA hypertension. Roentgenographic findings not expected based on a single or mixed valve lesion may reflect other valve disease.

Transthoracic echocardiography (TTE) is the most commonly used imaging modality for the diagnosis and characterization of multiple and/or mixed valvular heart disease and may often demonstrate findings not clinically suspected. Transesophageal echocardiography (TEE) may sometimes be required for more accurate assessment of valve anatomy (specifically, the mitral valve) and when IE is considered responsible for the clinical presentation. TTE findings of particular interest include those related to valve morphology and function, calcification, chamber size, ventricular wall thickness, biventricular function estimated PA systolic pressure, and the dimensions of the great vessels, including the root and ascending aorta, PA, and inferior vena cava. Exercise testing (with or without echocardiography) can be useful when the degree of functional limitation reported by the patient is not adequately explained by the findings on TTE performed at rest. An integrated assessment of the clinical and TTE findings is needed to help determine the dominant valve lesion(s) and establish an appropriate plan for treatment and follow-up. Natural history is usually influenced to a relatively greater degree by the dominant lesion.

Cardiac magnetic resonance (CMR) imaging can be used to provide additional anatomic and physiologic information when echocardiography proves suboptimal but is less well suited to the evaluation of valve morphology. Cardiac computed tomography (CT) has been used

to assess intracardiac structures in patients with complicated IE. It is invaluable in planning for transcatheter valve implantation. Coronary CT angiography provides a noninvasive alternative for the assessment of coronary artery anatomy prior to surgery or transcatheter intervention.

Invasive hemodynamic evaluation with right and left heart catheterization may be required to characterize more completely the individual contributions of each lesion in patients with either multiple or mixed valvular heart disease. It is strongly recommended when there is a discrepancy between the clinical and noninvasive findings in a symptomatic patient. Measurement of PA pressures and calculation of pulmonary vascular resistance (PVR) can help inform clinical decision-making in certain patient subsets, such as those with advanced mitral and tricuspid valve disease. It is important to identify any potential contribution to the clinical picture from pulmonary vascular disease. Attention to the accurate assessment of CO is essential. Coronary angiography (if indicated) can be performed as part of the procedure. Contrast ventriculography and great vessel angiography are performed infrequently.

## TREATMENT

### Multiple and Mixed Valve Disease

Management of patients with multiple or mixed valve disease can be challenging. As noted above, it is helpful to determine the dominant valve lesion and proceed according to the treatment and follow-up recommendations for it (**Chaps. 261–267**), being mindful of deviations from the expected course due to the contributions of more than one valve lesion. For example, AF that emerges in the course of moderate mitral valve disease may precipitate heart failure in patients with concomitant, severe aortic valve disease that was previously asymptomatic.

Medical therapies are limited and include diuretics when indicated for relief of congestion and anticoagulation to prevent stroke and thromboembolism in patients with AF. Blood pressure-lowering medications may be needed to treat systemic hypertension, which may aggravate left-sided regurgitant valve lesions, but should be initiated and titrated carefully. Pulmonary vasodilators to lower PVR are not generally effective in this context.

There is a paucity of evidence to inform practice guidelines for surgical and/or transcatheter valve intervention in patients with multiple or mixed valve disease. When there is a clear, dominant lesion, as for example in a patient with severe AS and mild AR, indications for intervention are straightforward and follow those recommended for patients with AS (**Chap. 261**). In other patients, however, there is less clarity, and decisions regarding intervention should be based on several considerations, including those related to lesion severity, ventricular remodeling, functional capacity, and PA pressures. In this regard, it is important to realize that patients with multiple and/or mixed valve disease may develop limiting symptoms or signs of physiologic impairment even with moderate valve lesions.

Concomitant aortic and mitral valve replacement surgery is associated with a significantly higher perioperative mortality risk than replacement of either valve alone, and operation should be carefully considered. Double valve replacement surgery is usually performed for treatment of severe (unrepairable) valve disease at both locations and for the combination of severe disease at one location with moderate disease at the other to avoid the hazards of reoperation in the intermediate to late term for progressive disease of the unoperated valve. In addition, the presence of a prosthesis in the aortic position significantly restricts surgical exposure of the native mitral valve. The need for double valve replacement may also impact the decision regarding the type of prosthesis (i.e., mechanical vs tissue).

Tricuspid valve repair for moderate or severe secondary (functional) TR at the time of left-sided valve surgery is now commonplace, particularly if there is dilation of the tricuspid annulus

(>40 mm). The addition of tricuspid valve repair, consisting usually of insertion of an annuloplasty ring, adds little time or complexity to the procedure and is well tolerated. Reoperation for repair (or replacement) of progressive TR years after initial surgery for left-sided valve disease, on the other hand, is associated with a relatively high perioperative mortality risk. Mitral valve repair or replacement for moderate or severe secondary MR at time of AVR for AS can usually be undertaken with acceptable risk for perioperative death or major complication.

The presence of moderate or severe MR in patients with rheumatic MS is a contraindication to percutaneous mitral balloon commissurotomy (PMBC). TAVI can be performed for mixed AS and AR when the anatomic findings related to annulus size, coronary height, and the distribution of calcium are favorable. Transcatheter management of both severe AS and severe primary or secondary MR (with deployment of an edge-to-edge clip) has been undertaken with increasing frequency in appropriately selected patients with prohibitive or high surgical risk. Further advances in transcatheter treatments for multiple and mixed valve disease are anticipated.

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## Congenital Heart Disease in the Adult

Anne Marie Valente, Michael J. Landzberg

### PREVALENCE

The number of adults with congenital heart disease (CHD) living in the United States is estimated to be at least 1.4 million, with just over one in five having a complex form of CHD. The majority of adults with CHD were diagnosed in childhood, although a substantial percentage may have CHD first recognized as adults. Lifelong follow-up in coordination with, or directly by, clinicians with expertise in adult congenital heart disease (ACHD) is recommended. In this chapter, we will review the current field of ACHD, with an introduction to CHD nomenclature and cardiac development. This is followed by a summary of the more common CHD lesions that may be diagnosed in adulthood. Lastly, some of the common repaired CHD lesions that are encountered in adults are discussed. Throughout the chapter, to aid in the understanding of congenital cardiac anatomy and physiology, we include figures displaying the passage of blood flow between blood vessels and cardiac chambers in various disorders (Fig. 269-1).

### THE CHANGING LANDSCAPE OF ADULT CHD

**A Relatively New Subspecialty in Cardiovascular Disease**  
Over the past decade, the field of caring for adults with CHD (ACHD) has blossomed, and several nationwide initiatives have been initiated in an attempt to standardize care. The American College of Cardiology and American Heart Association developed guidelines for the care of adults with CHD, first published in 2008 and revised in 2018. These guidelines emphasize the need for collaboration among primary care practitioners, cardiologists, and ACHD subspecialty cardiologists. The

body of medical knowledge and competencies attendant with ACHD combined with skill acquisition in coordination of complex care over a patient's medical lifetime led in 2015 to ACHD board certification examinations by the American Board of Medical Subspecialties, as well as the establishment of requirements for advanced fellowship training in ACHD care by the Accreditation Council for Graduate Medical Education. In temporal association, the Adult Congenital Heart Association (ACHA) developed a process for ACHD care program accreditation based on standardization of infrastructural components felt requisite to achieve quality outcomes for ACHD.

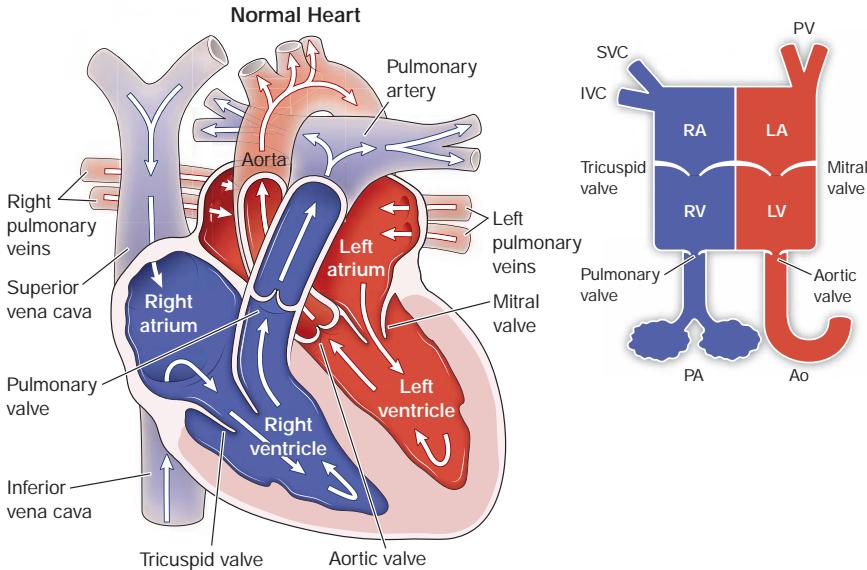
### SPECIAL CONSIDERATIONS FOR THE ACHD PATIENT

Adults with CHD may not recognize subtle changes in their exercise capacity, some of which are associated with worse survival; by the time symptoms are recognized, irreversible physiologic changes may have occurred. ACHD patients are, therefore, advised to undergo regular evaluations for surveillance of anatomic, hemodynamic, and electrophysiologic sequelae that may be present. In addition, specific situations may arise in which it is prudent to review care in consultation with an ACHD specialist, several of which are outlined below.

**Non-Cardiac Surgery** Nearly all adults with CHD can be classified with stage A (harboring risk) or greater degrees of heart failure. As such, adults with CHD may demonstrate limited hemodynamic reserve to altered myocardial perfusion or loading conditions and may have subclinical organ dysfunction that is not recognized by standard laboratory assessment. Comprehensive, multispecialty assessment and care strategy review are recommended in advance of invasive or operative procedures for adults with CHD. Table 269-1 lists the multiorgan considerations that should be considered in adults with CHD during perioperative resuscitation and convalescence. Anesthetic management requires particular knowledge of anatomy, physiologic consequence of underlying defects, myocardial and vascular performance, presence and nature of previous palliative procedures and residual shunts, alteration of venous or arterial pathways within the circulation, and status of noncardiovascular organ physiology.

**Pregnancy** Women with CHD should receive counseling regarding both maternal and fetal risks prior to conceiving a pregnancy and should be cared for in institutions with experience in treating CHD during pregnancy. Preconception evaluation includes detailed medical history, with particular attention to the women's functional capacity, which is closely linked to maternal and fetal outcomes. Table 269-2 lists the World Health Organization classification of risk during pregnancy in women with heart disease; women at risk should be strongly counseled about the significant risks of morbidity and mortality during pregnancy and the postpartum period. Normal physiologic hemodynamic changes of pregnancy are significant, occur over a relatively condensed period of time, and may be compounded in adults with CHD. Silversides and colleagues have developed a weighted-risk score for pregnant women with heart disease, based on a large registry known as CARPREG 2. The highest-weighted risk factors (weight of 3 points) include a prior history of cardiac events or arrhythmias, decreased functional status (New York Heart Association class III), and presence of a mechanical heart valve. Risk factors that account for 2 points include ventricular dysfunction, high-risk left-sided valve disease/left ventricular outflow tract obstruction, pulmonary hypertension, coronary artery disease, and high-risk aortopathy. One point is assigned for late pregnancy assessment or no prior cardiac intervention. In this cohort, 16% of women experienced an adverse cardiac outcome, primarily heart failure and arrhythmia related. The predicted risks for cardiac events stratified according to point score were as follows: 1 point, 5%; 2 points, 10%; 3 points, 15%; 4 points, 22%; and >4 points, 41%.

Prepregnancy medications should be reviewed to ensure their safety in pregnancy. Alternatives to angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and endothelin receptor blockers should be considered, as these agents are teratogenic and contraindicated during pregnancy and should be discontinued. Women requiring anticoagulation must be advised of the challenges of



**FIGURE 269-1 Normal heart.** Understanding of congenital cardiac anatomy and physiology is facilitated by use of box diagrams, displaying passage of blood flow between blood vessels and cardiac chambers. Labeling (e.g., structure names, arrows to denote direction of flow, coloring to represent oxygen saturation, connections or obstructions, chamber or vascular pressures, oxygen saturations) can aid in representation. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

managing anticoagulation during pregnancy, and individualized strategies should be developed. A fetal echocardiogram between 18 and 22 weeks of gestation is advised for patients with CHD. Additionally, both men and women with CHD should be counseled regarding the risk of CHD in their offspring.

### CONGENITAL TERMINOLOGY, DEVELOPMENT, AND GENETICS

**Congenital Nomenclature** One of the challenges in caring for adults with CHD is the inconsistent terminology used to describe the congenital heart lesions. Several classification systems have been proposed, from the initial descriptions by Maude Abbott, Maurice Lev, and Jesse Edwards, to the extensive characterizations by Stella and Richard Van Praagh and Robert Anderson. In this chapter, we follow a segmental approach. The heart is composed of several segments that are analyzed separately before formulating a comprehensive diagnosis. The principal segments are the atria, the ventricles, and the great arteries, which

are joined together by the atrioventricular canal and the conus (infundibulum). In the normal heart, the right ventricle (RV) is right-sided and organized inflow-to-outflow from right to left, while the left ventricle (LV) is left-sided and organized inflow-to-outflow from left to right. It is important to determine the segmental alignments, that is, what drains into what. For example, in the normal heart, the right atrium (RA) is aligned with the RV and the LV with the aorta. Finally, the segmental connections, the way in which adjacent segments are physically linked to each other, are described. For example, in the normal heart, the pulmonary artery (PA) is connected to the RV by a complete muscular conus (infundibulum), while the aorta is connected to the LV by aortic-mitral fibrous continuity (without a complete conus). Alignment and connection are different concepts and both are important, especially in complex defects.

**Cardiac Development** The heart starts to form in the third week of gestation and is nearly fully formed by 8 weeks' gestation. Mesodermal precardiac cells migrate to form the cardiac

crescents (primary heart fields) in anterior lateral plate mesoderm, which are then brought together to form a primary linear heart tube by ventral closure of the embryo. Cells of the second heart field continue to proliferate outside the heart and are added to the heart tube over the course of embryogenesis, contributing to the atria, the RV, and outflow tract. Additionally, cardiac neural crest cells migrate into the developing heart in the 5th–6th weeks and are essential for septation of the outflow, formation of the semilunar valves, and patterning of the aortic arches. Once formed, the heart tube grows and elongates by addition of cells from the second heart field. The ends of the heart tube are relatively fixed by the pericardial sac so that as it elongates it must loop (bend), and in the vast majority of hearts, the loop falls to the right (D-loop). Further elongation pushes the mid-portion of the tube (future ventricles) inferior or caudal to the inflow, resulting in the normal relationship between the atria and ventricles. Further growth pushes the outflow medially and is associated with outflow rotation, both processes essential for normal alignment of the outflow. Finally, the proximal part of the outflow is incorporated in the RV, shortening the outflow in association with further rotation. While this remodeling is occurring, the outflow is undergoing septation under the influence of cardiac neural crest cells. Septation proceeds from distal to proximal, culminating in formation and muscularization of the infundibular, or muscular, outflow septum, which inserts onto the superior endocardial cushion at the rightward rim of the outflow foramen, walling the aorta into the LV via the outflow foramen and the PA directly into the RV.

**Genetic Considerations** CHD is the most commonly occurring birth defect; etiologic contributors are increasingly recognized, although often speculated to be multifactorial. Children born with trisomy 21 have a 50% chance of having CHD, most commonly defects in the atrioventricular canal. Conotruncal defects are associated with a number of chromosomal abnormalities, most notably a deletion at chromosome 22q11 (DiGeorge syndrome). Echocardiographic clues to this association in patients with a conotruncal defect include an associated right aortic arch or aberrant subclavian artery. Many adults currently living with conotruncal defects may not have undergone testing for DiGeorge syndrome. This condition is important to recognize because a variety of psychiatric disorders and disabilities in cognitive function may be present and go untreated. Patients with Noonan

**TABLE 269-1 Multiorgan Considerations in Adult Congenital Heart Disease Patients**

Neurologic	Increased incidence of occult or clinically evident strokes Decreased level of executive functioning skills Anxiety, posttraumatic stress disorder, depression Psychosocial disorders
Lungs	Restrictive lung disease Pulmonary vascular disease
Renal	Decreased perfusion
Hepatic	Liver fibrosis
Peripheral vasculature	Increased chronic venous insufficiency
Lymphatic	Impaired reabsorption
Orthopedic	Scoliosis Kyphosis
Hematologic	Anemia Coagulopathies

TABLE 269-2 Modified World Health Organization (mWHO) Classification of Heart Disease in Pregnancy

	mWHO I	mWHO II	mWHO II-III	mWHO III	mWHO IV
<b>Diagnosis (if otherwise well and uncomplicated)</b>	Small or mild <ul style="list-style-type: none"> <li>Pulmonary stenosis</li> <li>Patent ductus arteriosus</li> <li>Mitral valve prolapse</li> </ul> Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated	Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias (supraventricular arrhythmias) Turner syndrome without aortic dilatation	Mild left ventricular impairment (EF >45%) Hypertrophic cardiomyopathy Native or tissue valve disease not considered WHO I or IV (mild mitral stenosis, moderate aortic stenosis) Marfan or other HTAD syndrome without aortic dilatation Aorta <45 mm in bicuspid aortic valve pathology Repaired coarctation Atrioventricular septal defect	Moderate left ventricular impairment (EF 30–45%) Previous peripartum cardiomyopathy without any residual left ventricular impairment Mechanical valve Systemic right ventricle with good or mildly decreased ventricular function Fontan circulation Fontan circulation with good clinical course and without associated comorbidities Unrepaired cyanotic heart disease Other complex heart disease Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve, Turner syndrome ASI 20–25 mm/m <sup>2</sup> , tetralogy of Fallot >50 mm) Ventricular tachycardia	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV) Previous peripartum cardiomyopathy with any residual left ventricular impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD, >50 mm in bicuspid aortic valve, Turner syndrome ASI >25 mm/m <sup>2</sup> , tetralogy of Fallot >50 mm) Vascular Ehlers-Danlos Severe (re)coarctation Fontan with any complication
<b>Risk</b>	No detectable increased risk of maternal mortality and no/mild increased risk in morbidity	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity	Significantly increased risk of maternal mortality or severe morbidity	Extremely high risk of maternal mortality or severe morbidity

Abbreviations: ASI, aortic size index; EF, ejection fraction; HTAD, heritable thoracic aortic disease.

syndrome commonly have a dysplastic pulmonary valve and have facial and lymphatic abnormalities. Several defects in specific genes have been associated with Noonan syndrome, most notably *PTPN11*. Adults with Williams syndrome (7q11.23 deletion) commonly have supravalvar aortic stenosis and diffuse arteriopathy, with a “cocktail-like” personality and hypercalcemia. There is a growing importance of genome-wide analyses in subjects with CHD.

### SPECIFIC CHD LESIONS

**Dilated Right Heart** There are many congenital etiologies for right heart dilation (Table 269-3). These include congenital valvular anomalies (such as Ebstein anomaly or pulmonary regurgitation), intrinsic RV myocardial anomalies (arrhythmogenic RV dysplasia, Uhl's anomaly), or shunt lesions occurring proximal to the tricuspid valve. Cardiac imaging is critical in determining the etiology of right heart dilation, and knowledge of the anatomy and physiology of various shunt lesions is essential.

**Atrial Septal Defect** One of the most common etiologies of right heart dilation is presence of an atrial septal defect (ASD; Fig. 269-2A).

Intracardiac communications allow blood transmission between chambers or spaces based on relative resistance, propulsion, and flow patterns. Patients with large ASDs often present in childhood; however, many ASDs are not discovered until adult life. The physiology of an ASD is predominantly that of a “left-to-right” shunt (flow of pulmonary venous, or oxygenated, blood toward systemic venous, or deoxygenated, chambers or vessels). The degree of left-to-right shunting determines the amount of right heart volume loading and is dictated by the size of the defect as well as the diastolic properties of the heart. As patients age, several factors, such as diabetes mellitus, systemic hypertension, and atherosclerosis, may contribute to decreased compliance of the left-sided cardiac chambers and contribute to increased left-to-right shunting and symptomatology. The classic physical examination finding is a wide, fixed splitting of the second heart sound, which is

due to prolonged RV ejection and increased PA capacitance, which, in turn, delay pulmonary valve closure. The surface electrocardiogram (ECG) commonly displays an incomplete right bundle branch block. Symptoms, when they occur, most commonly include exercise intolerance, arrhythmia, and dyspnea with exertion. It is not uncommon for adults to have incidentally noted asymptomatic ASD during evaluation of other comorbid issues. Right heart dilation, without additional etiology for such, in the setting of unrepaired ASD is considered a risk for progression toward symptomatic right heart failure, atrial arrhythmias, and potential development of pulmonary arterial hypertension (if such is not already present). Therefore, a patient with an ASD and right heart dilation, particularly with symptoms attributable to such, should be offered ASD closure. Pulmonary vascular disease leading to pulmonary hypertension develops in up to 10% of patients with unrepaired ASD, and Eisenmenger syndrome (ES) is a rare complication (see below). Management of patients with concomitant ASD and pulmonary hypertension should be coordinated with both ACHD and pulmonary hypertension experts.

Figure 269-2B illustrates the locations of various ASDs. The most common type of an ASD is a secundum ASD, which is a defect, or true deficiency in the atrial septum, in the region of the fossa ovalis. This should be differentiated from a patent foramen ovale (PFO), which is persistence of patency of the flap valve of the fossa ovalis (not associated with right-sided cardiac dilation) and persists in up to 25% of adults. Secundum ASDs can often be closed with occluder devices placed percutaneously. However, certain anatomic determinants make percutaneous closure less favorable, including large defects, inadequate tissue rims surrounding the defect, and concomitance of anomalous draining pulmonary veins. A primum ASD is a deficiency of the atrioventricular (AV) canal portion of the atrial septum; primum ASD is always associated with abnormal development of the AV valves, most commonly resulting in a cleft in the mitral valve. A coronary sinus defect is rare and involves an opening between the coronary sinus and the left atrium. A sinus venosus defect is not a defect in the atrial

**TABLE 269-3** Congenital Etiologies of Right Heart Dilation

Congenital tricuspid valve disease
Tricuspid valve dysplasia with regurgitation
Ebstein anomaly
Congenital pulmonary valve regurgitation
Pulmonary arterial hypertension
Myocardial abnormalities
Arrhythmogenic RV cardiomyopathy
Uhl's anomaly
Shunt lesions
Partial anomalous pulmonary venous return
Primum ASD
Secundum ASD
Sinus venosus defect
Coronary sinus septal defect
Gerbode defect (LV-RA shunt)
Coronary artery fistula to the RA, CS
Postoperative residual shunts

Abbreviations: ASD, atrial septal defect; CS, coronary sinus; LV, left ventricle; RA, right atrium; RV, right ventricle.

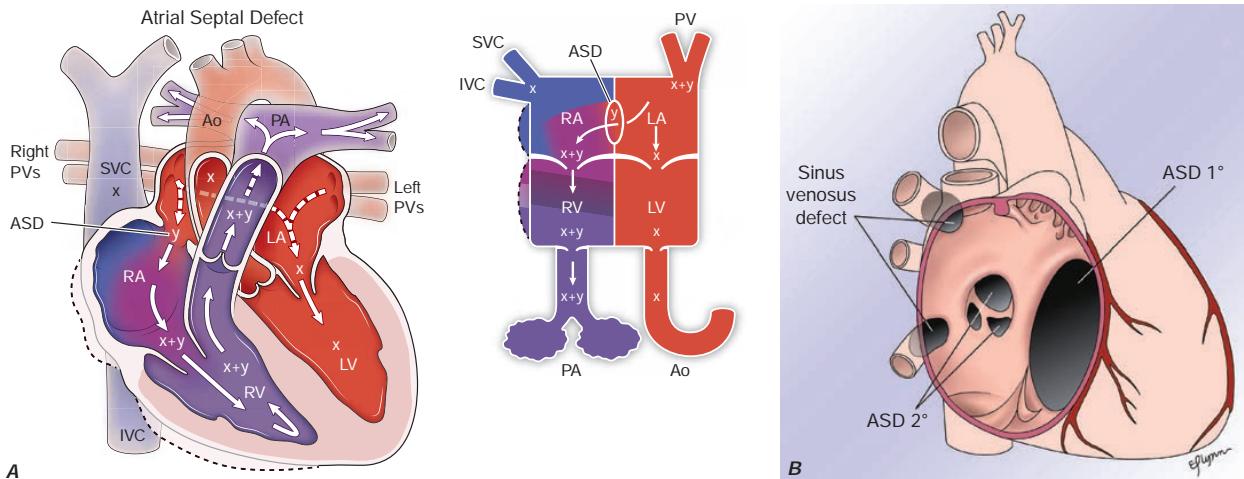
septum but, rather, a defect between either the right superior vena caval–atrial junction and the right upper pulmonary vein(s) or, less commonly, the inferior vena caval–atrial junction and the right lower pulmonary veins. Surgical closure is required for primum ASDs, sinus venosus defects, and coronary sinus septal defects.

**Partial Anomalous Pulmonary Venous Return** Partial anomalous pulmonary venous return (PAPVR) is occasionally discovered in adults with right heart dilation or incidentally on cross-sectional imaging (Fig. 269-3). There are several possible anomalous connections, with the most common being a left upper pulmonary vein to an ascending vertical vein into the innominate vein or the right upper pulmonary vein draining to the superior vena cava. In the latter case, careful attention should be paid to ensure that there is not an associated sinus venosus defect. Concomitant pulmonary hypertension can occur but is uncommon. Symptomatology may be absent, and a decision to repair isolated PAPVR should include variance in anatomy, lung ventilation and perfusion, hemodynamic response to shunt, symptoms, and surgical experience.

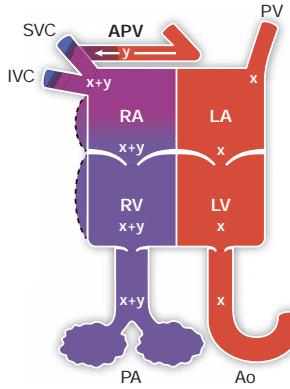
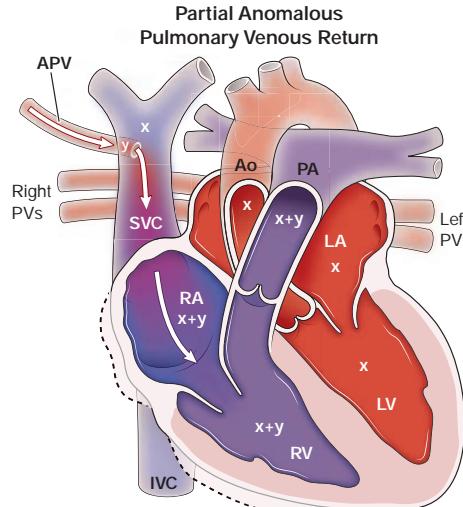
**Ebstein Anomaly** Ebstein anomaly (Fig. 269-4) is the result of embryologic failure of delamination, or “peeling away,” of the tricuspid valve leaflets from the ventricular myocardium, resulting in adherence of the valve leaflets to the underlying myocardium. This results in a wide variety of abnormalities, including apical and posterior displacement of the dilated tricuspid valve annulus, dilation of the “atrialized” portion of the RV, and fenestrations, redundancy, and tethering typically of the anterior leaflet of the tricuspid valve. The malformed tricuspid valve is usually regurgitant, but may occasionally be stenotic. The clinical presentation of Ebstein anomaly in the adult depends on several factors, including the extent of tricuspid valve leaflet distortion, degree of tricuspid regurgitation (TR), right atrial pressure, and presence of an atrial level shunt. The physical examination of a patient with Ebstein anomaly may vary depending on the severity of disease. In more severe cases, the first heart sound may be split and the second component of the first heart sound may have a distinctive snapping quality (known as the sail sign, due to the redundancy of the anterior tricuspid valve leaflet). Patients with significant TR may have prominent “v” waves of the jugular venous pulsations; however, this finding is often absent due to abnormal right atrial compliance. The ECG is often abnormal, with right atrial and ventricular enlargement. Up to 20% of patients have evidence of ventricular preexcitation (Wolff-Parkinson-White pattern). Surgical treatment includes a tricuspid valve repair or replacement, closure of any atrial level defects, and arrhythmia ablative procedures.

**Shunt Lesions Causing Left Heart Dilation** Intracardiac shunts or intravascular passages that occur below the level of the tricuspid valve result in left heart dilation. The two major types of congenital shunts that result in left heart dilation are a ventricular septal defect (VSD; Fig. 269-5A) and patent ductus arteriosus (PDA; Fig. 269-6).

**Ventricular Septal Defects** VSDs are the most common congenital anomaly recognized at birth; however, they account for only ~10% of CHD in the adult, due to the high rate of spontaneous closure of small VSDs during the early years of life. Large VSDs usually cause symptoms of heart failure and poor somatic growth and are most often surgically closed before adulthood. Several classification systems for VSDs exist. Figure 269-5B illustrates various locations of VSDs; the most common location is in the membranous septum (also referred to as perimembranous or outlet defects). Muscular defects that persist into adult life are often pressure and flow restricted, resulting in no significant hemodynamic consequence. AV canal defects, also referred



**FIGURE 269-2** **A.** Atrial septal defect. In the presence of an atrial septal defect, the difference in compliance between the (RA + RV) as compared to the (LA + LV), combined with the size of the defect itself, allows for a “shunt” of flow (“y”) of “red” (oxygenated) blood from the left side of the heart to the right side (deoxygenated). Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x + y”) in the RA, RV, and total blood flow to the lungs. If the volume or the sequelae of the shunted blood is sufficient, RA and RV can dilate (hatched lines), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; ASD, atrial septal defect; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava. **B.** Diagrammatic representation of the location of various atrial septal defects. ASD 1, primum atrial septal defect; ASD 2, secundum atrial septal defect. (Part B used with permission from Emily Flynn McIntosh, illustrator.)



**FIGURE 269-3 Partial anomalous pulmonary venous return.** In the presence of an anomalously draining pulmonary vein (typically to a systemic vein such as the left innominate vein, SVC, or rarely IVC), an obligate “shunt” of flow (“y”) of “red” (oxygenated) blood from the affected pulmonary vein to the right heart (deoxygenated) ensues. Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x+y”) in the SVC, RA, RV, and total blood flow to the lungs. If the volume or the sequelae of the shunted blood is sufficient, RA and RV can dilate (hatched lines), or shortness of breath can ensue. Ao, aorta; APV, anomalous pulmonary vein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

to as inlet defects, are located in the crux of the heart and are associated with abnormalities of the AV valve leaflets. Subpulmonary defects, also known as *conal septal defects*, are commonly associated with prolapse of the right coronary cusp and aortic insufficiency. The outcome for adults with small VSDs without evidence of ventricular dilation or pulmonary hypertension is generally excellent.

**Patent Ductus Arteriosus** A PDA courses between the aortic isthmus and the origin of one of the branch PAs. Small PDAs are often silent to auscultation and do not cause hemodynamic changes. The classic murmur is heard best just below the left clavicle and typically extends from systole past the second heart sound into diastole, reflecting flow turbulence and gradient between the aorta and the PAs (resulting in left-to-right shunting). Large PDAs will lead to left heart dilation and may lead to chronically elevated pulmonary vascular resistance, including the potential for ES.

## MODERATE AND COMPLEX CHD

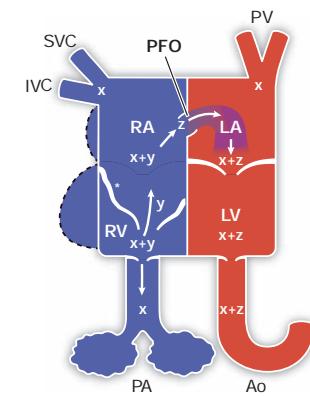
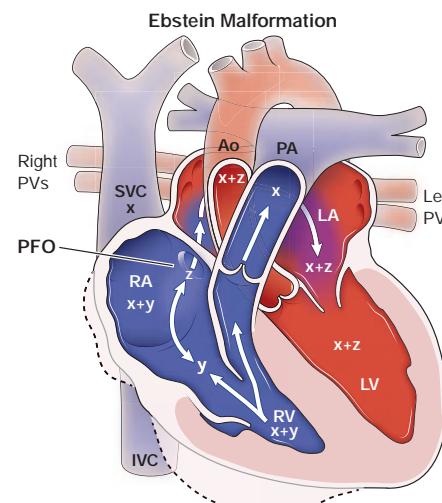
**Tetralogy of Fallot** Tetralogy of Fallot (TOF) is the most common form of cyanotic CHD, occurring in 0.5 per 1000 live births. It involves anterior deviation of the conal septum, resulting in RV outflow tract (RVOT) obstruction, a VSD, RV hypertrophy, and an overriding aorta (Fig. 269-7A, B). There is a large spectrum of severity of disease in TOF, from patients who have only mild pulmonary stenosis to those with complete pulmonary atresia (TOF/PA). Current surgical strategies involve primary repair in infancy (Fig. 269-7C); however, many adults may have first undergone palliative procedures (Blalock-Taussig, Potts, Waterston shunts) prior to a complete repair. The goal of surgical repair is to alleviate the pulmonary stenosis and close

the VSD. Up to 10% of patients with TOF have an anomalous coronary artery, most commonly, an anomalous left anterior descending coronary artery from the right coronary cusp. Patients with an anomalous coronary as well as those with TOF/PA may require an RV-to-PA conduit.

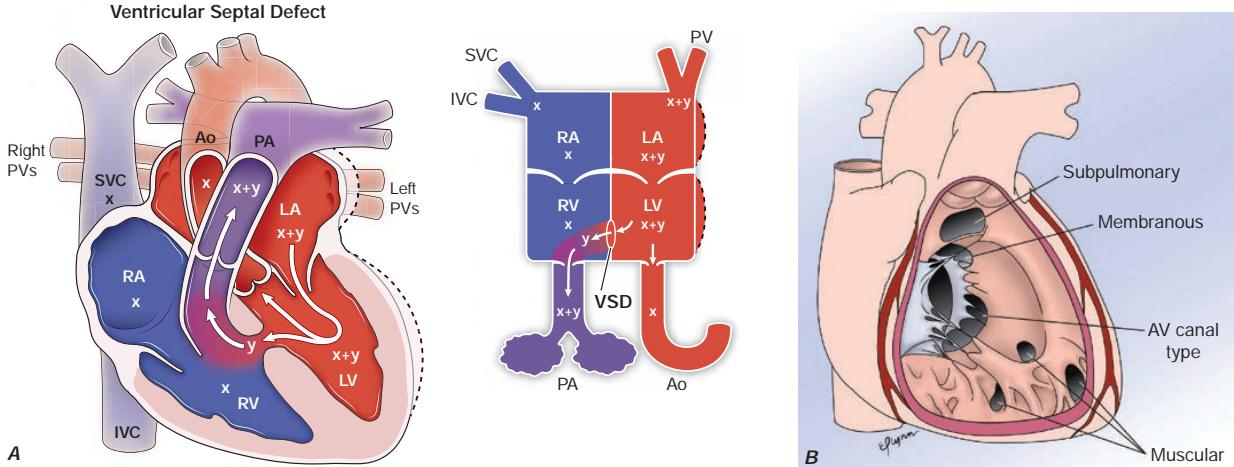
Adults with repaired TOF often have hemodynamic sequelae that may require reintervention in adulthood (Table 269-4). Pulmonary regurgitation is common following TOF repair and is usually associated with RV dilation. Accurate quantification of RV size, function, and mass is particularly important in adults after repair of TOF, as RV dilation, dysfunction, and hypertrophy are associated with adverse outcomes in these patients. Patients may also have residual RVOT obstruction, which may occur beneath the pulmonary valve, at the valve level, above the valve, or in the branch PAs. Cardiac magnetic resonance imaging is routinely used in the surveillance of these patients. Left ventricular dysfunction is present in at least 20% of adults with repaired TOF, particularly those who were repaired later in life, had prior palliative shunts, or have concomitant RV dysfunction.

As patients age with repaired TOF, both atrial and ventricular arrhythmias occur with increasing frequency. A QRS duration on a resting ECG of 180 ms or more has been associated with increased risk of ventricular tachycardia and sudden death in this patient population. In one

prospective follow-up study of 144 adults with repaired TOF, there was a 72% survival at 40 years, but only a 25% cumulative event-free survival. These events include need for reintervention (most commonly pulmonary valve replacement [PVR]), symptomatic arrhythmias, and heart failure.



**FIGURE 269-4 Ebstein malformation.** In the presence of Ebstein anomaly, the tricuspid valve leaflets can be redundant, fenestrated, and sail-like (typically seen in the anterior leaflet \*) or adherent to the underlying myocardium with apical displacement of the nonadherent components (typically the septal and posterior leaflets). Location and degree of leaflet coaptation are variable and account for varying degrees of tricuspid regurgitation, shift of the functional tricuspid valve anterior from the anatomic annulus into the right ventricle, “atrialization” of the right ventricle, and most commonly angulation of the tricuspid valve into the RV outflow tract. RA and RV dilation (hatched lines) can occur due to the effects of combined volume from systemic venous return (“x”) and tricuspid regurgitant flow (“y”). PFO is frequent; worsening compliance and elevation of pressure in the RA as compared to the LA can lead to increasing “right-to-left” (deoxygenated to oxygenated) shunt and cyanosis. RV myocardial function may be abnormal. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PFO, patent foramen ovale; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava; \*, anterior tricuspid valve leaflet.



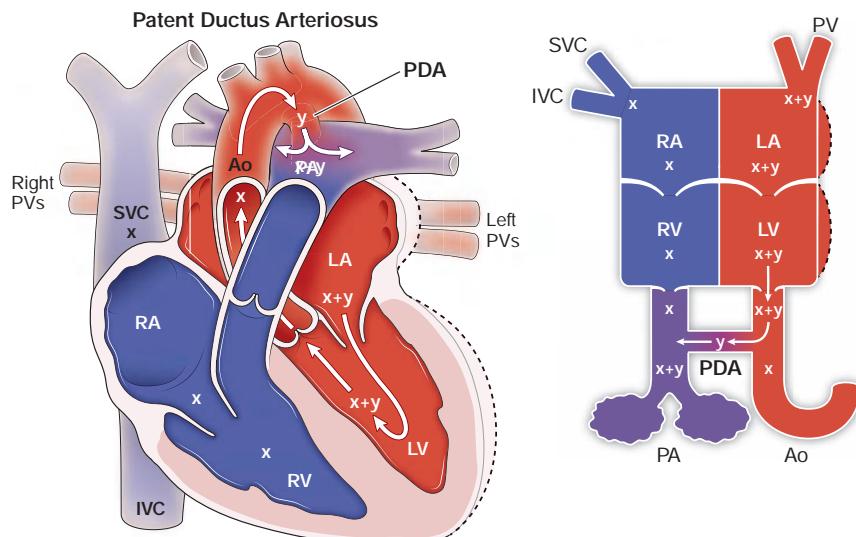
**FIGURE 269-5** **A.** Ventricular septal defect. In the presence of a ventricular septal defect, the difference in pressure and outflow resistance in systole (and the difference in compliance in diastole) between the RV and LV, combined with the size of the defect itself, allow for a “shunt” of flow (“y”) of “red” (oxygenated) blood from the left side of the heart to the right side (deoxygenated). Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x + y”) through the outflow of the RV into the lungs, and in the left atrium and left ventricle. If the volume or the sequelae of the shunted blood are sufficient, LA and LV can dilate (hatched lines), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava; VSD, ventricular septal defect. **B.** Diagrammatic representation of the location of various ventricular septal defects. (Part B used with permission from Emily Flynn McIntosh, illustrator.)

The most common reintervention in a repaired TOF patient is a PVR. However, optimal timing of PVR in these patients remains unclear. Although PVR has been shown to decrease RV volumes and subjectively improve symptoms, it has not been proven to result in an improved ejection fraction or less adverse outcomes, such as ventricular arrhythmias or death. Traditionally, PVR has been accomplished with a surgical procedure; however, percutaneous implantation of pulmonary valves is becoming increasingly utilized in clinical practice.

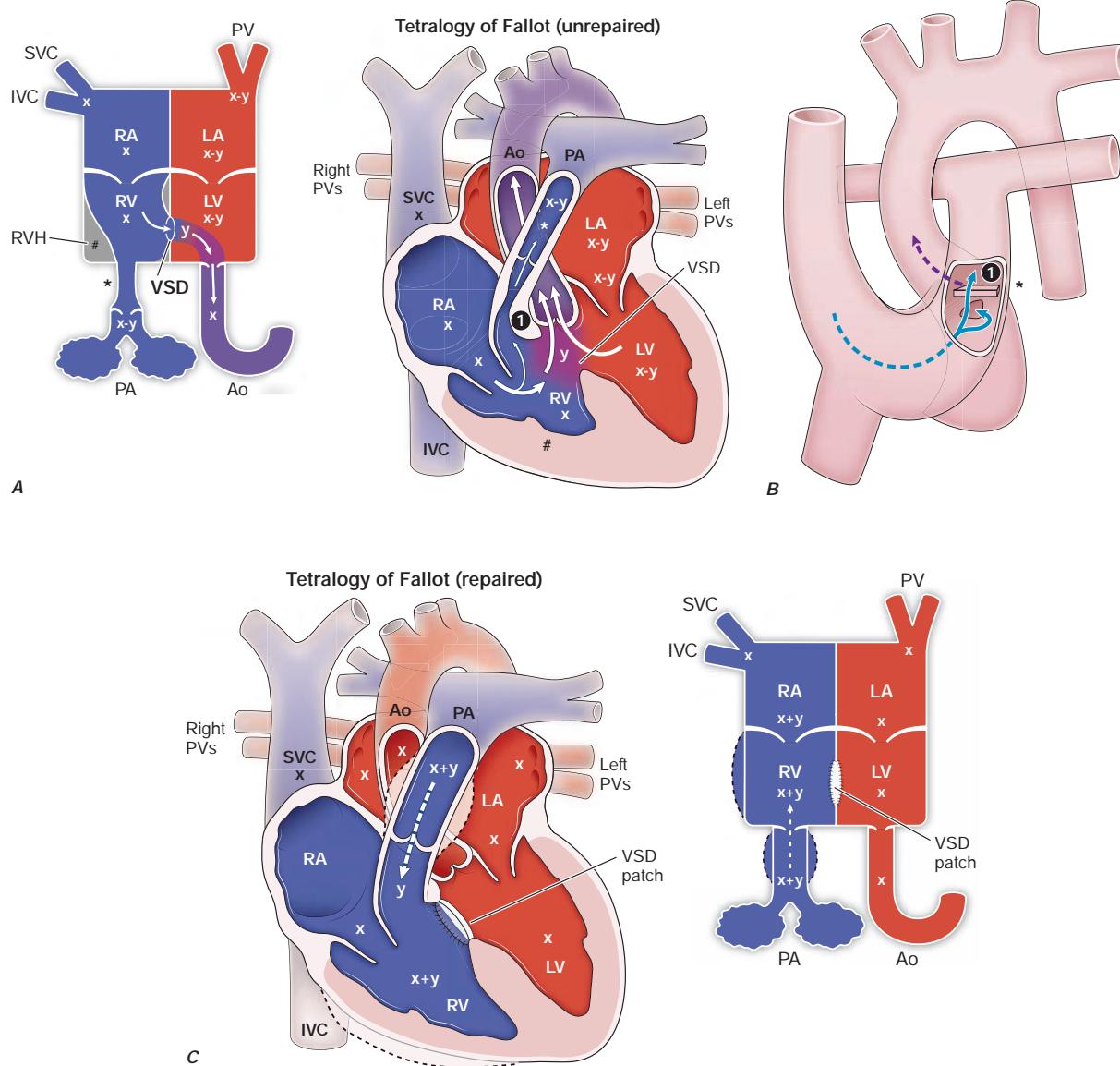
Patients with repaired TOF may also undergo interventions including closure of residual VSDs, dilation and/or stenting of the RVOT or branch PAs, and tricuspid valve repair. Patients with clinically significant arrhythmias may benefit from catheter ablation.

**Transposition of the Great Arteries** Transposition of the great arteries (TGA) is defined by the great arteries arising from the opposite side of the ventricular septum than normal; as such, the aorta arises from the RV and the PA from the LV. The more common form of TGA, known as *D-loop TGA*, involves AV concordance and ventricular-arterial discordance, resulting in a physiology that allows two circuits to be in parallel rather than in series (Fig. 269-8A) and intense cyanosis shortly after birth. This physiology is not compatible with long-term survival without surgical intervention. Patients with TGA may be born with additional congenital defects (most commonly a VSD).

The surgical repairs for D-loop TGA have evolved over time. In the late 1950s through the 1970s, the atrial switch procedure (Mustard,



**FIGURE 269-6** Patent ductus arteriosus. In the presence of a patent ductus arteriosus, the difference in pressure and resistance in both systole and diastole between the pulmonary arteries and the aorta, combined with the size of the ductus itself, allow for a “shunt” of flow (“y”) of “red” (oxygenated) blood from the aorta to the pulmonary arteries (deoxygenated). Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x + y”) in the lungs, the left atrium, the left ventricle, and out the aortic valve. If the volume or the sequelae of the shunted blood are sufficient, LA and LV can dilate (hatched lines), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PDA, patent ductus arteriosus; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.



**FIGURE 269-7** **A.** Tetralogy of Fallot involves anterior and superior malalignment of a bar of tissue (conal septum) (see \* in part **B**, which presents a cut-away view through the anterior surface of the RV, into the RV outflow), partially obstructing the right ventricular outflow (under the pulmonary valve, i.e., “subpulmonary stenosis”, labeled as 1), and leaving a gap in the interventricular septum (VSD). The pulmonary valve annulus is typically hypoplastic. Outflow obstruction prevents regression of right ventricular hypertrophy (\*), which was present in utero. The difference in pressure and outflow resistance in systole (and the difference in compliance in diastole) between the obstructed RV and the LV allows for a “shunt” of flow (“y”) of “blue” (deoxygenated) blood from the right side of the heart to the left side (oxygenated). Systemic venous return of pure deoxygenated blood (“x”) is decreased by the shunted blood (“y”), leading to a total decrease in the volume of blood (“ $x - y$ ”) passing beyond into the lungs. The deoxygenated shunted blood (“y”) mixes with fully oxygenated blood in the LV, contributing to systemic arterial cyanosis. **C.** Tetralogy of Fallot—repaired. After modern repair of tetralogy of Fallot, VSD has been patched closed, and outflow tract obstruction has been surgically removed, frequently at the expense of a patch enlarging the pulmonary valve annulus at the expense of sacrificing the integrity of the pulmonary valve (causing pulmonary regurgitation). The pulmonary regurgitant volume (“y”) is added to systemic venous return (“x”), contributing to RV chamber enlargement (hashed lines) and may be associated with tricuspid annular dilation and valve regurgitation, resulting in RA enlargement. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; RVH, right ventricular hypertrophy; SVC, superior vena cava; VSD, ventricular septal defect.

Senning procedures) was performed (Fig. 269-8B). These atrial switch procedures relieved the cyanosis but left the patient with a systemic RV. Despite moderate-term survival over decades, there are multiple long-term sequelae that may present following the atrial switch procedure. The most worrisome complication is that of systemic RV dysfunction. The prevalence of RV dysfunction in this population is not well defined. Limited study has failed to reveal medical therapies effective for systemic RV dysfunction.

A subset of patients with D-loop TGA, VSD, and PS may have undergone a Rastelli procedure. This intervention involves placing an RV-to-PA conduit and routing the LV to the aorta through the VSD, which results in relief of cyanosis and the benefit of a systemic LV.

In the 1980s, the arterial switch operation (ASO; Fig. 269-8C) became the surgical procedure of choice for D-loop TGA. This procedure involves transecting the great arteries above the sinuses and placing the PAs anteriorly to come into alignment with the RV, resulting in

**TABLE 269-4 Potential Sequelae of Repaired Tetralogy of Fallot**

Right atrial dilation
Right ventricular dilation
Right ventricular dysfunction
Right ventricular outflow tract obstruction
Pulmonary regurgitation
Branch pulmonary artery stenosis
Tricuspid regurgitation
Residual ventricular septal defect
Left ventricular dysfunction
Aortic root dilation
Atrial arrhythmias
Ventricular arrhythmias
Sudden cardiac death

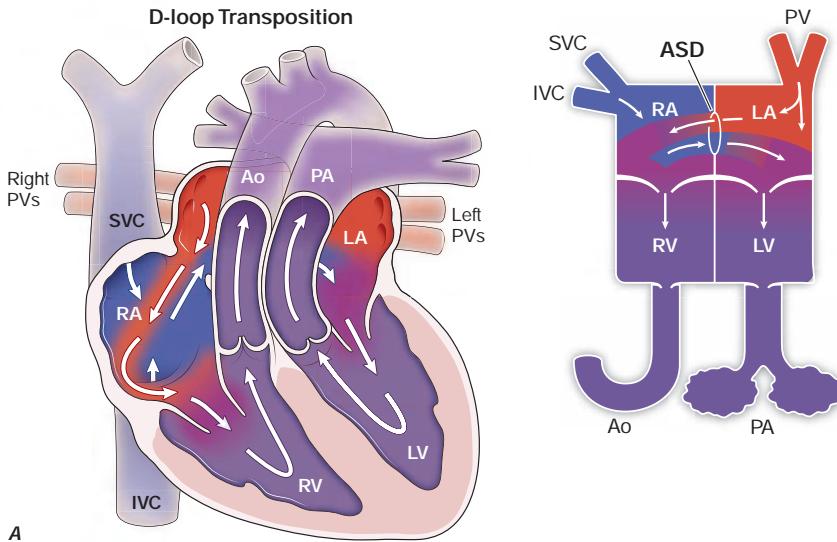
draping of the branch PAs over the ascending aorta. A coronary artery translocation is performed. The ASO has resulted in substantial long-term survival.

The potential long-term sequelae of the various surgical procedures for D-loop TGA are listed in **Table 269-5**.

The less common form of TGA, known as *L-loop TGA* (physiologically corrected or “congenitally corrected” TGA; **Fig. 269-9**), may not require surgical intervention but is presented here in relation to other forms of TGA. L-loop TGA involves both AV discordance (RA allowing passage of deoxygenated systemic venous return to the LV, and conversely, the left atrium conducting oxygenated pulmonary venous blood to the RV) as well as ventriculoarterial discordance (connections

of LV to PA, RV to aorta). This results in normal arterial oxygen saturation, yet an RV associated with the aorta. Patients with L-loop TGA commonly have associated congenital anomalies, including dextrocardia, ASDs, a dysplastic tricuspid valve, and pulmonary stenosis. Conduction disturbances are common, and complete heart block occurs in up to 30% of patients. Those patients without associated defects may not present until later in life, most commonly with heart failure, TR, or newly recognized conduction disease.

**Coarctation of the Aorta** Adults with coarctation of the aorta (**Fig. 269-10**) typically have a shelf-like obstruction at the level of the descending aorta that passes just posterior to the junction of the main and left PA; obstruction less commonly involves the transverse aortic arch. On physical examination, the lower extremity blood pressure and pulses are lower than (and delayed in timing, in contrast to) the upper extremity values, unless significant aortic collaterals have developed. A continuous murmur over the scapula may be present due to the collateral blood flow. Significant coarctation increases afterload to all proximal structures in the path of oxygenated blood, from LV and coronary arteries, to ascending and transverse aorta, to cerebral and arm vessels and proximal descending aorta. Bicuspid aortic valve (typically with right-left commissural fusion) is a common association. In women with short stature, webbed neck, lymphedema, and primary amenorrhea, a concomitant diagnosis of Turner syndrome should be considered, the presence of which indicates greater degree of, and risks from, sequelae from seemingly similar anatomy and physiology. Patients who have undergone surgical repair in general have a good prognosis; however, they remain at risk for systemic hypertension, premature atherosclerosis, LV failure, and aortic aneurysm, dissection, and recurrent coarctation.



**FIGURE 269-8** **A.** Transposition of the great arteries. When the great arteries are transposed, the aorta arises from the RV, and the pulmonary artery arises from the LV, leaving deoxygenated blood circulating from systemic veins to systemic arteries in separated fashion from oxygenated blood, which circulates from pulmonary veins to pulmonary arteries. Without interchamber or intravascular communications, this circulation is incompatible with life. Presence of an atrial septal defect (ASD), depicted here, ventricular septal defect (VSD), or patent ductus arteriosus (PDA) allows for some interchamber or intravascular mixing and, at best, partial relief of cyanosis and sustenance of life, at the expense of increased pulmonary blood flow. **B.** Atrial switch. Atrial level switch procedures (Mustard and Senning) were the first standardized surgeries to alter the natural course of complex congenital heart disease, utilizing intracardiac rerouting via a “baffle” to redirect blood flow. The atrial switch simulates inverted trousers, with each “pants leg” (\*) attaching to either the SVC or the IVC, transporting deoxygenated blood through the interior of the trousers to the “waist of the trousers” and directing blood through the mitral valve to the LV and out the PA. Surgical removal of the atrial septum allows pulmonary venous return to traverse from posterior left atrium through the space between the pants legs of the baffle, through the tricuspid valve to the RV (serving as the “systemic ventricle,” i.e., that pumps to the systemic arterial circulation), and out the aorta. Non-infrequent sequelae include sinus node dysfunction, atrial arrhythmias, systolic dysfunction of the RV, tricuspid regurgitation (from RV to LA), leaks in the baffle material allowing shunting of blood, and obstruction of the systemic or pulmonary venous baffles. **C.** Arterial switch. The arterial switch operation allowed both anatomic and physiologic correction for D-loop transposition of the great arteries. Successful surgical switching of the PA and the Ao above the level of the native roots (hatched lines) necessitated ability to transfer coronary artery origins contained within a button of tissue (\*) back to the neo-aorta (now supported by the LV). Deoxygenated blood flow from SVC and IVC passes from RA to RV to PA, and oxygenated blood passes from PV to LA to LV to Ao. Uncommon sequelae include obstruction at any of the surgical sites (supravalvar PA or Ao stenosis, coronary orifice obstruction) or more distal obstructions due to tension placed on the PA, Ao, or coronary arteries. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

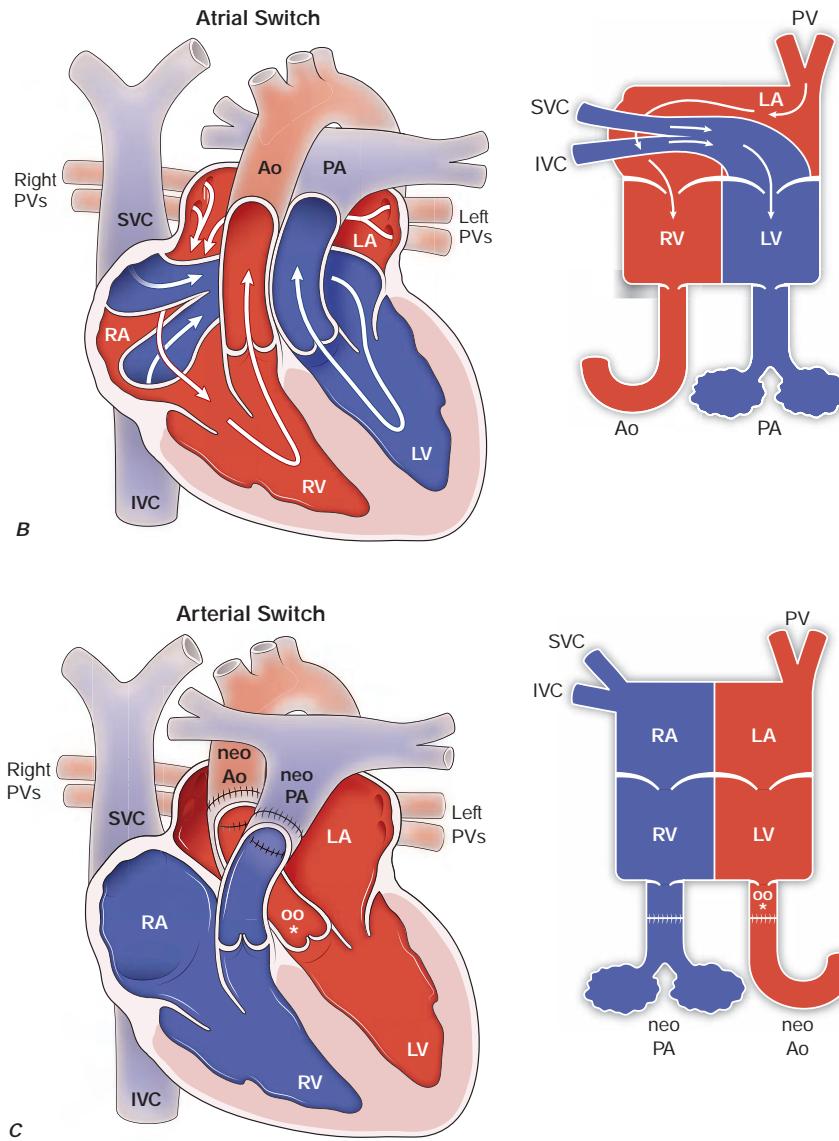


FIGURE 269-8 (Continued)

**Single Ventricle Physiology** The term *single ventricle heart disease* is imprecise but useful in some settings, as it refers to congenital heart conditions in which one ventricle or its valves preclude surgical creation of a biventricular circulation. Common congenital diagnoses in this category include tricuspid atresia, double inlet LV, and

hypoplastic left heart syndrome. Most patients with single ventricle physiology undergo a series of surgeries culminating in a Fontan procedure (Fig. 269-11A, B). Since its initial use for tricuspid valve atresia in 1971, multiple modifications of this procedure have occurred, with common features of near complete separation of the pulmonary and systemic circulations. The Fontan procedure utilizes the single ventricle to pump pulmonary venous (oxygenated) blood through the aorta to the body and allows for “passive” flow of systemic venous return of deoxygenated blood through surgically created connections to the lungs. Patients who have undergone a Fontan procedure are at risk for multiple comorbidities in adulthood, including atrial arrhythmias, heart failure, renal and hepatic dysfunction, and both venous and arterial thrombosis and embolism.

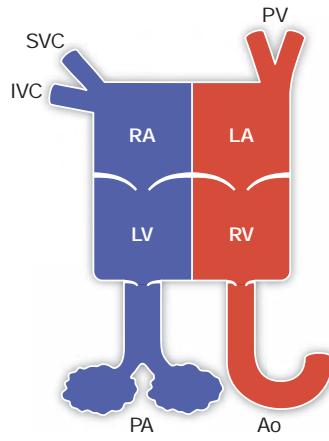
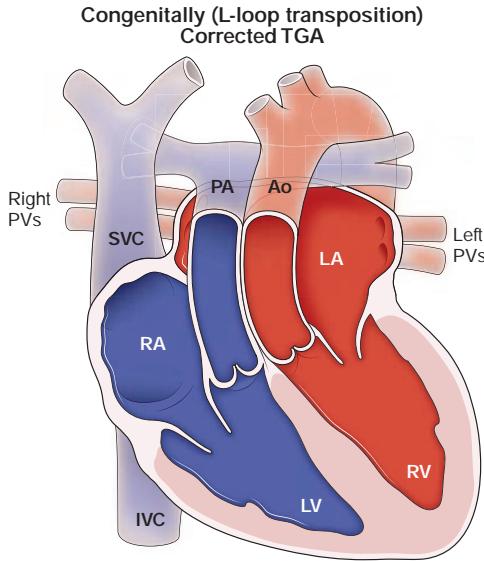
### UNREPAIRED CYANOTIC CHD

**Eisenmenger Syndrome** ES is felt to be the consequence of a long-standing high-volume or pressurized left-to-right shunt in which excessive blood flow to the pulmonary vasculature leads to severely increased pulmonary vascular resistance that eventually results in reversal of the shunt, creating bidirectional or right-to-left flow. ES is a

TABLE 269-5 Long-Term Sequelae of D-Loop TGA Surgery

ATRIAL SWITCH	ARTERIAL SWITCH	RASTELLI PROCEDURE
Systemic venous baffle	Arterial anastomosis stenosis	Subaortic stenosis
Pulmonary venous baffle	Branch PA stenosis	RV-PA conduit obstruction
RV (systemic) dysfunction	Neo-aortic root dilation	Pulmonary regurgitation
Tricuspid regurgitation	Neo-aortic regurgitation	Ventricular dysfunction
Baffle leaks	Coronary artery stenosis	
LVOT obstruction (PS)	LV dysfunction	

Abbreviations: LV, left ventricle; LVOT, left ventricular outflow tract; PA, pulmonary artery; RV, right ventricle; TGA, transposition of the great arteries.

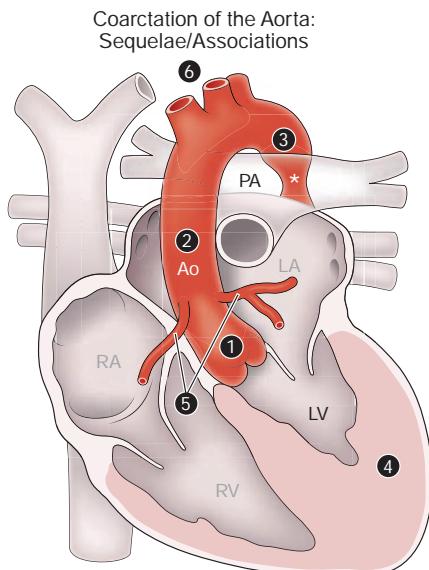


**FIGURE 269-9** Congenitally corrected transposition of the great arteries. Physiologically corrected transposition of the great arteries (also known as *congenitally corrected transposition of the great arteries*) is characterized by atrioventricular discordance and ventriculoarterial discordance. Systemic venous blood passes from the right atrium (RA) through the mitral valve into the morphologic left ventricle (LV) to the pulmonary artery (PA). Oxygenated blood then returns to the lungs to the left atrium (LA) through the tricuspid valve into the morphologic right ventricle (RV) and then out the aorta (Ao). IVC, inferior vena cava; PV, pulmonary veins; SVC, superior vena cava.

multiple-organ condition and may occur with any CHD with an initial left-to-right shunt. The natural history of ES is variable, and although there is significant morbidity, in general, adults with ES appear to survive longer than those with other forms of pulmonary arterial hypertension. Medical care recommendations have included sustaining adequate hydration, avoiding and treating anemia including iron supplementation when appropriate, and anticoagulation (although this remains controversial due to predisposition to bleeding and occurrence of clinical hemoptysis, which has frequently been associated with pulmonary vascular thrombosis). Elevation of hematocrit above that

considered appropriate for the degree of cyanosis can be managed in symptomatic patients by hydration alone or, on occasion, by performing phlebotomy with isovolumic replenishment. Routine phlebotomy in the asymptomatic adult with ES is contraindicated. Appropriate optimization of iron stores has been demonstrated to improve quality of life and functional performance in iron-deficient adults with ES. Contraception for women with ES who are of childbearing age is strongly recommended, avoiding use of estrogen, which may be thrombogenic. Pregnancy is contraindicated in these women due to the high risk of maternal mortality.

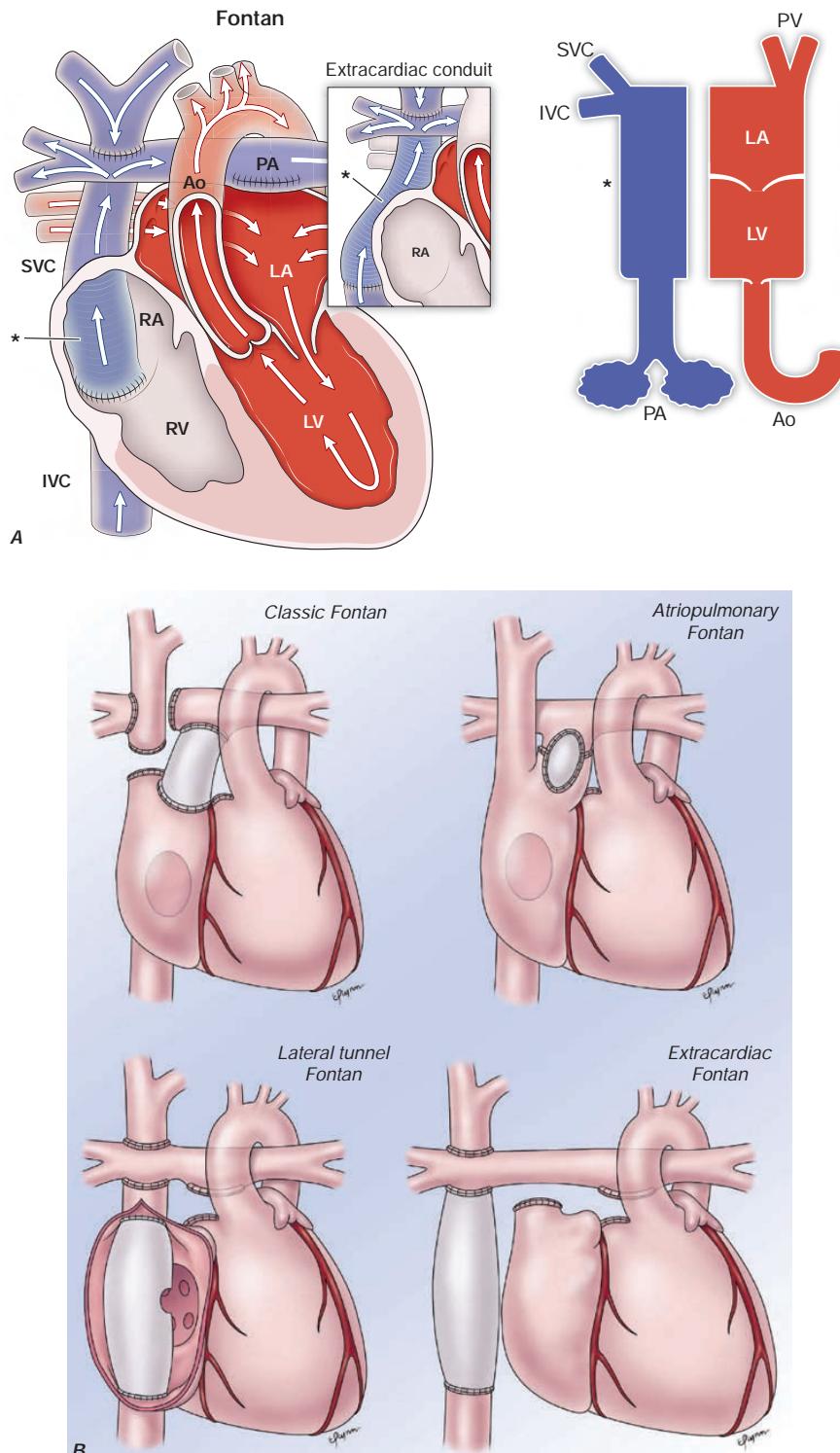
Recent evidence suggests that the use of selective pulmonary vasodilators, such as bosentan or sildenafil, may be efficacious in ES. Select patients may be candidates for combined heart-lung transplantation or preferably lung transplantation with concomitant repair of the intracardiac defect, if feasible.



**FIGURE 269-10** Aortic coarctation (\*). Bicuspid aortic valve (1) is most common concomitant lesion. Sequelae from aortic coarctation (unrepaired or repaired) include systemic arterial hypertension, ascending (2) or descending (3) aortic enlargement or aneurysm formation, left ventricular (LV) hypertrophy (4), LV diastolic and systolic heart failure, accelerated coronary (5) or cerebral (6) atherosclerosis, cerebral aneurysm formation, and recurrence of coarctation after repair. Ao, aorta; PA, pulmonary arteries.

**The Role of Palliative Care in ACHD** In aggregate, adults with CHD demonstrate both quality-of-life-limiting comorbidities and premature mortality far in excess of age-matched controls. The reported prevalence of pain, anxiety, depression, dyspnea, and fatigue appears similar to that reported for adults who are decades older and engaged in palliative care for acquired cardiovascular disease at end of life (EOL). Similarly, at EOL with ACHD, frequencies of hospitalization, intensive care admission, 30-day readmission, and increased length of hospital stay appear greater (despite younger age) than for adults with cancer. In a retrospective study of ACHD patients who died during a hospital admission, only a minority had engaged in EOL discussions with their providers. Surveys of both adults with CHD and their providers suggest that the overwhelming majority of patients wish to participate in advanced care planning and discussion of palliative care; this contrasts with statements from ACHD care providers noting their uncertainties regarding EOL prognostication and concerns over discussion about EOL. Palliative care specialists who are embedded within or aligned with ACHD care teams can play an important and iterative role in defining and addressing alignment of patient and clinician goals within the boundaries of frequently complex care decisions over the adult life span.

**Global Considerations** As survival patterns improve for all medically complex patients, the internist and general practitioner are faced with particular challenges and dilemmas; foremost is accrual of



**FIGURE 269-11** A. Fontan surgery creates a unique circulation in which deoxygenated blood is directed to the PAs from the SVC and IVC in a fashion that bypasses any pumping chamber. The SVC and IVC are connected (\*) via either an internal “tunnel” or an extracardiac conduit that guides flow to the PA. Pulmonary venous (oxygenated) return courses from PV to LA to LV to aorta. In contrast to physiology in normal adults (where pressure is generated by an RV to propel blood flow from a lower pressure RA to a higher pressure LA), in Fontan circulation, by definition, due to the absence of a pumping chamber to the PA, RA pressure is greater than LA pressure, permitting flow through the lungs. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; SVC, superior vena cava; \*, Fontan baffle. B. Diagrammatic representation of the location of various types of Fontan operations. (Part B used with permission from Emily Flynn McIntosh, illustrator.)

sufficient knowledge and competency so as to be able both to engage in patient care provision as well as to seek greater expertise, guidance, and support, when such is appropriate. Across the globe, lifelong care for adults with CHD typifies this growing demand. Care for adults with CHD within medical care centers that contain an ACHD specialty care program has been associated with improved overall survival. However, current analyses suggest that the majority of adults with CHD seek and receive their medical care outside of such ACHD specialty care centers and within the hands of the general practitioner, internist, and cardiologist. Under a surface of adaptability and determination, adults with CHD present a wide spectrum of cognitive and functional performance, multiple organ system comorbidities, abnormalities of systemic and pulmonary vasculature, and a near universal presence of heart failure of one stage or another, all over a lifetime. It appears incumbent on the ACHD specialist and ACHD specialty care centers to serve as a hub for partnering practitioners, encouraging engagement to the level of highest competencies, and providing education, oversight, and support, so as to achieve optimal outcomes.

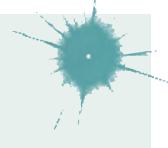
### FURTHER READING

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- Gurvitz M et al: Emerging research directions in adult congenital heart disease: A report from an NHLBI/ACHA Working Group. *J Am Coll Cardiol* 67:1956, 2016.
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270

## Pericardial Disease

Joseph Loscalzo



### NORMAL FUNCTIONS OF THE PERICARDIUM

The normal pericardium is a double-layered sac of the visceral pericardium and parietal pericardium. The visceral pericardium is a serous membrane that is separated from the fibrous parietal pericardium by a small quantity (15–50 mL) of fluid, an ultrafiltrate of plasma. The normal pericardium, by exerting a restraining force, prevents sudden dilation of the cardiac chambers, especially the right atrium and ventricle, e.g., during exercise. It also restricts the anatomic position of the heart and likely retards the spread of infections from the lungs and pleural cavities to the heart. Nevertheless, *total* absence of the pericardium, either congenital or after surgery, does not produce obvious clinical disease. In *partial* left pericardial defects, the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

### ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium (**Table 270-1**), has four principal diagnostic features:

1. *Chest pain* is usually present in acute infectious pericarditis and in many of the forms presumed to be related to hypersensitivity,

**TABLE 270-1 Classification of Pericarditis**

#### Clinical Classification

- I. Acute pericarditis (<6 weeks)
  - A. Fibrinous
  - B. Effusive (serous or sanguineous)
- II. Subacute pericarditis (6 weeks to 6 months)
  - A. Effusive-constrictive
  - B. Constrictive
- III. Chronic pericarditis (>6 months)
  - A. Constrictive
  - B. Adhesive (nonconstrictive)

#### Etiologic Classification

- I. Infectious pericarditis
  - A. Viral (coxsackievirus A and B, echovirus, herpesviruses, mumps, adenovirus, hepatitis, HIV)
  - B. Pyogenic (*pneumococcus*, *Streptococcus*, *Staphylococcus*, *Neisseria*, *Legionella*, *Chlamydia*)
  - C. Tuberculous
  - D. Fungal (*histoplasmosis*, *coccidioidomycosis*, *Candida*, *blastomycosis*)
  - E. Other infections (syphilitic, protozoal, parasitic)
- II. Noninfectious pericarditis
  - A. Acute idiopathic
  - B. Renal failure
  - C. Neoplasia
    - 1. Primary tumors (benign or malignant, mesothelioma)
    - 2. Tumors metastatic to pericardium (lung and breast cancer, lymphoma, leukemia)
  - D. Trauma (penetrating chest wall, nonpenetrating)
  - E. Aortic dissection (with leakage into pericardial sac)
  - F. Acute myocardial infarction
  - G. Postirradiation
  - H. Familial Mediterranean fever and other periodic fever syndromes
  - I. Familial pericarditis
    - 1. Mulibrey nanism<sup>a</sup>
  - J. Metabolic (myxedema, cholesterol)
- III. Pericarditis presumably related to autoimmunity
  - A. Rheumatic fever
  - B. Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, acute rheumatic fever, granulomatosis with polyangiitis [Wegener's])
  - C. Drug-induced (e.g., procainamide, hydralazine, phenytoin, isoniazid, minoxidil, anticoagulants, methysergide)
  - D. Postcardiac injury
    - 1. Postpericardiotomy
    - 2. Posttraumatic
    - 3. Postmyocardial infarction (Dressler's syndrome)

<sup>a</sup>An autosomal recessive syndrome characterized by growth failure, muscle hypotonia, hepatomegaly, ocular changes, enlarged cerebral ventricles, mental retardation, ventricular hypertrophy, and chronic constrictive pericarditis.

autoimmunity, or of unknown cause (idiopathic). The pain of acute pericarditis is often severe, retrosternal and/or left precordial, and referred to the neck, arms, or left shoulder. Frequently the pain is pleuritic, consequent to accompanying pleural inflammation (i.e., sharp and aggravated by inspiration and coughing); however, at times, it is steady, radiates to the trapezius ridge or into either arm, and resembles that of myocardial ischemia. For this reason, confusion with acute myocardial infarction (AMI) is common. Characteristically, pericardial pain may be intensified by lying supine and relieved by sitting up and leaning forward (**Chap. 14**). Pain is often absent in slowly developing tuberculous, postirradiation, neoplastic, and uremic pericarditis.

The differentiation of AMI from acute pericarditis may be challenging when, with the latter, serum biomarkers of myocardial damage such as troponin and creatine kinase-MB rise, presumably

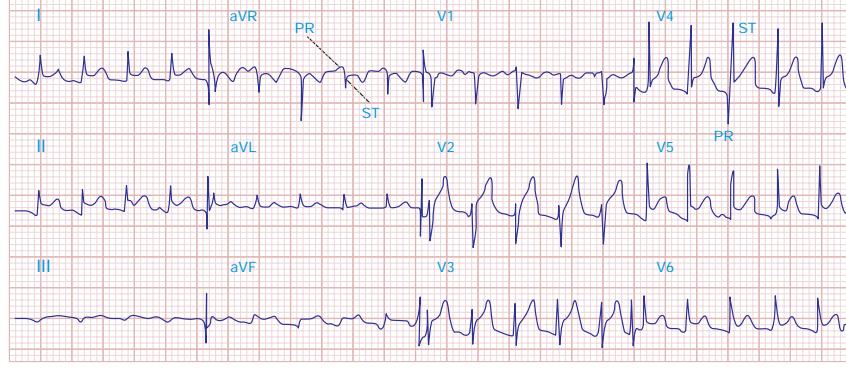
because of concomitant involvement of the epicardium in the inflammatory process (an epi-myocarditis) with resulting myocyte necrosis. If they occur, however, these elevations are quite modest compared to those in AMI, given the extensive electrocardiographic ST-segment elevation in pericarditis. This dissociation is useful in differentiating between these conditions.

2. A *pericardial friction rub* is audible at some point in the illness in about 85% of patients with acute pericarditis. The rub may have up to three components per cardiac cycle and is described as rasping, scratching, or grating (Chap. 239); it is heard most frequently at end expiration with the patient upright and leaning forward.
3. The *electrocardiogram* (ECG) in acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation (Fig. 270-1A), and typically evolves through four stages. In stage 1, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V<sub>1</sub>-V<sub>4</sub>, with reciprocal depressions only in aVR and occasionally V<sub>1</sub>. In addition, there is depression of the PR segment below the TP segment, reflecting atrial involvement, an early change that may occur prior to ST segment elevation. Usually there are no significant changes in QRS complexes unless a large pericardial effusion develops (see below). After several days, the ST segments return to normal (stage 2), and only then, or even later, do the T waves become inverted (stage 3). Weeks or months after the onset of acute pericarditis, the ECG returns to normal (stage 4). In contrast, in AMI, ST elevations are upwardly convex, and reciprocal

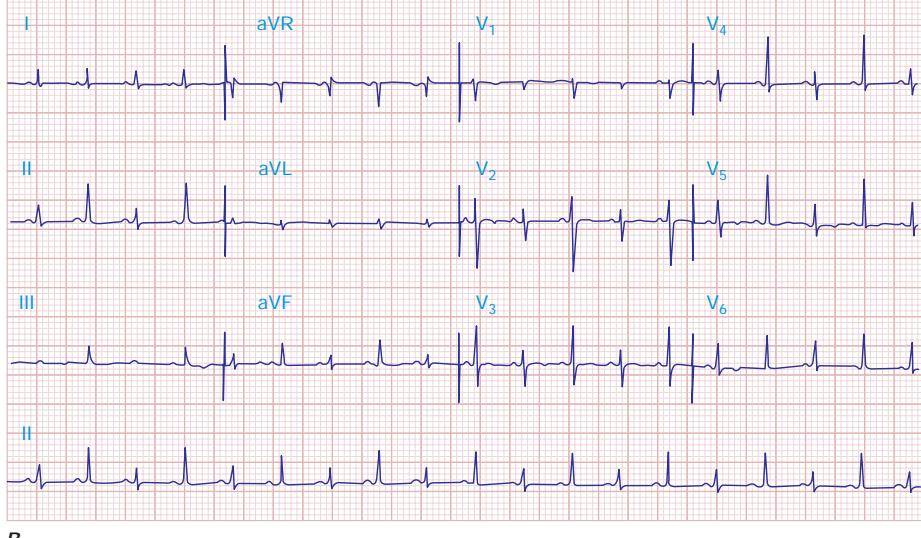
depression is usually more prominent; these changes may return to normal within a day or two. Q waves may develop, with loss of R-wave amplitude, and T-wave inversions; by contrast, with acute pericarditis, these changes are usually seen within hours *before* the ST segments have become isoelectric (Chaps. 274 and 275).

4. *Pericardial effusion* is usually associated with pain and/or the ECG changes mentioned above and, if the effusion is large, with electrical alternans (Fig. 270-1B). Pericardial effusion is especially important clinically when it develops within a relatively short time because it may lead to cardiac tamponade (see below). Differentiation from cardiac enlargement on physical examination may be difficult, but heart sounds may be fainter with large pericardial effusion. The friction rub and the apex impulse may disappear. The base of the left lung may be compressed by pericardial fluid, producing *Ewart's sign*, a patch of dullness, increased fremitus, and egophony beneath the angle of the left scapula. The chest roentgenogram may show enlargement of the cardiac silhouette, with a "water bottle" configuration, but may be normal in patients with small effusions.

**Diagnosis** *Echocardiography* (Chap. 241) is the most widely used imaging technique. It is sensitive, specific, simple, and noninvasive; may be performed at the bedside; and allows localization and estimation of the quantity of pericardial fluid. The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium and/or as a space between the anterior right

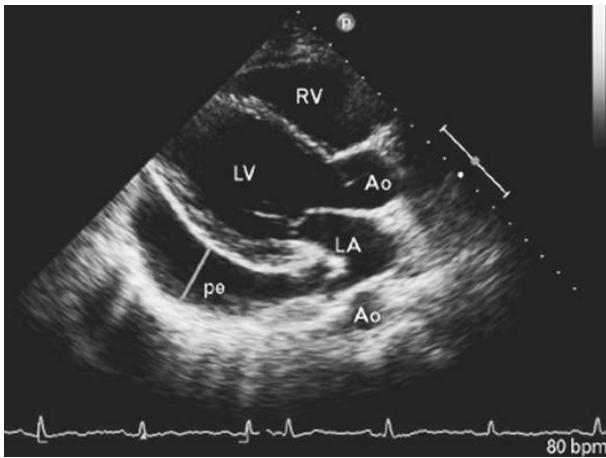


A



B

**FIGURE 270-1** **A.** Acute pericarditis. There are diffuse ST-segment elevations in leads I, II, aVF, and V<sub>1</sub>-V<sub>4</sub>). There is PR-segment depression due to a concomitant atrial injury current. **B.** Electrical alternans. This tracing was obtained from a patient with a large pericardial effusion with cardiac tamponade.



**FIGURE 270-2** Two-dimensional echocardiogram in lateral view in a patient with a large pericardial effusion. Ao, aorta; LA, left atrium; LV, left ventricle; pe, pericardial effusion; RV, right ventricle. (Reproduced with permission from Imazio M: Contemporary management of pericardial diseases. *Curr Opin Cardiol* 27:308, 2012.)

ventricle and the parietal pericardium just beneath the anterior chest wall (**Fig. 270-2**).

The diagnosis of pericardial fluid or thickening may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). These techniques may be superior to echocardiography in detecting loculated pericardial effusions, and pericardial thickening, and in the identification of pericardial masses. MRI is also helpful in detecting pericardial inflammation (**Fig. 270-3**).

## TREATMENT

### Acute Pericarditis

There is no specific therapy for acute idiopathic pericarditis, but bed rest should be recommended, and anti-inflammatory treatment with aspirin (2–4 g/d) or nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (600–800 mg tid) or indomethacin (25–50 mg tid), should be administered along with gastric protection (e.g., omeprazole 20 mg/d). In responsive patients, these doses should be continued for 1–2 weeks and then tapered over several weeks. In addition, colchicine (0.5 mg qd [ $<70$  kg] or 0.5 mg bid [ $>70$  kg]) should be administered for 3 months. Colchicine enhances the response to NSAIDs and also aids in reducing the risk of recurrent pericarditis. This drug is concentrated in and interferes with the migration of neutrophils, may cause diarrhea and other gastrointestinal side effects, and is contraindicated in patients with hepatic or renal dysfunction. Glucocorticoids (e.g.,

prednisone 1 mg/kg per day) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with or do not tolerate NSAIDs and colchicine. However, since they increase the risk of subsequent recurrence, full-dose corticosteroids should be given for only 2–4 days and then tapered. Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and tamponade.

In patients with multiple, frequent, and disabling recurrences that continue for  $>2$  years, are not prevented by continuing colchicine and other NSAIDs, and are not controlled by glucocorticoids, treatment with azathioprine or anakinra (an interleukin 1 receptor antagonist) has been reported to be of benefit. Rarely, pericardial stripping may be necessary; however, this procedure may not always terminate the recurrences.

The majority of patients with acute pericarditis can be managed as outpatients with careful follow-up. However, when specific causes (tuberculosis, neoplastic disease, bacterial infection) are suspected, or if any of the predictors of poor prognosis (fever  $>38^\circ\text{C}$ , subacute onset, or large pericardial effusion) are present, hospitalization is advisable.

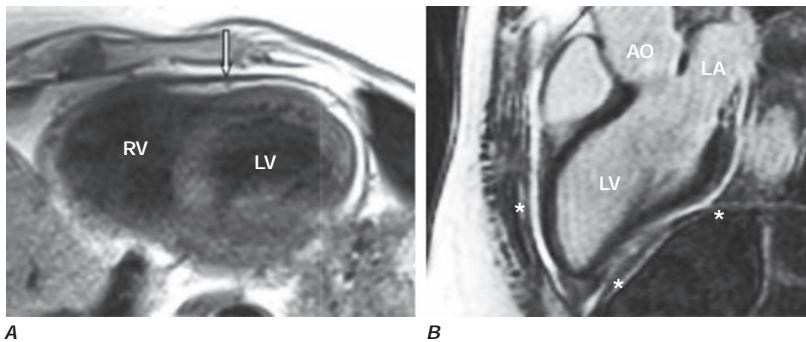
## CARDIAC TAMPONADE

The accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction of the inflow of blood into the ventricles results in cardiac tamponade. This complication may be fatal if it is not recognized and treated promptly. The most common causes of tamponade are idiopathic pericarditis and pericarditis secondary to neoplastic disease, tuberculosis, or bleeding into the pericardial space after leakage from an aortic dissection, cardiac operation, trauma, or treatment with anticoagulants.

The three principal features of tamponade (*Beck's triad*) are hypotension, soft or absent heart sounds, and jugular venous distention with a prominent x (early systolic) descent but an absent y (early diastolic) descent. The limitations to ventricular filling are responsible for reductions of cardiac output and arterial pressure. The quantity of fluid necessary to produce cardiac tamponade may be as small as 200 mL when the fluid develops rapidly or be as much as  $>2000$  mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume.

A high index of suspicion for cardiac tamponade is required because in many instances no obvious cause for pericardial disease is apparent. This diagnosis should be considered in any patient with otherwise unexplained sudden enlargement of the cardiac silhouette, hypotension, and elevation of jugular venous pressure. Reductions in amplitude of the QRS complexes and *electrical alternans* of the P, QRS, or T waves should also raise the suspicion of cardiac tamponade (**Fig. 270-1**).

**Table 270-2** lists the features that distinguish acute cardiac tamponade from constrictive pericarditis.



**FIGURE 270-3** Pericardial inflammation by cardiac magnetic resonance imaging. **A.** Short axis view. The pericardium is thickened and enhanced on T2 magnetic images. Note thickened white line denoted by arrow. **B.** Long axis view. Late gadolinium enhancement of thickened, inflamed pericardium. AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (From RY Kwong: *Cardiovascular magnetic resonance imaging*, in Braunwald's Heart Disease, 10th ed, Mann DL et al [eds]. Philadelphia: Elsevier, 2015, pp 320–40.)

TABLE 270-2 Features That Distinguish Cardiac Tamponade from Constrictive Pericarditis and Similar Clinical Disorders

CHARACTERISTIC	TAMPONADE	CONSTRICITIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY	RIGHT VENTRICULAR MYOCARDIAL INFARCTION	EFFUSIVE CONSTRICATIVE PERICARDITIS
<b>Clinical</b>					
Pulsus paradoxus	+++	+	+	+	+++
Jugular veins					
Prominent y descent	-	++	+	+	-
Prominent x descent	+++	++	+++	+	+++
Kussmaul's sign	-	+++	+	+++	++
Third heart sound	-	-	+	+	+
Pericardial knock	-	++	-	-	-
<b>Electrocardiogram</b>					
Low ECG voltage	++	++	+	-	+
Electrical alternans	++	-	-	-	+
<b>Echocardiogram</b>					
Thickened pericardium	-	+++	-	-	++
Pericardial calcification	-	++	-	-	-
Pericardial effusion	+++	-	-	-	++
RV size	Usually small	Usually normal	Usually normal	Enlarged	Usually normal
Exaggerated respiratory variation in flow velocity	+++	+++	-	+++	+
<b>CT/MRI</b>					
Thickened pericardium	-	+++	-		++
Equalization of diastolic pressures	+++	+++	-	++	++

Abbreviations: +++, always present; ++, usually present; +, rare; -, absent; DC, diastolic collapse; ECG, electrocardiogram; RV, right ventricle.

Source: Reproduced with permission from GM Brockington et al: Constrictive pericarditis. *Cardiol Clin* 8:645, 1990.

**Paradoxical Pulse** This important clue to the presence of cardiac tamponade consists of a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure. When severe, it may be detected by palpating weakness or even disappearance of the arterial pulse during inspiration, but usually sphygmomanometric measurement of systolic pressure during slow respiration is required.

Because both ventricles share a tight incompressible covering, i.e., the pericardial sac, the inspiratory enlargement of the right ventricle causes leftward bulging of the interventricular septum, reducing left ventricular volume, stroke volume, and arterial systolic pressure. Paradoxical pulse also occurs in approximately one-third of patients with constrictive pericarditis (see below), and in some cases of hypovolemic shock, acute and chronic obstructive airway disease, and pulmonary embolism. Right ventricular infarction (Chap. 275) may resemble cardiac tamponade with hypotension, elevated jugular venous pressure, an absent y descent in the jugular venous pulse, and occasionally, a paradoxical pulse (Table 270-2).

**Diagnosis** Because immediate treatment of cardiac tamponade may be lifesaving, prompt establishment of the diagnosis, usually by echocardiography, should be undertaken. When pericardial effusion causes tamponade, Doppler ultrasound shows that tricuspid and pulmonic valve flow velocities increase markedly during inspiration, whereas pulmonic vein, mitral, and aortic flow velocities decrease (as in constrictive pericarditis, see below) (Fig. 270-4). In tamponade, there is late diastolic inward motion (collapse) of the right ventricular free wall and the right atrium. Transesophageal echocardiography, CT, or cardiac MRI may be necessary to diagnose a loculated effusion responsible for cardiac tamponade.

## TREATMENT

### Cardiac Tamponade

Patients with acute pericarditis should be observed frequently for the development of an effusion. If a large effusion is present,

pericardiocentesis should be performed or the patient watched closely for signs of tamponade with serial echocardiography and monitoring of arterial and venous pressures.

### PERICARDIOCENTESIS

If manifestations of tamponade appear, pericardiocentesis using an apical, parasternal, or, most commonly, subxiphoid approach must be carried out at once because if left untreated, tamponade may be rapidly fatal. Whenever possible, this procedure should be carried out under echocardiographic guidance. Intravenous saline may be administered as the patient is being readied for the procedure, but the pericardiocentesis must not be delayed. If possible, intraperitoneal pressure should be measured before fluid is withdrawn, and

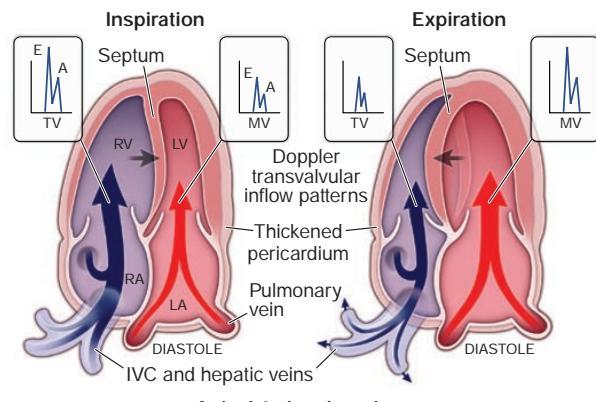


FIGURE 270-4 Constrictive pericarditis. Doppler schema of respirophasic changes in mitral and tricuspid inflow. Reciprocal patterns of ventricular filling are assessed on pulsed Doppler examination of mitral valve (MV) and tricuspid valve (TV) inflow. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Courtesy of Bernard E. Bulwer, MD.)

the pericardial cavity should be drained as completely as possible. A small, multiholed catheter may be advanced over the needle inserted into the pericardial cavity and left in place to allow draining of the pericardial space if fluid reaccumulates. Surgical drainage through a limited (subxiphoid) thoracotomy may be required in recurrent tamponade to remove loculated effusions and/or when it is necessary to obtain tissue for diagnosis.

Pericardial fluid obtained from an effusion may have the physical characteristics of an exudate. In developed nations, bloody fluid is most commonly due to neoplasm, renal failure, or after cardiac injury. In developing nations, tuberculosis, may also cause exudative and/or bloody effusion.

The pericardial fluid should be analyzed for red and white blood cells and cytology for neoplastic cells. Cultures should be obtained. The presence of DNA of *Mycobacterium tuberculosis* determined by the polymerase chain reaction strongly supports the diagnosis of tuberculous pericarditis; however, it is often necessary to obtain pericardial tissue to make this diagnosis (Chap. 178).

### VIRAL OR IDIOPATHIC ACUTE PERICARDITIS

In many instances, acute pericarditis occurs in association with or following illnesses of known or presumed viral origin and probably is caused by the same agent. There may be an antecedent infection of the respiratory tract, but viral isolation and serologic studies are usually negative. In some cases, Coxsackievirus A or B or the virus of influenza, echovirus, mumps, *Herpes simplex*, varicella/zoster, adenovirus, or cytomegalovirus has been isolated from pericardial fluid, and/or appropriate elevations in viral antibody titers have been observed. Frequently, a viral cause cannot be established, and the term *idiopathic acute pericarditis* is appropriate.

Viral or idiopathic acute pericarditis occurs at all ages but is most common in young adult males and is often associated with pleural effusion and pneumonitis. The almost simultaneous development of fever and precordial pain, often 10–12 days after a presumed viral illness, constitutes an important feature in the differentiation of acute pericarditis from AMI, in which chest pain precedes fever. The constitutional symptoms are usually mild to moderate, and a pericardial friction rub is often audible. The disease ordinarily runs its course in a few days to 4 weeks. Elevations of C-reactive protein and of the white blood cell count are common. The ST-segment alterations in the ECG usually disappear after 1 or more weeks, but the abnormal T waves may persist for as long as several years and be a source of confusion in persons without a clear history of pericarditis. Accumulation of some pericardial fluid is common, and both tamponade and constrictive pericarditis are possible, but infrequent, complications.

The most frequent complication is recurrent (relapsing) pericarditis, which occurs in about one-fourth of patients with acute idiopathic pericarditis. A smaller number of individuals have multiple recurrences.

**Postcardiac Injury Syndrome** Acute pericarditis may appear in a variety of circumstances that have one common feature—previous injury to the myocardium with blood in the pericardial cavity. The syndrome may develop after a cardiac operation (postpericardiectomy syndrome), after blunt or penetrating cardiac trauma (Chap. 272), or after perforation of the heart with a catheter; rarely, it follows AMI.

The clinical picture mimics acute viral or idiopathic pericarditis. The principal symptom is the pain of acute pericarditis, which usually develops 1–4 weeks after the cardiac injury. Recurrences are common and may occur up to 2 years or more following the injury. Fever, pleuritis, and pneumonitis are accompanying features, and the illness usually subsides in 1 or 2 weeks. The pericarditis may be of the fibrinous variety, or it may be a pericardial effusion, which is often serosanguinous and rarely causes tamponade. ECG changes typical of acute pericarditis may also occur. This syndrome is probably the result of a hypersensitivity (or autoimmune) reaction to antigen(s) that originate from injured myocardial tissue and/or pericardium.

Often no treatment is necessary aside from aspirin and analgesics. When the illness is severe or followed by a series of disabling

recurrences, therapy with another NSAID, colchicine, or a glucocorticoid, such as described for treatment of acute pericarditis, is usually effective.

### DIFFERENTIAL DIAGNOSIS

Because there is no specific test for *acute idiopathic pericarditis*, the diagnosis is one of exclusion. Consequently, all other disorders that may be associated with acute fibrinous pericarditis must be considered. A common diagnostic error is mistaking acute viral or idiopathic pericarditis for AMI and vice versa.

Pericarditis secondary to postcardiac injury is differentiated from acute idiopathic pericarditis chiefly by timing. If it occurs within a few days or weeks of a chest blow, a cardiac perforation, a cardiac operation, or an AMI, the two are probably related.

It is important to distinguish *pericarditis due to collagen vascular disease* from acute idiopathic pericarditis. Most important in the differential diagnosis is the pericarditis due to systemic lupus erythematosus (SLE; Chap. 356) or drug-induced (hydralazine or procainamide) lupus. When pericarditis occurs in the absence of any obvious underlying disorder, the diagnosis of SLE may be suggested by a rise in the titer of antinuclear antibodies. Acute pericarditis is an occasional complication of *rheumatoid arthritis*, *scleroderma*, and *polyarteritis nodosa*, and other evidence of these diseases is usually obvious at the time of presentation with acute pericarditis.

*Pyogenic (purulent) pericarditis* is usually secondary to cardiothoracic operations, by extension of infection from the lungs or pleural cavities, from rupture of the esophagus into the pericardial sac, or from rupture of a valvular ring abscess in a patient with infective endocarditis. It may also complicate the viral, bacterial, mycobacterial, and fungal infections that occur with HIV infection. It is generally accompanied by fever, chills, septicemia, and evidence of infection elsewhere, and generally has a poor prognosis. The diagnosis is made by examination of the pericardial fluid. It requires immediate drainage as well as vigorous antibiotic treatment.

*Pericarditis of renal failure (uremic pericarditis)* occurs in up to one-third of patients with severe renal dysfunction and is also seen in patients undergoing chronic dialysis who have normal levels of blood urea nitrogen (*dialysis-associated pericarditis*). These two forms of pericarditis may be fibrinous and are generally associated with serosanguinous effusions; frank hemorrhagic effusions may be seen in some cases of uremic pericarditis prior to the onset of dialysis. A pericardial friction rub is common, but pain is usually absent or mild. Treatment with an NSAID and intensification of dialysis are usually adequate. Occasionally, tamponade occurs and pericardiocentesis is required. When the pericarditis of renal failure is recurrent or persistent, a pericardial window should be created or pericardectomy may be necessary.

Pericarditis due to *neoplastic diseases* results from extension or invasion of metastatic tumors (most commonly carcinoma of the lung and breast, malignant melanoma, lymphoma, and leukemia) to the pericardium. The pain of pericarditis, tamponade, and atrial arrhythmias are complications that occur occasionally. Diagnosis is made by pericardial fluid cytology or pericardial biopsy. *Mediastinal irradiation* for neoplasm may cause acute pericarditis and/or chronic constrictive pericarditis. Unusual causes of acute pericarditis include syphilis, fungal infection (histoplasmosis, blastomycosis, aspergillosis, and candidiasis), and parasitic infestation (amebiasis, toxoplasmosis, echinococcosis, and trichinosis) (Table 270-1).

### CHRONIC PERICARDIAL EFFUSIONS

Chronic pericardial effusions are sometimes encountered in patients without an antecedent history of acute pericarditis. They may cause few symptoms per se, and their presence may be detected by finding an enlarged cardiac silhouette on a chest roentgenogram. *Tuberculosis* and *myxedema* may be causal. Neoplasms, SLE, rheumatoid arthritis, mycotic infections, radiation therapy to the chest, and chylopericardium may also cause chronic pericardial effusion and should be considered and specifically sought in such patients. Aspiration and analysis of the pericardial fluid are often helpful in diagnosis. Pericardial fluid

**2024** should be analyzed as described under pericardiocentesis. Grossly sanguineous pericardial fluid results most commonly from a neoplasm, tuberculosis, renal failure, or slow leakage from an aortic dissection. Pericardiocentesis may resolve large effusions, but pericardectomy may be required in patients with recurrence. Intrapericardial instillation of sclerosing agents may be used to prevent reaccumulation of fluid, most commonly in recurrent neoplastic effusions.

## CHRONIC CONSTRICTIVE PERICARDITIS

This disorder results when the healing of an acute fibrinous or serofibrinous pericarditis or the resorption of a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation tissue. The latter gradually contracts and forms a firm scar encasing the heart, which may become calcified. In developing nations, a high percentage of cases are of tuberculous origin, but this is now an uncommon cause in North America or Western Europe. Chronic constrictive pericarditis may follow acute or relapsing viral or idiopathic pericarditis, trauma with organized blood clot, or cardiac surgery of any type, or results from mediastinal irradiation, purulent infection, histoplasmosis, neoplastic disease (especially breast cancer, lung cancer, and lymphoma), rheumatoid arthritis, SLE, or chronic renal failure treated by chronic dialysis. In many patients, the cause of the pericardial disease is undetermined, and in these patients, an asymptomatic or forgotten bout of viral pericarditis, idiopathic or acute, may have been the inciting event.

The basic physiologic abnormality in patients with chronic constrictive pericarditis is the inability of the ventricles to fill owing to the limitations imposed by the rigid, thickened pericardium. Ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole. In both conditions, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and the mean pressures in the atria, pulmonary veins, and systemic veins are all elevated to similar levels (i.e., within 5 mmHg of one another). Despite these hemodynamic changes, systolic function may be normal or only slightly impaired at rest. However, in advanced cases, the fibrotic process may extend into the myocardium and cause myocardial scarring and atrophy, and venous congestion may then be due to the combined effects of the pericardial and myocardial lesions.

In constrictive pericarditis, the right and left atrial pressure pulses display an M-shaped contour, with prominent *x* and *y* descents. The *y* descent, which is absent or diminished in cardiac tamponade, is the most prominent deflection in constrictive pericarditis; it reflects rapid early filling of the ventricles. The *y* descent is interrupted by a rapid rise in atrial pressure during early diastole, when ventricular filling is impeded by the constricting pericardium. These characteristic changes are transmitted to the jugular veins, where they may be recognized by inspection. In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit characteristic "square root" signs during diastole. These hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis and may also be observed in restrictive cardiomyopathies (**Chap. 259, Table 259-2**).

### CLINICAL AND LABORATORY FINDINGS

Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, and edema are common. The patient often appears chronically ill, and in advanced cases, anasarca, skeletal muscle wasting, and cachexia may be present. Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe. The neck veins are distended and may remain so even after intensive diuretic treatment, and venous pressure may fail to decline during inspiration (*Kussmaul's sign*). The latter is common in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy.

The pulse pressure is normal or reduced. A paradoxical pulse can be detected in about one-third of cases. Congestive hepatomegaly is pronounced, may impair hepatic function, and may cause jaundice;

ascites is common and is usually more prominent than dependent edema. Pleural effusions and splenomegaly may also be present. The apical pulse is reduced and may retract in systole (*Broadbent's sign*). The heart sounds may be distant; an early third heart sound (i.e., a pericardial knock) occurring at the cardiac apex with the abrupt cessation of ventricular filling is often conspicuous.

The ECG frequently displays low voltage of the QRS complexes and diffuse flattening or inversion of the T waves. Atrial fibrillation is present in about one-third of patients. The *chest roentgenogram* shows a normal or slightly enlarged heart. Pericardial calcification is most common in tuberculous pericarditis. Pericardial calcification may, however, occur in the absence of constriction, and constriction may occur without calcification.

Inasmuch as the common physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement and dysfunction associated with jaundice and intractable ascites may lead to a mistaken diagnosis of hepatic cirrhosis. This error can be avoided if the neck veins are inspected and found to be distended.

The transthoracic *echocardiogram* often shows pericardial thickening, dilation of the inferior vena cava and hepatic veins, and a sharp halt to rapid left ventricular filling in early diastole, with normal ventricular systolic function and flattening of the left ventricular posterior wall. There is a distinctive pattern of transvalvular flow velocity on Doppler echocardiography (Fig. 270-4). During inspiration, there is an exaggerated reduction in blood flow velocity in the pulmonary veins and across the mitral valve, and a leftward shift of the ventricular septum; the opposite occurs during expiration. Diastolic flow velocity in the inferior vena cava into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration. However, echocardiography cannot definitively establish or exclude the diagnosis of constrictive pericarditis; CT and MRI are more accurate, with the latter useful in evaluating myocardial involvement.

### DIFFERENTIAL DIAGNOSIS

As with chronic constrictive pericarditis, *cor pulmonale* (**Chap. 257**) may be associated with marked systemic venous hypertension, little pulmonary congestion, a (left) heart that is not enlarged, and a paradoxical pulse. However, in *cor pulmonale*, advanced parenchymal pulmonary disease is usually apparent and venous pressure *falls* during inspiration (i.e., Kussmaul's sign is negative). *Tricuspid stenosis* (**Chap. 266**) may also simulate chronic constrictive pericarditis with congestive hepatomegaly, splenomegaly, ascites, and venous distention. However, the characteristic murmur and that of accompanying mitral stenosis are usually present.

Because it can be corrected surgically, it is important to distinguish chronic constrictive pericarditis from restrictive cardiomyopathy (**Chap. 259**), which has a similar pathophysiologic underpinning (i.e., restriction of ventricular filling). The differentiating features are summarized in Table 270-2. When a patient has progressive, disabling, and unresponsive congestive heart failure and displays any of the features of constrictive heart disease, Doppler echocardiography to record respiratory effects on transvalvular flow (Fig. 270-4) should be performed and an MRI or CT scan should be obtained to detect or exclude constrictive pericarditis because the latter is usually correctable.

### TREATMENT

#### Constrictive Pericarditis

Pericardial resection is the only definitive treatment of constrictive pericarditis and should be as complete as possible. Coronary arteriography should be carried out preoperatively in patients aged >50 years to exclude unsuspected accompanying coronary artery disease. The benefits derived from cardiac decortication are usually progressive over a period of months. The risk of this operation depends on the extent of penetration of the myocardium by the

fibrotic and calcific process, the severity of myocardial atrophy, the extent of secondary impairment of hepatic and/or renal function, and the patient's general condition. Operative mortality is in the range of 5–10% even in experienced centers; the patients with the most severe disease, especially secondary to radiation therapy, are at highest risk. Therefore, surgical treatment should, if possible, be carried out as early as possible.

**Subacute Effusive-Constrictive Pericarditis** This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened pericardium. As such, it shares a number of features with both chronic pericardial effusion producing cardiac compression and with pericardial constriction. It may be caused by tuberculosi (see below), multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, renal failure, scleroderma, and neoplasms. The heart is generally enlarged, and a paradoxical pulse is usually present. After pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction. Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal. The diagnosis can be established by pericardiocentesis followed by pericardial biopsy. Wide excision of both the visceral and parietal pericardium is usually effective therapy.

**Tuberculous Pericardial Disease** This chronic infection is a common cause of chronic pericardial effusion, especially in the developing world where active tuberculosis and HIV are endemic. Tuberculous pericarditis may present as pericardial effusion, chronic constrictive pericarditis, or subacute effusive-constrictive pericarditis (see above). The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion. It is important to consider this diagnosis in a patient with known tuberculosis, with HIV, and with fever, chest pain, weight loss, and enlargement of the cardiac silhouette of undetermined origin. If the etiology of chronic pericardial effusion remains obscure despite detailed analysis including culture of the pericardial fluid, a pericardial biopsy, preferably by a limited thoracotomy, should be performed. If definitive evidence is still lacking but the specimen shows granulomas with caseation, antituberculous chemotherapy (*Chap. 178*) is indicated.

If the biopsy specimen shows a thickened pericardium after 2–4 weeks of antituberculous therapy, pericardectomy should be performed to prevent the development of constriction. Tubercular cardiac constriction should be treated surgically while the patient is receiving antituberculous chemotherapy.

#### Acknowledgment

Eugene Braunwald wrote this chapter in the 20th edition, and some material from that chapter has been retained here.

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Cardiac tumors can be broadly classified into those that arise primarily in the heart and those that reflect metastatic disease from a distant primary source. Primary cardiac tumors can be further divided into those that are pathologically benign and those that are malignant. Overall, primary cardiac tumors are relatively uncommon, whereas secondary involvement of the heart or pericardium occurs in as many as 20% of patients with end-stage metastatic cancer. While patients with cardiac tumors may present with a variety of symptoms, many patients are asymptomatic at the time of diagnosis, the tumor being identified incidentally on imaging studies performed for other reasons. Cardiac tumors need to be differentiated from other cardiac masses such as vegetation, thrombus, inflammatory myofibroblastic tumors, or myocardial hypertrophy. Echocardiography is usually the initial imaging modality used to evaluate cardiac tumors; however, a variety of imaging modalities are now available, and a multimodality approach is often necessary for accurate diagnosis and clarification of treatment options (**Table 271-1**).

#### PRIMARY TUMORS

Primary tumors of the heart are rare, occurring in ~1 in 2000 patients in autopsy series. Approximately three-quarters are histologically benign, the majority of which are myxomas. Malignant tumors, almost all of which are sarcomas, account for 25% of primary cardiac tumors. All cardiac tumors, regardless of pathologic type, have the potential to cause life-threatening complications. Many tumors are now surgically curable; thus, early diagnosis is imperative.

**Clinical Presentation** Cardiac tumors may present with a wide array of cardiac and noncardiac manifestations. These manifestations, which depend in large part on the location and size of the tumor as well as its impact on surrounding cardiac structures, are often nonspecific features of more common forms of heart disease, and include chest

**TABLE 271-1 Imaging Modalities and Their Utility in the Evaluation of Cardiac Tumors**

MODALITY	UTILITY IN CARDIAC TUMOR EVALUATION
Transthoracic echocardiography (TTE) (including two-dimensional, three-dimensional, and contrast)	Assessment of tumor location and size and its impact on adjacent structures (e.g., valves, pericardium).
Transesophageal echocardiography (TEE)	Improved tumor characterization and spatial resolution compared with TTE. May aid in determining surgical approach.
Cardiac MRI with gadolinium contrast	Improved tissue characterization, definition of tumor size, and identification of local invasion when compared with TTE or TEE. May differentiate tumor from thrombus.
Gated cardiac CT	Provides anatomic assessment and tissue characterization of the tumor. Useful when patients cannot tolerate MRI or when MRI is not feasible (e.g., patients with implantable cardiac devices). Allows for better assessment of calcified lesions and evaluation of extracardiac tumor involvement.
Nuclear imaging (including <sup>18</sup> F-fluorodeoxyglucose positron emission tomography [FDG-PET])	Definition of extracardiac disease. May be useful in diagnosis of certain cardiac tumors (e.g., neuroendocrine tumors), but assessment of smaller tumors may be limited by surrounding myocardial FDG uptake.

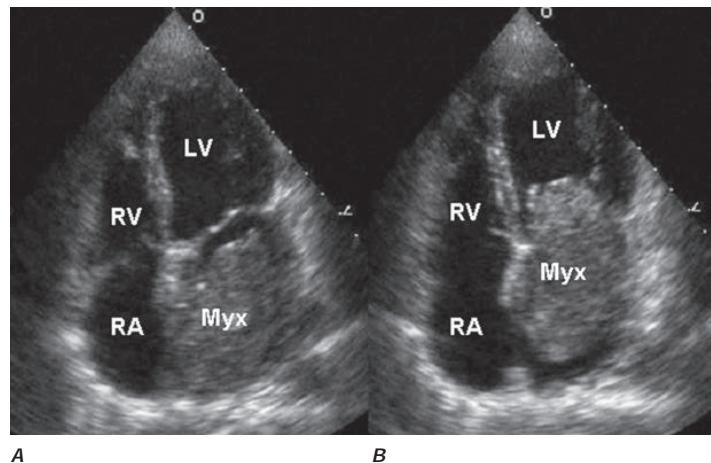
pain, syncope, congestive heart failure (CHF), murmurs, arrhythmias, conduction disturbances, pericardial effusion, and pericardial tamponade. Additionally, embolic phenomena and constitutional symptoms may occur.

**Myxoma** Myxomas are the most common type of primary cardiac tumor in adults, accounting for one-third to one-half of all cases at postmortem examination, and approximately three-quarters of the tumors treated surgically. They occur at all ages, most commonly in the third through sixth decades, with a female predilection. Approximately 90% of myxomas are sporadic; the remainder are familial with autosomal dominant transmission. The familial variety often occurs as part of a syndrome complex (Carney complex) that includes (1) myxomas (cardiac, skin, and/or breast), (2) lentigines and/or pigmented nevi, and (3) endocrine overactivity (primary nodular adrenal cortical disease with or without Cushing's syndrome, testicular tumors, and/or pituitary adenomas with gigantism or acromegaly). Certain constellations of findings have been referred to as the *NAME* syndrome (nevus, atrial myxoma, myxoid neurofibroma, and ephelides) or the *LAMB* syndrome (lentigines, atrial myxoma, and blue nevi), although these syndromes probably represent subsets of the Carney complex. The genetic basis of this complex has not been elucidated completely; however, inactivating mutations in the tumor-suppressor gene *PRKARIA*, which encodes the protein kinase A type I- regulatory subunit, have been identified in ~70% of patients with Carney complex.

Pathologically, myxomas are gelatinous structures that consist of myxoma cells embedded in a stroma rich in glycosaminoglycans. Most sporadic tumors are solitary, arise from the interatrial septum in the vicinity of the fossa ovalis (particularly in the left atrium), and are often pedunculated on a fibrovascular stalk. In contrast, familial or syndromic tumors tend to occur in younger individuals, are often multiple, may be ventricular in location, and are more likely to recur after initial resection.

Myxomas commonly present with obstructive signs and symptoms. The most common clinical presentation mimics that of mitral valve disease: either stenosis owing to tumor prolapse into the mitral orifice or regurgitation resulting from tumor-induced valvular trauma or distortion. Ventricular myxomas may cause outflow tract obstruction similar to that caused by subaortic or subpulmonic stenosis. The symptoms and signs of myxoma may be sudden in onset or positional in nature, owing to the effects of gravity on tumor position. A characteristic low-pitched sound, a "tumor plop," may be appreciated on auscultation during early or mid-diastole and is thought to result from the impact of the tumor against the mitral valve or ventricular wall. Myxomas also may present with peripheral or pulmonary embolic phenomenon (resulting from embolization of tumor fragments or tumor-associated thrombus) or with constitutional signs and symptoms, including fever, weight loss, cachexia, malaise, arthralgias, rash, digital clubbing, and Raynaud's phenomenon. These constitutional symptoms are likely the result of cytokines (e.g., interleukin 6) secreted by the myxoma. Laboratory abnormalities, such as hypergammaglobulinemia, anemia, polycythemia, leukocytosis, thrombocytopenia or thrombocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein level are often present. These features account for the frequent misdiagnosis of patients with myxomas as having endocarditis, collagen vascular disease, or a paraneoplastic syndrome.

Two-dimensional and three-dimensional transthoracic and/or transesophageal echocardiography are useful in the diagnosis of cardiac myxoma and allow for assessment of tumor size and determination of the site of tumor attachment, both of which are important considerations in the planning of surgical excision (Fig. 271-1). Computed tomography (CT) and magnetic resonance imaging (MRI) may provide important additional information regarding size, shape, composition, and surface characteristics of the tumor (Fig. 271-2) and may identify extracardiac intrathoracic involvement in patients in whom metastatic disease is suspected.



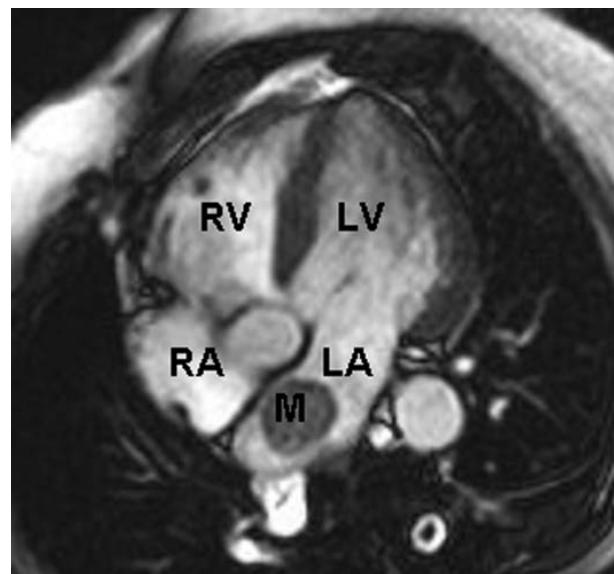
**FIGURE 271-1** Transthoracic echocardiogram demonstrating a large atrial myxoma. The myxoma (Myx) fills the entire left atrium in systole (**A**) and prolapses across the mitral valve and into the left ventricle (LV) during diastole (**B**). RA, right atrium; RV, right ventricle. (Courtesy of Dr. Michael Tsang; with permission.)

Although cardiac catheterization and angiography were previously performed routinely before tumor resection, they no longer are considered mandatory when adequate noninvasive information is available and other cardiac disorders (e.g., coronary artery disease) are not considered likely. Additionally, catheterization of the chamber from which the tumor arises carries the risk of tumor embolization. Because myxomas may be familial, echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young and has multiple tumors or features of a myxoma syndrome.

## TREATMENT

### Myxoma

Surgical excision using cardiopulmonary bypass is indicated regardless of tumor size and is generally curative. Myxomas recur in 12–22% of familial cases but in only 1–2% of sporadic cases. Tumor



**FIGURE 271-2** Cardiac magnetic resonance imaging demonstrating a rounded mass (M) within the left atrium (LA). Pathologic evaluation at the time of surgery revealed it to be an atrial myxoma. LV, left ventricle; RA, right atrium; RV, right ventricle.

recurrence most likely results from multifocal lesions in the former setting and incomplete tumor resection in the latter.

**Other Benign Tumors** Cardiac *lipomas*, although relatively common, are usually incidental findings at postmortem examination; however, they may grow as large as 15 cm, may present as an abnormality of the cardiac silhouette on chest x-ray, and should be resected if they produce symptoms owing to mechanical interference with cardiac function, arrhythmias, or conduction disturbances. *Papillary fibroelastomas* are friable tumors with frond-like projections that are usually solitary and are the most common tumors of the cardiac valves. Remnants of cytomegalovirus have been recovered from these tumors, raising the possibility that they arise as a result of chronic viral endocarditis. Although usually clinically silent, they can cause valve dysfunction and may embolize distally, resulting in transient ischemic attacks, stroke, or myocardial infarction. In general, these tumors should be resected even when asymptomatic, although a more conservative approach may be considered for small, right-sided lesions. *Rhabdomyomas* and *fibromas* are the most common cardiac tumors in infants and children and usually occur in the ventricles, where they may produce mechanical obstruction to blood flow, thereby mimicking valvular stenosis, CHF, restrictive or hypertrophic cardiomyopathy, or pericardial constriction. Rhabdomyomas are probably hamartomatous growths, are multiple in 90% of cases, occur in ~50% of children with tuberous sclerosis, and are associated with mutations in the tumor-suppressor genes *TSC1* and *TSC2* (Fig. 271-3). These tumors have a tendency to regress completely or partially; only tumors that cause obstruction require surgical resection. Fibromas are usually single, universally ventricular in location, often calcified, and may be associated with mutations in the tumor-suppressor gene *PTCH1*. Fibromas tend to grow and cause arrhythmias and obstructive symptoms and should be completely resected when possible. *Paragangliomas* are rare chromaffin cell tumors that represent extra-adrenal pheochromocytomas. Most are located in the roof of the left atrium and can be identified on cardiac CT or MRI or with nuclear scanning using 131-I-metiodobenzylguanidine. They are highly vascular and may be hormonally active, resulting in uncontrolled hypertension. Extensive surgical resection is usually required. *Hemangiomas* and *mesotheliomas* are generally small tumors, most often intramyocardial in location, and may cause atrioventricular (AV) conduction disturbances and even sudden death as a result of their propensity to develop in the region of the AV node. Other benign tumors arising from the heart include *teratoma*, *chemodectoma*, *neurilemoma*, *granular cell myoblastoma*, and *paraganglioma*.

**Malignant Tumors** Almost all malignant primary cardiac tumors are sarcomas, which may be of several histologic types; angiosarcomas

are the most common type in adults, whereas rhabdomyosarcomas are the most common type in children. In general, sarcomas are characterized by rapid progression that culminates in the patient's death within weeks to months from the time of presentation as a result of hemodynamic compromise, local invasion, or distant metastases. Almost one-third are metastatic at the time of initial diagnosis, usually involving the lungs. Sarcomas commonly involve the right side of the heart, are rapidly growing, frequently invade the pericardial space, and may obstruct the cardiac chambers or venae cavae. Sarcomas also may occur on the left side of the heart and may be mistaken for myxomas. Isolated cardiac lymphomas have been rarely described, but more commonly occur in the context of systemic disease. They are more common in men and in the elderly; usually involve the right heart; may represent with arrhythmias, syncope, CHF, or constitutional symptoms; and are usually of the large B-cell type.

## TREATMENT

### Malignant Tumors

The optimal therapy for cardiac sarcoma is complete resection, often with neoadjuvant and postoperative chemotherapy; however, at the time of presentation, many of these tumors have spread too extensively to allow for surgical excision. Although there are scattered reports of palliation with radiotherapy and/or chemotherapy, the response of cardiac sarcomas to these therapies is generally poor. The one exception appears to be cardiac lymphosarcomas, which may respond to a combination of chemo- and radiotherapy. Primary cardiac lymphoma is the most chemotherapy-sensitive primary cardiac malignancy, with long-term survival achieved in ~40% of treated individuals.

### TUMORS METASTATIC TO THE HEART

Metastatic cardiac tumors are much more common than primary cardiac tumors, and their incidence is likely to increase as the life expectancy of patients with various forms of malignant neoplasms is extended by more effective therapy and improved imaging modalities allow earlier identification of metastatic disease. Although cardiac metastases may occur with any tumor type, the relative incidence is especially high in malignant melanoma and, to a somewhat lesser extent, leukemia and lymphoma (Fig. 271-4). In absolute terms, the most common primary sites from which cardiac metastases originate are carcinoma of the breast and lung, reflecting the high incidence of these malignancies. Cardiac metastases almost always occur in the setting of widespread primary disease; most often, there is either primary or metastatic disease elsewhere in the thoracic cavity.

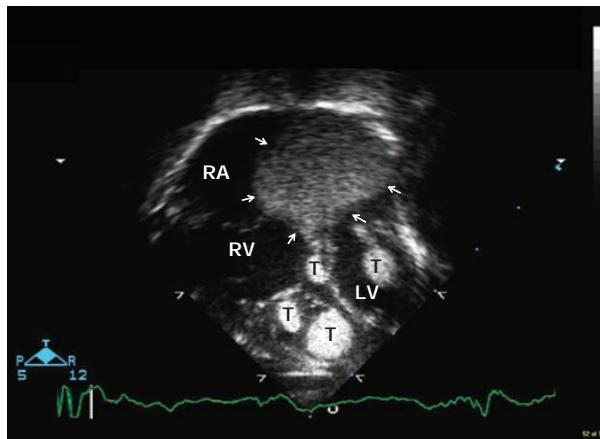


FIGURE 271-3 Transthoracic echocardiogram revealing multiple tumors (T) consistent with rhabdomyomas in a 1-day-old infant. The largest tumor (arrows) was located in the left atrioventricular groove and measured 2 cm × 2 cm. LV, left ventricle; RA, right atrium; RV, right ventricle.

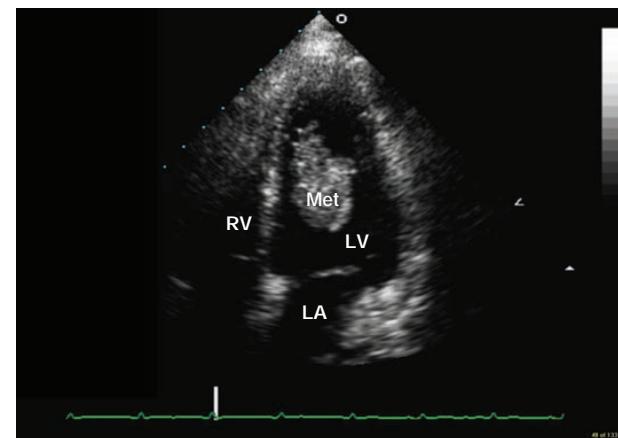


FIGURE 271-4 Large metastatic lesion (Met) in the left ventricle (LV) of a patient with diffusely metastatic bladder cancer. The mass arose from the interventricular septum and prolapsed into the aortic outflow tract during systole.

Cardiac metastases may occur via hematogenous or lymphangitic spread or by direct tumor invasion. While they generally manifest as small, firm nodules, diffuse infiltration also may occur, especially with sarcomas or hematologic neoplasms. The pericardium is most often involved, followed by myocardial involvement of any chamber and, rarely, by involvement of the endocardium or cardiac valves.

Cardiac metastases are clinically apparent only ~10% of the time, are usually not the cause of the patient's presentation, and rarely are the cause of death. The vast majority occur in the setting of a previously recognized malignant neoplasm. As with primary cardiac tumors, the clinical presentation reflects more the location and size of the tumor than its histologic type. When symptomatic, cardiac metastases may result in a variety of clinical features, including dyspnea, acute pericarditis, cardiac tamponade, ectopic tachyarrhythmias, heart block, and CHF. Importantly, many of these signs and symptoms may also result from myocarditis, pericarditis, or cardiomyopathy induced by radiotherapy or chemotherapy, and a high index of suspicion for cardiac involvement should be maintained for patients with malignant disease who develop these symptoms.

Electrocardiographic (ECG) findings are nonspecific but may reveal features consistent with pericarditis or may demonstrate low QRS voltage and electrical alternans in the setting of a large pericardial effusion. On chest x-ray, the cardiac silhouette is most often normal but may be enlarged or exhibit a bizarre contour. Echocardiography is useful for identifying and assessing the significance of pericardial effusions and visualizing larger metastases, although CT and radionuclide imaging may define the tumor burden more clearly. Cardiac MRI offers superb image quality and plays a central role in the diagnostic evaluation of cardiac metastases and cardiac tumors in general. Pericardiocentesis may allow for a specific cytologic diagnosis in patients with malignant pericardial effusions with a reported sensitivity of 67–92%. Angiography is rarely necessary but may help to delineate discrete myocardial lesions.

## TREATMENT

### Tumors Metastatic to the Heart

Most patients with cardiac metastases have advanced malignant disease; thus, therapy is generally palliative and consists of controlling symptoms and treatment of the primary tumor. Symptomatic malignant pericardial effusions should be drained by pericardiocentesis. Prolonged drainage (3–5 days) and concomitant instillation of a sclerosing agent (e.g., tetracycline or bleomycin) may delay or prevent reaccumulation of the effusion, and creation of a pericardial window allows drainage of the effusion to the adjacent pleural or peritoneal space. Given the overall poor prognosis of these patients, discussions regarding goals of care and involvement of palliative care services are often appropriate.

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## CARDIAC TRAUMA

Traumatic cardiac injury may be caused by either penetrating or non-penetrating trauma; the latter is often referred to as blunt cardiac injury (BCI). *Penetrating injuries* most often result from gunshot or knife wounds, and the site of entry is usually obvious. *Blunt cardiac injuries* most often occur during motor vehicle accidents, either from rapid deceleration or from impact of the chest against the steering wheel, but can also result from falls from heights, crush injuries, blast injuries, and violent assault. Importantly, rapid deceleration following motor vehicle accidents may be associated with significant cardiac injury even in the absence of external signs of thoracic trauma.

### BLUNT CARDIAC INJURY

*Myocardial contusion* is a nonspecific term that has been used to describe a broad spectrum of nonpenetrating cardiac injuries that result in abnormalities on electrocardiogram (ECG), elevation in cardiac biomarkers, and acute structural cardiac abnormalities (**Table 272-1**). Importantly, the cardiac injury may initially be overlooked in trauma patients as the clinical focus is directed toward other, more obvious injuries. Unfortunately, there is no one sign or symptom that confirms the diagnosis of BCI, and clinical, laboratory, and radiographic findings may be nonspecific in the setting of significant trauma. The physical examination may be challenging in the setting of chest wall injury; however, patients should be carefully examined to detect pericardial rubs, cardiac murmurs, and evidence of pericardial tamponade (**Chap. 270**). The mechanism of injury and the presence of other chest trauma should be considered when determining the index of suspicion for BCI; however, there is no proven association between sternal or rib fractures and the presence of BCI, and significant cardiac injury may be present in the absence of chest wall abnormalities.

Chest pain is common following thoracic trauma, and while it could indicate cardiac ischemia or pericardial injury, it often reflects musculoskeletal trauma. Nonetheless, myocardial necrosis may occur as a direct result of the blunt injury or as a result of traumatic coronary laceration, dissection, or thrombosis. The injured myocardium is pathologically similar to infarcted myocardium and may be associated with atrial or ventricular arrhythmias, conduction disturbances including bundle branch block, or abnormalities on ECG resembling those of infarction or pericarditis. Thus, it is important to obtain an ECG in all patients presenting with chest trauma and consider BCI as a cause of otherwise unexplained ECG abnormalities.

**TABLE 272-1 Spectrum of Cardiac Abnormalities Following Blunt Cardiac Injury**

ABNORMALITY	COMMENTS
ECG abnormalities	Sinus tachycardia, RBBB, ST-T wave abnormalities, atrial and ventricular arrhythmias
Elevated cardiac biomarkers	Troponin I and T are most specific
Focal wall motion abnormality or hematoma	Most commonly involving RV free wall, LV apex, and interventricular septum
Valvular insufficiency	Most commonly involving mitral and tricuspid valves and occasionally the aortic valve
Myocardial rupture	Ventricular septal defect or free wall rupture
Coronary artery injury	Most commonly involving the LAD, usually presents as STEMI
Pericardial effusion and tamponade	Resulting from free wall rupture or coronary artery laceration

Abbreviations: ECG, electrocardiogram; LAD, left anterior descending coronary artery; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle; STEMI, ST-segment elevation myocardial infarction.

Serum creatine kinase, myocardial band (CK-MB) isoenzyme levels are increased in ~20% of patients who experience blunt chest trauma but may be falsely elevated in the presence of massive skeletal muscle injury and should not be relied upon to confirm the diagnosis of BCI in the setting of trauma. Cardiac troponin levels are more specific for identifying cardiac damage; patients with normal serial troponin levels after chest trauma are very unlikely to have cardiac injury. When combined with a normal ECG, a normal troponin level at 6–8 h after chest trauma essentially excludes BCI. Echocardiography is the most useful modality for the detection of structural and functional sequelae of BCI, including regional wall motion abnormalities (most commonly involving the right ventricle, interventricular septum, or left ventricular apex), pericardial effusion, valvular dysfunction, and ventricular rupture. A transthoracic echocardiogram (TTE) should be performed in all patients with suspected BCI, especially in those with an abnormal ECG, elevated troponin, or hemodynamic instability; transesophageal echocardiography should be considered for patients in whom adequate TTE images cannot be obtained.

Traumatic rupture of the cardiac valves or their supporting structures, most commonly of the tricuspid or mitral valve, leads to acute valvular incompetence. This complication is usually heralded by the development of a loud murmur, may be associated with rapidly progressive heart failure, and can be diagnosed by either TTE or transesophageal echocardiography.

The most serious consequence of nonpenetrating cardiac injury is myocardial rupture, which may result in hemopericardium and tamponade (free wall rupture) or intracardiac shunting (ventricular septal rupture). Although generally fatal, up to 40% of patients with cardiac rupture have been reported to survive long enough to reach a specialized trauma center. Hemopericardium also may result from traumatic rupture of a pericardial vessel or a coronary artery. Additionally, pericarditis and/or pericardial effusion may develop weeks or even months after blunt chest trauma as a manifestation of the post–cardiac injury syndrome, an inflammatory condition that resembles the postpericardiotomy syndrome ([Chap. 270](#)).

Blunt, nonpenetrating, often innocent-appearing injuries to the chest may trigger ventricular fibrillation even in the absence of structural myocardial damage. This syndrome, referred to as *commotio cordis*, occurs most often in adolescents during sporting events (e.g., baseball, hockey, football, and lacrosse) and is an electrical phenomenon that probably results from an impact to the chest wall overlying the heart during the susceptible phase of repolarization (just before the peak of the T wave). Survival depends on prompt defibrillation. Sudden emotional or physical trauma, even in the absence of direct cardiac trauma, may precipitate a transient catecholamine-mediated cardiomyopathy referred to as *takotsubo syndrome* or *apical ballooning syndrome* ([Chap. 259](#)).

Rupture or transection of the aorta, usually just above the aortic valve or at the site of the ligamentum arteriosum, is a common consequence of nonpenetrating chest trauma and is the most common vascular deceleration injury. The clinical presentation may be similar to that of aortic dissection ([Chap. 280](#)); the arterial pressure and pulse amplitude may be increased in the upper extremities and decreased in the lower extremities, and chest x-ray may reveal mediastinal widening. Aortic rupture into the left thoracic space is almost universally fatal; however, the rupture may occasionally be contained by the aortic adventitia, resulting in a false, or *pseudo-*, aneurysm that may be discovered months or years after the initial injury.

## TREATMENT

### Blunt Cardiac Injury

The treatment of BCI depends on the specific injury sustained. Hemodynamically stable patients with a normal ECG and normal serial troponin levels are at low risk for BCI and usually do not require hospital admission for cardiac issues. Patients with an abnormal ECG and/or elevated troponin but normal echocardiogram usually warrant 24–48 h of telemetry monitoring; however,

other specific cardiac treatment is not usually required in the absence of the development of arrhythmias. Patients with mechanical complications (acute valvular insufficiency, myocardial rupture) require urgent operative correction.

## PENETRATING CARDIAC INJURY

*Penetrating injuries* of the heart produced by knife or bullet wounds usually result in rapid clinical deterioration and frequently in death as a result of hemopericardium/pericardial tamponade or massive hemorrhage. Nonetheless, up to half of such patients may survive long enough to reach a specialized trauma center if immediate resuscitation is performed. Prognosis in these patients relates to the mechanism of injury, the specific cardiac chamber(s) involved, and their clinical condition at presentation. In general, gunshot wounds are associated with a higher mortality than are knife wounds; up to 65% of stabbing victims survive versus <20% of shooting victims. This is likely in part because ballistic wounds are more frequently associated with multi-chamber cardiac injury. As a result of its anterior position in the chest, the right ventricle (RV) is the most frequently injured cardiac chamber, followed by the left ventricle (LV); isolated atrial injury is uncommon. Some studies suggest that RV injuries may be associated with a better prognosis than LV injuries, and most reports indicate that multichamber involvement carries a worse prognosis than single-chamber injury. Patients who are in hemodynamic collapse at presentation to the emergency department have a particularly poor prognosis with a mortality rate approaching 90%, whereas ~75% of patients who are stable enough to be brought to the operating room will survive.

Cardiac perforation of the right atrium, the RV free wall, or the interventricular septum may occur as a complication of cardiac procedures including during placement of central venous/intracardiac catheters, insertion of pacemaker/defibrillator leads, or performance of RV endomyocardial biopsies, and coronary arterial perforation can occur during deployment of intracoronary stents. These iatrogenic injuries are associated with a better prognosis than are other forms of penetrating cardiac trauma, likely related to a more limited degree of cardiac injury and the rapid availability of corrective therapies.

Traumatic rupture of a great vessel from penetrating injury is usually associated with hemothorax and, less often, hemopericardium, both of which are associated with significant mortality. Local hematoma formation may compress adjacent vessels and produce ischemic symptoms, and arteriovenous fistulas may develop, occasionally resulting in high-output heart failure.

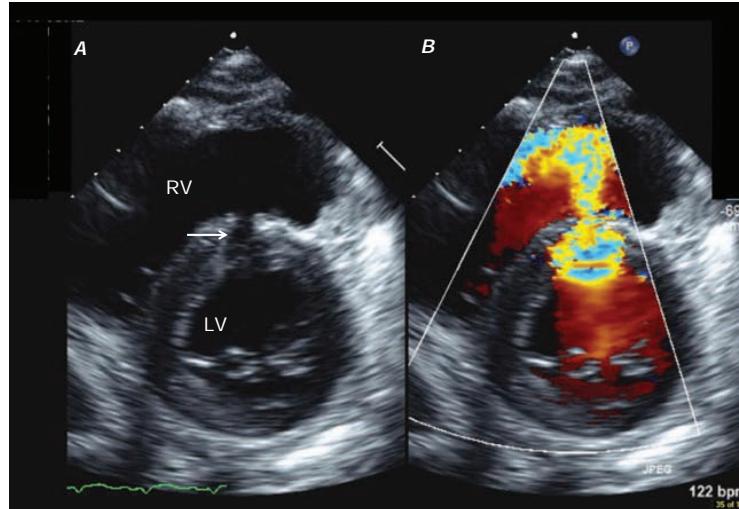
Some patients with penetrating chest injuries are hemodynamically stable at presentation and without symptoms to suggest cardiac injury; however, as many as 20% of these patients will have occult penetrating cardiac trauma. As a result, there should always be a high index of suspicion for cardiac injury in any patient with penetrating chest trauma, irrespective of clinical stability. TTE should be performed in all of these patients to assess for the presence of pericardial effusion or hematoma.

Occasionally, patients who survive penetrating cardiac injuries may subsequently present days or weeks later with a new cardiac murmur or heart failure as a result of mitral or tricuspid regurgitation or an intracardiac shunt (i.e., ventricular or atrial septal defect, aortopulmonary fistula, or coronary arteriovenous fistula) that was undetected at the time of the initial injury or developed subsequently ([Fig. 272-1](#)). Therefore, trauma patients should be examined carefully several weeks after the injury. If a mechanical complication is suspected, it can be confirmed by echocardiography or cardiac catheterization.

## TREATMENT

### Penetrating Cardiac Injury

Penetrating cardiac injury associated with hemodynamic instability is a surgical emergency and requires immediate resuscitative measures including endotracheal intubation, establishment of large-bore intravenous access to facilitate massive volume resuscitation, and immediate thoracotomy to allow for pericardial drainage and repair of cardiac injuries. Occasionally, cross-clamping of the



**FIGURE 272-1** Transthoracic echocardiogram demonstrating a traumatic ventricular septal defect. The patient underwent emergent repair of the right ventricle following a self-inflicted stab wound to the chest. Subsequent two-dimensional imaging (**A**) revealed a laceration of the interventricular septum (arrow) with color flow Doppler (**B**) demonstrating prominent left-to-right shunting across the defect. LV, left ventricle; RV, right ventricle.

descending aorta is required to preferentially perfuse the heart and brain until hemodynamic stability can be achieved. Hemodynamically stable patients in whom echocardiography reveals even a small pericardial effusion require urgent surgical exploration to evaluate for occult cardiac perforation. Pericardiocentesis may be lifesaving in patients with tamponade but is usually only a temporizing measure while awaiting definitive surgical therapy. In some survivors of penetrating cardiac injury, the pericardial hemorrhage predisposes to the development of constriction (**Chap. 270**), which may require surgical decortication.

#### FURTHER READING

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manifestations and treatment of IHD, while the subsequent chapters address the acute phases of IHD.

#### EPIDEMIOLOGY AND GLOBAL TRENDS

IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. IHD is the most common, serious, chronic, life-threatening illness in the United States, where 20.1 million persons have IHD. Although there is regional variation, ~3–4% of the population has sustained a myocardial infarction. Genetic factors, a high-fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD. In the United States and Western Europe, IHD is growing among low-income groups, but primary prevention has delayed the disease to later in life across socioeconomic groups. Despite these sobering statistics, it is worth noting that epidemiologic data show a decline in the rate of deaths due to IHD, about half of which is attributable to treatments and half to prevention by risk factor modification.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. These trends are occurring in the general context of population growth and as a result of the increase in the average age of the world's population. With urbanization in countries with emerging economies and a growing middle class, elements of the energy-rich Western diet are being adopted. As a result, the prevalence of risk factors for IHD and the prevalence of IHD itself are both increasing rapidly, so that in analyses of the global burden of disease, there is a shift from communicable to noncommunicable diseases, and it is estimated that globally 197.2 million people live with IHD. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East. IHD is a major contributor to the number of disability-adjusted life-years (DALYs) experienced globally.

#### PATHOPHYSIOLOGY

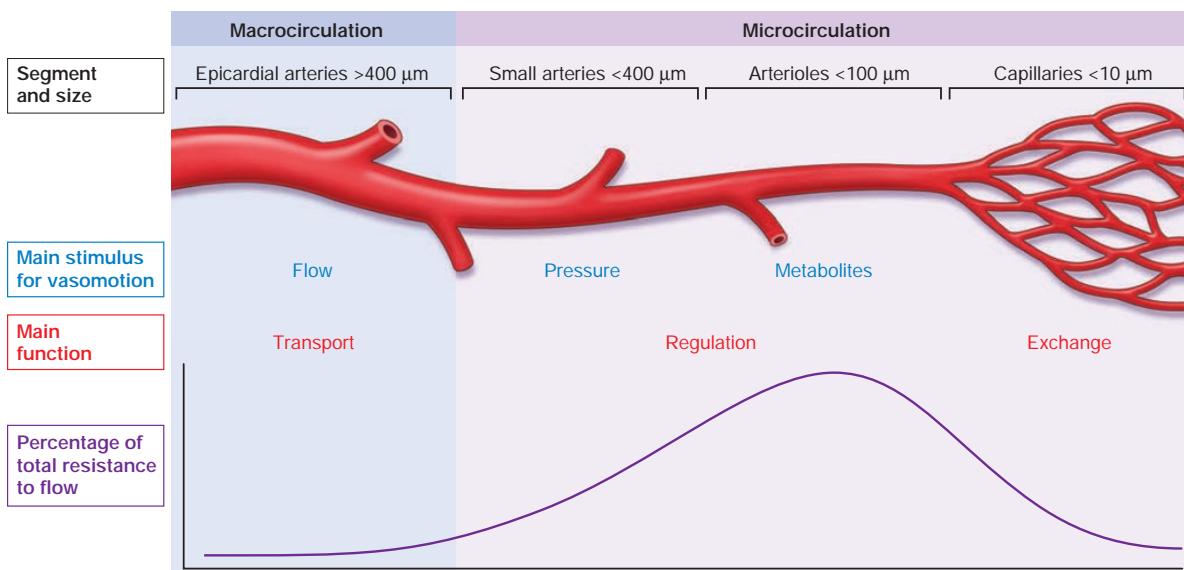
Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. In normal conditions, for any given level of a demand for oxygen, the myocardium will control the supply of oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction. The major determinants of myocardial oxygen demand ( $MVO_2$ ) are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood

## Section 5 Coronary and Peripheral Vascular Disease

### 273 Ischemic Heart Disease

Elliott M. Antman, Joseph Loscalzo

*Ischemic heart disease* (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. This chapter focuses on the chronic



**FIGURE 273-1** Macrocirculation and microcirculation across segments and sizes of the arteries. The location and size of the arteries supplying blood to the heart is shown at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. The main function of each of the arterial segments is shown next, followed by a depiction of the relative resistance to antegrade flow. (Reproduced with permission from B De Bruyne et al: Microvascular (dys)function and clinical outcome in stable coronary disease. *J Amer Coll Cardiol* 67:1170, 2016.)

flow. Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries: (1) large epicardial arteries ( $R_1$ ), (2) prearteriolar vessels ( $R_2$ ), and (3) arteriolar and intramyocardial capillary vessels ( $R_3$ ). In the absence of significant flow-limiting atherosclerotic obstructions,  $R_1$  is trivial; the major determinant of coronary resistance is found in  $R_2$  and  $R_3$  (Fig. 273-1). The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation ( $R_2$  and  $R_3$  decrease). For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and, in this manner, regulate the supply of oxygen and substrate to the myocardium (*metabolic regulation*). The coronary resistance vessels also adapt to physiologic alterations in blood pressure to maintain coronary blood flow at levels appropriate to myocardial needs (*autoregulation*).

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for more coronary flow occurs. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm (see Prinzmetal's angina in Chap. 274), arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities such as the origin of the left anterior descending coronary artery from the pulmonary artery may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults.

Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy (LVH) due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia (Chap. 261). A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction.

Not infrequently, two or more causes of ischemia coexist in a patient, such as an increase in oxygen demand due to LVH secondary

to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary resistance vessels also can cause ischemia. When it causes angina, this condition is referred to as *microvascular angina*.

## CORONARY ATHEROSCLEROSIS

Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis (high levels of plasma low-density lipoprotein [LDL], cigarette smoking, hypertension, and diabetes mellitus) vary in their relative impact on disturbing the normal functions of the vascular endothelium. These functions include local control of vascular tone, maintenance of an antithrombotic surface, and control of inflammatory cell adhesion and diapedesis. The loss of these defenses leads to inappropriate constriction, luminal thrombus formation, and abnormal interactions between blood cells, especially monocytes and platelets, and the activated vascular endothelium. Functional changes in the vascular milieu ultimately result in the subintimal collections of fat, smooth muscle cells, fibroblasts, and intercellular matrix that define the atherosclerotic plaque. Rather than viewing atherosclerosis strictly as a vascular problem, it is useful to consider it in the context of alterations in the nature of the circulating blood (hyperglycemia; increased concentrations of LDL cholesterol, tissue factor, fibrinogen, von Willebrand factor, coagulation factor VII, and platelet microparticles). The combination of a "vulnerable vessel" in a patient with "vulnerable blood" promotes a state of hypercoagulability and hypofibrinolysis. This is especially true in patients with diabetes mellitus.

Atherosclerosis develops at irregular rates in different segments of the epicardial coronary tree and leads eventually to segmental reductions in cross-sectional area, i.e., plaque formation. There is also a predilection for atherosclerotic plaques to develop at sites of increased turbulence in coronary flow, such as at branch points in the epicardial arteries. When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet increased myocardial demand. When the diameter is reduced by ~80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically to cause myocardial ischemia at rest or with minimal stress.

Segmental atherosclerotic narrowing of epicardial coronary arteries is caused most commonly by the formation of a plaque, which is

subject to rupture or erosion of the cap separating the plaque from the bloodstream. Upon exposure of the plaque contents to blood, two important and interrelated processes are set in motion: (1) platelets are activated and aggregate, and (2) the coagulation cascade is activated, leading to deposition of fibrin strands. A thrombus composed of platelet aggregates and fibrin strands traps red blood cells and can reduce coronary blood flow, leading to the clinical manifestations of myocardial ischemia.

The location of the obstruction influences the quantity of myocardium rendered ischemic and determines the severity of the clinical manifestations. Thus, critical obstructions in vessels, such as the left main coronary artery and the proximal left anterior descending coronary artery, are particularly hazardous. Chronic severe coronary narrowing and myocardial ischemia frequently are accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can by themselves provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand.

With progressive worsening of a stenosis in a proximal epicardial artery, the distal resistance vessels (when they function normally) dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances, ischemia, manifest clinically by angina or electrocardiographically by ST-segment deviation, can be precipitated by increases in myocardial oxygen demand caused by physical activity, emotional stress, and/or tachycardia. Changes in the caliber of the stenosed coronary artery resulting from physiologic vasomotion, loss of endothelial control of dilation (as occurs in atherosclerosis), pathologic spasm (Prinzmetal's angina), or small platelet-rich plugs also can upset the critical balance between oxygen supply and demand and thereby precipitate myocardial ischemia.

### EFFECTS OF ISCHEMIA

During episodes of inadequate perfusion caused by coronary atherosclerosis, myocardial tissue oxygen tension falls and may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium (Fig. 273-2). Coronary atherosclerosis is a focal process that usually causes nonuniform ischemia. During ischemia, regional disturbances of ventricular contractility cause segmental

hypokinesia, akinesia, or, in severe cases, bulging (dyskinesia), which can reduce myocardial pump function.

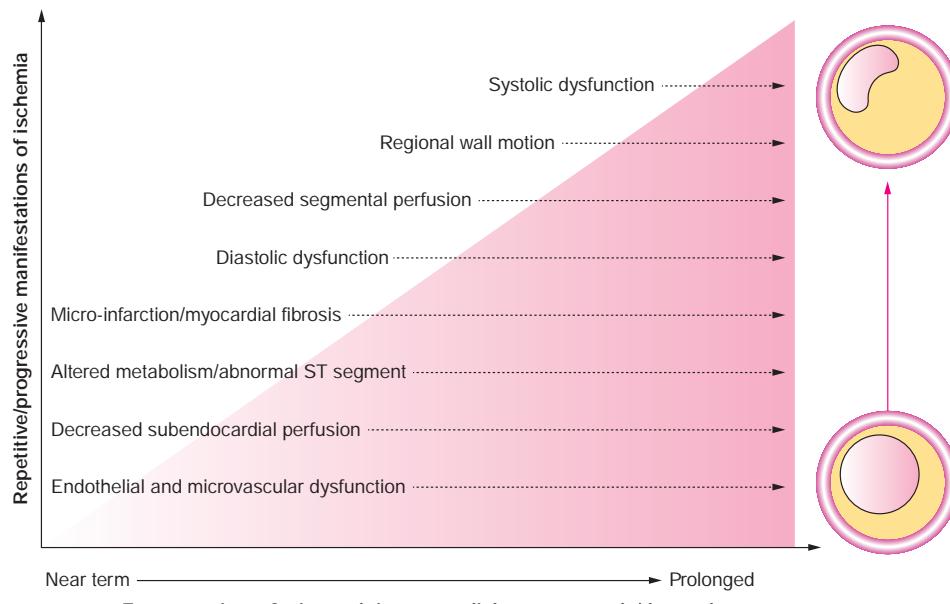
The abrupt development of severe ischemia, as occurs with total or subtotal coronary occlusion, is associated with near instantaneous failure of normal muscle relaxation and then diminished contraction. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall (compared with the subepicardial region). Ischemia of large portions of the ventricle causes transient left ventricular (LV) failure, and if the papillary muscle apparatus is involved, mitral regurgitation can occur. When ischemia is transient, it may be associated with angina pectoris; when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction (Chap. 275).

A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, i.e., ATP and creatine phosphate. Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes as well as an increase in cytosolic calcium. The severity and duration of the imbalance between myocardial oxygen supply and demand determine whether the damage is reversible (20 min for total occlusion in the absence of collaterals) or permanent, with subsequent myocardial necrosis (>20 min).

Ischemia also causes characteristic changes in the electrocardiogram (ECG) such as repolarization abnormalities, as evidenced by inversion of T waves and, when more severe, displacement of ST segments (Chap. 240). Transient T-wave inversion probably reflects nontransmural, intramyocardial ischemia; transient ST-segment depression often reflects patchy subendocardial ischemia; and ST-segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to isolated ventricular premature beats or even ventricular tachycardia or ventricular fibrillation (Chaps. 254 and 255). Most patients who die suddenly from IHD do so as a result of ischemia-induced ventricular tachyarrhythmias (Chap. 306).

### ASYMPTOMATIC VERSUS SYMPTOMATIC IHD

Although the prevalence is decreasing, postmortem studies of accident victims and military casualties in Western countries show that



**FIGURE 273-2** Cascade of mechanisms and manifestations of ischemia. (Reproduced with permission from LJ Shaw et al: Women and ischemic heart disease: Evolving knowledge. *J Am Coll Cardiol* 54:1561, 2009.)

coronary atherosclerosis can begin before age 20 and is present among adults who were asymptomatic during life. Exercise stress tests in asymptomatic persons may show evidence of silent myocardial ischemia, i.e., exercise-induced ECG changes not accompanied by angina pectoris; coronary angiographic studies of such persons may reveal coronary artery plaques and previously unrecognized obstructions (**Chap. 242**). Coronary artery calcifications (CACs) may be seen on CT images of the heart, can be quantified in a CAC score, and may be used as adjunctive information to support a diagnosis of IHD. However, they should not be used as the primary screening modality or as the isolated basis on which to formulate therapeutic decisions. (See further discussion below.) Postmortem examination of patients with such obstructions without a history of clinical manifestations of myocardial ischemia often shows macroscopic scars secondary to myocardial infarction in regions supplied by diseased coronary arteries, with or without collateral circulation. According to population studies, ~25% of patients who survive acute myocardial infarction may not come to medical attention, and these patients have the same adverse prognosis as do those who present with the classic clinical picture of acute myocardial infarction (**Chap. 275**). Sudden death may be unheralded and is a common presenting manifestation of IHD (**Chap. 306**).

Patients with IHD also can present with cardiomegaly and heart failure secondary to ischemic damage of the LV myocardium that may have caused no symptoms before the development of heart failure; this condition is referred to as *ischemic cardiomyopathy*. In contrast to the asymptomatic phase of IHD, the symptomatic phase is characterized by chest discomfort due to either angina pectoris or acute myocardial infarction (**Chap. 275**). Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or die suddenly.

## STABLE ANGINA PECTORIS

This episodic clinical syndrome is a result of transient myocardial ischemia. Various diseases that cause myocardial ischemia and the numerous forms of discomfort with which it may be confused are discussed in **Chap. 14**. Males constitute ~70% of all patients with angina pectoris and an even greater proportion of those aged <50 years. It is, however, important to note that angina pectoris in women may be atypical in presentation (see below).

## HISTORY

The typical patient with angina is a man >50 years or a woman >60 years of age who complains of episodes of chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, he or she typically places a hand over the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort (Levine's sign). Angina is usually crescendo-decrescendo in nature (typically with the severity of the discomfort not at its most intense level at the outset of symptoms), typically lasts 2–5 min, and can radiate to either shoulder and to both arms (especially the ulnar aspects of the forearm and hand). It also can arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium. Angina is rarely localized below the umbilicus or above the mandible. A useful finding in assessing a patient with chest discomfort is the fact that myocardial ischemic discomfort does not radiate to the trapezius muscles; that radiation pattern is more typical of pericarditis.

Although episodes of angina typically are caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or frustration) and are relieved by rest, they also may occur at rest (**Chap. 274**) and while the patient is recumbent (angina decubitus). The patient may be awakened at night by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia, diminished oxygenation as the respiratory pattern changes during sleep, or expansion of the intrathoracic blood volume that occurs with recumbency; the latter causes an increase in cardiac size (end-diastolic volume), wall tension, and myocardial oxygen demand that can lead to ischemia and transient LV failure.

The threshold for the development of angina pectoris may vary by time of day and emotional state. Many patients report a fixed threshold for angina, occurring predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. In other patients, the threshold for angina may vary considerably within any particular day and from day to day. In such patients, variations in myocardial oxygen supply, most likely due to changes in coronary vasomotor tone, may play an important role in defining the pattern of angina. A patient may report symptoms upon minor exertion in the morning yet by midday be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar circumstances, a heavy meal, exposure to cold, or a combination of these factors.

Exertional angina typically is relieved in 1–5 min by slowing or ceasing activities and even more rapidly by rest and sublingual nitroglycerin (see below). Indeed, the diagnosis of angina should be suspect if it does not respond to the combination of these measures. The severity of angina can be conveniently summarized by the Canadian Cardiac Society functional classification (**Table 273-1**). Its impact on the patient's functional capacity can be described by using the New York Heart Association functional classification (Table 273-1).

Sharp, fleeting chest pain or a prolonged, dull ache localized to the left submammary area is rarely due to myocardial ischemia. However, especially in women and diabetic patients, angina pectoris may be atypical in location and not strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, occurring more frequently in the winter in temperate climates. Anginal "equivalents" are symptoms of myocardial ischemia other than angina. They include dyspnea,

**TABLE 273-1** Cardiovascular Disease Classification Chart

CLASS	NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION
I	Patients have cardiac disease but <i>without</i> the resulting <i>limitations</i> of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, <i>does not cause angina</i> . Angina present with strenuous or rapid or prolonged exertion at work or recreation.
II	Patients have cardiac disease resulting in <i>slight limitation</i> of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	<i>Slight limitation</i> of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
III	Patients have cardiac disease resulting in <i>marked limitation</i> of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	<i>Marked limitation</i> of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs at normal pace.
IV	Patients have cardiac disease resulting in <i>inability</i> to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	<i>Inability</i> to carry on any physical activity without discomfort—anginal syndrome <i>may</i> be present at rest.

*Source:* Reproduced with permission from L Goldman et al: Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. Circulation 64:1227, 1981.

Systematic questioning of a patient with suspected IHD is important to uncover the features of an unstable syndrome associated with increased risk, such as angina occurring with less exertion than in the past, occurring at rest, or awakening the patient from sleep. Since coronary atherosclerosis often is accompanied by similar lesions in other arteries, a patient with angina should be questioned and examined for peripheral arterial disease (intermittent claudication [Chap. 281]), stroke, or transient ischemic attacks (Chap. 426). It is also important to uncover a family history of premature IHD (<55 years in first-degree male relatives and <65 in female relatives) and the presence of diabetes mellitus, hyperlipidemia, hypertension, cigarette smoking, and other risk factors for coronary atherosclerosis.

The history of typical angina pectoris establishes the diagnosis of IHD until proven otherwise. Given the importance of the history, clinicians should move beyond unstructured interviews with the patient and consider using a validated questionnaire (e.g., Seattle Angina Questionnaire) to establish the presence and severity of IHD. The coexistence of advanced age, male sex, the postmenopausal state, and risk factors for atherosclerosis increases the likelihood of hemodynamically significant coronary disease. A particularly challenging problem is the evaluation and management of patients with persistent ischemic-type chest discomfort but no flow-limiting obstructions in their epicardial coronary arteries. This situation arises more often in women than in men. Potential etiologies include microvascular coronary disease (detectable on coronary reactivity testing in response to vasoactive agents such as intracoronary adenosine, acetylcholine, and nitroglycerin) and abnormal cardiac nociception. Treatment of microvascular coronary disease should focus on efforts to improve endothelial function, including nitrates, beta blockers, calcium antagonists, statins, and angiotensin-converting enzyme (ACE) inhibitors. Abnormal cardiac nociception is more difficult to manage and may be ameliorated in some cases by imipramine.

## PHYSICAL EXAMINATION

The physical examination is often normal in patients with stable angina when they are asymptomatic. However, because of the increased likelihood of IHD in patients with diabetes and/or peripheral arterial disease, clinicians should search for evidence of atherosclerotic disease at other sites, such as an abdominal aortic aneurysm, carotid arterial bruits, and diminished arterial pulses in the lower extremities. The physical examination also should include a search for evidence of risk factors for atherosclerosis such as xanthelasmas and xanthomas. Evidence for peripheral arterial disease should be sought by evaluating the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (ankle-brachial index). Examination of the fundi may reveal an increased light reflex and arteriovenous nicking as evidence of hypertension. There also may be signs of anemia, thyroid disease, and nicotine stains on the finger-tips from cigarette smoking.

Palpation may reveal cardiac enlargement and abnormal contraction of the cardiac impulse (LV dyskinesia). Auscultation can uncover arterial bruits, a third and/or fourth heart sound, and, if acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left lateral decubitus position. Aortic stenosis, aortic regurgitation (Chap. 261), pulmonary hypertension (Chap. 283), and hypertrophic cardiomyopathy (Chap. 259) must be excluded, since these disorders may cause angina in the absence of coronary atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient LV failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema. Tenderness of the chest wall, localization of the discomfort with a single fingertip on the chest, or reproduction of the pain with palpation of the chest makes it unlikely that the pain is caused by myocardial ischemia. A protuberant abdomen may indicate that the patient has the metabolic syndrome and is at increased risk for atherosclerosis.

## LABORATORY EXAMINATION

Although the diagnosis of IHD can be made with a high degree of confidence from the history and physical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol—total, LDL, high-density lipoprotein [HDL]—and triglycerides), glucose (hemoglobin A<sub>1c</sub>), creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray may be helpful in demonstrating the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the degree of cardiac damage. Evidence exists that an elevated level of high-sensitivity C-reactive protein (CRP) (specifically, between 1 and 3 mg/L) is an independent risk factor for IHD and may be useful in therapeutic decision-making about the initiation of hypolipidemic treatment. The major benefit of high-sensitivity CRP is in reclassifying the risk of IHD in patients in the “intermediate” risk category on the basis of traditional risk factors.

## ELECTROCARDIOGRAM

A 12-lead ECG recorded at rest may be normal in patients with typical angina pectoris, but there may also be signs of an old myocardial infarction (Chap. 240). Although repolarization abnormalities, i.e., ST-segment and T-wave changes, as well as LVH and disturbances of cardiac rhythm or intraventricular conduction, are suggestive of IHD, they are nonspecific, since they also can occur in pericardial, myocardial, and valvular heart disease or, in the case of the former, transiently with anxiety, changes in posture, drugs, or esophageal disease. The presence of LVH is a significant indication of increased risk of adverse outcomes from IHD. Of note, even though LVH and cardiac rhythm disturbances are nonspecific indicators of the development of IHD, they may be contributing factors to episodes of angina in patients in whom IHD has developed as a consequence of conventional risk factors. Dynamic ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific.

## STRESS TESTING

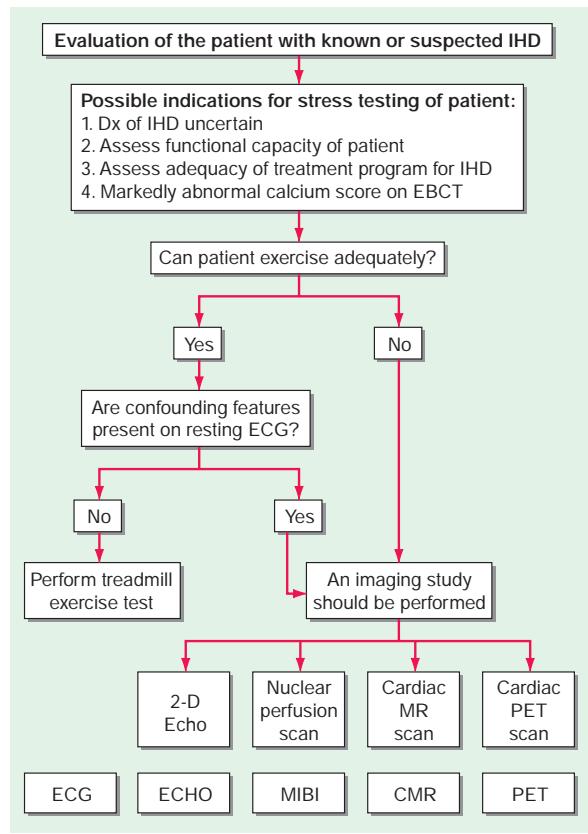
**Electrocardiographic** The most widely used test for both the diagnosis of IHD and the estimation of risk and prognosis involves recording of the 12-lead ECG before, during, and after exercise, usually on a treadmill (Fig. 273-3). The test consists of a standardized incremental increase in external workload (Table 273-2) while symptoms, the ECG, and arm blood pressure are monitored. Exercise duration is usually symptom-limited, and the test is discontinued upon evidence of chest discomfort, severe shortness of breath, dizziness, severe fatigue, ST-segment depression >0.2 mV (2 mm), a fall in systolic blood pressure >10 mmHg, or the development of a ventricular tachyarrhythmia. This test is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort. The ischemic ST-segment response generally is defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s (Fig. 273-2). Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered nondiagnostic.

In interpreting ECG stress tests, the probability that coronary artery disease (CAD) exists in the patient or population under study (i.e., pretest probability) should be considered. A positive result on exercise indicates that the likelihood of CAD is 98% in males who are >50 years with a history of typical angina pectoris and who develop chest discomfort during the test. The likelihood decreases if the patient has atypical or no chest pain by history and/or during the test.

The incidence of false-positive tests is significantly increased in patients with low probabilities of IHD, such as asymptomatic men age <40 or premenopausal women with no risk factors for premature atherosclerosis. It is also increased in patients taking cardioactive drugs, such as digitalis and antiarrhythmic agents, and in those with intraventricular conduction disturbances, resting ST-segment and T-wave abnormalities, ventricular hypertrophy, or abnormal serum potassium levels. Obstructive disease limited to the circumflex coronary artery may result in a false-negative stress test since the posterolateral portion of the heart that this vessel supplies is not well represented on the surface 12-lead ECG. Since the overall sensitivity of an exercise stress

ECG is only ~75%, a negative result does not exclude CAD, although it makes the likelihood of three-vessel or left main CAD extremely unlikely.

A medical professional should be present throughout the exercise test. It is important to measure total duration of exercise, the times to the onset of ischemic ST-segment change and chest discomfort, the external work performed (generally expressed as the stage of exercise), and the internal cardiac work performed, i.e., by the heart rate–blood pressure product. The depth of the ST-segment depression and the time needed for recovery of these ECG changes are also important. Because the risks of exercise testing are small but real—estimated at one fatality



A

**FIGURE 273-3 Evaluation of the patient with known or suspected ischemic heart disease.** On the left of the figure is an algorithm for identifying patients who should be referred for stress testing and the decision pathway for determining whether a standard treadmill exercise with electrocardiogram (ECG) monitoring alone is adequate. A specialized imaging study is necessary if the patient cannot exercise adequately (pharmacologic challenge is given) or if there are confounding features on the resting ECG (symptom-limited treadmill exercise may be used to stress the coronary circulation). Panels B–E on the next page are examples of the data obtained with ECG monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; IHD, ischemic heart disease; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron emission tomography. **A.** Lead V<sub>4</sub> at rest (top panel) and after 4.5 min of exercise (bottom panel). There is 3 mm (0.3 mV) of horizontal ST-segment depression, indicating a positive test for ischemia. (Reproduced with permission from BR Chaitman, in E Braunwald et al [eds]: *Braunwald's heart disease: A textbook of cardiovascular medicine, Single Volume (Heart Disease)* (Braunwald), 8th ed. Philadelphia, Saunders, 2008.) **B.** A 45-year-old avid jogger who began experiencing classic substernal chest pressure underwent an exercise echo study. With exercise the patient's heart rate increased from 52 to 153 beats/min. The left ventricular chamber dilated with exercise, and the septal and apical portions became akinetic to dyskinetic (red arrow). These findings are strongly suggestive of a significant flow-limiting stenosis in the proximal left anterior descending artery, which was confirmed at coronary angiography. (Modified from SD Solomon, in E Braunwald et al [eds]: *Primary Cardiology*, 2nd ed, Philadelphia, Saunders, 2003.) **C.** Stress and rest myocardial perfusion single-photon emission computed tomography images obtained with 99m-technetium sestamibi in a patient with chest pain and dyspnea on exertion. The images demonstrate a medium-size and severe stress perfusion defect involving the inferolateral and basal inferior walls, showing nearly complete reversibility, consistent with moderate ischemia in the right coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.) **D.** A patient with a prior myocardial infarction presented with recurrent chest discomfort. On cardiac magnetic resonance (CMR) cine imaging, a large area of anterior akinesia was noted (marked by the arrows in the top left and right images, systolic frame only). This area of akinesia was matched by a larger extent of late gadolinium-DTPA enhancements consistent with a large transmural myocardial infarction (marked by arrows in the middle left and right images). Resting (bottom left) and adenosine vasodilating stress (bottom right) first-pass perfusion images revealed reversible perfusion abnormality that extended to the inferior septum. This patient was found to have an occluded proximal left anterior descending coronary artery with extensive collateral formation. This case illustrates the utility of different modalities in a CMR examination in characterizing ischemic and infarcted myocardium. DTPA, diethylenetriamine penta-acetic acid. (Images provided by Dr. Raymond Kwong, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.) **E.** Stress and rest myocardial perfusion PET images obtained with rubidium-82 in a patient with chest pain on exertion. The images demonstrate a large and severe stress perfusion defect involving the mid and apical anterior, anterolateral, and anteroapical walls and the left ventricular apex, showing complete reversibility, consistent with extensive and severe ischemia in the mid-left anterior descending coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.)

Rest



Stress

**B**

Rest



Stress

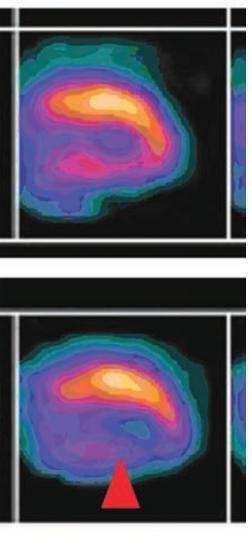
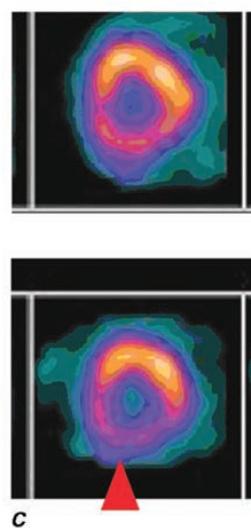
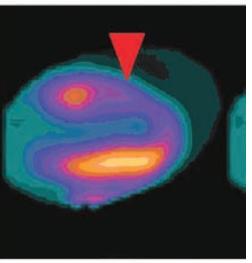
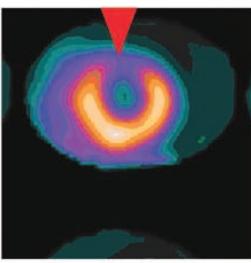
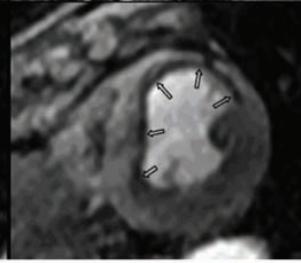
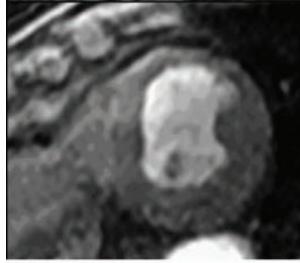
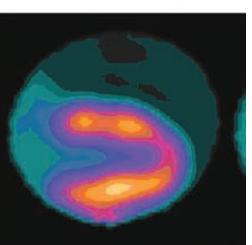
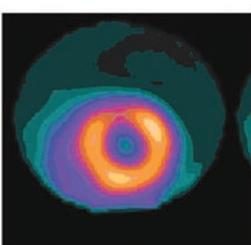
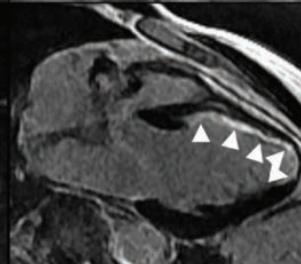
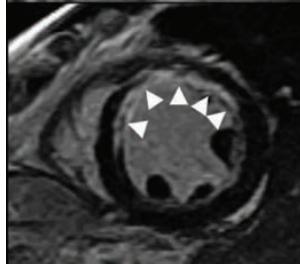
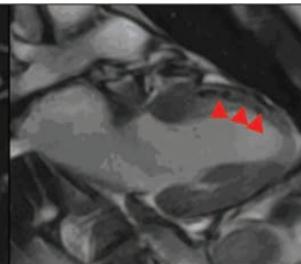
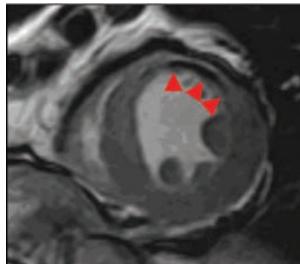
**C****E****D**

FIGURE 273-3 (Continued)

**TABLE 273-2 Relation of Metabolic Equivalent Tasks (METs) to Stages in Various Testing Protocols**

FUNCTIONAL CLASS	CLINICAL STATUS			$\text{O}_2 \text{ COST}$ mL/kg/min	METs	TREADMILL PROTOCOLS			
						BRUCE Modified 3 min Stages		BRUCE 3 min Stages	
NORMAL AND I	HEALTHY, DEPENDENT ON AGE, ACTIVITY	SEDENTARY, HEALTHY	LIMITED			MPH	%GR	MPH	%GR
						6.0	22	6.0	22
						5.5	20	5.2	20
						5.0	18	5.0	18
						56.0	16		
						52.5	15		
						49.0	14		
						45.5	13	4.2	16
						42.0	12		
						38.5	11	3.4	14
II		SYMPTOMATIC				35.0	10		
						31.5	9		
						28.0	8		
						24.5	7	2.5	12
						21.0	6		
III						17.5	5	1.7	10
						14.0	4		
						10.5	3	1.7	5
						7.0	2	1.7	0
						3.5	1		
IV									

Note: The standard Bruce treadmill protocol (right-hand column) begins at 1.7 MPH and 10% gradient (GR) and progresses every 3 min to a higher speed and elevation. The corresponding oxygen consumption and clinical status of the patient are shown in the center and left-hand columns.

Abbreviations: GR, grade; MPH, miles per hour.

Source: Reproduced with permission from GF Fletcher et al: Exercise standards for testing and training. Circulation 104:1694, 2001.

and two nonfatal complications per 10,000 tests—equipment for resuscitation should be available. Modified (heart rate–limited rather than symptom-limited) exercise tests can be performed safely in patients as early as 6 days after uncomplicated myocardial infarction (Table 273-2). Contraindications to exercise stress testing include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

The normal response to graded exercise includes progressive increases in heart rate and blood pressure. Failure of the blood pressure to increase or an actual decrease with signs of ischemia during the test is an important adverse prognostic sign, since it may reflect ischemia-induced global LV dysfunction. The development of angina and/or severe (>0.2 mV) ST-segment depression at a low workload, i.e., before completion of stage II of the Bruce protocol, and/or ST-segment depression that persists >5 min after the termination of exercise increases the specificity of the test and suggests severe IHD and a high risk of future adverse events.

**Cardiac Imaging** (See also Chap. 241) When the resting ECG is abnormal (e.g., preexcitation syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial radionuclide perfusion imaging after the intravenous administration of thallium-201 or 99m-technetium sestamibi during exercise (or with pharmacologic) stress. Contemporary data also suggest positron emission tomography (PET) imaging (with exercise or pharmacologic stress) using N-13 ammonia or rubidium-82 as another technique for assessing perfusion. Images obtained immediately after cessation of exercise to detect regional ischemia are compared with those obtained at rest to confirm reversible ischemia and regions of persistently absent uptake that signify infarction.

A sizable fraction of patients who need noninvasive stress testing to identify myocardial ischemia and increased risk of coronary events cannot exercise because of peripheral vascular or musculoskeletal

disease, exertional dyspnea, or deconditioning. In these circumstances, an intravenous pharmacologic challenge is used in place of exercise. For example, adenosine can be given to create a coronary “steal” by temporarily increasing flow in nondiseased segments of the coronary vasculature at the expense of diseased segments. Alternatively, a graded incremental infusion of dobutamine may be administered to increase  $\text{MVO}_2$ . A variety of imaging options are available to accompany these pharmacologic stressors (Fig. 273-3). The development of a transient perfusion defect with a tracer such as thallium-201 or 99m-technetium sestamibi is used to detect myocardial ischemia.

Echocardiography is used to assess LV function in patients with chronic stable angina and patients with a history of a prior myocardial infarction, pathologic Q waves, or clinical evidence of heart failure. Two-dimensional echocardiography can assess both global and regional wall motion abnormalities of the left ventricle that are transient when due to ischemia. Stress (exercise or dobutamine) echocardiography may cause the emergence of regions of akinesis or dyskinesis that are not present at rest. Stress echocardiography, like stress myocardial perfusion imaging, is more sensitive than exercise electrocardiography in the diagnosis of IHD. Cardiac magnetic resonance (CMR) stress testing is also evolving as an alternative to radionuclide, PET, or echocardiographic stress imaging. CMR stress testing performed with dobutamine infusion can be used to assess wall motion abnormalities accompanying ischemia, as well as myocardial perfusion. CMR can be used to provide more complete ventricular evaluation using multislice magnetic resonance imaging (MRI) studies.

Atherosclerotic plaques become progressively calcified over time, and coronary calcification in general increases with age. For this reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. These methods involve computed tomography (CT) applications that achieve rapid acquisition of images (electron beam [EBCT] and multidetector [MDCT] detection). Coronary calcium detected by these imaging techniques most commonly is quantified by using the Agatston score, which is based on the area and density of calcification.

## CORONARY ARTERIOGRAPHY

(See also Chap. 242) This diagnostic method outlines the lumina of the coronary arteries and can be used to detect or exclude serious coronary obstruction. However, coronary arteriography provides no information about the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Of note, atherosclerotic plaques characteristically are scattered throughout the coronary tree, tend to occur more frequently at branch points, and grow progressively in the intima and media of an epicardial coronary artery at first without encroaching on the lumen, causing an outward bulging of the artery—a process referred to as remodeling. Later in the course of the disease, further growth causes luminal narrowing.

**Indications** The ISCHEMIA trial informs decision-making about referral for coronary arteriography (with intent to perform revascularization) in patients with stable IHD and an ejection fraction >35% even in the presence of moderate-severe ischemia on noninvasive functional testing. Over the course of 4 years of follow-up, early referral for an invasive strategy was not associated with a reduction in the risk of myocardial infarction or death but was more effective than an initial conservative, medical strategy in relieving angina. Thus, coronary arteriography is indicated in (1) patients with chronic stable angina pectoris who are severely symptomatic despite medical therapy and are being considered for revascularization, i.e., a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); (2) patients with troublesome symptoms that present diagnostic difficulties in whom there is a need to confirm or rule out the diagnosis of IHD; (3) patients with known or possible angina pectoris who have survived cardiac arrest; and (4) patients with angina or evidence of ischemia on noninvasive testing with clinical or laboratory evidence of ventricular dysfunction.

Examples of other indications for coronary arteriography include the following:

1. Patients with chest discomfort suggestive of angina pectoris but a negative or nondiagnostic stress test who require a definitive diagnosis for guiding medical management, alleviating psychological stress, career or family planning, or insurance purposes.
2. Patients who have been admitted repeatedly to the hospital for a suspected acute coronary syndrome (Chaps. 274 and 275), but in whom this diagnosis has not been established and in whom it is considered clinically important to determine the presence or absence of CAD.
3. Patients with careers that involve the safety of others (e.g., pilots, firefighters, police) who have questionable symptoms or suspicious or positive noninvasive tests and in whom there are reasonable doubts about the state of the coronary arteries.
4. Patients with aortic stenosis or hypertrophic cardiomyopathy and angina in whom the chest pain could be due to IHD.
5. Male patients >45 years and females >55 years who are to undergo a cardiac operation such as valve replacement or repair and who may or may not have clinical evidence of myocardial ischemia.
6. Patients after myocardial infarction, especially those who are at high risk after myocardial infarction because of the recurrence of angina or the presence of heart failure, frequent ventricular premature contractions, or signs of ischemia on the stress test.
7. Patients in whom coronary spasm or another nonatherosclerotic cause of myocardial ischemia (e.g., coronary artery anomaly, Kawasaki disease) is suspected.

Noninvasive alternatives to diagnostic coronary arteriography include CT angiography and CMR angiography (Chap. 241). Although these new imaging techniques can provide information about obstructive lesions in the epicardial coronary arteries, their exact role in clinical practice has not been rigorously defined. Important aspects of their use that should be noted include the substantially higher radiation exposure with CT angiography compared to conventional diagnostic arteriography and the limitations on CMR imposed by cardiac movement during the cardiac cycle, especially at high heart rates.

## PROGNOSIS

The principal prognostic indicators in patients known to have IHD are age, the functional state of the left ventricle, the location(s) and severity of coronary artery narrowing, and the severity or activity of myocardial ischemia. Angina pectoris of recent onset, unstable angina (Chap. 274), early postmyocardial infarction angina, angina that is unresponsive or poorly responsive to medical therapy, and angina accompanied by symptoms of congestive heart failure all indicate an increased risk for adverse coronary events. The same is true for the physical signs of heart failure, episodes of pulmonary edema, transient third heart sounds, and mitral regurgitation and for echocardiographic or radioisotopic (or roentgenographic) evidence of cardiac enlargement and reduced (<0.40) ejection fraction.

Most important, any of the following signs during noninvasive testing indicates a high risk for coronary events: inability to exercise for 6 min, i.e., stage II (Bruce protocol) of the exercise test; a strongly positive exercise test showing onset of myocardial ischemia at low workloads ( $<0.1$  mV ST-segment depression before completion of stage II,

$0.2$  mV ST-segment depression at any stage, ST-segment depression for  $>5$  min after the cessation of exercise, a decline in systolic pressure  $>10$  mmHg during exercise, or the development of ventricular tachyarrhythmias during exercise); the development of large or multiple perfusion defects or increased lung uptake during stress radioisotope perfusion imaging; and a decrease in LV ejection fraction during exercise on radionuclide ventriculography or during stress echocardiography. Conversely, patients who can complete stage III of the Bruce exercise protocol and have a normal stress perfusion scan or negative stress echocardiographic evaluation are at very low risk for future coronary events. The finding of frequent episodes of ST-segment deviation on ambulatory ECG monitoring (even in the absence of symptoms) is also an adverse prognostic finding.

On cardiac catheterization, elevations of LV end-diastolic pressure and ventricular volume and reduced ejection fraction are the most important signs of LV dysfunction and are associated with a poor prognosis. Patients with chest discomfort but normal LV function and normal coronary arteries have an excellent prognosis. Obstructive lesions of the left main ( $>50\%$  luminal diameter) or left anterior descending coronary artery proximal to the origin of the first septal artery are associated with a greater risk than are lesions of the right or left circumflex coronary artery because of the greater quantity of myocardium at risk. Atherosclerotic plaques in epicardial arteries with fissuring or filling defects indicate increased risk. These lesions go through phases of inflammatory cellular activity, degeneration, endothelial dysfunction, abnormal vasomotion, platelet aggregation, and fissuring or hemorrhage. These factors can temporarily worsen the stenosis and cause thrombosis and/or abnormal reactivity of the vessel wall, thus exacerbating the manifestations of ischemia. The recent onset of symptoms, the development of severe ischemia during stress testing (see above), and unstable angina pectoris (Chap. 274) all reflect episodes of rapid progression in coronary lesions.

With any degree of obstructive CAD, mortality is greatly increased when LV function is impaired; conversely, at any level of LV function, the prognosis is influenced importantly by the quantity of myocardium perfused by critically obstructed vessels. Therefore, it is essential to collect all the evidence substantiating past myocardial damage (evidence of myocardial infarction on ECG, echocardiography, radioisotope imaging, or left ventriculography), residual LV function (ejection fraction and wall motion), and risk of future damage from coronary events (extent of coronary disease and severity of ischemia defined by noninvasive stress testing). The larger the quantity of established myocardial necrosis is, the less the heart is able to withstand additional damage and the poorer the prognosis is. Risk estimation must include age, presenting symptoms, all risk factors, signs of arterial disease, existing cardiac damage, and signs of impending damage (i.e., ischemia).

The greater the number and severity of risk factors for coronary atherosclerosis (advanced age [ $>75$  years], hypertension, dyslipidemia, diabetes, morbid obesity, accompanying peripheral and/or cerebrovascular disease, previous myocardial infarction), the worse the prognosis of an angina patient. Evidence exists that elevated levels of CRP in the

plasma, extensive coronary calcification on EBCT (see above), and increased carotid intimal thickening on ultrasound examination also indicate an increased risk of coronary events.

## TREATMENT

### Stable Angina Pectoris

Once the diagnosis of IHD has been made, each patient must be evaluated individually with respect to his or her level of understanding, expectations and goals, control of symptoms, and prevention of adverse clinical outcomes such as myocardial infarction and premature death. The degree of disability and the physical and emotional stress that precipitates angina must be recorded carefully to set treatment goals. The management plan should include the following components: (1) explanation of the problem and reassurance about the ability to formulate a treatment plan, (2) identification and treatment of aggravating conditions, (3) recommendations for adaptation of activity as needed, (4) treatment of risk factors that will decrease the occurrence of adverse coronary outcomes, (5) drug therapy for angina, and (6) consideration of revascularization.

#### EXPLANATION AND REASSURANCE

Patients with IHD need to understand their condition and realize that a long and productive life is possible even though they have angina pectoris or have experienced and recovered from an acute myocardial infarction. Offering results of clinical trials showing improved outcomes can be of great value in encouraging patients to resume or maintain activity and return to work. A planned program of rehabilitation can encourage patients to lose weight, improve exercise tolerance, and control risk factors with more confidence.

#### IDENTIFICATION AND TREATMENT OF AGGRAVATING CONDITIONS

A number of conditions may increase oxygen demand or decrease oxygen supply to the myocardium and may precipitate or exacerbate

angina in patients with IHD. LVH, aortic valve disease, and hypertrophic cardiomyopathy may cause or contribute to angina and should be excluded or treated. Obesity, hypertension, and hyperthyroidism should be treated aggressively to reduce the frequency and severity of anginal episodes. Decreased myocardial oxygen supply may be due to reduced oxygenation of the arterial blood (e.g., in pulmonary disease or, when carboxyhemoglobin is present, due to cigarette or cigar smoking) or decreased oxygen-carrying capacity (e.g., in anemia). Correction of these abnormalities, if present, may reduce or even eliminate angina pectoris.

#### ADAPTATION OF ACTIVITY

Myocardial ischemia is caused by a discrepancy between the demand of the heart muscle for oxygen and the ability of the coronary circulation to meet that demand. Most patients can be helped to understand this concept and utilize it in the rational programming of activity. Many tasks that ordinarily evoke angina may be accomplished without symptoms simply by reducing the speed at which they are performed. Patients must appreciate the diurnal variation in their tolerance of certain activities and should reduce their energy requirements in the morning, immediately after meals, and in cold or inclement weather. On occasion, it may be necessary to recommend a change in employment or residence to avoid physical stress.

Physical conditioning usually improves the exercise tolerance of patients with angina and has substantial psychological benefits. A regular program of isotonic exercise that is within the limits of the individual patient's threshold for the development of angina pectoris and that does not exceed 80% of the heart rate associated with ischemia on exercise testing should be strongly encouraged. Based on the results of an exercise test, the number of metabolic equivalent tasks (METs) performed at the onset of ischemia can be estimated (Table 273-2) and a practical exercise prescription can be formulated to permit daily activities that will fall below the ischemic threshold (**Table 273-3**).

**TABLE 273-3 Energy Requirements for Some Common Activities**

LESS THAN 3 METs	3–5 METs	5–7 METs	7–9 METs	MORE THAN 9 METs
<b>Self-Care</b>				
Washing/shaving	Cleaning windows	Easy digging in garden	Heavy shoveling	Carrying loads upstairs (objects >90 lb)
Dressing	Raking	Level hand lawn mowing	Carrying objects (60–90 lb)	Climbing stairs (quickly)
Light housekeeping	Power lawn mowing	Carrying objects (30–60 lb)		Shoveling heavy snow
Desk work	Bed making/stripping			
Driving auto	Carrying objects (15–30 lb)			
<b>Occupational</b>				
Sitting (clerical/assembly)	Stocking shelves (light objects)	Carpentry (exterior)	Digging ditches (pick and shovel)	Heavy labor
Desk work	Light welding/carpentry	Shoveling dirt		
Standing (store clerk)		Sawing wood		
<b>Recreational</b>				
Golf (cart)	Dancing (social)	Tennis (singles)	Canoeing	Squash
Knitting	Golf (walking)	Snow skiing (downhill)	Mountain climbing	Ski touring
	Sailing	Light backpacking		Vigorous basketball
	Tennis (doubles)	Basketball		
		Stream fishing		
<b>Physical Conditioning</b>				
Walking (2 mph)	Level walking (3–4 mph)	Level walking (4.5–5.0 mph)	Level jogging (5 mph)	Running more than 6 mph
Stationary bike	Level biking (6–8 mph)	Bicycling (9–10 mph)	Swimming (crawl stroke)	Bicycling (more than 13 mph)
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine	Rope jumping
			Heavy calisthenics	Walking uphill (5 mph)
			Bicycling (12 mph)	

Abbreviation: METs, metabolic equivalent tasks.

Source: Modified from WL Haskell: Rehabilitation of the coronary patient, in NK Wenger, HK Hellerstein (eds): *Design and Implementation of Cardiac Conditioning Program*. New York, Churchill Livingstone, 1978.

A *family history* of premature IHD is an important indicator of increased risk and should trigger a search for treatable risk factors such as hyperlipidemia, hypertension, and diabetes mellitus. *Obesity* impairs the treatment of other risk factors and increases the risk of adverse coronary events. In addition, obesity often is accompanied by three other risk factors: diabetes mellitus, hypertension, and hyperlipidemia. The treatment of obesity and these accompanying risk factors is an important component of any management plan. A diet low in saturated and *trans*-unsaturated fatty acids and a reduced caloric intake to achieve optimal body weight are a cornerstone in the management of chronic IHD. It is especially important to emphasize weight loss and regular exercise in patients with the metabolic syndrome or overt diabetes mellitus.

*Cigarette smoking* accelerates coronary atherosclerosis in both sexes and at all ages and increases the risk of thrombosis, plaque instability, myocardial infarction, and death. In addition, by increasing myocardial oxygen needs and reducing oxygen supply, it aggravates angina. Smoking cessation studies have demonstrated important benefits with a significant decline in the occurrence of these adverse outcomes. Noncombustible tobacco in the form of electronic cigarettes (nicotine delivery systems) may also increase the frequency of anginal episodes. The physician's message must be clear and strong and supported by programs that achieve and monitor abstinence from all tobacco product use (*Chap. 454*).

*Hypertension* (*Chap. 277*) may coexist with other risk factors for IHD and is associated with an increased risk of adverse clinical events from coronary atherosclerosis as well as stroke. In addition, the LVH that results from sustained hypertension aggravates ischemia. There is evidence that long-term effective treatment of hypertension can decrease the occurrence of adverse coronary events (*Chap. 277*).

*Diabetes mellitus* (*Chap. 403*) accelerates coronary and peripheral atherosclerosis and is frequently associated with dyslipidemia and increases in the risk of angina, myocardial infarction, and sudden coronary death. Aggressive control of the dyslipidemia (target LDL cholesterol <70 mg/dL) and hypertension (blood pressure <130/80 mmHg) that are frequently found in diabetic patients is highly effective and therefore essential, as described below.

#### DYSLIPIDEMIA

The treatment of dyslipidemia is central in aiming for long-term relief from angina, reduced need for revascularization, and reduction in myocardial infarction and death. The control of lipids can be achieved by the combination of a diet low in saturated and *trans*-unsaturated fatty acids, exercise, and weight loss. Nearly always, HMG-CoA reductase inhibitors (statins) are required and can lower LDL cholesterol (25–50%), raise HDL cholesterol (5–9%), and lower triglycerides (5–30%). A powerful treatment effect of statins on atherosclerosis, IHD, and outcomes is seen regardless of the pretreatment LDL cholesterol level. Fibrates, niacin, and icosapent ethyl can be used to lower triglycerides (*Chap. 407*). Controlled trials with lipid-regulating regimens have shown equal proportional benefit for men, women, the elderly, diabetic patients, and smokers. Injectable monoclonal antibodies against PCSK9 are now available and are important disease-modifying treatments capable of producing dramatic lowering of LDL cholesterol beyond that achieved with a statin alone or a combination of a statin plus ezetimibe.

Compliance with the health-promoting behaviors listed above is generally very poor, and a conscientious physician must not underestimate the major effort required to meet this challenge. Many patients who are discharged from the hospital with proven coronary disease do not receive adequate treatment for dyslipidemia. In light of the proof that treating dyslipidemia brings major benefits, physicians need to establish treatment pathways, monitor compliance, and follow up regularly.

#### RISK REDUCTION IN WOMEN WITH IHD

The incidence of clinical IHD in premenopausal women is very low; however, after menopause, the atherogenic risk factors increase

TABLE 273-4 Nitrate Therapy in Patients with Ischemic Heart Disease

PREPARATION OF AGENT	DOSE	SCHEDULE
Nitroglycerin <sup>a</sup>	0.5–2 in.	Two or three times daily
	Transdermal patch 0.2–0.8 mg/h	Every 24 h; remove at bedtime for 12–14 h
	Sublingual tablet 0.3–0.6 mg	As needed, up to three doses 5 min apart
	Spray One or two sprays	As needed, up to three doses 5 min apart
Isosorbide dinitrate <sup>a</sup>	10–40 mg	Two or three times daily
	Oral sustained release 80–120 mg	Once or twice daily (eccentric schedules)
Isosorbide 5-mononitrate	20 mg	Twice daily (given 7–8 h apart)
	Oral sustained release 30–240 mg	Once daily

<sup>a</sup>A 10- to 12-h nitrate-free interval is recommended.

*Source:* Reproduced with permission from DA Morrow, WE Boden: Stable ischemic heart disease. In RO Bonow et al (eds): *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th ed. Philadelphia, Saunders, 2012.

(e.g., increased LDL) and the rate of clinical coronary events accelerates to the levels observed in men. Diabetes mellitus, which is more common in women, greatly increases the occurrence of clinical IHD and amplifies the deleterious effects of hypertension, hyperlipidemia, and smoking. Cardiac catheterization and coronary revascularization are underused in women and are performed at a later and more severe stage of the disease than in men. When cholesterol lowering, beta blockers after myocardial infarction, and CABG are applied in the appropriate patient groups, women benefit to the same degree as men.

#### DRUG THERAPY

The commonly used drugs for the treatment of angina pectoris are summarized in **Tables 273-4 through 273-6**. Pharmacotherapy for IHD is designed to reduce the frequency of anginal episodes,

TABLE 273-5 Properties of Beta Blockers in Clinical Use for Ischemic Heart Disease

DRUGS	SELECTIVITY	PARTIAL AGONIST ACTIVITY	USUAL DOSE FOR ANGINA
Acetbutolol	$\beta_1$	Yes	200–600 mg twice daily
Atenolol	$\beta_1$	No	50–200 mg/d
Betaxolol	$\beta_1$	No	10–20 mg/d
Bisoprolol	$\beta_1$	No	10 mg/d
Esmolol (intravenous) <sup>a</sup>	$\beta_1$	No	50–300 $\mu$ g/kg/min
Labetalol <sup>b</sup>	None	Yes	200–600 mg twice daily
Metoprolol	$\beta_1$	No	50–200 mg twice daily
Nadolol	None	No	40–80 mg/d
Nebivolol	$\beta_1$ (at low doses)	No	5–40 mg/d
Pindolol	None	Yes	2.5–7.5 mg 3 times daily
Propranolol	None	No	80–120 mg twice daily
Timolol	None	No	10 mg twice daily

<sup>a</sup>Esmolol is an ultra-short-acting beta blocker that is administered as a continuous intravenous infusion. Its rapid offset of action makes esmolol an attractive agent to use in patients with relative contraindications to beta blockade. <sup>b</sup>Labetalol is a combined alpha and beta blocker.

*Note:* This list of beta blockers that may be used to treat patients with angina pectoris is arranged alphabetically. It is preferable to use a sustained-release formulation that may be taken once daily to improve the patient's compliance with the regimen.

*Source:* Data from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

DRUGS	USUAL DOSE	DURATION OF ACTION	SIDE EFFECTS
<b>Dihydropyridines</b>			
Amlodipine	5–10 mg qd	Long	Headache, edema
Felodipine	5–10 mg qd	Long	Headache, edema
Iradipine	2.5–10 mg bid	Medium	Headache, fatigue
Nicardipine	20–40 mg tid	Short	Headache, dizziness, flushing, edema
Nifedipine	Immediate release: 30–90 mg daily orally  Slow release: 30–180 mg orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
Nisoldipine	20–40 mg qd	Short	Similar to nifedipine
<b>Nondihydropyridines</b>			
Diltiazem	Immediate release: 30–80 mg 4 times daily  Slow release: 120–320 mg qd	Short  Long	Hypotension, dizziness, flushing, bradycardia, edema
Verapamil	Immediate release: 80–160 mg tid  Slow release: 120–480 mg qd	Short  Long	Hypotension, myocardial depression, heart failure, edema, bradycardia

<sup>a</sup>May be associated with increased risk of mortality if administered during acute myocardial infarction.

**Note:** This list of calcium channel blockers that may be used to treat patients with angina pectoris is divided into two broad classes, dihydropyridines and nondihydropyridines, and arranged alphabetically within each class. Among the dihydropyridines, the greatest clinical experience has been obtained with amlodipine and nifedipine. After the initial period of dose titration with a short-acting formulation, it is preferable to switch to a sustained-release formulation that may be taken once daily to improve patient compliance with the regimen.

**Source:** Data from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

myocardial infarction, and coronary death. Trial data emphasize how important medical management is when added to the health-promoting behaviors discussed above. To achieve maximum benefit from medical therapy for IHD, it is frequently necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects.

## NITRATES

The organic nitrates are a valuable class of drugs in the management of angina pectoris (Table 273-4). Their major mechanisms of action include systemic venodilation with concomitant reduction in LV end-diastolic volume and pressure, thereby reducing myocardial wall tension and oxygen requirements; dilation of epicardial coronary vessels; and increased blood flow in collateral vessels. When metabolized, organic nitrates release nitric oxide (NO) that binds to guanylyl cyclase in vascular smooth muscle cells, leading to an increase in cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle. Nitrates also exert antithrombotic activity by NO-dependent activation of platelet guanylyl cyclase, impairment of intraplatelet calcium flux, and platelet activation.

The absorption of these agents is rapid and complete through mucous membranes. For this reason, nitroglycerin is most commonly administered sublingually in tablets of 0.4 or 0.6 mg. Patients with angina should be instructed to take the medication both to relieve angina and also ~5 min before activities that are likely to induce an episode.

Nitrates improve exercise tolerance in patients with chronic angina and relieve ischemia in patients with unstable angina as well as patients with Prinzmetal's variant angina (Chap. 274). A diary of angina and nitroglycerin use may be valuable for detecting changes in the frequency, severity, or threshold for discomfort that may

signify the development of unstable angina pectoris and/or herald an impending myocardial infarction.

**Long-Acting Nitrates** None of the long-acting nitrates is as effective as sublingual nitroglycerin for the acute relief of angina. These organic nitrate preparations can be swallowed, chewed, or administered as a patch or paste by the transdermal route (Table 273-4). They provide effective plasma levels for up to 24 h, but the therapeutic response is highly variable. Different preparations and/or administration during the daytime should be tried only to prevent discomfort while avoiding side effects such as headache and dizziness. Individual dose titration is important to prevent side effects. To minimize the effects of nitrate tolerance, the minimum effective dose should be used and a minimum of 8 h each day kept free of the drug to restore any useful response(s).

**-Adrenergic Blockers** These drugs represent an important component of the pharmacologic treatment of angina pectoris (Table 273-5). They reduce myocardial oxygen demand by inhibiting the increases in heart rate, arterial pressure, and myocardial contractility caused by adrenergic activation. Beta blockade reduces these variables most strikingly during exercise but causes only small reductions at rest. Long-acting beta-blocking drugs or sustained-release formulations offer the advantage of once-daily dosing (Table 273-5). The therapeutic aims include relief of angina and ischemia. These drugs also can reduce mortality and reinfarction rates in patients after myocardial infarction and are moderately effective antihypertensive agents.

Relative contraindications include asthma and reversible airway obstruction in patients with chronic lung disease, atrioventricular conduction disturbances, severe bradycardia, Raynaud's phenomenon, and a history of mental depression. Side effects include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia (sometimes severe), impaired atrioventricular conduction, LV failure, bronchial asthma, worsening claudication, and intensification of the hypoglycemia produced by oral hypoglycemic agents and insulin. Reducing the dose or even discontinuation may be necessary if these side effects develop and persist. Since sudden discontinuation can intensify ischemia, the doses should be tapered over 2 weeks. Beta blockers with relative  $\beta_1$ -receptor specificity such as metoprolol and atenolol may be preferable in patients with mild bronchial obstruction and insulin-requiring diabetes mellitus.

**Calcium Channel Blockers** Calcium channel blockers (Table 273-6) are coronary vasodilators that produce variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective. Because of differences in the dose-response relationship on cardiac electrical activity between the dihydropyridine and nondihydropyridine calcium channel blockers, verapamil and diltiazem may produce symptomatic disturbances in cardiac conduction and bradyarrhythmias. They also exert negative inotropic actions and are more likely to aggravate LV failure, particularly when used in patients with LV dysfunction, especially if the patients are also receiving beta blockers. Although useful effects usually are achieved when calcium channel blockers are combined with beta blockers and nitrates, individual titration of the doses is essential with these combinations. Variant (Prinzmetal's) angina responds particularly well to calcium channel blockers (especially members of the dihydropyridine class), supplemented when necessary by nitrates (Chap. 274).

Verapamil ordinarily should not be combined with beta blockers because of the combined adverse effects on heart rate and contractility. Diltiazem can be combined with beta blockers in patients with normal ventricular function and no conduction disturbances. Amlodipine and beta blockers have complementary actions on coronary blood supply and myocardial oxygen demands. Whereas the

former decreases blood pressure and dilates coronary arteries, the latter slows heart rate and decreases contractility. Amlodipine and the other second-generation dihydropyridine calcium antagonists (nicardipine, isradipine, long-acting nifedipine, and felodipine) are potent vasodilators and are useful in the simultaneous treatment of angina and hypertension. Short-acting dihydropyridines should be avoided because of the risk of precipitating infarction, particularly in the absence of concomitant beta blocker therapy.

**Choice Between Beta Blockers and Calcium Channel Blockers for Initial Therapy** Since beta blockers have been shown to improve life expectancy after acute myocardial infarction (**Chaps. 274 and 275**) and calcium channel blockers have not, the former may also be preferable in patients with angina and a damaged left ventricle. However, calcium channel blockers are indicated in patients with the following: (1) inadequate responsiveness to the combination of beta blockers and nitrates; many of these patients do well with a combination of a beta blocker and a dihydropyridine calcium channel blocker; (2) adverse reactions to beta blockers such as depression, sexual disturbances, and fatigue; (3) angina and a history of asthma or chronic obstructive pulmonary disease; (4) sick-sinus syndrome or significant atrioventricular conduction disturbances; (5) Prinzmetal's angina; or (6) symptomatic peripheral arterial disease.

A comparison of the common side effects, contraindications, and potential drug interactions of many of the frequently presented antianginal agents is shown in **Table 273-7**.

**Antiplatelet Drugs** Aspirin is an irreversible inhibitor of platelet cyclooxygenase and thereby interferes with platelet activation. Chronic administration of 75–325 mg orally per day has been shown to reduce coronary events in asymptomatic adult men over age 50, patients with chronic stable angina, and patients who have or have survived unstable angina and myocardial infarction. There is a dose-dependent increase in bleeding when aspirin is used chronically. It is preferable to use an enteric-coated formulation in the range of 81–162 mg/d. Administration of this drug should be considered in all patients with IHD in the absence of gastrointestinal bleeding, allergy, or dyspepsia. Clopidogrel (300–600 mg loading and 75 mg/d) is an oral agent that blocks P2Y<sub>12</sub> ADP receptor-mediated platelet aggregation. It provides benefits similar to those of aspirin

in patients with stable chronic IHD and may be substituted for aspirin if aspirin causes the side effects listed above. Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with an acute coronary syndrome (**Chap. 274**) and also reduces the risk of thrombus formation in patients undergoing implantation of a stent in a coronary artery (**Chap. 276**). Alternative antiplatelet agents that block the P2Y<sub>12</sub> platelet receptor such as prasugrel and ticagrelor have been shown to be more effective than clopidogrel for prevention of ischemic events after placement of a stent for an acute coronary syndrome but are associated with an increased risk of bleeding. Although combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with an acute coronary syndrome treated with implantation of a drug-eluting stent, studies have not shown any benefit from the routine addition of clopidogrel to aspirin in patients with chronic stable IHD.

### OTHER THERAPIES

The ACE inhibitors are widely used in the treatment of survivors of myocardial infarction, patients with hypertension or chronic IHD including angina pectoris, and those at high risk of vascular diseases such as diabetes. The benefits of ACE inhibitors are most evident in IHD patients at increased risk, especially if diabetes mellitus or LV dysfunction is present, and those who have not achieved adequate control of blood pressure and LDL cholesterol on beta blockers and statins. However, the routine administration of ACE inhibitors to IHD patients who have normal LV function and have achieved blood pressure and LDL goals on other therapies does not reduce the incidence of events and therefore is not cost-effective.

Despite treatment with nitrates, beta blockers, or calcium channel blockers, some patients with IHD continue to experience angina, and additional medical therapy is now available to alleviate their symptoms. Ranolazine, a piperazine derivative, may be useful for patients with chronic angina despite standard medical therapy (Table 273-7). Its antianginal action is believed to occur via inhibition of the late inward sodium current (I<sub>Na</sub>). The benefits of I<sub>Na</sub> inhibition include limitation of the Na overload of ischemic myocytes and prevention of Ca<sup>2+</sup> overload via the Na<sup>+</sup>-Ca<sup>2+</sup> exchanger. A dose of 500–1000 mg orally twice daily is usually well tolerated. Ranolazine is contraindicated in patients with hepatic impairment

**TABLE 273-7 Antianginal Agents**

AGENT	COMMON SIDE EFFECTS	CONTRAINdicATIONS	POTENTIAL DRUG INTERACTIONS
<b>Agents That Have a Physiologic Effect</b>			
Short-acting and long-acting nitrates	Headache, flushing, hypotension, syncope and postural hypotension, reflex tachycardia, methemoglobinemia	Hypertrophic obstructive cardiomyopathy	Phosphodiesterase type 5 inhibitors (sildenafil and similar agents), beta-adrenergic blockers, calcium channel blockers
Beta blockers	Fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, masked signs of hypoglycemia	Low heart rate or heart conduction disorder, cardiogenic shock, asthma, severe peripheral vascular disease, decompensated heart failure, vasospastic angina; use with caution in patients with COPD (cardioselective beta blockers may be used if patient receives adequate treatment with long-acting beta agonists)	Heart rate-lowering calcium channel blockers, sinus node or AV conduction depressors
Calcium-channel blockers Heart rate-lowering agents	Bradycardia, heart conduction defect, low ejection fraction, constipation, gingival hyperplasia	Cardiogenic shock, severe aortic stenosis, obstructive cardiomyopathy	CYP3A4 substrates (digoxin, simvastatin, cyclosporine)
Dihydropyridine	Headache, ankle swelling fatigue, flushing, reflex tachycardia	Low heart rate or heart rhythm disorder, sick-sinus syndrome, congestive heart failure, low blood pressure	Agents with cardiotropic effects (beta blockers, flecainide), CYP3A4 substrates
<b>Agents That Affect Myocardial Metabolism</b>			
Ranolazine	Dizziness, constipation, nausea, QT interval prolongation	Liver cirrhosis	CYP3A4 substrates (digoxin, simvastatin, cyclosporine), drugs that prolong the corrected QT interval

Abbreviations: AV, atrioventricular; COPD, chronic obstructive pulmonary disease; CYP3A4, cytochrome P450 3A4.

Source: Data from SE Husted: Lancet 386:691, 2015, and EM Ohman: N Engl J Med 374:1167, 2016.

or with conditions or drugs associated with QT<sub>c</sub> prolongation and when drugs that inhibit the CYP3A metabolic system (e.g., ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and large quantities of grapefruit juice) are being used.

Originally introduced for the management of diabetes mellitus, the sodium-glucose cotransporter-2 inhibitor (SGLT2i) drugs have emerged as important agents with cardiovascular and renal protective effects. They promote weight loss, lower blood pressure, and reduce plasma volume—all of which are desirable in patients with IHD. In addition, they decrease intraglomerular hypertension and hyperfiltration. Evidence exists that they are helpful in patients with and without diabetes who have a reduced LV ejection fraction. Nonsteroidal anti-inflammatory drug (NSAID) use in patients with IHD may be associated with a small but finite increased risk of myocardial infarction and mortality. For this reason, they generally should be avoided in IHD patients. If they are required for symptom relief, it is advisable to coadminister aspirin and strive to use an NSAID associated with the lowest risk of cardiovascular events, in the lowest dose required, and for the shortest period of time.

Another class of agents opens ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. The major drug in this class is nicorandil, which typically is administered orally in a dose of 20 mg twice daily for prevention of angina. (Nicorandil is not available for use in the United States but is used in several other countries.)

Ivabradine (2.5–7.5 mg orally twice daily) is a specific sinus node inhibiting agent that may be helpful for preventing cardiovascular events in patients with IHD who have a resting heart rate >70 beats/min (alone or in combination with a beta blocker) and LV systolic dysfunction.

**Angina and Heart Failure** Transient LV failure with angina can be controlled by the use of nitrates. For patients with established congestive heart failure, the increased LV wall tension raises myocardial oxygen demand. Treatment of congestive heart failure (Chap. 257) reduces heart size, wall tension, and myocardial oxygen demand, which helps control angina and ischemia. If the symptoms and signs of heart failure are controlled, an effort should be made to use beta blockers not only for angina but because trials in heart failure have shown significant improvement in survival. A trial of the intravenous ultra-short-acting beta blocker esmolol may be useful to establish the safety of beta blockade in selected patients. Nocturnal angina often can be relieved by the treatment of heart failure.

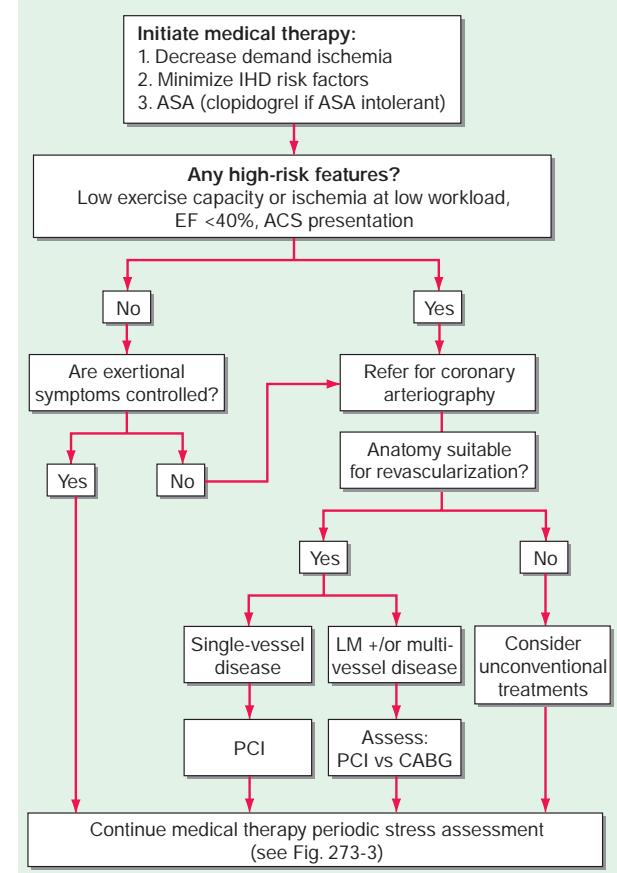
The combination of congestive heart failure and angina in patients with IHD usually indicates a poor prognosis and warrants serious consideration of cardiac catheterization and coronary revascularization.

## CORONARY REVASCULARIZATION

Clinical trials have confirmed that with the initial diagnosis of stable IHD, it is first appropriate to initiate a medical regimen as described above. Revascularization should be considered in the presence of unstable phases of the disease, intractable symptoms, high-risk coronary anatomy, diabetes, and impaired LV function. *Revascularization should be employed in conjunction with but not replace the continuing need to modify risk factors and assess medical therapy.* An algorithm for integrating medical therapy and revascularization options in patients with IHD is shown in Fig. 273-4.

### PERCUTANEOUS CORONARY INTERVENTION

(See also Chap. 276) PCI involving balloon dilatation usually accompanied by coronary stenting is widely used to achieve revascularization of the myocardium in patients with symptomatic IHD and suitable stenoses of epicardial coronary arteries. Whereas patients with stenosis of the left main coronary artery and those with three-vessel IHD (especially with diabetes and/or impaired LV function) who require revascularization are best treated with CABG, PCI is widely employed in patients with symptoms and evidence of ischemia due to stenoses



**FIGURE 273-4 Algorithm for management of a patient with ischemic heart disease.** All patients should receive the core elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should be considered for unconventional treatments. See text for further discussion. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main.

of one or two vessels and even in selected patients with three-vessel disease (and, perhaps, in some patients with left main disease) and may offer many advantages over surgery.

**Indications and Patient Selection** The most common clinical indication for PCI is symptom-limiting angina pectoris, despite medical therapy, accompanied by evidence of ischemia during a stress test. PCI is more effective than medical therapy for the relief of angina. PCI improves outcomes in patients with unstable angina or when used early in the course of myocardial infarction with and without cardiogenic shock. However, in patients with stable exertional angina, clinical trials have confirmed that PCI does not reduce the occurrence of death or myocardial infarction compared to optimum medical therapy. PCI can be used to treat stenoses in native coronary arteries as well as in bypass grafts in patients who have recurrent angina after CABG.

**Risks** When coronary stenoses are discrete and symmetric, two and even three vessels can be treated in sequence. However, case selection is essential to avoid a prohibitive risk of complications, which are usually due to dissection or thrombosis with vessel occlusion, uncontrolled ischemia, and ventricular failure (Chap. 276). Oral aspirin, a P2Y<sub>12</sub> antagonist, and an antithrombin agent are given to reduce coronary thrombus formation. Left main coronary artery stenosis generally is

regarded as a lesion that should be treated with CABG. In selected cases such as patients with prohibitive surgical risks, PCI of an unprotected left main can be considered, but such a procedure should be performed only by a highly skilled operator; importantly, there are regional differences in the use of this approach internationally.

**Efficacy** Primary success, with relief of angina, is achieved in >95% of cases. Recurrent stenosis of the dilated vessels occurs in ~20% of cases within 6 months of PCI with bare metal stents, and angina will recur within 6 months in 10% of cases. Restenosis is more common in patients with diabetes mellitus, arteries with small caliber, incomplete dilation of the stenosis, long stents, occluded vessels, obstructed vein grafts, dilation of the left anterior descending coronary artery, and stenoses containing thrombi. In diseased vein grafts, procedural success has been improved by the use of capture devices or filters that prevent embolization, ischemia, and infarction.

It is usual clinical practice to administer oral aspirin indefinitely and a P2Y<sub>12</sub> antagonist for 1–3 months after the implantation of a bare metal stent. Although aspirin in combination with a thienopyridine may help prevent coronary thrombosis during and shortly after PCI with stenting, there is no evidence that these medications reduce the incidence of restenosis.

The use of current-generation drug-eluting stents that locally deliver antiproliferative drugs can reduce restenosis to <5%. Advances in PCI, especially the availability of drug-eluting stents, have vastly extended the use of this revascularization option in patients with IHD. Of note, however, the delayed endothelial healing in the region of a drug-eluting stent also extends the period during which the patient is at risk for subacute stent thrombosis. Aspirin should be administered indefinitely and a P2Y<sub>12</sub> antagonist daily (dual antiplatelet therapy [DAPT]) for at least 1 year after implantation of a drug-eluting stent. Evidence exists of a benefit of continuing DAPT for up to 30 months, albeit at the cost of a higher risk of bleeding.

Efforts are underway to develop new antithrombotic regimens. These include (1) shortening the duration of DAPT by eliminating aspirin after 3 months and continuing a potent P2Y<sub>12</sub> antagonist (e.g., ticagrelor) and (2) switching from DAPT to dual pathway inhibition with an antiplatelet agent and a low-dose direct oral anticoagulant (a particularly attractive option for IHD patients who also have atrial fibrillation). The relative benefits of such new regimens have not been established and no consensus has been achieved, as yet.

When a situation arises in which temporary discontinuation of antiplatelet therapy is necessary, the clinical circumstances should be reviewed with the operator who performed the PCI and a coordinated plan should be established for minimizing the risk of late stent thrombosis; central to this plan is the discontinuation of antiplatelet therapy for the shortest acceptable period. The risk of stent thrombosis is dependent on stent size and length, complexity of the lesions, age, diabetes, and technique. However, compliance with DAPT and individual responsiveness to platelet inhibition are very important factors as well.

Successful PCI produces effective relief of angina in >95% of cases. The majority of patients with symptomatic IHD who require revascularization can be treated initially by PCI. Successful PCI is less invasive and expensive than CABG and permits savings in the *initial* cost of care. Successful PCI avoids the risk of stroke associated with CABG surgery and allows earlier return to work and resumption of an active life. However, the early health-related and economic benefits of PCI are reduced over time because of the greater need for follow-up and the increased need for repeat procedures. When directly compared in patients with diabetes or three-vessel or left main CAD, CABG was superior to PCI in preventing major adverse cardiac or cerebrovascular events over a 12-month follow-up.

### CORONARY ARTERY BYPASS GRAFTING

Anastomosis of one or both of the internal mammary arteries or a radial artery to the coronary artery distal to the obstructive lesion is the preferred procedure. For additional obstructions that cannot be bypassed by an artery, a section of a vein (usually the saphenous) is used to form a venous bypass conduit between the aorta and the coronary artery distal to the obstructive lesion.

Although some indications for CABG are controversial, certain areas of agreement exist:

1. The operation is relatively safe, with mortality rates <1% in patients without serious comorbid disease and normal LV function and when the procedure is performed by an experienced surgical team.
2. Intraoperative and postoperative mortality rates increase with the severity of ventricular dysfunction, comorbidities, age >80 years, and lack of surgical experience. The effectiveness and risk of CABG vary widely depending on case selection and the skill and experience of the surgical team.
3. Occlusion of venous grafts is observed in 10–20% of patients during the first postoperative year and in ~2% per year during 5- to 7-year follow-up and 4% per year thereafter. Long-term patency rates are considerably higher for internal mammary and radial artery implantations than for saphenous vein grafts. In patients with left anterior descending coronary artery obstruction, survival is better when coronary bypass involves the internal mammary artery rather than a saphenous vein. Graft patency and outcomes are improved by meticulous treatment of risk factors, particularly dyslipidemia.
4. Angina is abolished or greatly reduced in ~90% of patients after complete revascularization. Although this usually is associated with graft patency and restoration of blood flow, the pain may also have been alleviated as a result of infarction of the ischemic segment or a placebo effect.
5. Survival may be improved by operation in patients with stenosis of the left main coronary artery as well as in patients with three- or two-vessel disease with significant obstruction of the proximal left anterior descending coronary artery. The survival benefit is greater in patients with abnormal LV function (ejection fraction <50%). Survival may also be improved in the following patients: (a) patients with obstructive CAD who have survived sudden cardiac death or sustained ventricular tachycardia; (b) patients who have undergone previous CABG and have multiple saphenous vein graft stenoses, especially of a graft supplying the left anterior descending coronary artery; and (c) patients with recurrent stenosis after PCI and high-risk criteria on noninvasive testing.
6. Minimally invasive CABG through a small thoracotomy and/or off-pump surgery can reduce morbidity and shorten convalescence in suitable patients but does not appear to reduce significantly the risk of neurocognitive dysfunction postoperatively.
7. Among patients with type 2 diabetes mellitus and multivessel coronary disease, CABG surgery plus optimal medical therapy is superior to optimal medical therapy alone in preventing major cardiovascular events, a benefit mediated largely by a significant reduction in nonfatal myocardial infarction. The benefits of CABG are especially evident in diabetic patients treated with an insulin-sensitizing strategy as opposed to an insulin-providing strategy. CABG has also been shown to be superior to PCI (including the use of drug-eluting stents) in preventing death, myocardial infarction, and repeat revascularization in patients with diabetes mellitus and multivessel IHD.

Indications for CABG usually are based on the severity of symptoms, coronary anatomy, and ventricular function. The ideal candidate has no other complicating disease and has troublesome or disabling angina that is not adequately controlled by medical therapy or does not tolerate medical therapy. Great symptomatic benefit can be anticipated if a patient wishes to lead a more active life and has severe stenoses of two or three epicardial coronary arteries with objective evidence of myocardial ischemia as a cause of the chest discomfort. Congestive heart failure and/or LV dysfunction, advanced age (>80 years), reoperation, urgent need for surgery, and the presence of diabetes mellitus are all associated with a higher perioperative mortality rate.

LV dysfunction can be due to noncontractile or hypocontractile segments that are viable but are chronically ischemic (hibernating myocardium). As a consequence of chronic reduction in myocardial blood flow, these segments downregulate their contractile function. They can be detected by using radionuclide scans of myocardial perfusion and metabolism, PET, cardiac MRI, or delayed scanning with

thallium-201 or by improvement of regional functional impairment provoked by low-dose dobutamine. In such patients, revascularization improves myocardial blood flow, can return function, and can improve survival.

**The Choice Between PCI and CABG** All the clinical characteristics of each individual patient must be used to decide on the method of revascularization (e.g., LV function, diabetes, lesion complexity). A number of randomized clinical trials have compared PCI and CABG in patients with multivessel CAD who were suitable technically for both procedures. The redevelopment of angina requiring repeat coronary angiography and repeat revascularization is higher with PCI. This is a result of restenosis in the stented segment (a problem largely solved with drug-eluting stents) and the development of new stenoses in unstented portions of the coronary vasculature. It has been argued that PCI with stenting focuses on culprit lesions, whereas a bypass graft to the target vessel also provides a conduit around future culprit lesions proximal to the anastomosis of the graft to the native vessel (Fig. 273-5). By contrast, stroke rates are lower with PCI.

Based on available evidence, it is now recommended that patients with an unacceptable level of angina despite optimal medical management be considered for coronary revascularization. Patients with single- or two-vessel disease with normal LV function and anatomically suitable lesions ordinarily are advised to undergo PCI (Chap. 276). Patients with three-vessel disease (or two-vessel disease that includes the proximal left descending coronary artery) and impaired global LV function (LV ejection fraction <50%) or diabetes mellitus and those with left main CAD or other lesions unsuitable for catheter-based procedures should be considered for CABG as the initial method of revascularization. In light of the complexity of the decision-making, it is desirable to have a multidisciplinary team, including a cardiologist and a cardiac surgeon in conjunction with the patient's primary care physician, provide input along with ascertaining the patient's preferences before committing to a particular revascularization option.

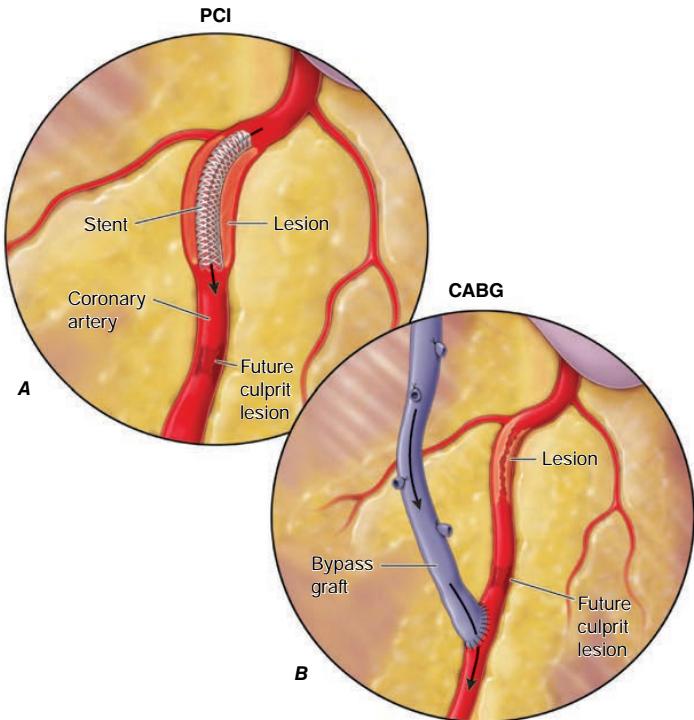
### UNCONVENTIONAL TREATMENTS FOR IHD

On occasion, clinicians will encounter a patient who has persistent, disabling angina despite maximally tolerated medical therapy and for whom revascularization is not an option (e.g., small diffusely diseased vessels not amenable to stent implantation or acceptable targets for bypass grafting). In such situations, unconventional treatments should be considered.

*Enhanced external counterpulsation* utilizes pneumatic cuffs on the lower extremities to provide diastolic augmentation and systolic unloading of blood pressure to decrease cardiac work and oxygen consumption while enhancing coronary blood flow. Clinical trials have shown that regular application improves angina, exercise capacity, and regional myocardial perfusion. Experimental approaches, such as stem cell therapies and cardiac repair with small noncoding RNA molecules (miRNA), are also under active study.

### ASYMPTOMATIC (SILENT) ISCHEMIA

Obstructive CAD, acute myocardial infarction, and transient myocardial ischemia can occur in the absence of symptoms. During continuous ambulatory ECG monitoring, the majority of ambulatory patients with typical chronic stable angina are found to have objective evidence of myocardial ischemia (ST-segment depression) during episodes of chest discomfort while they are active outside the hospital. In addition, many of these patients also have more frequent episodes of asymptomatic ischemia. Frequent episodes of ischemia (symptomatic and asymptomatic) during daily life appear to be associated with an increased likelihood of adverse coronary events (death and myocardial infarction). In addition, patients with asymptomatic ischemia after a myocardial infarction are at greater risk for a second coronary event.



**FIGURE 273-5** Difference in the approach to the lesion with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the "culprit" lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, proximal to the insertion of the vein graft, a difference that may account for the superiority of CABG, at least in the intermediate term, in patients with multivessel disease. (From BJ Gersh: Methods of coronary revascularization—Things may not be as they seem. *N Engl J Med* 352:2235, 2005. Copyright © 2005 Massachusetts Medical Society Reprinted with permission from Massachusetts Medical Society.)

The widespread use of exercise ECG during routine examinations has also identified some of these previously unrecognized patients with asymptomatic CAD. Longitudinal studies have demonstrated an increased incidence of coronary events in asymptomatic patients with positive exercise tests.

## TREATMENT

### Asymptomatic Ischemia

The management of patients with asymptomatic ischemia must be individualized. When coronary disease has been confirmed, the aggressive treatment of hypertension and dyslipidemia is essential and will decrease the risk of infarction and death. In addition, the physician should consider the following: (1) the degree of positivity of the stress test, particularly the stage of exercise at which ECG signs of ischemia appear; the magnitude and number of the ischemic zones of myocardium on imaging; and the change in LV ejection fraction that occurs on radionuclide ventriculography or echocardiography during ischemia and/or during exercise; (2) the ECG leads showing a positive response, with changes in the anterior precordial leads indicating a less favorable prognosis than changes in the inferior leads; and (3) the patient's age, occupation, and general medical condition.

Most would agree that an asymptomatic 45-year-old commercial airline pilot with significant (0.4-mV) ST-segment depression in leads V<sub>1</sub> to V<sub>4</sub> during mild exercise should undergo coronary arteriography, whereas an asymptomatic, sedentary 85-year-old retiree with 0.1-mV ST-segment depression in leads II and III during maximal activity need not. However, there is no consensus about the most appropriate approach in the large majority of patients for whom the situation is less extreme. Asymptomatic patients with silent

ischemia, three-vessel CAD, and impaired LV function may be considered appropriate candidates for CABG.

The treatment of risk factors, particularly lipid lowering and blood pressure control as described above, and the use of aspirin, statins, and beta blockers after infarction have been shown to reduce events and improve outcomes in asymptomatic as well as symptomatic patients with ischemia and proven CAD. Although the incidence of asymptomatic ischemia can be reduced by treatment with beta blockers, calcium channel blockers, and long-acting nitrates, it is not clear whether this is necessary or desirable in patients who have not had a myocardial infarction.

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# Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)

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Eugene Braunwald



Patients with acute coronary syndrome (ACS) are commonly classified into two groups to facilitate evaluation and management, namely patients with acute myocardial infarction (MI) with ST-segment elevation (STEMI) on their presenting electrocardiogram (ECG) (**Chap. 275**) and those with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). The latter include patients with non-ST-segment elevation MI (NSTEMI), who, by definition, have evidence of myocyte necrosis, and those with unstable angina (UA), who do not (**Fig. 274-1**).

The incidence of NSTEMI is rising due to the increasing burden of obesity, diabetes, and chronic kidney disease in an aging population and the increasing detection of myocardial necrosis by troponin (see below), whereas the incidence of STEMI is declining due to greater use of aspirin, statins, and less smoking. Among patients with NSTE-ACS, the proportion with NSTEMI is increasing while that with UA is falling because of the wider use of highly sensitive troponin (hsTn) assays (see below) with enhanced detection of myocyte necrosis, thereby reclassifying UA to NSTEMI.

## PATHOPHYSIOLOGY

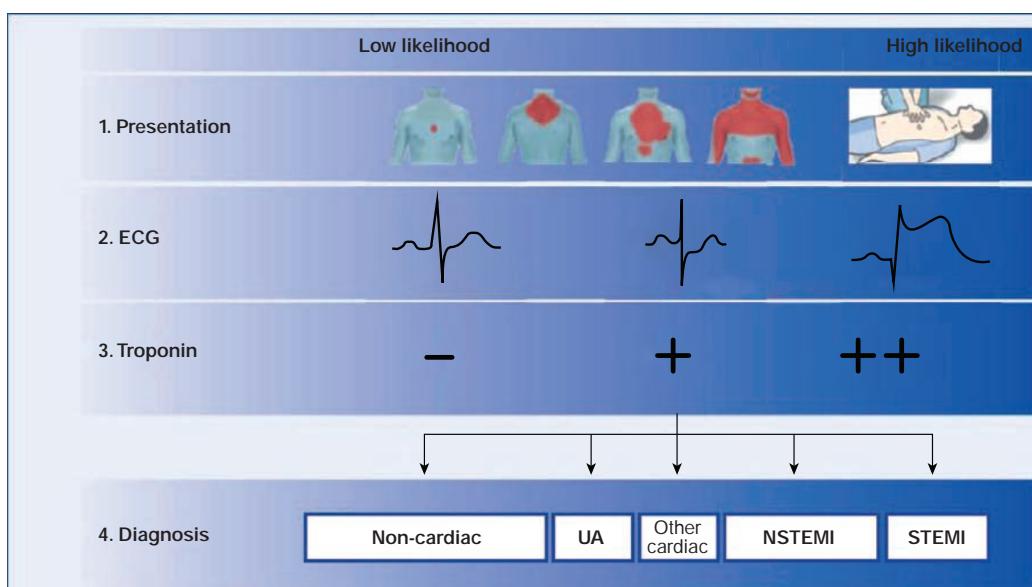
NSTE-ACS is caused by an imbalance between myocardial oxygen supply and demand resulting from one or more of three processes that lead to coronary arterial thrombosis: (1) plaque fissure with inflammation—the inflammatory response is reflected by an increased activity of effector T cells as part of an adaptive immunity dysregulation; (2) plaque fissure without inflammation; and (3) plaque erosion, which is present in at least one-third of ACS and is recognized with increasing frequency (**Fig. 274-2**). The so-called “vulnerable plaques” responsible for ACS may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck on coronary angiography. Such plaques usually are composed of a lipid-rich core with a thin fibrous cap. Patients with NSTE-ACS frequently have multiple such plaques that are at risk of disruption. A fourth process, without thrombosis, may be caused by epicardial or microvascular spasm or increased myocardial oxygen demand in the presence of fixed epicardial coronary obstruction.

Among patients with NSTE-ACS studied at angiography, ~10% have stenosis of the left main coronary artery, 35% have three-vessel coronary artery disease, 20% have two-vessel disease, 20% have single-vessel disease, and 15% have no apparent critical epicardial coronary artery stenosis; some of the latter may have obstruction of the coronary microcirculation and/or spasm of the epicardial vessels.

## CLINICAL PRESENTATION

**Diagnosis** The diagnosis of NSTE-ACS is based largely on a combination of the history and clinical findings (age, the electrocardiogram, and circulating troponin) (**Table 274-1**, **Fig. 274-3**).

**History and Physical Examination** Typically, chest discomfort is severe and has at least one of three features: (1) occurrence at rest (or with minimal exertion), lasting >10 min; (2) of relatively recent onset (i.e., within the prior 2 weeks); and/or (3) a crescendo pattern, i.e., distinctly more severe, prolonged, or frequent than previous episodes. The diagnosis of NSTEMI is established if a patient with any of



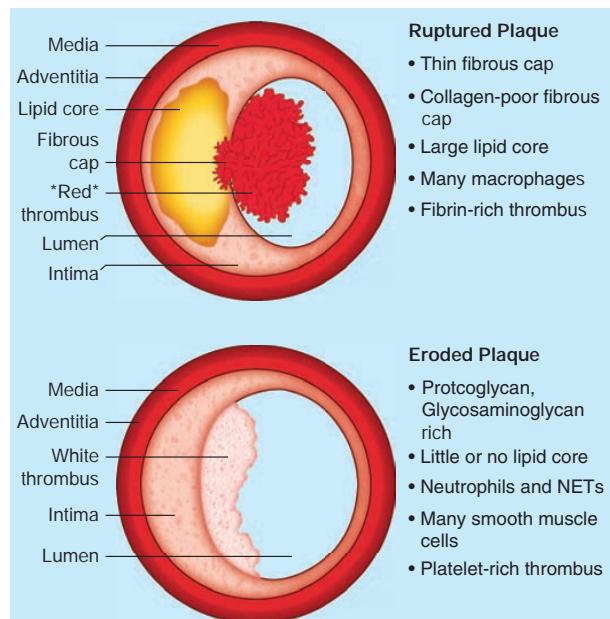
**FIGURE 274-1** Assessment of patients with suspected acute coronary syndromes. The initial assessment is based on the integration of low-likelihood and/or high-likelihood features derived from clinical presentation (i.e., symptoms, vital signs), 12-lead electrocardiogram (ECG), and cardiac troponin. The proportion of the final diagnoses derived from the integration of these parameters is visualized by the size of the respective boxes. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina. (Reproduced with permission from M Roffi et al: ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 37:267, 2016. <https://doi.org/10.1093/eurheartj/ehv320>, Translated and reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology.)

these features (without electrocardiographic ST-segment elevations) develops evidence of myocardial necrosis, as reflected in abnormally elevated levels of circulating troponin, in the absence of another explanation (see below). The chest discomfort is typically located in the substernal region and radiates to the left arm, left shoulder, and/or superiorly to the neck and jaw. Anginal equivalents such as dyspnea,

epigastric discomfort, nausea, or weakness may occur instead of chest discomfort. These equivalents are more frequent in women, the elderly, and patients with diabetes mellitus. The physical examination resembles that in patients with stable angina (Chap. 273) and may be unremarkable. However, if the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis; pale, cool skin; sinus tachycardia; a third and/or fourth heart sound; basilar rales; and hypotension.

**Electrocardiogram** New ST-segment depression occurs in about one-third of patients with NSTE-ACS. It may be transient but can persist for as long as several days following NSTEMI. T-wave changes are more common but are a less specific sign of ischemia, unless they are new and deep T-wave inversions ( $0.3$  mV).

**Cardiac Biomarkers** Patients with NSTEMI have elevated biomarkers of necrosis, such as cardiac troponin (cTn) I or T (cTnI or cTnT). cTns are sensitive, relatively specific, and the preferred markers of myocardial necrosis. Elevated levels of cTn with a dynamic early change



**FIGURE 274-2** Comparison of the characteristics of human atheromata complicated by thrombosis and causing acute coronary syndrome. The column on the left highlights some of the characteristics demonstrated by analyses of human coronary arterial lesions that have undergone thrombosis by these two diverse mechanisms. NETs, neutrophil extracellular traps (Reproduced with permission from P Libby et al: Reassessing the mechanisms of acute coronary syndromes the “vulnerable plaque” and superficial erosion. Circ Res 124:150, 2019.)

**TABLE 274-1** TIMI Risk Score for NSTE-ACS

RISK MARKERS	
• Age $\geq 65$ years	• ↑ cardiac markers
• Known CAD ( $\geq 50\%$ stenosis)	• 2 original episodes in prior 24 h
• ST deviation $>0.5$ mm on presenting ECG	• Prior angina
	• 3 CAD risk factors
NO. OF RISK MARKERS	INCIDENCE OF ADVERSE CARDIAC EVENTS* (%)
0/1	5
2	8
3	13
4	20
5	26
6/7	41

\*Risk at 14 days of death, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization.

Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; TIMI, Thrombolysis in Myocardial Infarction.

<b>TABLE 274-2 Reasons for the Elevation of Cardiac Troponin Values as a Result of Myocardial Injury</b>	
<b>Myocardial injury related to acute myocardial infarction</b>	
Atherosclerotic plaque disruption or erosion with thrombosis	
<b>Myocardial injury related to acute myocardial ischemia because of oxygen supply/demand imbalance</b>	
Reduced myocardial perfusion	
• Coronary artery spasm, microvascular dysfunction	
• Coronary embolism	
• Coronary artery dissection	
• Sustained bradycardia	
• Hypotension or shock	
• Respiratory failure	
• Severe anemia	
<i>Increased myocardial oxygen demand</i>	
• Sustained tachyarrhythmia	
• Severe hypertension	
<b>Other causes of myocardial injury</b>	
<i>Cardiac conditions</i>	
• Heart failure	
• Myocarditis	
• Cardiomyopathy (any type)	
• Takotsubo syndrome	
• Recent coronary revascularization	
• Cardiac procedure other than revascularization	
• Catheter ablation	
• Defibrillator shocks	
• Cardiac contusion	
<i>Systemic conditions</i>	
• Sepsis	
• Chronic kidney disease	
• Stroke, subarachnoid hemorrhage	
• Pulmonary embolism	
• Infiltrative diseases, e.g., amyloidosis, sarcoidosis	
• Chemotherapeutic agents	
• Critical illness	
• Strenuous exercise	

*Note:* For a more comprehensive listing, see the Fourth Universal Definition of Myocardial Infarction (source).

*Source:* Reproduced with permission from K Thygesen et al: Fourth universal definition of myocardial infarction (2018). Circulation 72:2231, 2018.

distinguish patients with NSTEMI from those with UA. In patients with NSTEMI, there is a characteristic temporal rise of the plasma concentration, peaking at 12–24 h after onset of symptoms and gradually decreasing thereafter. There is a direct relationship between the degree of elevation and mortality. The 1-h rapid rule-out MI algorithm (no abnormal elevation of hsTn at 0 or 1 hour after presentation) has been recommended by recent practice guidelines. It is important to distinguish myocardial injury from myocardial necrosis; the former is defined by elevations of cTn >99th percentile of the upper reference limit in patients *without* a clear clinical history or electrocardiographic features of acute myocardial ischemia. Myocardial injury may be caused by a variety of noncardiac and cardiac conditions other than MI (**Table 274-2**).

## IMAGING

Coronary computed tomographic angiography (CCTA) may be useful in improving the accuracy and speed of the diagnostic evaluation. The goals are to recognize or exclude epicardial coronary artery disease.

## RISK STRATIFICATION

Patients with documented NSTE-ACS exhibit a wide spectrum of early (30 days) risk of death, ranging from 1 to 10%, and a recurrent ACS rate of 5–15% during the first year. Assessment of risk

can be accomplished by one of several clinical risk scoring systems, including those developed from the Thrombolysis in Myocardial Infarction (TIMI) Trials, the Global Registry of Acute Coronary Event (GRACE), and the HEART (history, electrocardiogram, age, risk factors, troponin) score (**Fig. 274-3**). Multibiomarker strategies are now gaining favor, both to define more fully the pathophysiologic mechanisms underlying a patient's presentation and to stratify the patient's risk further. Early risk assessment is useful in identifying patients who would derive the greatest benefit from an early invasive strategy (see below).

## TREATMENT

### Non-ST-Segment Elevation Acute Coronary Syndrome

Patients with a low likelihood of ischemia can usually be managed in an emergency department or a dedicated "chest pain unit." Evaluation of such patients includes clinical monitoring for recurrent ischemic discomfort and continuous monitoring of ECGs, stress testing to detect and grade ischemia (**Chap. 273**), CCTA to assess epicardial coronary artery obstruction, and serum troponin.

#### MEDICAL TREATMENT

Patients who "rule-in" for NSTE-ACS by clinical features, cTn, or ST-T-wave changes on the ECG should be admitted to the hospital. Patients should be placed on bed rest with continuous ECG monitoring for ST-segment deviation and cardiac arrhythmias, preferably on a specialized cardiac unit. Ambulation is permitted if the patient shows no recurrence of ischemia (symptoms or ECG changes) and does not develop an elevation of cTn for 24 h. They may proceed to stress testing to detect ischemia and, if it is present, to assess its severity.

Medical therapy consists of an acute phase focused on the clinical symptoms and stabilization of the culprit lesion(s) and a longer-term phase that involves therapies directed at the prevention of disease progression and future recurrent NSTE-ACS.

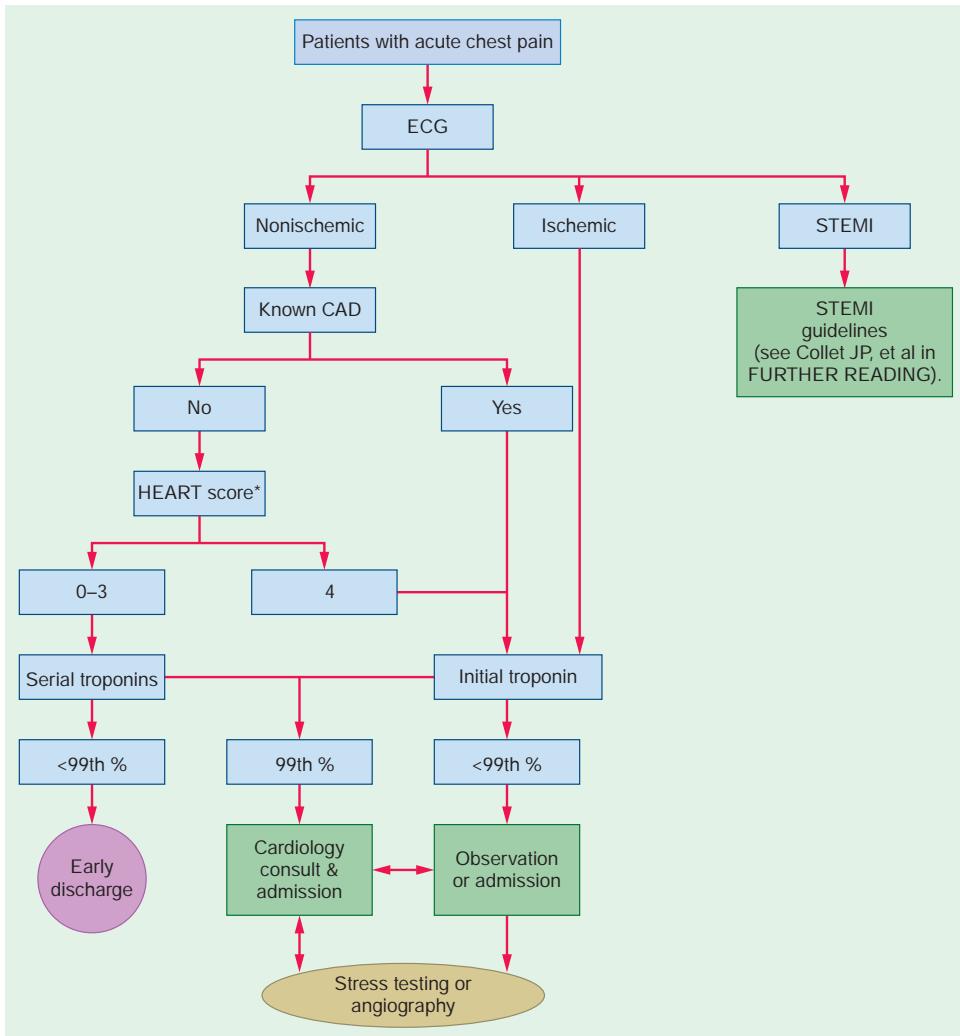
#### ANTI-ISCHEMIC TREATMENT (TABLE 274-3)

To provide relief of pain and discomfort, initial treatment, in addition to bed rest, includes nitrates,  $\beta$ -adrenergic blockers, and inhaled oxygen in patients with hypoxemia (arterial O<sub>2</sub> saturation <90%) and/or in those with heart failure and rales.

**Nitrates** Nitroglycerin should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic discomfort. If symptoms persist after three doses given 5 min apart, intravenous nitroglycerin (5–10  $\mu$ g/min, using nonabsorbing tubing) is recommended. The infusion rate may be increased by 10  $\mu$ g/min every 3–5 min until symptoms are relieved, systolic arterial pressure falls to <90 mmHg, or the dose reaches 200  $\mu$ g/min. Topical or oral nitrates (**Chap. 273**) can be used when the pain has resolved, or they may replace intravenous nitroglycerin when the patient has been symptom-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the recent use of a phosphodiesterase type 5 (PDE-5) inhibitor, sildenafil or vardenafil (within 24 h), or tadalafil (within 48 h).

**$\beta$ -Adrenergic Blockers and Other Agents** Beta blockers are the other mainstay of anti-ischemic treatment because they reduce myocardial oxygen needs. They may be started by the intravenous route in patients with severe ischemia but should be avoided in the presence of acute or severe heart failure, low cardiac output, hypotension, or contraindications (e.g., high-degree atrioventricular block, active bronchospasm). Ordinarily, oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended.

Heart rate-slslowing calcium channel blockers, e.g., verapamil or diltiazem, are recommended for patients who have persistent symptoms or ECG signs of ischemia after treatment with full-dose nitrates and beta blockers and in patients with contraindications to either class of these agents. Patients who have continuing severe



**FIGURE 274-3** The HEART pathway for evaluation of acute chest pain. CAD, coronary artery disease; ECG, electrocardiogram; STEMI, ST-segment elevation myocardial infarction. \*The Heart Score assigns 0, 1, or 2 points depending on the extent of abnormality for each of the History, ECG, Age, Risk factors, and Troponin. (Six AJ, Backus BE, and Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J* 16:191, 2008). (Reproduced with permission from JL Januzzi et al: Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC scientific expert panel. *J Am Coll Cardiol* 73:1068, 2019.)

chest pain despite maximal anti-ischemic therapy and are without contraindications to morphine may receive this drug intravenously (1–5 mg every 5–30 min). Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Early administration of intensive HMG-CoA reductase inhibitors (statins), such as atorvastatin 80 mg/d or rosuvastatin 40 mg/d, prior to percutaneous coronary intervention (PCI), and continued thereafter, has been suggested to reduce periprocedural MI and recurrences of ACS. In patients who do not have an adequate response to maximally tolerated statin (i.e., <50% decrease in low-density lipoprotein cholesterol [LDL-C]), addition of ezetimibe 10 mg daily and/or a PCSK9 inhibitor (alirocumab, evolocumab) early after ACS have been shown to further reduce the LDL-C and prevent future cardiovascular events.

#### ANTITHROMBOTIC THERAPY

Antithrombotic therapy consisting of antiplatelet and anticoagulant drugs represents the second major cornerstone of treatment (Table 274-4).

**Antiplatelet Drugs (See Chap. 118)** Initial treatment should begin with the cyclooxygenase inhibitor aspirin with a dose of at least 162 mg of a rapidly acting preparation (oral non-enteric-coated

or intravenous). Lower doses (75–100 mg/d) are recommended thereafter since they maintain efficacy while causing less bleeding. Contraindications are severe active bleeding and aspirin allergy.

In the absence of a high risk for bleeding, patients with NSTE-ACS, irrespective of whether an invasive or conservative strategy (see below) is selected, should also receive a platelet P2Y<sub>12</sub> receptor blocker to inhibit platelet activation. There are now three oral and one intravenous P2Y<sub>12</sub> inhibitors to choose from. The thienopyridine clopidogrel is an inactive prodrug that is converted into an active metabolite that causes irreversible blockade of the platelet P2Y<sub>12</sub> receptor. The loading dose of clopidogrel is 600 mg, whereas the maintenance dose is 75 mg daily. When clopidogrel is added to aspirin, so-called dual antiplatelet therapy (DAPT), in patients with NSTE-ACS, it confers a 20% relative reduction in cardiovascular death, MI, or stroke, compared to aspirin alone but is associated with a moderate (absolute 1%) increase in major bleeding.

Two other P2Y<sub>12</sub> inhibitors have been shown to be superior to clopidogrel in preventing recurrent cardiac ischemic events but both increase bleeding. Prasugrel, also a thienopyridine, achieves a more rapid onset and higher level of irreversible platelet inhibition than clopidogrel. It has been approved for ACS patients following angiography when PCI is planned; it should be administered at a

**TABLE 274-3 Recommendations for Anti-Ischemic Drugs in the Acute Phase of NSTE-ACS**

THERAPY	RECOMMENDATION	WHEN TO AVOID
Nitrates	<ul style="list-style-type: none"> <li>Use sublingual or intravenous nitrates to relieve angina</li> <li>Use intravenous nitrates if recurrent angina, uncontrolled hypertension, or signs of heart failure</li> <li>Consider in patients with vasospastic angina</li> </ul>	<ul style="list-style-type: none"> <li>Recent use of a PDE-5 inhibitor<sup>a</sup></li> <li>Hypotension</li> <li>Right ventricular infarct</li> <li>Severe aortic stenosis</li> </ul>
Beta blockers	<ul style="list-style-type: none"> <li>Initiate early for ischemic symptoms</li> <li>Continue chronic therapy</li> </ul>	<ul style="list-style-type: none"> <li>PR interval &gt;0.24 s</li> <li>2nd or 3rd atrioventricular block</li> <li>Heart rate &lt;50 beats/min</li> <li>Systolic pressure &lt;90 mmHg</li> <li>Shock or Killip class III or IV heart failure</li> <li>Severe reactive airways disease</li> </ul>
Calcium channel blockers	<ul style="list-style-type: none"> <li>Consider in patients with vasospastic angina</li> <li>Consider in patients with contraindications to beta blockers</li> </ul>	<ul style="list-style-type: none"> <li>Systolic pressure &lt;90 mmHg</li> <li>Pulmonary edema</li> <li>Left ventricular dysfunction<sup>b</sup></li> </ul>
Morphine or other narcotic analgesics <sup>c</sup>	<ul style="list-style-type: none"> <li>Continued severe angina despite 3 sublingual nitroglycerin tablets</li> <li>Recurrent ischemia despite adequate anti-ischemic therapy</li> </ul>	<ul style="list-style-type: none"> <li>Hypotension</li> <li>Respiratory depression</li> <li>Confusion or obtundation</li> </ul>

<sup>a</sup>Sildenafil or vardenafil <24 h or tadalafil <48 h.<sup>b</sup>Diltiazem or verapamil.  
<sup>c</sup>Concomitant administration may delay the absorption and blunt the antiplatelet effect of oral P2Y<sub>12</sub> inhibitors.

Abbreviations: NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PDE-5, phosphodiesterase type 5.

Source: Modified from M Roffi et al: Eur Heart J 37:267, 2017.

loading dose of 60 mg followed by 10 mg/d. Compared to clopidogrel, prasugrel significantly reduces the combined risk of cardiovascular death, MI, stroke, and stent thrombosis but increases bleeding. Prasugrel is contraindicated in patients with prior stroke or transient ischemic attack or at high risk for bleeding.

Ticagrelor, a potent, *reversible* platelet P2Y<sub>12</sub> inhibitor, reduces the risk of cardiovascular death, total mortality, or MI compared to clopidogrel across a broad spectrum of patients with ACS. After a loading dose of 180 mg, 90 mg bid is administered as maintenance. Like prasugrel, ticagrelor increases the risk of bleeding. Unlike prasugrel, ticagrelor demonstrated benefit whether patients were managed conservatively or with an early invasive strategy (see below). Some patients may develop dyspnea soon after administration, although the symptoms are often transient and infrequently serious.

Up to one-third of patients have an inadequate response to clopidogrel, and a substantial proportion of these cases are related to a genetic variant of the cytochrome P450 system involving the 2C19 gene that leads to reduced conversion of clopidogrel into its active metabolite. Thus, alternate P2Y<sub>12</sub> blockers (prasugrel or ticagrelor) should be considered in patients with NSTE-ACS who develop a new coronary event while receiving clopidogrel and aspirin.

DAPT should continue for at least 3 months (preferably 12 months) in patients with NSTE-ACS without an indication for long-term full-dose anticoagulation; the duration of DAPT is dependent upon the risk of bleeding versus thrombosis. Clinicians should select the antiplatelet regimen that provides the best balance of efficacy and safety based on the individual patient characteristics and clinical scenario. Longer duration DAPT is favored in patients

**TABLE 274-4 Clinical Use of Antithrombotic Therapy**

Oral Antiplatelet Therapy	
Aspirin	Loading dose of 150–325 mg orally of nonenteric formulation followed by 75–100 mg/d of an enteric or a nonenteric formulation
Clopidogrel	Loading dose of 600 mg (if PCI planned) or 300 mg (if no PCI planned), followed by 75 mg/d
Prasugrel	Pre-PCI: Loading dose of 60 mg followed by 10 mg/d In patient with body weight <60 kg or >75 years old, maintenance dose of 5 mg/d
Ticagrelor	Loading dose of 180 mg followed by 90 mg twice daily
Intravenous Antiplatelet Therapy at the Time of PCI	
Cangrelor	30 µg/kg bolus followed by 4 µg/kg/min infusion for 2 h or duration of procedure
Eptifibatide	180 µg/kg bolus followed in 10 min by second bolus of 180 µg/kg with infusion of 2.0 µg/kg/min for up to 18 h
Tirofiban	25 µg/kg per min over 3 minutes, followed by infusion of 0.15 µg/kg/min for up to 18 h
Parenteral Anticoagulants <sup>a</sup>	
Unfractionated heparin	Bolus 70–100 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg per h titrated to ACT 250–300 s
Enoxaparin	0.5 mg/kg IV bolus at the time of PCI or 1 mg/kg subcutaneous every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine clearance <30 mL/min
Bivalirudin	Initial IV bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg per h
Fondaparinux	2.5 mg subcutaneously daily (only prior to PCI)
Oral Anticoagulant Drugs (concomitant treatment after PCI)	
VKA	Dosing based on INR value and the respective clinical indication
Apixaban	Maintenance dose 5 mg (dose reduced to 2.5 mg) twice daily
Dabigatran	Maintenance dose 150 mg (dose reduced to 75 mg) twice daily in the United States, outside the United States either 110 or 150 mg twice daily may be used.
Edoxaban	Maintenance dose 60 mg (dose reduced to 30 mg) once daily
Rivaroxaban	Maintenance dose 20 mg (dose reduced to 15 mg) once daily In patients without atrial fibrillation or venous thromboembolism 2.5 mg bid may be used

Note: All dose reductions for patients meeting criteria. (See also Chap. 118.)

Abbreviations: ACT, activated clotting time; INR, international normalized ratio; PCI, percutaneous coronary intervention; VKA, vitamin K antagonists (e.g., warfarin).

Source: Modified from FJ Neumann: Eur Heart J 40:137, 2019.

with high atherothrombotic risk (e.g., due to stenting of the left main coronary artery or proximal left anterior descending or proximal bifurcating coronary arteries, recurrent MI, stent thrombosis).

An intravenous, direct, and rapidly acting P2Y<sub>12</sub> inhibitor, can-grelor, has also shown benefit relative to clopidogrel in patients who underwent PCI following a NSTE-ACS and reduced the risk of the primary composite outcome of death, MI, stent thrombosis, and ischemia-driven revascularization but at the expense of increased major bleeding events. This drug is approved as an adjunct to PCI for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with an oral P2Y<sub>12</sub> platelet inhibitor or an intravenous glycoprotein IIb/IIIa inhibitor.

In the 1990s and early 2000s, several trials of glycoprotein IIb/IIIa inhibitors in patients with NSTE-ACS had shown modest benefit counterbalanced by an increase in major bleeding. However, the majority of earlier studies were performed without concomitant P2Y<sub>12</sub> inhibitor treatment, and more recent studies in patients receiving the latter failed to show a benefit of routine early initiation of a glycoprotein IIb/IIIa inhibitor. Because of the increased risk of

bleeding, the addition of a glycoprotein IIb/IIIa inhibitor to aspirin and a P2Y<sub>12</sub> inhibitor (i.e., triple antiplatelet therapy) should be reserved for unstable patients undergoing PCI (e.g., recurrent ischemia on DAPT, or high coronary thrombus burden on angiography) because of the increased risk of bleeding.

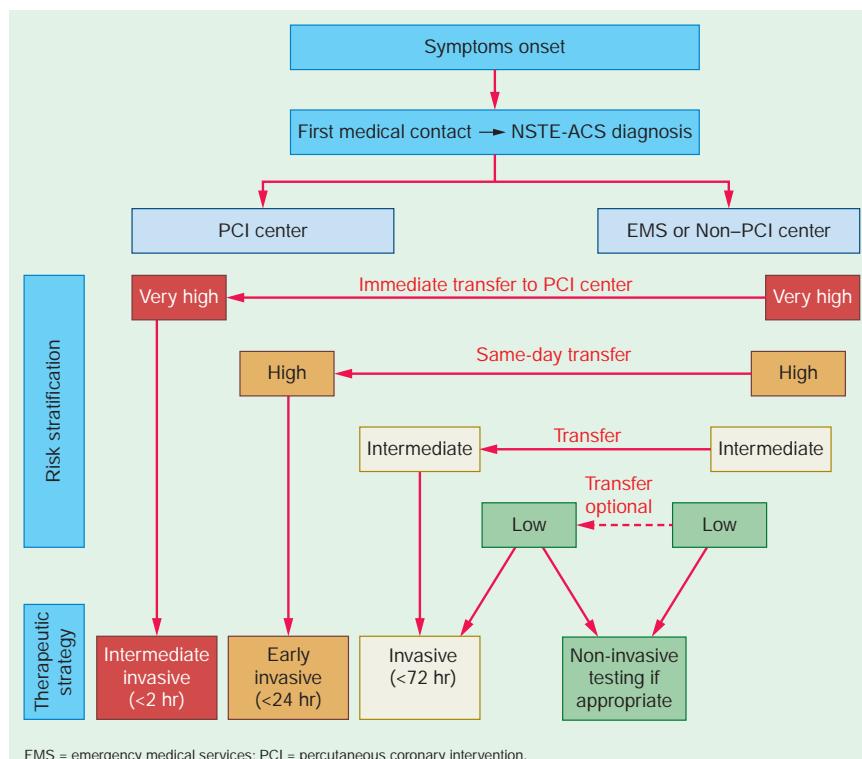
**Anticoagulants (See Chap. 118)** Four parenteral options are available for anticoagulant therapy to be added to antiplatelet agents: (1) unfractionated heparin (UFH), long the mainstay of therapy; (2) the low-molecular-weight heparin (LMWH) enoxaparin, which has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy (however, it is accompanied by a slight increase in bleeding); (3) bivalirudin, a direct thrombin inhibitor that is similar in efficacy to either UFH or LMWH and is used just prior to and/or during PCI; and (4) fondaparinux, a synthetic factor Xa inhibitor that is equivalent in efficacy to enoxaparin but has a lower risk of major bleeding. While UFH and enoxaparin have been widely studied in patients managed either with an early conservative or invasive strategy, bivalirudin is rarely used in conservatively managed patients, while fondaparinux requires supplemental UFH to prevent procedure-related thrombosis. In patients who develop NSTE-ACS while receiving treatment with a direct oral anticoagulant (DOAC), the DOAC should be held when one of the four parenteral anticoagulants is begun.

If an early invasive strategy is indicated (see below), radial arterial access is recommended to reduce the risk of bleeding. Excessive bleeding is the most important adverse effect of all antithrombotic agents, including both antiplatelet agents and anticoagulants. Therefore, attention must be directed to the doses of antithrombotic agents, accounting for age, body weight, creatinine clearance, and a previous history of excessive bleeding. Patients who have experienced a stroke are at higher risk of intracranial bleeding with potent

antiplatelet agents and combinations of antithrombotic drugs. In patients with atrial fibrillation (including patients with NSTE-ACS) treated with an oral anticoagulant who undergo PCI, the duration of DAPT should be shortened (e.g., stop aspirin after hospital discharge or up to 4 weeks post PCI, except in patients at very high risk for ischemic events), and continue P2Y12 inhibitor plus DOAC for 1 year. After 1 year, the majority of patients should be transitioned to oral anticoagulation monotherapy without concomitant antiplatelet treatment.

#### INVASIVE VERSUS CONSERVATIVE STRATEGY (FIG. 274-4)

In an invasive strategy, following initiation of anti-ischemic and antithrombotic agents as described above, coronary arteriography is carried out within ~48 h of presentation, followed by coronary revascularization (PCI or coronary artery bypass grafting), depending on the coronary anatomy (Fig. 274-4). Multiple clinical trials have demonstrated the benefit of this strategy in high-risk patients (i.e., patients with multiple clinical risk factors, ST-segment deviation, and/or positive biomarkers). Two studies comparing an immediate invasive strategy (median time to intervention of 1.4 and 4.7 h after presentation) reduced the rate of death or new MI compared to a delayed invasive strategy (median time of intervention of 61 and 62 h), with a greater benefit among patients with a high-risk score. In patients at low risk, the outcomes from an invasive strategy are similar to those obtained from a conservative strategy. The latter consists of anti-ischemic and antithrombotic therapy followed by a "selective invasive approach," in which the patient is observed closely and coronary arteriography is carried out if coronary computed angiography shows the presence of epicardial coronary stenosis, rest pain or ST-segment changes recur, a biomarker of necrosis becomes positive, or there is evidence of severe ischemia on a stress test.



**FIGURE 274-4 Selection of NSTE-ACS treatment strategy and timing according to initial risk stratification.** EMS, emergency medical services; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention. (Reproduced from ROFFI M et al: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology. Eur Heart J 37:296, 2016.)

The time of hospital discharge is a “teachable moment” for the patient with NSTE-ACS, when the caregiver can review and optimize the medical regimen. Risk factor modification is key, and the importance of smoking cessation, following an appropriate diet, achieving and maintaining optimal weight, daily exercise, blood pressure control, and control of hyperglycemia (in diabetic patients) should be emphasized. There is evidence of benefit with long-term therapy with several classes of drugs. Beta blockers, intensive lipid-lowering therapies to achieve an LDL-C <55 mg/dL, ACE inhibitors or angiotensin receptor blockers, and sodium-glucose co transport-2 or glucagon-like peptide 1 agonists in selected patients with type 2 diabetes mellitus (see Chap. 404), are recommended. The recommended antiplatelet regimen consists of the combination of low-dose (75–100 mg/d) aspirin and a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel, or ticagrelor) for 12 months, unless there is a high risk of bleeding. Antiplatelet monotherapy should be continued thereafter, unless long-term full-dose anticoagulation is indicated, in which case anticoagulant without antiplatelet therapy is recommended after 1 year (see above). A recent trial in patients (the majority after NSTE-ACS) who had received DAPT for 3 months after PCI and were then randomized to aspirin versus placebo on a background of continued ticagrelor for 12 months showed that ticagrelor monotherapy reduced clinically relevant bleeding without an increase in ischemic events compared to continuation of DAPT. In selected patients at high ischemic risk (e.g., those with prior MI, diabetes mellitus, coronary vein graft, heart failure) who are also at low risk of bleeding and not on an anticoagulant, continuation of DAPT to 3 years has been shown to be beneficial. Addition of rivaroxaban 2.5 mg twice daily to DAPT reduced MI, stent thrombosis, and cardiovascular death, while major bleeding was increased; however, the net outcome of fatal or irreversible events was reduced with the addition of the low-dose anti-factor Xa inhibitor.

Registries have shown that women and racial minorities, as well as patients with NSTE-ACS at high risk, including the elderly and patients with diabetes or chronic kidney disease, are less likely to receive evidence-based pharmacologic and interventional therapies with resultant poorer clinical outcomes and quality of life. Special attention should be directed to these groups.

### PRINZMETAL'S VARIANT ANGINA

In 1959, Prinzmetal and colleagues described a syndrome of severe ischemic pain that usually occurs at rest and is associated with ST-segment elevation. Prinzmetal's variant angina (PVA) is caused by focal spasm of an epicardial coronary artery with resultant transmural ischemia and abnormalities in left ventricular function that may lead to acute MI, ventricular tachycardia or fibrillation, and sudden cardiac death. The cause of the spasm is not well defined, but it may be related to hypercontractility of coronary arterial smooth muscle due to adrenergic vasoconstrictors, leukotrienes, or serotonin. For reasons that are not clear, the prevalence of PVA has decreased substantially during the past few decades, although it remains much more frequent in Japan than in North America or Western Europe.

**Clinical and Angiographic Manifestations** Patients with PVA are generally younger and, with the exception of cigarette smoking, have fewer coronary risk factors than do patients with NSTE-ACS. Cardiac examination is usually unremarkable in the absence of ischemia. However, a minority of patients have a generalized vasospastic disorder associated with migraine and/or Raynaud's phenomenon. The clinical diagnosis of PVA is made by the detection of transient ST-segment elevation with rest pain, although many patients may also exhibit episodes of silent ischemia.

Coronary angiography demonstrates transient coronary spasm as the diagnostic hallmark of PVA. Atherosclerotic plaques in at least one proximal coronary artery occur in about half of patients. Hyperventilation and intracoronary acetylcholine have been used to provoke focal coronary stenosis on angiography or to provoke rest angina with ST-segment elevation to establish the diagnosis. In patients with no obstructive coronary atherosclerosis and suspected coronary

vasomotor abnormalities, a positive provocative test for spasm has been shown to be safe, identifies a high-risk subgroup, and is endorsed by guidelines since it permits selection of therapy most appropriate for the underlying pathophysiology.

### TREATMENT

#### Prinzmetal's Variant Angina

Nitrates and calcium channel blockers are the main therapeutic agents. Aspirin may actually increase the severity of ischemic episodes, possibly as a result of the sensitivity of coronary tone to modest changes in the synthesis of prostacyclin. Statin therapy has been shown to reduce the risk of major adverse events, although the precise mechanism is not established. The response to beta blockers is variable. Coronary revascularization may be helpful in patients who also have discrete, flow-limiting, proximal fixed obstructive lesions. Patients who have had ischemia-associated ventricular fibrillation despite maximal medical therapy should receive an implantable cardioverter-defibrillator.

**Prognosis** Many patients with PVA pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after presentation, after which there may be a tendency for symptoms and cardiac events to diminish over time. Survival at 5 years is excellent (~90–95%), but as many as 20% of patients experience an MI. Patients with no or mild fixed coronary obstruction experience a lower incidence of cardiac death or MI compared to patients with associated severe obstructive lesions. Patients with PVA who develop serious arrhythmias during spontaneous episodes of pain are at a higher risk for sudden cardiac death. In most patients who survive an infarction or the initial 3- to 6-month period of frequent episodes, there is a tendency for symptoms and cardiac events to diminish over time.

### GLOBAL CONSIDERATIONS

Ischemic heart disease (IHD), and its most dangerous manifestation, ACS, remains the most frequent cause of death and disability worldwide. In the mid-twentieth century, these conditions were most common in high-income countries. The elucidation of risk factors leading to IHD, their management, and the development of therapies to reduce the deleterious consequences of ACS were responsible for dramatic reductions in these events that result in cardiovascular mortality. However, these advances have not affected all population groups equally. In Europe, there remains a northeast to southwest gradient, with higher prevalence in northern Russia and the Baltic nations and considerably lower prevalence in France, Italy, and Spain. In the United States, there remain racial and economic disparities, with poorer outcomes in minorities and low-income populations.

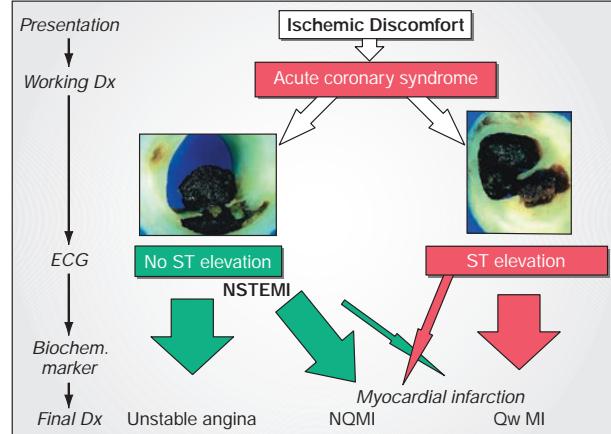
Simultaneous with these important advances in the high-income countries, the low- and middle-income countries have moved in the opposite direction. The improvements in agriculture, nutrition, sanitation, prevention and treatment of infections, and management of maternal/early childhood disorders, urbanization, and a reduction of physical labor have, in combination, led to marked increases in coronary risk factors—hypertension, cigarette smoking, obesity, diabetes mellitus, and elevations of circulating LDL-C. These, in turn, have been responsible for marked increases in ACS events and cardiovascular mortality. These changes have been most prominent in central Asia, India, and Pakistan, as well as in the more developed regions of sub-Saharan Africa.

The current challenge is to apply what was learned in high-income countries to the large populations in the low- and middle-income countries that are now at high risk. This will require large educational efforts directed at both the populations and their caregivers. An additional challenge will be to provide the trained specialized personnel, facilities, drugs, and devices to deal with these threats. The successful implementation of these measures is now principally a socio-politico-economic issue. One mitigating factor is that many of the important drugs to prevent and treat these disorders, such as statins,

ACE inhibitors, diuretics, beta blockers, and calcium antagonists, are off patent and are now inexpensive.

## FURTHER READING

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**FIGURE 275-1 Acute coronary syndromes.** Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (*right*) or subtotally occlusive thrombus (*left*). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority (*wide red arrow*) ultimately develop a Q wave on the ECG (Qw MI), while a minority (*thin red arrow*) do not develop Q wave and, in older literature, were said to have sustained a non-Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina or a non-ST-segment elevation MI (NSTEMI) (*wide green arrows*), a distinction that is ultimately made based on the presence or absence of a serum cardiac biomarker such as CK-MB or a cardiac troponin detected in the blood. The majority of patients presenting with NSTEMI do not develop a Q wave on the ECG; a minority develop a Qw MI (*thin green arrow*). Dx, diagnosis; ECG, electrocardiogram; MI, myocardial infarction. (Adapted from CW Hamm et al: *Lancet* 358:1533, 2001, and MJ Davies: *Heart* 83:361, 2000; from the BMJ Publishing Group.)

## 275

### ST-Segment Elevation Myocardial Infarction

Elliott M. Antman, Joseph Loscalzo

Acute myocardial infarction (AMI) is a common diagnosis in hospitalized patients in industrialized countries. In the United States, ~605,000 patients experience a new AMI, and 200,000 experience a recurrent AMI each year. About half of AMI-related deaths occur before the stricken individual reaches the hospital. Of note, the in-hospital mortality rate after admission for AMI has declined from 10 to ~5%. The 1-year mortality rate after AMI is ~15%. Mortality is approximately fourfold higher in elderly patients (aged >75) as compared with younger patients.

When patients with prolonged ischemic discomfort at rest are first seen, the working clinical diagnosis is that they are suffering from an acute coronary syndrome (Fig. 275-1). The 12-lead electrocardiogram (ECG) is a pivotal diagnostic and triage tool because it is at the center of the decision pathway for management, permitting distinction of those patients presenting with ST-segment elevation from those presenting without ST-segment elevation. Serum cardiac biomarkers are obtained to distinguish unstable angina (UA) from non-ST-segment elevation myocardial infarction (NSTEMI) and to assess the magnitude of an ST-segment elevation myocardial infarction (STEMI). Epidemiologic studies indicate there has been a shift in the pattern of AMI over the past several decades with more patients with NSTEMI than STEMI. This chapter focuses on the evaluation and management of patients with STEMI, while Chap. 274 discusses UA/NSTEMI.

## PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE

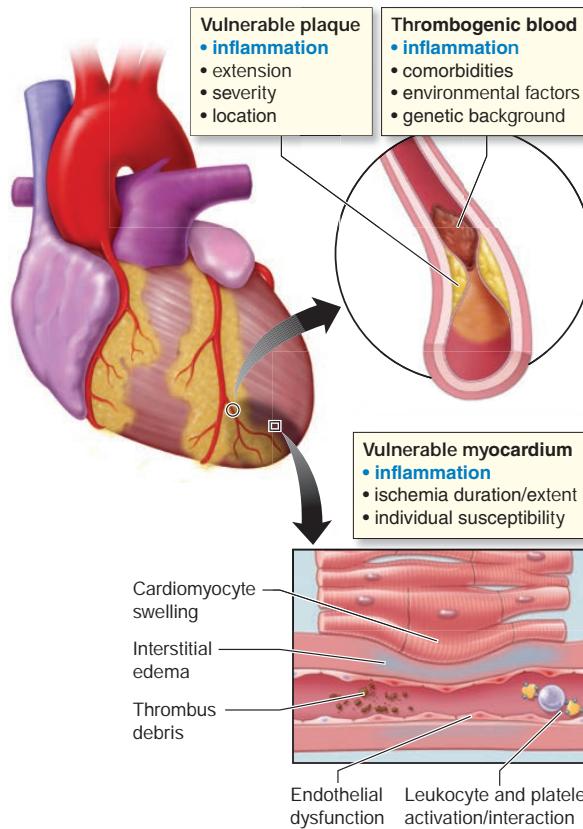
STEMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery

stenoses do not typically precipitate STEMI because of the development of a rich collateral network over time. Instead, STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or facilitated by factors such as cigarette smoking, hypertension, and lipid accumulation. In most cases, STEMI occurs when the surface of an atherosclerotic plaque becomes disrupted (exposing its contents to the blood) and conditions (local or systemic) favor thrombogenesis. A mural thrombus forms at the site of plaque disruption, and the involved coronary artery becomes occluded. Histologic studies indicate that the coronary plaques prone to disruption are those with a rich lipid core and a thin fibrous cap. After an initial platelet monolayer forms at the site of the disrupted plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A<sub>2</sub> (a potent local vasoconstrictor) is released, further platelet activation occurs, and potential resistance to fibrinolysis develops.

In addition to the generation of thromboxane A<sub>2</sub>, activation of platelets by agonists promotes a conformational change in the glycoprotein IIb/IIIa receptor (Chap. 115). Once converted to its functional state, this receptor develops a high affinity for soluble adhesive proteins (i.e., integrins) such as fibrinogen. Since fibrinogen is a multivalent molecule, it can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation.

The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin (Chap. 116). Fluid-phase and clot-bound thrombin participate in an autoamplification reaction leading to further activation of the coagulation cascade. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands (Fig. 275-2).

In rare cases, STEMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic—particularly inflammatory—diseases.



**FIGURE 275-2 Critical determinants of myocardial infarction injury.** The overlapping of vulnerable plaque and thrombogenic blood are critical determinants for myocardial infarction occurrence and extension. In addition, myocardial vulnerability, which is largely due to coronary microvascular dysfunction, contributes to extension and severity of ischemic injury. In the most severe form (known as no-reflow), structural and functional impairments sustain vascular obstruction. Endothelial dysfunction triggers leukocyte and platelet activation/interaction, whereas thrombotic debris may worsen the obstruction. Furthermore, cardiomyocyte swelling, interstitial edema, and tissue inflammation promote extravascular compression. (Modified from F Montecucco, F Carbone, TH Schindler. Pathophysiology of ST-segment elevation myocardial infarction: Novel mechanisms and treatments. *Eur Heart J* 37:1268, 2016.)

The amount of myocardial damage caused by coronary occlusion depends on (1) the territory supplied by the affected vessel, (2) whether or not the vessel becomes totally occluded, (3) the duration of coronary occlusion, (4) the quantity of blood supplied by collateral vessels to the affected tissue, (5) the demand for oxygen of the myocardium whose blood supply has been suddenly limited, (6) endogenous factors that can produce early spontaneous lysis of the occlusive thrombus, and (7) the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

Patients at increased risk for developing STEMI include those with multiple coronary risk factors and those with UA (Chap. 274). Less common underlying medical conditions predisposing patients to STEMI include hypercoagulability, collagen vascular disease, cocaine abuse, and intracardiac thrombi or masses that produce coronary emboli.

There have been major advances in the management of STEMI with recognition that the “chain of survival” involves a highly integrated system starting with prehospital care and extending to early hospital management so as to provide expeditious implementation of a reperfusion strategy.

## CLINICAL PRESENTATION

In up to one-half of cases, a precipitating factor appears to be present before STEMI, such as vigorous physical exercise, emotional stress, or a medical or surgical illness. Although STEMI may commence at any

time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening.

Pain is the most common presenting complaint in patients with STEMI. The pain is deep and visceral; adjectives commonly used to describe it are *heavy*, *squeezing*, and *crushing*; although, occasionally, it is described as stabbing or burning (Chap. 14). It is similar in character to the discomfort of angina pectoris (Chap. 273) but commonly occurs at rest, is usually more severe, and lasts longer. Typically, the pain involves the central portion of the chest and/or the epigastrium, and, on occasion, it radiates to the arms. Less common sites of radiation include the abdomen, back, lower jaw, and neck. The frequent location of the pain beneath the xiphoid and epigastrium and the patients’ denial that they may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion. The pain of STEMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom. The pain may commence when the patient is at rest, but when it begins during a period of exertion, it does not usually subside with cessation of activity, in contrast to angina pectoris.

The pain of STEMI can simulate pain from acute pericarditis (Chap. 270), pulmonary embolism (Chap. 279), acute aortic dissection (Chap. 280), costochondritis, and gastrointestinal disorders. These conditions should therefore be considered in the differential diagnosis. Radiation of discomfort to the trapezius is not seen in patients with STEMI and may be a useful distinguishing feature that suggests pericarditis is the correct diagnosis. However, *pain is not uniformly present in patients with STEMI*. The proportion of painless STEMIs is greater in patients with diabetes mellitus, and it increases with age. In the elderly, STEMI may present as sudden-onset breathlessness, which may progress to pulmonary edema. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of peripheral embolism, or merely an unexplained drop in arterial pressure.

## PHYSICAL FINDINGS

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggests STEMI. Although many patients have a normal pulse rate and blood pressure within the first hour of STEMI, patients with anterior infarction may have manifestations of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and those with inferior infarction may show evidence of parasympathetic hyperactivity (bradycardia and/or hypotension).

The precordium is usually quiet, and the apical impulse may be difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop in the periapical area within the first days of the illness and then may resolve. Other physical signs of ventricular dysfunction include fourth and third heart sounds, decreased intensity of the first heart sound, and paradoxical splitting of the second heart sound (Chap. 239). A transient midsystolic or late systolic apical systolic murmur due to dysfunction of the mitral valve apparatus may be present. A pericardial friction rub may be heard in patients with transmural STEMI at some time in the course of the illness, if they are examined frequently. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. Temperature elevations up to 38°C may be observed during the first week after STEMI. The arterial pressure is variable; in most patients with transmural infarction, systolic pressure declines by ~10–15 mmHg from the preinfarction state.

## LABORATORY FINDINGS

STEMI progresses through the following temporal stages: (1) acute (first few hours–7 days), (2) healing (7–28 days), and (3) healed (~29 days). The myocardium undergoes a series of cellular responses in the infarct

zone, beginning with recruitment of polymorphonuclear leukocytes (for removal of dead cells and clearance of extracellular macromolecules) followed by proinflammatory monocytes (that recruit fibroblasts) and ultimately reparative monocytes (that promote angiogenesis and interstitial collagen production).

When evaluating the results of diagnostic tests for STEMI, the temporal phase of the infarction must be considered. The laboratory tests of value in confirming the diagnosis may be divided into four groups: (1) ECG, (2) serum cardiac biomarkers, (3) cardiac imaging, and (4) nonspecific indices of tissue necrosis and inflammation.

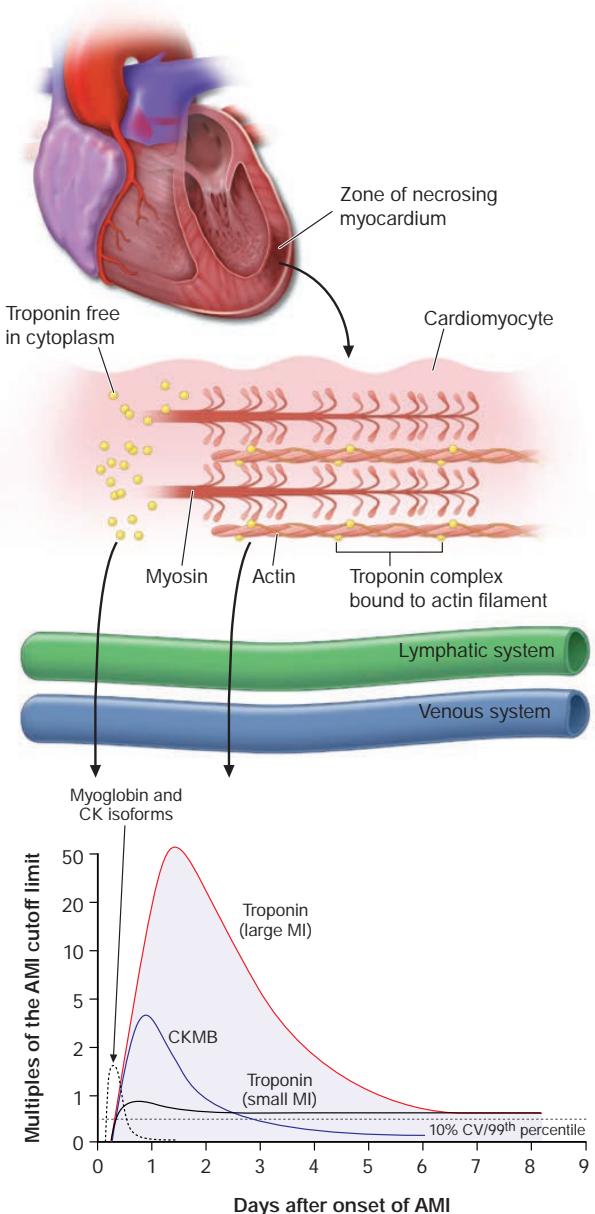
### ELECTROCARDIOGRAM

The electrocardiographic manifestations of STEMI are described in **Chap. 240**. During the initial stage, total occlusion of an epicardial coronary artery produces ST-segment elevation. Most patients initially presenting with ST-segment elevation ultimately evolve Q waves on the ECG. However, Q waves in the leads overlying the infarct zone may vary in magnitude and appear only transiently, depending on the reperfusion status of the ischemic myocardium and restoration of transmembrane potentials over time. A small proportion of patients initially presenting with ST-segment elevation will not develop Q waves when the obstructing thrombus is not totally occlusive, obstruction is transient, or a rich collateral network is present. Among patients presenting with ischemic discomfort but *without* ST-segment elevation, if a serum cardiac biomarker of necrosis (see below) is detected, the diagnosis of NSTEMI is ultimately made (Fig. 275-1). A minority of patients who present initially without ST-segment elevation may develop a Q-wave myocardial infarction (MI). Previously, it was believed that transmural MI is present if the ECG demonstrates Q waves or loss of R waves, and nontransmural MI may be present if the ECG shows only transient ST-segment and T-wave changes. However, electrocardiographic-pathologic correlations are far from perfect, and terms such as *Q-wave MI*, *non-Q-wave MI*, *transmural MI*, and *nontransmural MI* have been replaced by STEMI and NSTEMI (Fig. 275-1). Contemporary studies using magnetic resonance imaging (MRI) suggest that the development of a Q wave on the ECG is more dependent on the volume of infarcted tissue rather than the transmurality of infarction.

### SERUM CARDIAC BIOMARKERS

Certain proteins, referred to as serum cardiac biomarkers, are released from necrotic heart muscle after STEMI. The rate of liberation of specific proteins differs depending on their intracellular location, their molecular weight, and the local blood and lymphatic flow. Cardiac biomarkers become detectable in the peripheral blood once the capacity of the cardiac lymphatics to clear the interstitium of the infarct zone is exceeded and spillover into the venous circulation occurs. The temporal pattern of protein release is of diagnostic importance. The criteria for AMI require a rise and/or fall in cardiac biomarker values with at least one value above the 99th percentile of the upper reference limit for normal individuals.

*Cardiac-specific troponin T* (cTnT) and *cardiac-specific troponin I* (cTnI) have amino-acid sequences that differ from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI using highly specific monoclonal antibodies. cTnT and cTnI may increase after STEMI to levels many times higher than the upper reference limit (the highest value seen in 99% of a reference population not suffering from MI), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI (Fig. 275-3). With improvements in the assays for the cardiac-specific troponins, it is now possible to detect concentrations <1 ng/L in patients without ischemic-type chest discomfort. The cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury or a small MI that may be below the detection limit for creatine phosphokinase (CK) and its MB isoenzyme (CK-MB), and they are, therefore, of particular value in distinguishing UA from NSTEMI. In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI. Contemporary urgent reperfusion strategies necessitate making a decision (based



**FIGURE 275-3** The zone of necrosing myocardium is shown at the top of the figure, followed in the middle portion of the figure by a diagram of a cardiomyocyte that is in the process of releasing biomarkers. The biomarkers that are released into the interstitium are first cleared by lymphatics followed subsequently by spillover into the venous system. After disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first (left-most arrow in bottom portion of figure). Markers such as myoglobin and CK isoforms are rapidly released, and blood levels rise quickly above the cutoff limit; this is then followed by a more protracted release of biomarkers from the disintegrating myofilaments that may continue for several days. Cardiac troponin levels rise to about 20–50 times the upper reference limit (the 99th percentile of values in a reference control group) in patients who have a “classic” acute myocardial infarction (MI) and sustain sufficient myocardial necrosis to result in abnormally elevated levels of the MB fraction of creatine kinase (CK-MB). Clinicians can now diagnose episodes of microinfarction by sensitive assays that detect cardiac troponin elevations above the upper reference limit, even though CK-MB levels may still be in the normal reference range (not shown). CV, coefficient of variation. (Modified from EM Antman: Decision making with cardiac troponin tests. *N Engl J Med* 346:2079, 2002, and: bottom image: Reproduced with permission from AS Jaffe: Biomarkers in acute cardiac disease: The present and the future. *J Am Coll Cardiol* 48:1, 2006.)

largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. Levels of cTnI and cTnT may remain elevated for 7–10 days after STEMI.

CK rises within 4–8 h and generally returns to normal by 48–72 h (Fig. 275-3). An important drawback of total CK measurement is its lack of specificity for STEMI, as CK may be elevated with skeletal muscle disease or trauma, including intramuscular injection. The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and, therefore, is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. A ratio (relative index) of CK-MB mass to CK activity 2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CK-MB elevation.

Many hospitals are using cTnT or cTnI rather than CK-MB as the routine serum cardiac marker for diagnosis of STEMI, although any of these analytes remains clinically acceptable. It is *not* cost-effective to measure both a cardiac-specific troponin and CK-MB at all time points in every patient.

While it has long been recognized that the total quantity of protein released correlates with the size of the infarct, the peak protein concentration correlates only weakly with infarct size. Recanalization of a coronary artery occlusion (either spontaneously or by mechanical or pharmacologic means) in the early hours of STEMI causes earlier peaking of biomarker measurements (Fig. 275-3) because of a rapid washout from the interstitium of the infarct zone, quickly overwhelming lymphatic clearance of the proteins.

The *nonspecific reaction* to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days; the white blood cell count often reaches levels of 12,000–15,000/ $\mu\text{L}$ . The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

## CARDIAC IMAGING

Abnormalities of wall motion on *two-dimensional echocardiography* (Chap. 241) are almost universally present. Although acute STEMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool in the emergency department setting. When the ECG is not diagnostic of STEMI, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether the patient should receive reperfusion therapy (e.g., fibrinolysis or a percutaneous coronary intervention [PCI]). Echocardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for therapy with an inhibitor of the renin-angiotensin-aldosterone system. Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of STEMI.

Several *radionuclide imaging techniques* (Chap. 241) are available for evaluating patients with suspected STEMI. However, these imaging modalities are used less often than echocardiography because they are more cumbersome and lack sensitivity and specificity in many clinical circumstances. Myocardial perfusion imaging with [ $^{201}\text{Tl}$ ] or [ $^{99m}\text{Tc}$ ]-sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium (Chap. 273), reveals a defect ("cold spot") in most patients during the first few hours after development of a transmural infarct. Although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and, thus, is not specific for the diagnosis of *acute MI*. Radionuclide ventriculography, carried out with [ $^{99m}\text{Tc}$ ]-labeled red blood cells, frequently demonstrates wall motion disorders and reduction in the ventricular ejection fraction in patients with STEMI. While of value in assessing the hemodynamic consequences of infarction and in aiding

in the diagnosis of RV infarction when the RV ejection fraction is depressed, this technique is nonspecific, as many cardiac abnormalities other than MI alter the radionuclide ventriculogram.

MI can be detected accurately with high-resolution cardiac MRI (Chap. 241) using a technique referred to as late enhancement. A standard imaging agent (gadolinium) is administered and images are obtained after a 10-min delay. Since little gadolinium enters normal myocardium, where there are tightly packed myocytes, but does permeate into the intercellular region of the infarct zone, there is a bright signal in areas of infarction that appears in stark contrast to the dark areas of normal myocardium.

An Expert Consensus Task Force for the Universal Definition of Myocardial Infarction has provided a comprehensive set of criteria for the definition of MI that integrates the clinical and laboratory findings discussed earlier (Table 275-1) as well as a classification of MI into five types that reflect the clinical circumstances in which it may occur (Fig. 275-4).

## INITIAL MANAGEMENT

### PREHOSPITAL CARE

The prognosis in STEMI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical complications ("pump failure"). Most out-of-hospital deaths from STEMI result from the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 h of the onset of symptoms, and of these, over half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected STEMI include (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable of performing resuscitative maneuvers, including defibrillation; (3) expeditious transportation of the patient to a hospital facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias and providing advanced cardiac life support; and (4) expeditious implementation of reperfusion therapy. The greatest delay usually occurs not during transportation to the hospital but, rather, between the onset of pain and the patient's decision to call for help. This delay can best be reduced by health care professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention. Regular office visits with patients having a history of, or who are at risk for, ischemic heart disease are important "teachable moments" for clinicians to review the symptoms of STEMI and the appropriate action plan.

Increasingly, monitoring and treatment are carried out by trained personnel in the ambulance, further shortening the time between the onset of the infarction and appropriate treatment. General guidelines for initiation of fibrinolysis in the prehospital setting include the ability to transmit 12-lead ECGs to confirm the diagnosis, the presence of paramedics in the ambulance, training of paramedics in the interpretation of ECGs and management of STEMI, and online medical command and control that can authorize the initiation of treatment in the field.

### MANAGEMENT IN THE EMERGENCY DEPARTMENT

In the emergency department, the goals for the management of patients with suspected STEMI include control of cardiac discomfort, rapid identification of patients who are candidates for urgent reperfusion therapy, triage of lower-risk patients to the appropriate location in the hospital, and avoidance of inappropriate discharge of patients with STEMI. Many aspects of the treatment of STEMI are initiated in the emergency department and then continued during the in-hospital phase of management (Fig. 275-5). The overarching goal is to minimize the time from first medical contact to initiation of reperfusion therapy. This may involve transfer from a non-PCI hospital to one that is PCI capable, with a goal of initiating PCI within 120 min of first medical contact (Fig. 275-5).

*Aspirin* is essential in the management of patients with suspected STEMI and is effective across the entire spectrum of acute coronary

**TABLE 275-1 Definitions of Myocardial Injury and Infarction****Criteria for Myocardial Injury**

The term *myocardial injury* should be used when there is evidence of elevated cardiac troponin (cTn) levels with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

**Criteria for Acute Myocardial Infarction (types 1, 2, and 3 MI)**

The term *acute myocardial infarction* (MI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischemia
- New ischemic electrocardiographic (ECG) changes
- Development of pathologic Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs)

Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values became available or abnormal meets criteria for *type 3 MI*.

**Criteria for Coronary Procedure–Related MI (types 4 and 5 MI)**

Percutaneous coronary intervention (PCI)–related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG)–related MI is termed *type 5 MI*.

Coronary procedure–related MI <48 h after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn levels are stable (<20% variation) or falling, must meet the criteria for a >5- or >10-fold increase and manifest a change from the baseline value of >20%. In addition, they must have at least one of the following:

- New ischemic ECG changes (this criterion is related to *type 4a MI* only)
- Development of new pathologic Q waves
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion–thrombus, disruption of collateral flow, or distal embolization

Isolated development of new pathologic Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn levels are elevated and rising, but less than the prespecified thresholds for PCI and CABG.

Other types of type 4 MI include *type 4B MI*/stent thrombosis and *type 4C MI* restenosis that both meet *type 1 MI* criteria.

Postmortem demonstration of a procedure-related thrombus meets the *type 4a MI* and *type 5 MI* criteria if associated with a stent.

**Criteria for Prior or Silent/Unrecognized MI**

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of nonischemic causes
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology
- Pathoanatomical findings of a prior MI

*Source:* Reproduced with permission from K Thygesen et al: Fourth universal definition of myocardial infarction (2018). Circulation 138:e618, 2018.

syndromes (Fig. 275-5). Rapid inhibition of cyclooxygenase-1 in platelets followed by a reduction of thromboxane A<sub>2</sub> levels is achieved by buccal absorption of a chewed 160–325-mg tablet in the emergency department. This measure should be followed by daily oral administration of aspirin in a dose of 75–162 mg.

In patients whose arterial oxygen (O<sub>2</sub>) saturation is normal, supplemental O<sub>2</sub> is of limited if any clinical benefit and therefore is not

cost-effective. However, when hypoxemia is present, O<sub>2</sub> should be administered by nasal prongs or face mask (2–4 L/min) for the first 6–12 h after infarction; the patient should then be reassessed to determine if there is a continued need for such treatment.

**CONTROL OF DISCOMFORT**

Sublingual *nitroglycerin* can be given safely to most patients with STEMI. Up to three doses of 0.4 mg should be administered at about 5-min intervals. In addition to diminishing or abolishing chest discomfort, nitroglycerin may be capable of both decreasing myocardial oxygen demand (by lowering preload) and increasing myocardial oxygen supply (by dilating infarct-related coronary vessels or collateral vessels). In patients whose initially favorable response to sublingual nitroglycerin is followed by the return of chest discomfort, particularly if accompanied by other evidence of ongoing ischemia such as further ST-segment or T-wave shifts, the use of intravenous nitroglycerin should be considered. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<90 mmHg) or in whom there is clinical suspicion of RV infarction (inferior infarction on ECG, elevated jugular venous pressure, clear lungs, and hypotension). Nitrates should not be administered to patients who have taken a phosphodiesterase-5 inhibitor for erectile dysfunction within the preceding 24 h, because it may potentiate the hypotensive effects of nitrates. An idiosyncratic reaction to nitrates, consisting of sudden marked hypotension, sometimes occurs but can usually be reversed promptly by the rapid administration of intravenous atropine.

*Morphine* is a very effective analgesic for the pain associated with STEMI. However, it may reduce sympathetically mediated arteriolar and venous constriction, and the resulting venous pooling may reduce cardiac output and arterial pressure. These hemodynamic disturbances usually respond promptly to elevation of the legs, but in some patients, volume expansion with intravenous saline is required. The patient may experience diaphoresis and nausea, but these events usually pass and are replaced by a feeling of well-being associated with the relief of pain. Morphine also has a vagotonic effect and may cause bradycardia or advanced degrees of heart block, particularly in patients with inferior infarction. These side effects usually respond to atropine (0.5 mg intravenously). Morphine is routinely administered by repetitive (every 5 min) intravenous injection of small doses (2–4 mg), rather than by the subcutaneous administration of a larger quantity, because absorption may be unpredictable by the latter route.

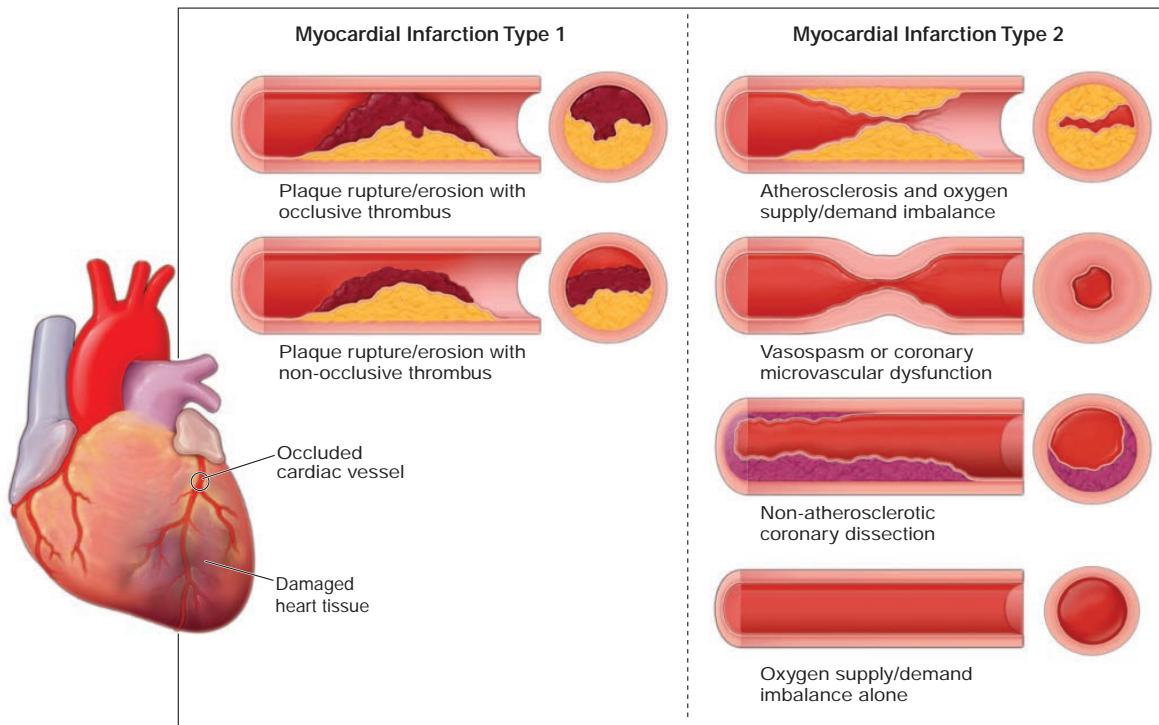
Intravenous *beta blockers* are also useful in the control of the pain of STEMI. These drugs control pain effectively in some patients, presumably by diminishing myocardial O<sub>2</sub> demand and hence ischemia. More important, there is evidence that intravenous beta blockers reduce the risks of reinfarction and ventricular fibrillation (see “Beta-Adrenoceptor Blockers” below). A commonly employed regimen is metoprolol, 5 mg every 2–5 min for a total of three doses, provided the patient has a heart rate >60 beats/min, systolic pressure >100 mmHg, a PR interval <0.24 s, and rales that are no higher than 10 cm up from the diaphragm. Fifteen minutes after the last intravenous dose, an oral regimen is initiated of 50 mg every 6 h for 48 h, followed by 100 mg every 12 h.

Patient selection is important when considering beta blockers for STEMI. Oral beta blocker therapy should be initiated in the first 24 h for patients who do not have any of the following: (1) signs of heart failure, (2) evidence of a low-output state, (3) increased risk for cardiogenic shock, or (4) other relative contraindications to beta blockade (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease).

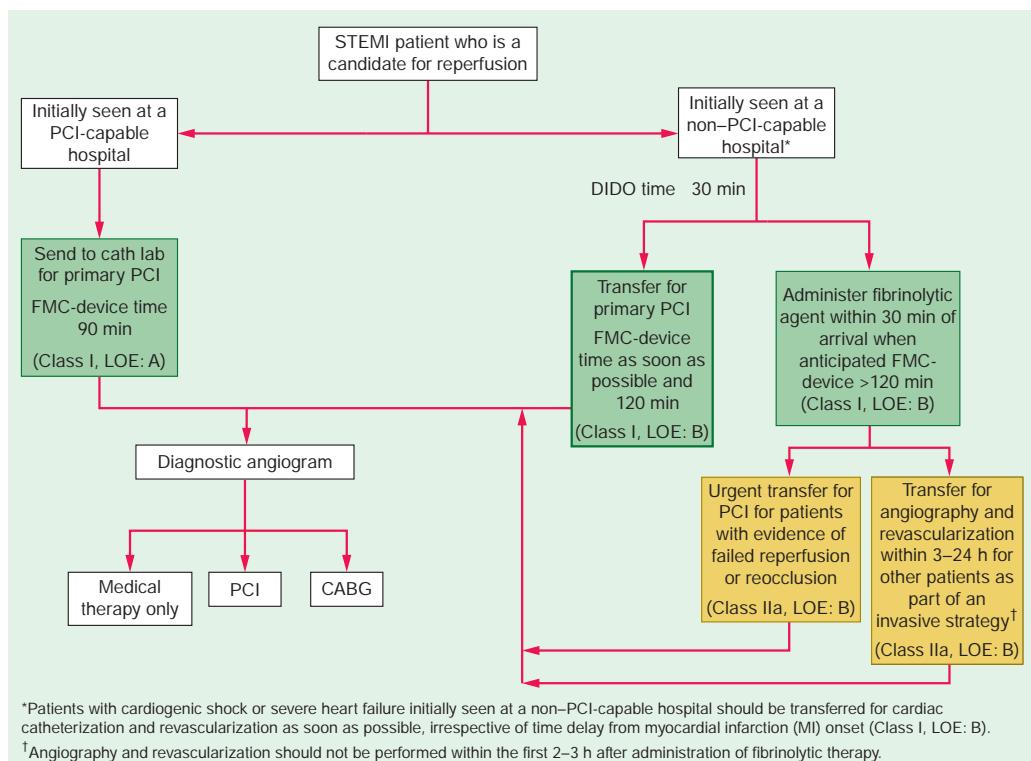
Unlike beta blockers, calcium antagonists are of little value in the acute setting, and there is evidence that short-acting dihydropyridines may be associated with an increased mortality risk.

**MANAGEMENT STRATEGIES**

The primary tool for screening patients and making triage decisions is the initial 12-lead ECG. When ST-segment elevation of at least 2 mm in two contiguous precordial leads and 1 mm in two adjacent limb leads is present, a patient should be considered a candidate for *reperfusion therapy* (Figs. 275-1 and 275-5). The process of selecting patients for



**FIGURE 275-4** Distinction between type 1 and type 2 myocardial infarction (MI). **A.** Type 1 MIs are caused by atherosclerotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion). The relative burden of atherosclerosis and thrombosis in the culprit lesion varies greatly. **B.** The pathophysiological mechanism leading to ischemic myocardial injury in the context of a mismatch between oxygen supply and demand has been classified as type 2 MI, while the infarct-related coronary artery is typically occluded in Type 1 MI's, subtotal occlusion may be present in Type II MI's. (Adapted from K Thygesen: *Circulation* 138:e618, 2018.)



**FIGURE 275-5** Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI). The bold arrows and boxes are the preferred strategies. Performance of percutaneous coronary intervention (PCI) is dictated by an anatomically appropriate culprit stenosis. CABG, coronary artery bypass graft; DDO, door-in-door-out; FMC, first medical contact; LOE, level of evidence. Colors correspond to the class of recommendation in the guideline. While the infarct-related coronary artery is typically occluded in Type 1 MI's, subtotal occlusion may be present in Type II MI's. (Reproduced with permission from PT O'Gara: 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction. *Circulation* 127:e362, 2013.)

fibrinolysis versus primary PCI (angioplasty or stenting; **Chap. 276**) is discussed below. In the absence of ST-segment elevation, fibrinolysis is not helpful, and evidence exists suggesting that it may be harmful.

## LIMITATION OF INFARCT SIZE

The quantity of myocardium that becomes necrotic as a consequence of a coronary artery occlusion is determined by factors other than just the site of occlusion. While the central zone of the infarct contains necrotic tissue that is irretrievably lost, the fate of the surrounding ischemic myocardium (ischemic penumbra) may be improved by timely restoration of coronary perfusion, reduction of myocardial O<sub>2</sub> demands, prevention of the accumulation of noxious metabolites, and blunting of the impact of mediators of reperfusion injury (e.g., calcium overload and oxygen-derived free radicals). Up to one-third of patients with STEMI may achieve *spontaneous* reperfusion of the infarct-related coronary artery within 24 h and experience improved healing of infarcted tissue. Reperfusion, either pharmacologically (by fibrinolysis) or by PCI, accelerates the opening of infarct-related arteries in those patients in whom spontaneous fibrinolysis ultimately would have occurred and also greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished. Timely restoration of flow in the epicardial infarct-related artery combined with improved perfusion of the downstream zone of infarcted myocardium results in a limitation of infarct size. Protection of the ischemic myocardium by the maintenance of an optimal balance between myocardial O<sub>2</sub> supply and demand through pain control, treatment of congestive heart failure (CHF), and minimization of tachycardia and hypertension extends the “window” of time for the salvage of myocardium by reperfusion strategies.

Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in patients with STEMI. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition, they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

## PRIMARY PERCUTANEOUS CORONARY INTERVENTION

(See also **Chap. 276**) PCI, usually angioplasty and/or stenting without preceding fibrinolysis, referred to as *primary PCI*, is effective in restoring perfusion in STEMI when carried out on an emergency basis in the first few hours of MI. It has the advantage of being applicable to patients who have contraindications to fibrinolytic therapy (see below) but otherwise are considered appropriate candidates for reperfusion. It appears to be more effective than fibrinolysis in opening occluded coronary arteries and, when performed by experienced operators in dedicated medical centers, is associated with better short-term and long-term clinical outcomes. Compared with fibrinolysis, primary PCI is generally preferred when the diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for at least 2–3 h when the clot is more mature and less easily lysed by fibrinolytic drugs. However, PCI is expensive in terms of personnel and facilities, and its applicability is limited by its availability, around the clock, in only a minority of hospitals (Fig. 275-5). Whereas prior trials suggested that the only vessel upon which an intervention should be performed is the infarct-related artery, more contemporary studies (PRAMI, CvLPRIT, COMPLETE) provide evidence that performing PCI on nonculprit coronary vessels results in a lower rate of cardiovascular events and a lower need for subsequent ischemia-driven revascularization.

## FIBRINOLYSIS

If no contraindications are present (see below), fibrinolytic therapy should ideally be initiated within 30 min of presentation (i.e., door-to-needle time < 30 min). The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. The fibrinolytic agents tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK), and reteplase (rPA) have been approved by the U.S. Food and Drug Administration for intravenous use in patients with STEMI. These drugs all

act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non-fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative, as some degree of systemic fibrinolysis occurs with the former agents. TNK and rPA are referred to as *bolus fibrinolysis* since their administration does not require a prolonged intravenous infusion.

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the *Thrombolysis in Myocardial Infarction (TIMI) grading system*: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction, but without perfusion of the distal coronary bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed, but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow. The latter is the goal of reperfusion therapy, because full perfusion of the infarct-related coronary artery yields far better results in terms of limiting infarct size, maintenance of LV function, and reduction of both short- and long-term mortality rates. Additional methods of angiographic assessment of the efficacy of fibrinolysis include counting the number of frames on the cine film required for dye to flow from the origin of the infarct-related artery to a landmark in the distal vascular bed (*TIMI frame count*) and determining the rate of entry and exit of contrast dye from the microvasculature in the myocardial infarct zone (*TIMI myocardial perfusion grade*). These methods have an even tighter correlation with outcomes after STEMI than the more commonly employed TIMI flow grade.

tPA and the other relatively fibrin-specific plasminogen activators, rPA and TNK, are more effective than streptokinase at restoring full perfusion—i.e., TIMI grade 3 coronary flow—and have a small edge in improving survival as well. The current recommended regimen of tPA consists of a 15-mg bolus followed by 50 mg intravenously over the first 30 min, followed by 35 mg over the next 60 min. Streptokinase is administered as 1.5 million units (MU) intravenously over 1 h. rPA is administered in a double-bolus regimen consisting of a 10-MU bolus given over 2–3 min, followed by a second 10-MU bolus 30 min later. TNK is given as a single weight-based intravenous bolus of 0.53 mg/kg over 10 s. In addition to the fibrinolytic agents discussed earlier, pharmacologic reperfusion typically involves adjunctive antiplatelet and antithrombotic drugs, as discussed subsequently.

Clear contraindications to the use of fibrinolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure >180 mmHg and/or a diastolic pressure >110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). While advanced age is associated with an increase in hemorrhagic complications, the benefit of fibrinolytic therapy in the elderly appears to justify its use if no other contraindications are present and the amount of myocardium in jeopardy appears to be substantial.

*Relative contraindications* to fibrinolytic therapy, which require assessment of the risk-to-benefit ratio, include current use of anticoagulants (international normalized ratio > 2), a recent (<2 weeks) invasive or surgical procedure or prolonged (>10 min) cardiopulmonary resuscitation, known bleeding diathesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

*Allergic reactions* to streptokinase occur in ~2% of patients who receive it. While a minor degree of hypotension occurs in 4–10% of patients given this agent, marked hypotension occurs, although rarely, in association with severe allergic reactions.

*Hemorrhage* is the most frequent and potentially the most serious complication. Because bleeding episodes that require transfusion are

more common when patients require invasive procedures, unnecessary venous or arterial interventions should be avoided in patients receiving fibrinolytic agents. Hemorrhagic stroke is the most serious complication and occurs in ~0.5–0.9% of patients being treated with these agents. This rate increases with advancing age, with patients >70 years experiencing roughly twice the rate of intracranial hemorrhage as those <65 years. Large-scale trials have suggested that the rate of intracranial hemorrhage with tPA or rPA is slightly higher than with streptokinase.

### INTEGRATED REPERFUSION STRATEGY

Evidence has emerged that suggests timely performance of PCI is the preferred reperfusion strategy in the management of STEMI. Prior approaches that segregated the pharmacologic and catheter-based approaches to reperfusion have now been replaced with an integrated approach to triage and transfer STEMI patients to receive PCI (Fig. 275-5). To achieve the degree of integration required to care for a patient with STEMI, all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of emergency medical services and hospital-based activities.

Cardiac catheterization and coronary angiography should be carried out after fibrinolytic therapy if there is evidence of either (1) failure of reperfusion (persistent chest pain and ST-segment elevation >90 min), in which case a *rescue PCI* should be considered; or (2) coronary artery reocclusion (re-elevation of ST segments and/or recurrent chest pain) or the development of recurrent ischemia (such as recurrent angina in the early hospital course or a positive exercise stress test before discharge), in which case an *urgent PCI* should be considered. Routine angiography and *elective PCI* even in asymptomatic patients following administration of fibrinolytic therapy are used with less frequency, given the numerous technologic advances that have occurred in the catheterization laboratory and the increasing number of skilled interventionalists. Coronary artery bypass surgery should be reserved for patients whose coronary anatomy is unsuited to PCI but in whom revascularization appears to be advisable because of extensive jeopardized myocardium or recurrent ischemia.

## HOSPITAL PHASE MANAGEMENT

### CORONARY CARE UNITS

These units are routinely equipped with a system that permits continuous monitoring of the cardiac rhythm of each patient and hemodynamic monitoring in selected patients. Defibrillators, respirators, noninvasive transthoracic pacemakers, and facilities for introducing pacing catheters and flow-directed balloon-tipped catheters are also usually available. Equally important is the organization of a highly trained team of nurses who can recognize arrhythmias; adjust the dosage of antiarrhythmic, vasoactive, and anticoagulant drugs; and perform cardiac resuscitation, including electroshock, when necessary.

Patients should be admitted to a coronary care unit early in their illness when it is expected that they will derive benefit from the sophisticated and expensive care provided. The availability of electrocardiographic monitoring and trained personnel outside the coronary care unit has made it possible to admit lower-risk patients (e.g., those not hemodynamically compromised and without active arrhythmias) to “intermediate care units.”

The duration of stay in the coronary care unit is dictated by the ongoing need for intensive care. If symptoms are controlled with oral therapy, patients may be transferred out of the coronary care unit. Also, patients who have a confirmed STEMI but who are considered to be at low risk (no prior infarction and no persistent chest discomfort, CHF, hypotension, or cardiac arrhythmias) may be safely transferred out of the coronary care unit within 24 h.

**Activity** Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients with STEMI should be kept at bed rest for the first 6–12 h. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first

24 h. This practice is psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, patients typically are ambulating in their room with increasing duration, anticipating that they may be discharged after 3–5 days.

**Diet** Because of the risk of emesis and aspiration soon after STEMI, patients should receive either nothing or only clear liquids by mouth for the first 4–12 h. The typical coronary care unit diet should provide 30% of total calories as fat and have a cholesterol content of 300 mg/d. Complex carbohydrates should make up 50–55% of total calories. Portions should not be unusually large, and the menu should be enriched with foods that are high in potassium, magnesium, and fiber, but low in sodium. Diabetes mellitus and hypertriglyceridemia are managed by restriction of concentrated sweets in the diet.

**Bowel Management** Bed rest and the effect of the narcotics used for the relief of pain often lead to constipation. A bedside commode rather than a bedpan, a diet rich in bulk, and the routine use of a stool softener such as dioctyl sodium sulfosuccinate (200 mg/d) are recommended. If the patient remains constipated despite these measures, a laxative can be prescribed. Contrary to prior belief, it is safe to perform a gentle rectal examination on patients with STEMI.

**Sedation** Many patients require sedation during hospitalization to withstand the period of enforced inactivity with tranquility. Diazepam (5 mg), oxazepam (15–30 mg), or lorazepam (0.5–2 mg), given three to four times daily, is usually effective. An additional dose of any of the above medications may be given at night to ensure adequate sleep. Attention to this problem is especially important during the first few days in the coronary care unit, where the atmosphere of 24-h vigilance may interfere with the patient’s sleep. However, sedation is no substitute for reassuring, quiet surroundings. Many drugs used in the coronary care unit, such as atropine, H<sub>2</sub> blockers, and narcotics, can produce delirium, particularly in the elderly. This effect should not be confused with agitation, and it is wise to conduct a thorough review of the patient’s medications before arbitrarily prescribing additional doses of anxiolytics.

## PHARMACOTHERAPY

### ANTITHROMBOTIC AGENTS

The use of antiplatelet and anticoagulant therapy during the initial phase of STEMI is based on extensive laboratory and clinical evidence that thrombosis plays an important role in the pathogenesis of this condition. The primary goal of treatment with antiplatelet and anticoagulant agents is to maintain patency of the infarct-related artery, in conjunction with reperfusion strategies. A secondary goal is to reduce the patient’s tendency to thrombosis and, thus, the likelihood of mural thrombus formation or deep-venous thrombosis. The degree to which antiplatelet and anticoagulant therapy achieves these goals partly determines how effectively it reduces the risk of mortality from STEMI.

As noted previously (see “Management in the Emergency Department” earlier), aspirin is the standard antiplatelet agent for patients with STEMI. The most compelling evidence for the benefits of antiplatelet therapy (mainly with aspirin) in STEMI is found in the comprehensive overview by the Antiplatelet Trialists’ Collaboration. Data from nearly 20,000 patients with MI enrolled in 15 randomized trials were pooled and revealed a relative reduction of 27% in the mortality rate, from 14.2% in control patients to 10.4% in patients receiving antiplatelet agents.

Inhibitors of the P2Y<sub>12</sub> ADP receptor prevent activation and aggregation of platelets. The addition of the P2Y<sub>12</sub> inhibitor clopidogrel to background treatment with aspirin to STEMI patients reduces the risk of clinical events (death, reinfarction, stroke) and, in patients receiving fibrinolytic therapy, has been shown to prevent reocclusion of a successfully reperfused infarct artery. Newer P2Y<sub>12</sub> ADP receptor antagonists, such as prasugrel and ticagrelor, are more effective than clopidogrel in preventing ischemic complications in STEMI patients

undergoing PCI but are associated with an increased risk of bleeding. Glycoprotein IIb/IIIa receptor inhibitors are useful for preventing thrombotic complications in patients with STEMI undergoing PCI.

The standard anticoagulant agent used in clinical practice is unfractionated heparin (UFH). The available data suggest that when UFH is added to a regimen of aspirin and a non-fibrin-specific thrombolytic agent such as streptokinase, additional mortality benefit occurs (about 5 lives saved per 1000 patients treated). The immediate administration of intravenous UFH, in addition to a regimen of aspirin and relatively fibrin-specific fibrinolytic agents (tPA, rPA, or TNK), helps to maintain patency of the infarct-related artery. This effect is achieved at the cost of a small increased risk of bleeding. The recommended dose of UFH is an initial bolus of 60 U/kg (maximum 4000 U) followed by an initial infusion of 12 U/kg per h (maximum 1000 U/h). The activated partial thromboplastin time during maintenance therapy should be 1.5–2 times the control value.

Alternatives to UFH for anticoagulation of patients with STEMI are the low-molecular-weight heparin (LMWH) preparations, a synthetic version of the critical pentasaccharide sequence (fondaparinux), and the direct antithrombin bivalirudin. Advantages of LMWHs include high bioavailability permitting administration subcutaneously, reliable anticoagulation without monitoring, and greater anti-Xa:IIa activity. Enoxaparin has been shown to reduce significantly the composite endpoints of death/nonfatal reinfarction and death/nonfatal reinfarction/urgent revascularization compared with UFH in STEMI patients who receive fibrinolysis. Treatment with enoxaparin is associated with higher rates of serious bleeding, but net clinical benefit—a composite endpoint that combines efficacy and safety—still favors enoxaparin over UFH. Interpretation of the data on fondaparinux is difficult because of the complex nature of the pivotal clinical trial evaluating it in STEMI (OASIS-6). Fondaparinux appears superior to placebo in STEMI patients not receiving reperfusion therapy, but its relative efficacy and safety compared with UFH is less certain. Owing to the risk of catheter thrombosis, fondaparinux should not be used alone at the time of coronary angiography and PCI but should be combined with another anticoagulant with antithrombin activity such as UFH or bivalirudin. Trials of bivalirudin used an open-label design to evaluate its efficacy and safety compared with UFH plus a glycoprotein IIb/IIIa inhibitor. Bivalirudin was associated with a lower rate of bleeding, largely driven by reductions in vascular access site hematomas 5 cm or the administration of blood transfusions.

Patients with an anterior location of the infarction, severe LV dysfunction, heart failure, a history of embolism, two-dimensional echocardiographic evidence of mural thrombus, or atrial fibrillation are at increased risk of systemic or pulmonary thromboembolism. Such individuals should receive full therapeutic levels of anticoagulant therapy (LMWH or UFH) while hospitalized, followed by at least 3 months of warfarin therapy.

### BETA-ADRENOCEPTOR BLOCKERS

The benefits of beta blockers in patients with STEMI can be divided into those that occur immediately when the drug is given acutely and those that accrue over the long term when the drug is given for secondary prevention after an infarction. Acute intravenous beta blockade improves the myocardial O<sub>2</sub> supply-demand relationship, decreases pain, reduces infarct size, and decreases the incidence of serious ventricular arrhythmias. In patients who undergo fibrinolysis soon after the onset of chest pain, no incremental reduction in mortality rate is seen with beta blockers, but recurrent ischemia and reinfarction are reduced.

Thus, beta-blocker therapy after STEMI is useful for most patients (including those treated with an angiotensin-converting enzyme [ACE] inhibitor) except those in whom it is specifically contraindicated (patients with heart failure or severely compromised LV function, heart block, orthostatic hypotension, or a history of asthma) and perhaps those whose excellent long-term prognosis (defined as an expected mortality rate of <1% per year, patients <55 years, no previous MI, with normal ventricular function, no complex ventricular ectopy, and no angina) markedly diminishes any potential benefit.

### INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ACE inhibitors reduce the mortality rate after STEMI, and the mortality benefits are additive to those achieved with aspirin and beta blockers. The maximum benefit is seen in high-risk patients (those who are elderly or who have an anterior infarction, a prior infarction, and/or globally depressed LV function), but evidence suggests that a short-term benefit occurs when ACE inhibitors are prescribed unselectively to all hemodynamically stable patients with STEMI (i.e., those with a systolic pressure >100 mmHg). The mechanism involves a reduction in ventricular remodeling after infarction (see “Ventricular Dysfunction” later) with a subsequent reduction in the risk of CHF. The rate of recurrent infarction may also be lower in patients treated chronically with ACE inhibitors after infarction.

ACE inhibitors should be continued indefinitely in patients who have clinically evident CHF, in patients in whom an imaging study shows a reduction in global LV function or a large regional wall motion abnormality, or in those who are hypertensive.

Angiotensin receptor blockers (ARBs) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiologic signs of heart failure. Long-term mineralocorticoid receptor inhibition (spironolactone, eplerenone) should be prescribed for STEMI patients without significant renal dysfunction (creatinine 2.5 mg/dL in men and 2.0 mg/dL in women) or hyperkalemia (potassium 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LV ejection fraction <40%, and have either symptomatic heart failure or diabetes mellitus. A multidrug regimen for inhibiting the renin-angiotensin-aldosterone system has been shown to reduce both heart failure-related and sudden cardiac death-related cardiovascular mortality after STEMI.

### OTHER AGENTS

Favorable effects on the ischemic process and ventricular remodeling (see below) previously led many physicians to routinely use *intravenous nitroglycerin* (5–10 µg/min initial dose and up to 200 µg/min as long as hemodynamic stability is maintained) for the first 24–48 h after the onset of infarction. However, the benefits of routine use of intravenous nitroglycerin are less in the contemporary era where beta-adrenoceptor blockers and ACE inhibitors are routinely prescribed for patients with STEMI.

Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients with STEMI. Therefore, the routine use of calcium antagonists cannot be recommended. Strict control of blood glucose in diabetic patients with STEMI has been shown to reduce the mortality rate. Serum magnesium should be measured in all patients on admission, and any demonstrated deficits should be corrected to minimize the risk of arrhythmias.

### COMPLICATIONS AND THEIR MANAGEMENT

#### VENTRICULAR DYSFUNCTION

After STEMI, the left ventricle undergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as *ventricular remodeling* and generally precedes the development of clinically evident CHF in the months to years after infarction. Soon after STEMI, the left ventricle begins to dilate. Acutely, this results from expansion of the infarct, i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone, resulting in disproportionate thinning and elongation of the infarct zone. Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation following infarction of the anterior wall and apex of the left ventricle and causing more marked hemodynamic impairment, more frequent heart failure, and a poorer prognosis. Progressive dilation and its clinical consequences may be ameliorated by therapy with ACE inhibitors and other vasodilators (e.g., nitrates). In patients with an ejection

2062 fraction <40%, regardless of whether or not heart failure is present, ACE inhibitors or ARBs should be prescribed (see “Inhibition of the Renin-Angiotensin-Aldosterone System” earlier).

## HEMODYNAMIC ASSESSMENT

Pump failure is now the primary cause of in-hospital death from STEMI. The extent of infarction correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and  $S_3$  and  $S_4$  gallop sounds. Pulmonary congestion is also frequently seen on the chest roentgenogram. Elevated LV filling pressure and elevated pulmonary artery pressure are the characteristic hemodynamic findings, but these findings may result from a reduction of ventricular compliance (diastolic failure) and/or a reduction of stroke volume with secondary cardiac dilation (systolic failure) (Chap. 257).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate heart failure as evidenced by rales at the lung bases,  $S_3$  gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe heart failure, pulmonary edema; and class IV, shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and oliguria. When this classification was established in 1967, the expected hospital mortality rate of patients in these classes was as follows: class I, 0–5%; class II, 10–20%; class III, 35–45%; and class IV, 85–95%. With advances in management, the mortality rate in each class has fallen, perhaps by as much as one-third to one-half.

Hemodynamic evidence of abnormal global LV function appears when contraction is seriously impaired in 20–25% of the left ventricle. Infarction of 40% of the left ventricle usually results in cardiogenic shock (Chap. 305). Positioning of a balloon flotation (Swan-Ganz) catheter in the pulmonary artery permits monitoring of LV filling pressure; this technique is useful in patients who exhibit hypotension and/or clinical evidence of CHF. Cardiac output can also be determined with a pulmonary artery catheter. With the addition of intraarterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients with STEMI have markedly elevated LV filling pressures (>22 mmHg) and normal cardiac indices (2.6–3.6 L/[min/m<sup>2</sup>]), while others have relatively low LV filling pressures (<15 mmHg) and reduced cardiac indices. The former patients usually benefit from diuresis, while the latter may respond to volume expansion.

## HYPVOLEMIA

This is an easily corrected condition that may contribute to the hypotension and vascular collapse associated with STEMI in some patients. It may be secondary to previous diuretic use, to reduced fluid intake during the early stages of the illness, and/or to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with STEMI and hypotension before more vigorous forms of therapy are begun. Central venous pressure reflects RV rather than LV filling pressure and is an inadequate guide for adjustment of blood volume because LV function is almost always affected much more adversely than RV function in patients with STEMI. The optimal LV filling or pulmonary artery wedge pressure may vary considerably among patients. Each patient's ideal level (generally ~20 mmHg) is reached by cautious fluid administration during careful monitoring of oxygenation and cardiac output. Eventually, the cardiac output plateaus, and further increases in LV filling pressure only increase congestive symptoms and decrease systemic oxygenation without raising arterial pressure.

## TREATMENT

### Congestive Heart Failure

The management of CHF in association with STEMI is similar to that of acute heart failure secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic

support) (Chap. 257), except that the benefits of digitalis administration to patients with STEMI are unimpressive. By contrast, diuretic agents are extremely effective, as they diminish pulmonary congestion in the presence of systolic and/or diastolic heart failure. LV filling pressure falls and orthopnea and dyspnea improve after the intravenous administration of furosemide or other loop diuretics. These drugs should be used with caution, however, as they can result in a massive diuresis with associated decreases in plasma volume, cardiac output, systemic blood pressure, and, hence, coronary perfusion. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, and intravenous nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present, as ischemia causes an elevation of LV filling pressure. Vasodilators must be used with caution to prevent serious hypotension. As noted earlier, ACE inhibitors are an ideal class of drugs for management of ventricular dysfunction after STEMI, especially for the long term. (See “Inhibition of the Renin-Angiotensin-Aldosterone System” earlier.)

## CARDIOGENIC SHOCK

Prompt reperfusion, efforts to reduce infarct size, and treatment of ongoing ischemia and other complications of MI appear to have reduced the incidence of cardiogenic shock from 20 to ~7%. Among those who exhibit cardiogenic shock, only 10% of patients with this condition present with it on admission, while 90% develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of “piecemeal” necrosis extending outward from the original infarct zone. **The evaluation and management of cardiogenic shock and severe power failure after STEMI are discussed in detail in Chap. 305.**

## RIGHT VENTRICULAR INFARCTION

Approximately one-third of patients with inferior infarction demonstrate at least a minor degree of RV necrosis. An occasional patient with inferoposterior LV infarction also has extensive RV infarction, and rare patients present with infarction limited primarily to the RV. Clinically significant RV infarction causes signs of severe RV failure (jugular venous distention, Kussmaul's sign, hepatomegaly [Chap. 239]) with or without hypotension. ST-segment elevations of right-sided precordial ECG leads, particularly lead V<sub>4</sub>R, are frequently present in the first 24 h in patients with RV infarction. Two-dimensional echocardiography is helpful in determining the degree of RV dysfunction. Catheterization of the right side of the heart often reveals a distinctive hemodynamic pattern resembling constrictive pericarditis (steep right atrial “y” descent and an early diastolic dip and plateau in RV waveforms) (Chap. 270). Therapy consists of volume expansion to maintain adequate RV preload and efforts to improve LV performance with attendant reduction in pulmonary capillary wedge and pulmonary arterial pressures.

## ARRHYTHMIAS

(See also Chaps. 244 and 246) The incidence of arrhythmias after STEMI is higher in patients seen early after the onset of symptoms. The mechanisms responsible for infarction-related arrhythmias include autonomic nervous system imbalance, electrolyte disturbances, ischemia, and slowed conduction in zones of ischemic myocardium. An arrhythmia can usually be managed successfully if trained personnel and appropriate equipment are available when it develops. Since most deaths from arrhythmia occur during the first few hours after infarction, the effectiveness of treatment relates directly to the speed with which patients come under medical observation. The prompt management of arrhythmias constitutes a significant advance in the treatment of STEMI.

**Ventricular Premature Beats** Infrequent, sporadic ventricular premature depolarizations occur in almost all patients with STEMI and do not require therapy. Whereas in the past, frequent, multifocal, or early diastolic ventricular extrasystoles (so-called warning arrhythmias)

were routinely treated with antiarrhythmic drugs to reduce the risk of development of ventricular tachycardia and ventricular fibrillation, pharmacologic therapy is now reserved for patients with sustained ventricular arrhythmias. Prophylactic antiarrhythmic therapy (either intravenous lidocaine early or oral agents later) is contraindicated for ventricular premature beats in the absence of clinically important ventricular tachyarrhythmias because such therapy may actually increase the mortality rate. Beta-adrenoceptor blocking agents are effective in abolishing ventricular ectopic activity in patients with STEMI and in the prevention of ventricular fibrillation. As described earlier (see “Beta-Adrenoceptor Blockers”), they should be used routinely in patients without contraindications. In addition, hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation in patients with STEMI; to reduce the risk, the serum potassium concentration should be adjusted to ~4.5 mmol/L and magnesium to ~2.0 mmol/L.

**Ventricular Tachycardia and Fibrillation** Within the first 24 h of STEMI, ventricular tachycardia and fibrillation can occur without prior warning arrhythmias. The occurrence of ventricular fibrillation can be reduced by prophylactic administration of intravenous lidocaine. However, prophylactic use of lidocaine has not been shown to reduce overall mortality from STEMI. In fact, in addition to causing possible noncardiac complications, lidocaine may predispose to an excess risk of bradycardia and asystole. For these reasons, and with earlier treatment of active ischemia, more frequent use of beta-blocking agents, and the nearly universal success of electrical cardioversion or defibrillation, routine prophylactic antiarrhythmic drug therapy *is no longer recommended*.

Sustained ventricular tachycardia that is well tolerated hemodynamically should be treated with an intravenous regimen of amiodarone (bolus of 150 mg over 10 min, followed by infusion of 1.0 mg/min for 6 h and then 0.5 mg/min). A less desirable but alternative regimen is procainamide (bolus of 15 mg/kg over 20–30 min; infusion of 1–4 mg/min). If ventricular tachycardia does not stop promptly, electroversion should be used (*Chap. 246*). An unsynchronized discharge of 200–300 J (monophasic waveform; ~50% of these energies with biphasic waveforms) is used immediately in patients with ventricular fibrillation or when ventricular tachycardia causes hemodynamic deterioration. Ventricular tachycardia or fibrillation that is refractory to electroshock may be more responsive after the patient is treated with epinephrine (1 mg intravenously or 10 mL of a 1:10,000 solution via the intracardiac route) or amiodarone (a 75–150-mg bolus).

Ventricular arrhythmias, including the unusual form of ventricular tachycardia known as *torsades des pointes* (*Chaps. 252 and 254*), may occur in patients with STEMI as a consequence of other concurrent problems (such as hypoxia, hypokalemia, or other electrolyte disturbances) or of the toxic effects of an agent being administered to the patient (such as digoxin or quinidine). A search for such secondary causes should always be undertaken.

Although the in-hospital mortality rate is increased, the long-term survival is excellent in patients who survive to hospital discharge after primary ventricular fibrillation; i.e., ventricular fibrillation that is a primary response to acute ischemia that occurs during the first 48 h and is not associated with predisposing factors such as CHF, shock, bundle branch block, or ventricular aneurysm. This result is in sharp contrast to the poor prognosis for patients who develop ventricular fibrillation *secondary* to severe pump failure. For patients who develop ventricular tachycardia or ventricular fibrillation late in their hospital course (i.e., after the first 48 h), the mortality rate is increased both in-hospital and during long-term follow-up. Such patients should be considered for electrophysiologic study and implantation of a cardioverter-defibrillator (ICD) (*Chap. 252*). A more challenging issue is the prevention of sudden cardiac death from ventricular fibrillation late after STEMI in patients who have not exhibited sustained ventricular tachyarrhythmias during their index hospitalization. An algorithm for selection of patients who warrant prophylactic implantation of an ICD is shown in *Fig. 275-6*.

**Accelerated Idioventricular Rhythm** Accelerated idioventricular rhythm (AIVR, “slow ventricular tachycardia”), a ventricular

rhythm with a rate of 60–100 beats/min, often occurs transiently during fibrinolytic therapy at the time of reperfusion. For the most part, AIVR, whether it occurs in association with fibrinolytic therapy or spontaneously, is benign and does not presage the development of classic ventricular tachycardia. Most episodes of AIVR do not require treatment if the patient is monitored carefully, as degeneration into a more serious arrhythmia is rare.

**Supraventricular Arrhythmias** Sinus tachycardia is the most common supraventricular arrhythmia. If it occurs secondary to another cause (such as anemia, fever, heart failure, or a metabolic derangement), the primary problem should be treated first. However, if it appears to be due to sympathetic overstimulation (e.g., as part of a hyperdynamic state), then treatment with a beta blocker is indicated. Other common arrhythmias in this group are atrial flutter and atrial fibrillation, which are often secondary to LV failure. Digoxin is usually the treatment of choice for supraventricular arrhythmias if heart failure is present. If heart failure is absent, beta blockers, verapamil, and diltiazem are suitable alternatives for controlling the ventricular rate, as they may also help to control ischemia. If the abnormal rhythm persists for >2 h with a ventricular rate >120 beats/min or if tachycardia induces heart failure, shock, or ischemia (as manifested by recurrent pain or ECG changes), a synchronized electroshock (100–200 J monophasic waveform) should be used.

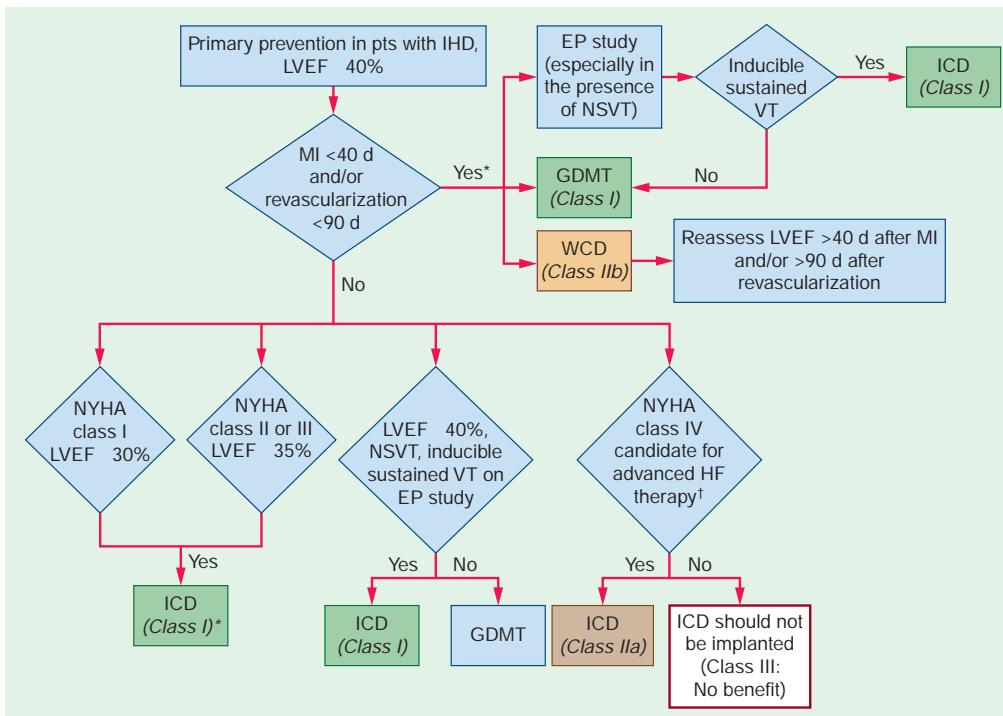
Accelerated junctional rhythms have diverse causes but may occur in patients with inferoposterior infarction. Digitalis excess must be ruled out. In some patients with severely compromised LV function, the loss of appropriately timed atrial systole results in a marked reduction of cardiac output. Right atrial or coronary sinus pacing is indicated in such instances.

**Sinus Bradycardia** Treatment of sinus bradycardia is indicated if hemodynamic compromise results from the slow heart rate. Atropine is the most useful drug for increasing heart rate and should be given intravenously in doses of 0.5 mg initially. If the rate remains <50–60 beats/min, additional doses of 0.2 mg, up to a total of 2.0 mg, may be given. Persistent bradycardia (<40 beats/min) despite atropine may be treated with electrical pacing. Isoproterenol should be avoided.

**Atrioventricular and Intraventricular Conduction Disturbances** (*See also Chap. 244*) Both the in-hospital mortality rate and the post-discharge mortality rate of patients who have complete atrioventricular (AV) block in association with anterior infarction are markedly higher than those of patients who develop AV block with inferior infarction. This difference is related to the fact that heart block in inferior infarction is commonly a result of increased vagal tone and/or the release of adenosine and therefore is transient. In anterior wall infarction, however, heart block is usually related to ischemic malfunction of the conduction system, which is commonly associated with extensive myocardial necrosis.

Temporary electrical pacing provides an effective means of increasing the heart rate of patients with bradycardia due to AV block. However, acceleration of the heart rate may have only a limited impact on prognosis in patients with anterior wall infarction and complete heart block in whom the large size of the infarct is the major factor determining outcome. It should be carried out if it improves hemodynamics. Pacing does appear to be beneficial in patients with inferoposterior infarction who have complete heart block associated with heart failure, hypotension, marked bradycardia, or significant ventricular ectopic activity. A subgroup of these patients, those with RV infarction, often respond poorly to ventricular pacing because of the loss of the atrial contribution to ventricular filling. In such patients, dual-chamber AV sequential pacing may be required.

External noninvasive pacing electrodes should be positioned in a “demand” mode for patients with sinus bradycardia (rate <50 beats/min) that is unresponsive to drug therapy, Mobitz II second-degree AV block, third-degree heart block, or bilateral bundle branch block (e.g., right bundle branch block plus left anterior fascicular block). Retrospective studies suggest that permanent pacing may reduce the long-term risk of sudden death due to bradyarrhythmias in the rare



**FIGURE 275-6 Primary prevention of SCD in patients with ischemic heart disease, including recent MI.** Colors correspond to class of recommendation in the guideline (green = Class I; yellow = Class IIa; amber = Class IIb; red = Class III). \*Scenarios exist for early ICD placement in select circumstances such as patients with a pacing indication or syncope. †Advanced HF therapy includes CRT, cardiac transplant, and left ventricular assist device. CRT, cardiac resynchronization therapy; EP, electrophysiologic; GDMT, guideline-directed management and therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; pts, patients; SCD, sudden cardiac death; VT, ventricular tachycardia; WCD, wearable cardioverter-defibrillator. The available evidence does not suggest there is a survival advantage to the use of an ICD early after MI, and the WCD is a potential option while waiting until the ejection fraction is reassessed (see figure). While the WCD appears to be effective in patients who wear the device, it is associated with frequent alarms, skin irritation, and emotional distress, which results in reduced wear time in a large number of patients. (Reproduced with permission from SM Al-Khatib et al: 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation* 138:e272, 2018.)

patient who develops combined persistent bifascicular and transient third-degree heart block during the acute phase of MI.

## OTHER COMPLICATIONS

**Recurrent Chest Discomfort** Because recurrent or persistent ischemia often heralds extension of the original infarct or reinfarction in a new myocardial zone and is associated with a near tripling of mortality after STEMI, patients with these symptoms should be referred for prompt coronary arteriography and mechanical revascularization. Administration of a fibrinolytic agent is an alternative to early mechanical revascularization.

**Pericarditis** (See also Chap. 270) Pericardial friction rubs and/or pericardial pain are frequently encountered in patients with STEMI involving the epicardium. This complication can usually be managed with aspirin (650 mg four times daily). It is important to diagnose the chest pain of pericarditis accurately because failure to recognize it may lead to the erroneous diagnosis of recurrent ischemic pain and/or infarct extension, with resulting inappropriate use of anticoagulants, nitrates, beta blockers, or coronary arteriography. When it occurs, complaints of pain radiating to either trapezius muscle is helpful because such a pattern of discomfort is typical of pericarditis but rarely occurs with ischemic discomfort. Anticoagulants potentially could cause tamponade in the presence of acute pericarditis (as manifested by either pain or persistent rub) and therefore should not be used unless there is a compelling indication.

**Thromboembolism** Clinically apparent thromboembolism complicates STEMI in ~10% of cases, but embolic lesions are found in 20% of patients in necropsy series, suggesting that thromboembolism is often clinically silent. Thromboembolism is considered to be an

important contributing cause of death in 25% of patients with STEMI who die after admission to the hospital. Arterial emboli originate from LV mural thrombi, while most pulmonary emboli arise in the leg veins.

Thromboembolism typically occurs in association with large infarcts (especially anterior), CHF and an LV thrombus detected by echocardiography. The incidence of arterial embolism from a clot originating in the ventricle at the site of an infarction is small but real. Two-dimensional echocardiography reveals LV thrombi in about one-third of patients with anterior wall infarction but in few patients with inferior or posterior infarction. Arterial embolism often presents as a major complication, such as hemiparesis when the cerebral circulation is involved or hypertension if the renal circulation is compromised. When a thrombus has been clearly demonstrated by echocardiographic or other techniques or when a large area of regional wall motion abnormality is seen even in the absence of a detectable mural thrombus, systemic anticoagulation should be undertaken (in the absence of contraindications), as the incidence of embolic complications appears to be markedly lowered by such therapy. The appropriate duration of therapy is unknown, but 3–6 months is probably prudent.

**Left Ventricular Aneurysm** The term *ventricular aneurysm* is usually used to describe *dyskinesis* or local expansile paradoxical wall motion. Normally functioning myocardial fibers must shorten more if stroke volume and cardiac output are to be maintained in patients with ventricular aneurysm; if they cannot, overall ventricular function is impaired. True aneurysms are composed of scar tissue and neither predispose to nor are associated with cardiac rupture.

The complications of LV aneurysm do not usually occur for weeks to months after STEMI; they include CHF, arterial embolism, and ventricular arrhythmias. Apical aneurysms are the most common and the most easily detected by clinical examination. The physical finding

of greatest value is a double, diffuse, or displaced apical impulse. Ventricular aneurysms are readily detected by two-dimensional echocardiography, which may also reveal a mural thrombus in an aneurysm.

Rarely, myocardial rupture may be contained by a local area of pericardium, along with organizing thrombus and hematoma. Over time, this *pseudoaneurysm* enlarges, maintaining communication with the LV cavity through a narrow neck. Because a pseudoaneurysm often ruptures spontaneously, it should be surgically repaired if recognized.

## POSTINFARCTION RISK STRATIFICATION AND MANAGEMENT

Many clinical and laboratory factors have been identified that are associated with an increase in cardiovascular risk after initial recovery from STEMI. Some of the most important factors include persistent ischemia (spontaneous or provoked), depressed LV ejection fraction (<40%), rales above the lung bases on physical examination or congestion on chest radiograph, and symptomatic ventricular arrhythmias. Other features associated with increased risk include a history of previous MI, age >75, diabetes mellitus, prolonged sinus tachycardia, hypotension, ST-segment changes at rest without angina ("silent ischemia"), an abnormal signal-averaged ECG, nonpatency of the infarct-related coronary artery (if angiography is undertaken), and persistent advanced heart block or a new intraventricular conduction abnormality on the ECG. Therapy must be individualized on the basis of the relative importance of the risk(s) present.

The goal of preventing reinfarction and death after recovery from STEMI has led to strategies to evaluate risk after infarction. In stable patients, submaximal exercise stress testing may be carried out before hospital discharge to detect residual ischemia and ventricular ectopy and to provide the patient with a guideline for exercise in the early recovery period. Alternatively, or in addition, a maximal (symptom-limited) exercise stress test may be carried out 4–6 weeks after infarction. Evaluation of LV function is usually warranted as well. Recognition of a depressed LV ejection fraction by echocardiography or radionuclide ventriculography identifies patients who should receive medications to inhibit the renin-angiotensin-aldosterone system. Patients in whom angina is induced at relatively low workloads, those who have a large reversible defect on perfusion imaging or a depressed ejection fraction, those with demonstrable ischemia, and those in whom exercise provokes symptomatic ventricular arrhythmias should be considered at high risk for recurrent MI or death from arrhythmia (Fig. 275-6). Cardiac catheterization with coronary angiography and/or invasive electrophysiologic evaluation is advised.

Exercise tests also aid in formulating an individualized exercise prescription, which can be much more vigorous in patients who tolerate exercise without any of the previously mentioned adverse signs. In addition, predischarge stress testing may provide an important psychological benefit, building the patient's confidence by demonstrating a reasonable exercise tolerance.

In many hospitals, a cardiac rehabilitation program with progressive exercise is initiated in the hospital and continued after discharge. Ideally, such programs should include an educational component that informs patients about their disease and its risk factors.

The usual duration of hospitalization for an uncomplicated STEMI is about 3–5 days. The remainder of the convalescent phase may be accomplished at home. During the first 1–2 weeks, the patient should be encouraged to increase activity by walking about the house and outdoors in good weather. Normal sexual activity may be resumed during this period. After 2 weeks, the physician should regulate the patient's activity on the basis of exercise tolerance. Most patients will be able to return to work within 2–4 weeks.

## SECONDARY PREVENTION

Various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates after STEMI. Long-term treatment with an antiplatelet agent (usually aspirin) after STEMI is associated with a 25% reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality (36 fewer events for every 1000 patients treated). An alternative antiplatelet agent that may be

used for secondary prevention in patients intolerant of aspirin is clopidogrel (75 mg orally daily). ACE inhibitors or ARBs and, in appropriate patients, aldosterone antagonists should be used indefinitely by patients with clinically evident heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.

The chronic routine use of oral beta-adrenoceptor blockers for at least 2 years after STEMI is supported by well-conducted, placebo-controlled trials.

Evidence suggests that warfarin lowers the risk of late mortality and the incidence of reinfarction after STEMI. Most physicians prescribe aspirin routinely for all patients without contraindications and add warfarin for patients at increased risk of embolism (see "Thromboembolism" earlier). Several studies suggest that in patients <75 years old a low dose of aspirin (75–81 mg/d) in combination with warfarin administered to achieve an international normalized ratio >2.0 is more effective than aspirin alone for preventing recurrent MI and embolic cerebrovascular accident. However, there is an increased risk of bleeding and a high rate of discontinuation of warfarin that has limited clinical acceptance of combination antithrombotic therapy. There is an increased risk of bleeding when warfarin is added to dual antiplatelet therapy (see Chap. 273). However, patients who have had a stent implanted and have an indication for anticoagulation should receive dual antiplatelet therapies in combination with warfarin. (See Chap. 273 for further discussion.) Such patients should also receive a proton pump inhibitor to minimize the risk of gastrointestinal bleeding and should have regular monitoring of their hemoglobin levels and stool hematest while on combination antithrombotic therapy.

Finally, risk factors for *atherosclerosis* (Chap. 237) should be discussed with the patient and, when possible, favorably modified.

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## 276

# Percutaneous Coronary Interventions and Other Interventional Procedures

David P. Faxon, Deepak L. Bhatt

Percutaneous transluminal coronary angioplasty (PTCA) was first introduced by Andreas Gruentzig in 1977 as an alternative to coronary bypass surgery. The concept was initially demonstrated by Charles Dotter in 1964 in peripheral vessels. The development of a small inelastic balloon catheter by Gruentzig allowed expansion of the technique into smaller peripheral and coronary vessels. Initial coronary experience was limited to single-vessel coronary disease and discrete proximal lesions due to the technical limitations of the equipment. Advances in technology with smaller profile balloon catheters and movable steerable guidewires and greater operator experience allowed the procedure to grow rapidly with expanded use in patients with more complex lesions and multivessel disease. The introduction of coronary stents in 1994 was one of the major advances in the field. These devices reduced acute complications and reduced by half the significant problems of acute thrombosis and late restenosis (or recurrence of the stenosis). Further reductions in restenosis were achieved by the introduction of drug-eluting stents in 2003. These stents slowly release antiproliferative drugs directly into the plaque over a few months. Percutaneous coronary intervention (PCI) is the most common revascularization procedure in the United States and is performed more than twice as often as coronary artery bypass surgery: >900,000 patients a year.

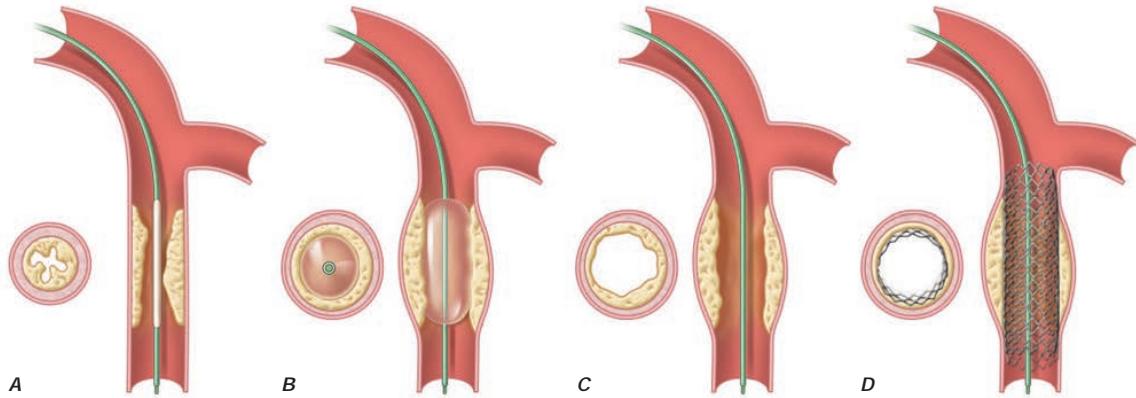
Interventional cardiology is a separate discipline in cardiology that requires a dedicated 1- or 2-year interventional cardiology fellowship following a 3-year general cardiology fellowship in order to obtain a separate board certification. The discipline has also expanded to include interventions for structural heart disease including treatment of congenital heart disease and valvular heart disease; it also includes interventions to treat peripheral vascular disease, including atherosclerotic and nonatherosclerotic lesions in the carotid, renal, aortic, and peripheral arterial and venous circulations.

## TECHNIQUE

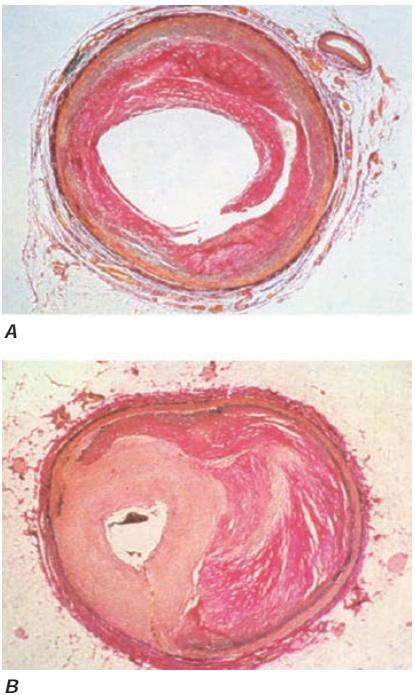
The initial procedure is performed in a similar manner as a diagnostic cardiac catheterization ([Chap. 242](#)). Arterial access is obtained via the radial or femoral artery. To prevent thrombotic complications during the procedure, patients who are anticipated to need an angioplasty are given aspirin (325 mg) and may be given a platelet P2Y<sub>12</sub> inhibitor such as clopidogrel (loading dose of 600 mg), prasugrel (loading dose of 60 mg), or ticagrelor (loading dose of 180 mg) before the procedure. Cangrelor, a potent IV P2Y<sub>12</sub> inhibitor, is approved for use in patients who have not received an oral agent prior to the procedure. During the procedure, anticoagulation is achieved by administration of unfractionated heparin, enoxaparin (a low-molecular-weight heparin), or bivalirudin (a direct thrombin inhibitor). In patients with ST-segment elevation myocardial infarction (STEMI), high-risk acute coronary syndrome, or a large thrombus in the coronary artery, an intravenous glycoprotein IIb/IIIa inhibitor (abciximab, tirofiban, or eptifibatide) may also be given, although cangrelor appears to be as effective with less bleeding risk.

Following placement of an introducing sheath into the artery, pre-formed guiding catheters are used to cannulate selectively the origins of the coronary arteries. Through the guiding catheter, a flexible, steerable guidewire is negotiated down the coronary artery lumen using fluoroscopic guidance; it is then advanced through the stenosis and into the vessel beyond. This guidewire then serves as a "rail" over which angioplasty balloons, stents, or other therapeutic devices can be advanced to enlarge the narrowed segment of coronary artery. The artery is usually dilated with a balloon catheter followed by placement of a stent. The catheters and introducing sheath are removed and the artery manually held, or in the case of radial access, an inflatable cuff is used. One of several femoral arterial closure devices can also be used to achieve hemostasis. Because PCI is performed under local anesthesia and mild sedation, it requires only a short (1-day or less) hospitalization.

Angioplasty works by stretching the artery and displacing the plaque away from the lumen, enlarging the entire vessel ([Fig. 276-1](#) and [Fig. 276-2](#)). The procedure rarely results in embolization of atherosclerotic



**FIGURE 276-1** Schematic diagram of the primary mechanisms of balloon angioplasty and stenting. **A**, A balloon angioplasty catheter is positioned into the stenosis over a guidewire under fluoroscopic guidance. **B**, The balloon is inflated, temporarily occluding the vessel. **C**, The lumen is enlarged primarily by stretching the vessel, often resulting in small dissections in the neointima. **D**, A stent mounted on a deflated balloon is placed into the lesion and pressed against the vessel wall with balloon inflation (not shown). The balloon is deflated and removed, leaving the stent permanently against the wall acting as a scaffold to hold the dissections against the wall and prevent vessel recoil. (Reproduced with permission from EJ Topol: *Textbook of Cardiovascular Medicine*, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2002.)



**FIGURE 276-2** Pathology of acute effects of balloon angioplasty with intimal dissection and vessel stretching (**A**) and an example of neointimal hyperplasia and restenosis showing renarrowing of the vessel (**B**). (Panel A reprinted from M Ueda et al: The early phenomena of restenosis following percutaneous transluminal coronary angioplasty. *Eur Heart J* 12:937, 1991; with permission. Panel B reprinted from CE Essed, M Van den Brand, AE Becker: Transluminal coronary angioplasty and early restenosis. Fibrocellular occlusion after wall laceration. *Br Heart J* 49:393, 1983; with permission.)

material. Owing to inelastic elements in the plaque, the stretching of the vessel by the balloon results in small localized dissections that can protrude into the lumen and be a nidus for acute thrombus formation. If the dissections are severe, then they can obstruct the lumen or induce a thrombotic occlusion of the artery (acute closure). Stents have largely prevented this complication by holding the dissection flaps up against the vessel wall (Fig. 276-1).

Stents are currently used in >90% of coronary angioplasty procedures. Stents are wire meshes (usually made of stainless steel or other metals, such as cobalt chromium or nitinol) that are compressed over a deflated angioplasty balloon. When the balloon is inflated, the stent is enlarged to approximate the “normal” vessel lumen. The balloon is then deflated and removed, leaving the stent behind to provide a permanent scaffold in the artery. Owing to the design of the struts, these devices are flexible, allowing their passage through diseased and tortuous coronary vessels. Stents are rigid enough to prevent elastic recoil of the vessel and have dramatically improved the success and safety of the procedure as a result.

Drug-eluting stents further enhanced the efficacy of PCI. An antiproliferative agent is attached to the metal stent by use of a thin polymer coating. The antiproliferative drug elutes from the stent over a 1- to 3-month period or longer after implantation. Drug-eluting stents have been shown to reduce clinical restenosis by 50%, so that in uncomplicated lesions, symptomatic restenosis occurs in 5–10% of patients. Not surprisingly, this led to the rapid acceptance of these devices; currently >90% of all stents implanted are drug-eluting. The first-generation devices were coated with either sirolimus or paclitaxel. Second-generation drug-eluting stents use newer agents such as everolimus, biolimus, and zotarolimus. These second-generation drug-eluting stents appear to be more effective with fewer complications, such as early or late stent thrombosis, than the first-generation devices and, therefore, have replaced the first-generation stents. Biodegradable polymers that are used to attach the drugs to the stents may be theoretically superior to

permanent polymers in preventing late stent thrombosis. In addition, the first-generation everolimus-eluting biodegradable vascular scaffold (BVS) stent had been shown to be reasonably safe with gradual degradation over several years, although concerns about late and very late stent thrombosis ultimately led to its withdrawal from clinical practice. Additional bioresorbable stents are under investigation. Drug-coated balloons are covered with an antiproliferative drug that can also reduce restenosis and are used primarily to treat in-stent restenosis.

Other interventional devices include atherectomy devices and thrombectomy catheters. These devices are designed to remove atherosclerotic plaque or thrombus and are used in conjunction with balloon dilatation and stent placement. Rotational atherectomy is the most commonly used adjunctive device and is modeled after a dentist's drill, with small round burrs of 1.25–2.5 mm at the tip of a flexible wire shaft. The burr is passed over the guidewire up to the stenosis and drills away atherosclerotic material. Because the atherosclerotic particles are  $\approx 25 \mu\text{m}$ , they pass through the coronary microcirculation and rarely cause problems. The device is particularly useful in heavily calcified plaques that are resistant to balloon dilatation. Given the current advances in stents, rotational atherectomy is infrequently used. Orbital atherectomy is a newer approach to calcified lesions that also relies on a spinning burr. Directional atherectomy catheters that slice off the plaque and remove it are not used in the coronaries any longer but are sometimes used in peripheral artery disease. In acute STEMI, specialized catheters without a balloon can be used to aspirate thrombus in order to prevent embolization down the coronary vessel and to improve blood flow before angioplasty and stent placement. Current studies show that manual catheter thrombus aspiration should not be used routinely but, in certain cases of a large thrombus burden, can improve blood flow in primary PCI.

PCI of degenerated saphenous vein graft lesions has been associated with a significant incidence of distal embolization of atherosclerotic material, unlike PCI of native vessel disease. A number of distal protection devices have been shown to significantly reduce embolization and myocardial infarction in this setting. Most devices work by using a collapsible wire filter at the end of a guidewire that is expanded in the distal vessel before PCI. If atherosclerotic debris is dislodged, the basket captures the material, and at the end of the PCI, the basket is pulled into a delivery catheter, and the debris safely removed from the patient.

## SUCCESS AND COMPLICATIONS

A successful procedure (angiographic success), defined as a reduction of the stenosis to less than a 20% diameter narrowing, occurs in 95–99% of patients. Lower success rates are seen in patients with tortuous, small, or calcified vessels or chronic total occlusions. Chronic total occlusions have the lowest success rates and their recanalization is significantly better if the occlusion is recent (within 3 months) or there are favorable anatomic features. Improvements in equipment and complex antegrade and retrograde techniques have increased the success rates of recanalization of chronic total occlusions to 70–80%.

Serious complications are rare but include a mortality rate of 0.1–0.3% for elective cases, a large myocardial infarction in <3%, and stroke in 0.1–0.4%. Patients who are older (>65 years), undergoing an emergent or urgent procedure, have chronic kidney disease, present with STEMI, or are in shock have significantly higher risk. Scoring systems can help to estimate the risk of the procedure. Myocardial infarction during PCI can occur for multiple reasons including an acute occluding thrombus, severe coronary dissection, embolization of thrombus or atherosclerotic material, or closure of a side branch vessel at the site of angioplasty or stent placement. Most myocardial infarctions are small and only detected by a rise in the creatine phosphokinase (CPK) or troponin level after the procedure. Only those with significant enzyme elevations (>10 times the upper limit of normal) are associated with a less favorable long-term outcome. Coronary stents have largely prevented occlusive coronary dissections due to the scaffolding effect of the stent.

All types of stents are prone to stent thrombosis (1–3%), either acute (<24 h) or subacute (1–30 days), which can be ameliorated by greater attention to full initial stent deployment and the use of dual antiplatelet therapy (DAPT) (aspirin, plus a platelet P2Y<sub>12</sub> receptor

blocker [clopidogrel, prasugrel, or ticagrelor]). Late (30 days–1 year) and very late (>1 year) stent thromboses occur very infrequently with stents but are slightly more common with first-generation drug-eluting stents, necessitating DAPT for up to 1 year or longer. Use of the second-generation stents is associated with lower rates of late and very late stent thromboses, and shorter durations of DAPT (6 months) are recommended for the stent, although longer durations may be useful depending on the underlying atherothrombotic and bleeding risks. Premature discontinuation of DAPT, particularly in the first month after implantation, is associated with a significantly increased risk for stent thrombosis (three- to ninefold greater). Stent thrombosis results in death in 10–20% and myocardial infarction in 30–70% of patients. Elective surgery that requires discontinuation of antiplatelet therapy after drug-eluting stent implantation should be postponed until after 3 months and preferably after 6 months, if at all possible.

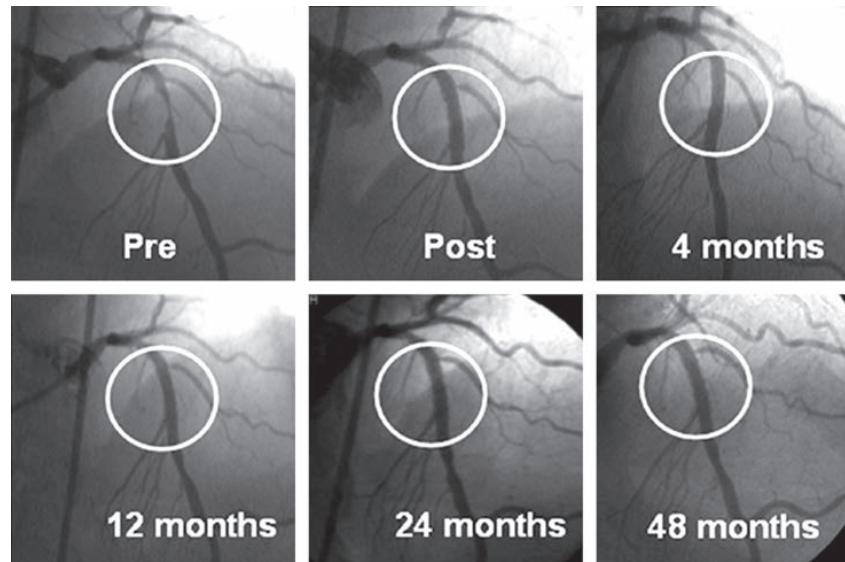
Restenosis, or renarrowing of the dilated coronary stenosis, is the most common complication of angioplasty and occurs in 20–50% of patients with balloon angioplasty alone, 10–30% of patients with bare metal stents, and 5–15% of patients with drug-eluting stents within the first year. The fact that stent placement provides a larger acute luminal area than balloon angioplasty alone reduces the incidence of subsequent restenosis. Drug-eluting stents further reduce restenosis through a reduction in excessive neointimal growth over the stent. If restenosis does not occur, the long-term outcome is excellent (Fig. 276-3). Clinical restenosis is recognized by recurrence of angina or symptoms within 12 months of the procedure. Less frequently, patients with restenosis can present with non-ST-segment elevation myocardial infarction (NSTEMI) (10%) or STEMI (2%) as well. Very late stent thrombosis and restenosis after 1 year is more likely to be due to neatherosclerosis than intimal hyperplasia seen within the first year. Clinical restenosis requires confirmation of a significant stenosis at the site of the prior PCI. Target lesion revascularization (TLR) or target vessel revascularization (TVR) is defined as angiographic restenosis with repeat PCI or coronary artery bypass grafting (CABG). By angiography, the incidence of restenosis is significantly higher than clinical restenosis (TLR or TVR) because many patients have mild restenosis that does not result in a recurrence of symptoms. The management of clinical restenosis is usually to repeat the PCI with balloon dilatation and placement of another drug-eluting stent. Once a patient has had restenosis, the risk of a second restenosis is further increased. The risk factors for restenosis are diabetes, myocardial infarction, long lesions, small-diameter vessels, and suboptimal initial PCI result. Treatments

for symptomatic recurrent restenosis include re-stenting (three layers of stent), brachytherapy, drug-coated balloons, or coronary bypass surgery.

## INDICATIONS

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines extensively review the indications for PCI in patients with stable angina, unstable angina, NSTEMI, and STEMI and should be referred to for a comprehensive discussion of the indications. Briefly, the two principal indications for coronary revascularization in patients with *chronic stable angina* (Chap. 273) are (1) to improve angina symptoms in patients who remain symptomatic despite adequate medical therapy and (2) to reduce mortality rates in patients with severe and extensive coronary disease. In patients with stable angina who are well controlled on medical therapy, studies such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trials have shown that initial revascularization does not lead to better outcomes (death or myocardial infarction) and can be safely delayed until symptoms worsen or evidence of severe ischemia on noninvasive testing occurs. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial was the largest trial comparing optimal medical therapy to revascularization with PCI or CABG in stable patients with moderate ischemia on stress testing but without left main or reduced left ventricular function (<35% ejection fraction). It showed that optimal medical therapy was similar to revascularization in a composite of cardiovascular death or hospitalization or in cardiovascular death and myocardial infarction at a median of 3.3 years. This trial confirms prior studies and supports conservative management in most stable patients. When revascularization is indicated due to unacceptable symptoms, the choice of PCI or CABG depends on a number of clinical and anatomic factors.

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with the paclitaxel drug-eluting stent to CABG in 1800 patients with three-vessel coronary disease or left main disease. The study found no difference in death or myocardial infarction at 1 year, but repeat revascularization was significantly higher in the stent-treated group (13.5 vs 5.9%), while stroke was significantly higher in the surgical group (2.2 vs 0.6%). The primary endpoint of death, myocardial infarction, stroke, or revascularization was significantly better with CABG, particularly in those



**FIGURE 276-3** Long-term results from one of the first patients to receive a sirolimus-eluting stent from early São Paulo experience. (From GW Stone, in D Baim [ed]: *Cardiac Catheterization, Angiography and Intervention*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2006; with permission.)

with the most extensive coronary artery disease such as three-vessel disease. The 10-year results confirm these findings. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes and multivessel disease and found a significantly lower primary endpoint of death, myocardial infarction, or stroke with CABG than PCI. Recent trials comparing PCI with CABG have shown similar outcomes for those with less extensive disease, but a better outcome when the coronary disease is severe and extensive. These studies support CABG for those with the most severe left main and three-vessel disease or those with diabetes. Lesser degrees of multivessel disease in patients with or without diabetes have an equal outcome with PCI, including left main disease with favorable angiographic characteristics.

The choice of PCI versus CABG is also related to the anticipated procedural success and complications of PCI and the risks of CABG. For PCI, the characteristics of the coronary anatomy are critically important. The location of the lesion in the vessel (proximal or distal), the degree of tortuosity, and the size of the vessel are considered. In addition, the lesion characteristics, including the degree of the stenosis, the presence of calcium, lesion length, and presence of thrombus, are assessed. The most common reason to decide not to do PCI is that the lesion(s) felt to be responsible for the patient's symptoms is not treatable. This is most commonly due to the presence of a chronic total occlusion (>3 months in duration) with unfavorable characteristics. A lesion classification to characterize the likelihood of success or failure of PCI has been developed by the ACC/AHA. Lesions with the highest success are called type A lesions (such as proximal noncalcified subtotal lesions), and those with the lowest success or highest complication rate are type C lesions (such as chronic total occlusions). Intermediate lesions are classified as type B1 or B2 depending on the number of unfavorable characteristics. Approximately 25–30% of patients will not be candidates for PCI due to unfavorable anatomy, whereas only 5% of CABG patients will not be candidates for surgery due to coronary anatomy. The primary reason for being considered inoperable with CABG is the presence of severe comorbidities such as advanced age, frailty, severe chronic obstructive pulmonary disease (COPD), poor left ventricular function, or lack of suitable surgical conduits or poor distal targets for bypass.

Another consideration in choosing a revascularization strategy is the degree of revascularization. In patients with multivessel disease, bypass grafts can usually be placed to all vessels >2 mm with significant stenosis, whereas PCI may be able to treat only some of the lesions due to the presence of unfavorable anatomy. Assessment of the significance of intermediate lesions using fractional flow reserve (FFR) or the instantaneous wave-free ratio (iFR) ([Chap. 242](#)) can assist in determining which lesions should be revascularized. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial showed a 30% reduction in adverse events when revascularization by PCI was restricted to those lesions that were hemodynamically significant (FFR 0.80) rather than when guided by angiography alone. Trials have shown that iFR is as predictive as FFR but is quicker and easier to perform, especially if there are sequential lesions or multivessel disease. Thus, complete revascularization of all functionally significant lesions should be favored and considered when choosing the optimal revascularization strategy. Given the multiple factors that need to be considered in choosing the best revascularization for an individual patient with multivessel disease, it is optimal to have a discussion among the cardiac surgeon, interventional cardiologist, and the physicians caring for the patient (so-called Heart Team) to weigh the choices properly.

Patients with acute coronary syndrome are at excess risk of short- and long-term mortality. Randomized clinical trials have shown that PCI is superior to intensive medical therapy in reducing mortality and myocardial infarction, with the benefit largely confined to those patients who are high risk. High-risk non-ST-segment elevation acute coronary syndrome patients are defined as those with any one of the following: refractory ischemia, recurrent angina, positive cardiac-specific enzymes, new ST-segment depression, transient ST-segment elevation, low ejection fraction, severe arrhythmias, or a recent PCI

or CABG. PCI is preferred over surgical therapy in most high-risk patients with acute coronary syndromes unless they have severe multivessel disease or the culprit lesion responsible for the unstable presentation cannot be adequately determined or treated. In STEMI, thrombolysis and PCI (primary PCI) are effective methods to restore coronary blood flow and salvage myocardium within the first 12 h after onset of chest pain. Because PCI is more effective in restoring flow than thrombolysis, it is preferred if readily available within 90 min of presentation to the hospital. PCI is also performed following thrombolysis to facilitate adequate reperfusion or as a rescue procedure in those who do not achieve reperfusion from thrombolysis, who cannot be rapidly transferred to a hospital that can perform primary PCI, or who develop cardiogenic shock. The Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI (COMPLETE) trial supports complete revascularization of nonculprit lesions in STEMI either in the hospital or in the few weeks after discharge.

## OTHER INTERVENTIONAL TECHNIQUES

### STRUCTURAL HEART DISEASE

Interventional treatment for structural heart disease (adult congenital heart disease and valvular heart disease) is a significant and growing component of the field of interventional cardiology.

The most common adult congenital lesion to be treated with percutaneous techniques is closure of atrial septal defects ([Chap. 269](#)). The procedure is done as in a diagnostic right heart catheterization with the passage of a catheter up the femoral vein into the right atrium. With echo and fluoroscopic guidance, the size and location of the defect can be accurately defined, and closure is accomplished using one of several approved devices. All devices use a left atrial and right atrial wire mesh or covered disk that are pulled together to capture the atrial septum around the defect and seal it off. The Amplatzer Septal Occluder device (AGA Medical, Minneapolis, Minnesota) is the most commonly used in the United States. The success rate in selected patients is 85–95%, and the device complications are rare and include device embolization, infection, or erosion. Closure of patent foramen ovale (PFO) is done in a similar way. PFO closure may be considered in patients who have had recurrent paradoxical stroke or transient ischemic attack (TIA) despite adequate medical therapy including anticoagulation or antiplatelet therapy or who are at high risk for recurrent stroke. The CLOSURE I trial (Evaluation of the STARflex Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale) randomized 909 patients with cryptogenic stroke or TIA who had a PFO. Closure did not reduce the primary endpoint of death within 30 days or death following a neurologic cause during 2 years of follow-up or stroke/TIA within 2 years. Other short-term trials confirmed these findings. However, the 10-year follow-up from the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial did find a benefit of closure in reducing the risk for recurrent cryptogenic stroke, as have meta-analyses examining the longer-term effects of closures in appropriate patients. The use in the treatment of migraine is not supported by the current data.

Similar devices can also be used to close patent ductus arteriosus and ventricular septal defects. Other congenital diseases that can be treated percutaneously include coarctation of the aorta, pulmonic stenosis, peripheral pulmonary stenosis, and other abnormal communications between the cardiac chambers or vessels.

The treatment of valvular heart disease is the most rapidly growing area in interventional cardiology. In the past, the only available techniques were balloon valvuloplasty for the treatment of aortic, mitral, or pulmonic stenosis ([Chap. 261](#)). Mitral valvuloplasty is the preferred treatment for symptomatic patients with rheumatic mitral stenosis who have favorable anatomy. The outcome in these patients is equal to that of surgical commissurotomy. The success is highly related to the echocardiographic appearance of the valve. The most favorable setting is commissural fusion without calcification or subchordal fusion and the absence of significant mitral regurgitation. Access is obtained from

the femoral vein using a transseptal technique in which a long metal catheter with a needle tip is advanced from the femoral vein through the right atrium and atrial septum at the level of the foramen ovale into the left atrium. A guidewire is advanced into the left ventricle, and a balloon-dilatation catheter is negotiated across the mitral valve and inflated to a predetermined size to enlarge the valve. The most commonly used dilatation catheter is the Inoue balloon. The technique splits the commissural fusion and commonly results in a doubling of the mitral valve area. The success of the procedure in favorable anatomy is 95%, and severe complications are rare (1–2%). The most common complications are tamponade due to puncture into the pericardium during the transseptal puncture or the creation of severe mitral regurgitation due to damage to the valve leaflets.

Severe mitral regurgitation can be treated percutaneously using the MitraClip (Abbott, Abbott Park, Illinois) device. The procedure involves the passage of a catheter into the left atrium using the trans-septal technique. A special catheter with a metallic clip on the end is passed through the mitral valve and retracted to catch and clip together the mid portion of the anterior and posterior mitral valve leaflets. The clip creates a double opening in the mitral valve and thereby reduces mitral regurgitation similar to the surgical Alfieri repair. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) trial, the device was less effective than surgical repair or replacement but was shown to be safe. Subsequent trials have shown it to be reasonably effective for patients who are not good candidates for surgical repair, particularly when the regurgitation is due to functional causes. The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial showed that, in patients with heart failure and functional mitral regurgitation who were carefully selected based on clinical and echocardiographic features, the procedure can reduce mortality.

Severe aortic stenosis can be treated with balloon valvuloplasty as well. In this setting, the valvuloplasty balloon catheter is placed retrograde across the aortic valve from the femoral artery and briefly inflated to stretch open the valve. The success is much less favorable, with only 50% achieving an aortic valve area of  $>1 \text{ cm}^2$  and a restenosis rate of 25–50% after 6–12 months. This poor success rate has limited its use to patients who are not surgical candidates or as a bridge to surgery or transcatheter aortic valve replacement (TAVR). In this setting, the intermediate-term mortality rate of the procedure is high (10%). Repeat aortic valvuloplasty as a treatment for aortic valve restenosis has been reported.

Percutaneous TAVR has been shown to be an effective treatment for low-, intermediate-, and high-risk patients and inoperable patients with aortic stenosis. Currently, three valve models, the Edwards SAPIEN valve (Edwards Lifescience, Irvine, California), the CoreValve ReValving system (Medtronic, Minneapolis, Minnesota), and the Lotus valve (Boston Scientific, Natick, Massachusetts), are available. Data to date show excellent durability of the valves, although long-term outcomes of 10 years are not yet available. The CoreValve and Lotus valves are self-expanding, whereas the Edwards valve is balloon expanded. The cannulas are large (14–22 French), and retrograde access via the femoral artery is most commonly chosen, if possible. In patients with peripheral artery disease, access via the subclavian artery, aorta, or transapically through a surgical incision can be used. Following balloon valvuloplasty, the valve is positioned across the valve and deployed with postdeployment balloon inflation to ensure full contact with the aortic annulus. The success rate is >90%, and the 30-day mortality rate is 2–15% based on preoperative risk. The Placement of Aortic Transcatheter Valve (PARTNER) randomized trial of the Edwards valve showed a 55% reduction in 1-year mortality and major adverse events in the extreme-risk group randomized to TAVR compared with medical therapy. In separate

randomized trials, low-, moderate-, and high-risk patients had similar outcomes to surgical valve replacement at 1 year. As a result, this valve is approved for low-, intermediate-, high-, and extreme-risk patients with severe symptomatic aortic stenosis.

Aortic and mitral bioprosthetic valve degeneration can be treated with repeat surgery or, in high-risk patients, with a valve-in-valve procedure where a percutaneous valve is placed inside of the prior surgical valve. It has been shown to be effective for aortic and mitral valves.

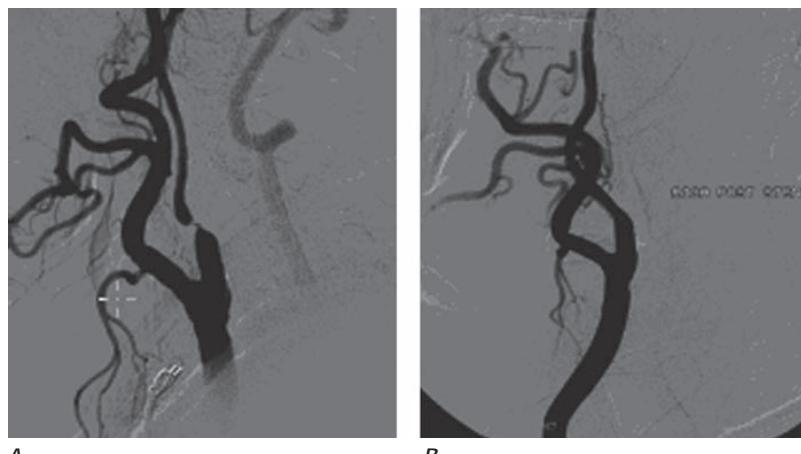
Pulmonic stenosis can also be effectively treated with balloon valvuloplasty and percutaneously replaced with the Melody valve (Medtronic). Tricuspid valve interventions are increasingly being performed.

## PERIPHERAL ARTERY INTERVENTIONS

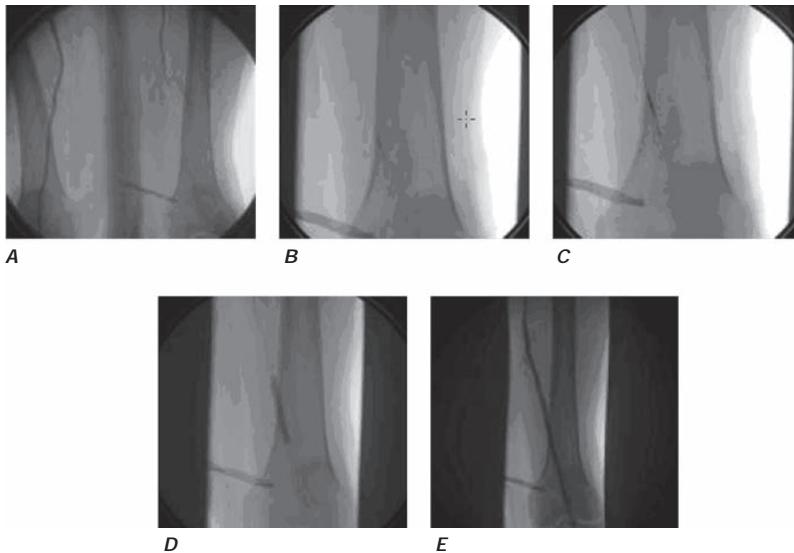
The use of percutaneous interventions to treat symptomatic patients with arterial obstruction in the carotid, renal, aortic, and peripheral vessels is an effective alternative to vascular surgery. Randomized clinical trial data support the use of carotid stenting in patients at high risk of complications from carotid endarterectomy (Fig. 276-4). Recent trials suggest similar outcomes with carotid stenting and carotid endarterectomy in patients at average risk, although depending on the patient's risk for perioperative stroke or myocardial infarction, one procedure may be preferred over the other. The success rate of peripheral artery interventional procedures has been improving, including treatment for long segments of occlusive disease historically treated by peripheral bypass surgery (Fig. 276-5). The use of drug-coated balloons and drug-eluting stents has shown to reduce restenosis when compared with balloon angioplasty alone. Peripheral intervention is increasingly part of the training of an interventional cardiologist, and most programs now require an additional year of training after the interventional cardiology training year. The techniques and outcomes are described in detail in the chapter on peripheral vascular disease (Chap. 281).

## CIRCULATORY SUPPORT TECHNIQUES

The use of circulatory support techniques is indicated for the management of patients with shock or hemodynamic instability and occasionally is needed in order to safely perform PCI on hemodynamically unstable patients. It also can be useful in helping to stabilize patients before surgical interventions. The most commonly used device is the percutaneous intraaortic balloon pump developed in the early 1960s. A 7- to 10-French, 25- to 50-mL balloon catheter is placed retrograde from the femoral artery into the descending aorta between the aortic arch and the abdominal aortic bifurcation. It is connected to a helium gas inflation system that synchronizes the inflation to coincide with early diastole with deflation by mid-diastole. As a result, it increases early diastolic pressure, lowers systolic pressure, and lowers late diastolic pressure through displacement of blood from the descending



**FIGURE 276-4** *A*, An example of a high-risk patient who requires carotid revascularization but who is not a candidate for carotid endarterectomy. *B*, Carotid artery stenting resulted in an excellent angiographic result. (From M Belkin, DL Bhatt: Carotid stenting in the elderly: Is 80 the new 60? *Circulation* 119:2302; 2009; with permission.)



**FIGURE 276-5** Peripheral interventional procedures have become highly effective at treating anatomic lesions previously amenable only to bypass surgery. **A.** Complete occlusion of the left superficial femoral artery. **B.** Wire and catheter advanced into subintimal space. **C.** Intravascular ultrasound positioned in the subintimal space to guide retrograde wire placement through the occluded vessel. **D.** Balloon dilation of the occlusion. **E.** Stent placement with excellent angiographic result. (Reprinted from A Almahameed, DL Bhatt: Contemporary management of peripheral arterial disease: III. Endovascular and surgical management. *Cleve Clin J Med* 2006; 73(suppl 4):S45-S51. With permission from The Cleveland Clinic Foundation. © 2006. The Cleveland Clinic Foundation. All rights reserved.)

aorta (counterpulsation). This results in an increase in coronary blood flow and a decrease in afterload. It is contraindicated in patients with aortic regurgitation, aortic dissection, or severe peripheral artery disease. The major complications are vascular and thrombotic. Intravenous heparin is given in order to reduce thrombotic complications.

Another support device is the Impella (Abiomed, Danvers, Massachusetts). The Impella catheter is placed percutaneously from the femoral artery into the left ventricle. The catheter has a small microaxial pump at its tip that can pump up to 2.5–5 L/min from the left ventricle to the aorta. The smaller devices can be placed percutaneously, but the larger devices need surgical access. Other support devices include TandemHeart (CardiacAssist, Pittsburgh, Pennsylvania), which involves placement of a large 21-French catheter from the femoral vein through the right atrium into the left atrium using the transseptal technique and a catheter in the femoral artery. A centrifugal pump can deliver 5 L of blood per minute. It may be useful in patients in shock or with STEMI or very-high-risk PCI. Patients can also be placed on peripheral extracorporeal membrane oxygenation (ECMO) using large cannulas placed in the femoral artery and vein. This technique can be performed emergently or electively in the catheterization laboratory and is useful for support of patients with acute respiratory failure or cardiac failure.

### INTERVENTIONS FOR PULMONARY EMBOLISM

The treatment of deep vein thrombosis is intravenous anticoagulation, with placement of an inferior vena cava filter if recurrent pulmonary emboli (PE) occur or anticoagulation is not possible. Post-phlebitic syndrome is a serious condition due to chronic venous obstruction that can lead to chronic leg edema and venous ulcers. Randomized data show that mechanical treatments may have a selective role in treatment of large iliofemoral deep-vein thrombosis.

PE should be treated with fibrinolytic agents if massive and in some cases if submassive. Surgical pulmonary embolectomy is an option for the treatment of massive PE with hemodynamic instability in patients who have contraindications for systemic fibrinolysis or those in whom it has failed. Catheter-based therapies for submassive and massive PEs are still evolving, but studies have shown promise. The techniques employed include the use of aspiration of the clot with a large catheter (10 French), intraclot infusion of a thrombolytic agent followed by aspiration, ultrasound-assisted catheter-directed thrombolysis, and use of rheolytic thrombectomy. Success for these techniques has been reported to be 80–90%, with major complications occurring in 2–4% of patients.

### INTERVENTIONS FOR REFRACTORY HYPERTENSION

The recent recognition of the importance of the renal sympathetic nerves in modulating blood pressure has led to a technique to selectively denervate renal sympathetic nerves in patients with refractory hypertension. The procedure involves applying low-power radiofrequency treatment via a catheter along the length of both renal arteries. Despite promising nonrandomized data, in the randomized Symplicity HTN-3 trial, renal denervation did not significantly reduce blood pressure compared with medical therapy. Further optimization of the technique is ongoing with some evidence from small randomized trials of modest efficacy, with larger scale evaluation ongoing.

### CONCLUSION

Interventional cardiology continues to expand its borders. Treatment for coronary artery disease, including complex anatomic subsets, continues to advance. Technological advances such as drug-eluting stents, now already in their second generation, are improving the results of PCI. PCI is the treatment of choice for patients with acute coronary syndromes. For patients with stable coronary disease, PCI is effective in symptom alleviation. Use of a Heart Team is the best way to make decisions concerning which revascularization—PCI or CABG—is best for an individual patient. Treatment of peripheral and cerebrovascular disease can be effective with percutaneous techniques. Structural heart disease is increasingly being treated with percutaneous options, with interventional approaches such as TAVR becoming preferred over surgical aortic valve replacement. Further growth of invasive procedures is anticipated in years to come.

### FURTHER READING

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Hypertension is one of the leading causes of the global burden of disease. Elevated blood pressure affects more than one billion individuals and causes an estimated 9.4 million deaths per year. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease (PAD). It often is associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors. Although antihypertensive therapy reduces the risks of cardiovascular and renal disease, large segments of the hypertensive population are either untreated or inadequately treated.

## EPIDEMIOLOGY

Blood pressure levels, the rate of age-related increases in blood pressure, and the prevalence of hypertension vary among countries and among subpopulations within a country. Hypertension is present in all populations except for small numbers of individuals living in isolated societies. In industrialized societies, blood pressure increases steadily during the first two decades of life. In children and adolescents, blood pressure is associated with growth and maturation, and blood pressure "tracks" over time in children and between adolescence and young adulthood. In the United States, average systolic blood pressure is higher for men than for women during early adulthood, although among older individuals the age-related rate of rise is steeper for women. Diastolic blood pressure also increases progressively with age until ~55 years, after which it tends to decrease. The consequence is a widening of pulse pressure (the difference between systolic and diastolic blood pressure) beyond age 60.

In the United States, based on criteria for defining hypertension prior to 2018, ~78 million adults have hypertension. Hypertension prevalence is 33.5% in non-Hispanic blacks, 28.9% in non-Hispanic whites, and 20.7% in Mexican Americans. Among individuals aged 60 years, the prevalence is 65.4%. Recent evidence suggests that the prevalence of hypertension in the United States may be increasing, possibly as a consequence of increasing obesity. The prevalence of hypertension and stroke mortality rates is higher in the southeastern United States than in other regions. In African Americans, hypertension appears earlier, is generally more severe, and results in higher rates of morbidity and mortality from stroke, left ventricular hypertrophy, CHF, and end-stage renal disease (ESRD) than in white Americans. In the United States, hypertension awareness, treatment, and control rates have been improving for decades. According to National Health and Nutrition Examination Survey (NHANES) data, in 2009–2012, prevalence estimates for men and women, respectively, were 80.2% and 85.4% for hypertension awareness, 70.9% and 80.6% for treatment (88.4% and 94.4% in those who were aware), 69.5% and 68.5% for control in those being treated, and 49.3% and 55.2% for overall control in adults with hypertension.

Both environmental and genetic factors may contribute to variations in hypertension prevalence. Studies of societies undergoing "acculturation" and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension. Hypertension prevalence is also related to dietary NaCl intake, and the age-related increase in blood pressure may be augmented by a high NaCl intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. The urine sodium-to-potassium ratio (an index of both sodium and potassium intakes) is a stronger correlate of blood pressure than is either sodium or potassium alone. Alcohol consumption, psychosocial stress, and low levels of physical activity also may contribute to hypertension.

\*Deceased.

## GENETIC CONSIDERATIONS

Although specific genetic variants have been identified in rare Mendelian forms of hypertension, these variants are not applicable to the vast majority (>98%) of patients with hypertension. For most individuals, it is likely that hypertension represents a polygenic disorder in which a combination of genes acts in concert with environmental exposures to make only a modest contribution to blood pressure. Furthermore, different subsets of genes may lead to different phenotypes associated with hypertension, e.g., obesity, dyslipidemia, insulin resistance.

Adoption, twin, and family studies document a significant heritable component to blood pressure levels and hypertension. Animal models (including selectively bred rats and congenic rat strains) have identified a number of genetic loci and genes associated with hypertension. Clinically, although replication has been a challenge, results of candidate gene studies and genome-wide association studies have identified >25 rare mutations and >100 hypertension-related polymorphisms. A number of these polymorphisms are involved in pathways that regulate arterial pressure. However, blood pressure-related polymorphisms account for only ~3.5% of blood pressure variance, whereas based on family studies, heritability of hypertension is estimated to be in the range of 30–40%. One hypothesis to account for the "missing heritability" is that epigenetic modifications of DNA contribute to the heritability of blood pressure. Epigenetic processes are changes in gene expression that occur without changes in DNA sequence. In contrast to DNA sequence, the epigenome is relatively susceptible to modification by environmental exposures.

Preliminary evidence suggests that there may also be genetic and epigenetic determinants of target organ damage and vascular disease attributed to hypertension, including left ventricular hypertrophy and nephropathy. Specific genetic variants have been linked to CHD and stroke. Additionally, recent studies have identified specific genome-wide epigenetic modifications of DNA associated with hypertension and with risk of future myocardial infarction and CHD.

## MECHANISMS OF HYPERTENSION

To provide a framework for understanding the pathogenesis and treatment options for hypertensive disorders, it is useful to understand factors involved in the regulation of both normal and elevated arterial pressure. Cardiac output and peripheral resistance are the two determinants of arterial pressure (Fig. 277-1). Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries (lumen diameter 100–400 µm) and arterioles.

## INTRAVASCULAR VOLUME

The kidney is both a target and a cause of hypertension. Primary renal disease is the most common etiology of secondary hypertension. Mechanisms of kidney-related hypertension include a diminished capacity to excrete sodium, excessive renin secretion in relation to volume status, and sympathetic nervous system overactivity. Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds the capacity of the kidney to excrete sodium, vascular volume may initially expand and cardiac output may increase. Many vascular beds have the capacity

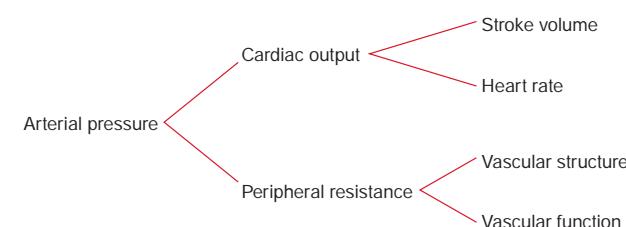


FIGURE 277-1 Determinants of arterial pressure.

to autoregulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase, since

$$\text{Blood flow} = \frac{\text{Pressure across the vascular bed}}{\text{Vascular resistance}}$$

The initial elevation of blood pressure in response to vascular volume expansion may be related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal. Whether this hypothesized sequence of events occurs in the pathogenesis of hypertension is not clear. What is clear is that salt can activate a number of neural, endocrine/paracrine, and vascular mechanisms, which have the potential to increase arterial pressure. The effect of sodium on blood pressure is related to the provision of sodium with chloride; non-chloride salts of sodium have little or no effect on blood pressure. As arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this "pressure-natriuresis" phenomenon may involve a subtle increase in the glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance.

NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due either to intrinsic renal disease or to increased production of a salt-retaining hormone (mineralocorticoid) resulting in increased renal tubular reabsorption of sodium. Renal tubular sodium reabsorption also may be augmented by increased neural activity to the kidney. In each of these situations, a higher arterial pressure may be required to achieve sodium balance. Conversely, salt-wasting disorders are associated with low blood pressure levels. End stage renal disease (ESRD) is an extreme example of volume-dependent hypertension. In ~80% of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20%, the mechanism of hypertension is related to increased activity of the renin-angiotensin system and is likely to be responsive to pharmacologic blockade of renin-angiotensin.

### AUTONOMIC NERVOUS SYSTEM

Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure. Norepinephrine, epinephrine, and dopamine all play important roles in tonic and phasic cardiovascular regulation.

The activities of the adrenergic receptors are mediated by guanine nucleotide-binding regulatory proteins (G proteins) and by intracellular concentrations of downstream second messengers. In addition to receptor affinity and density, physiologic responsiveness to catecholamines may be altered by the efficiency of receptor-effector coupling at a site "distal" to receptor binding. Receptor sites are relatively specific both for the transmitter substance and for the response that occupancy of the receptor site elicits. Based on their physiology and pharmacology, adrenergic receptors have been divided into two principal types:  $\alpha_1$  and  $\alpha_2$ . These types have been differentiated further into  $\beta_1$  and  $\beta_2$  receptors. Recent molecular cloning studies have identified several additional subtypes. Receptors are occupied and activated more avidly by norepinephrine than by epinephrine, and the reverse is true for  $\beta_2$  receptors.  $\alpha_1$  Receptors are located on postsynaptic cells in smooth muscle and elicit vasoconstriction.  $\alpha_2$  Receptors are localized on presynaptic membranes of postganglionic nerve terminals that synthesize norepinephrine. When activated by catecholamines,  $\alpha_2$  receptors act as negative feedback controllers, inhibiting further norepinephrine release. In the kidney, activation of  $\alpha_1$ -adrenergic receptors increases renal tubular reabsorption of sodium. Different classes of antihypertensive agents either inhibit  $\alpha_1$  receptors or act as agonists of  $\alpha_2$  receptors and reduce systemic sympathetic outflow. Activation

of myocardial  $\alpha_1$  receptors stimulates the rate and strength of cardiac contraction and consequently increases cardiac output.  $\alpha_1$  Receptor activation also stimulates renin release from the kidney. Another class of antihypertensive agents acts by inhibiting  $\alpha_1$  receptors. Activation of  $\alpha_2$  receptors by epinephrine relaxes vascular smooth muscle and results in vasodilation.

Circulating catecholamine concentrations may affect the number of adrenoceptors in various tissues. Downregulation of receptors may be a consequence of sustained high levels of catecholamines and provides an explanation for decreasing responsiveness, or tachyphylaxis, to catecholamines. For example, orthostatic hypotension is frequently observed in patients with pheochromocytoma, possibly due to the lack of norepinephrine-induced vasoconstriction with assumption of the upright posture. Conversely, with chronic reduction of neurotransmitter substances, adrenoceptors may increase in number or be upregulated, resulting in increased responsiveness to the neurotransmitter. Chronic administration of agents that block adrenergic receptors may result in upregulation, and abrupt withdrawal of those agents may produce a condition of temporary hypersensitivity to sympathetic stimuli. For example, clonidine is an antihypertensive agent that is a centrally acting  $\alpha_2$  agonist that inhibits sympathetic outflow. Rebound hypertension may occur with the abrupt cessation of clonidine therapy, probably as a consequence of upregulation of  $\alpha_1$  receptors.

Several reflexes modulate blood pressure on a minute-to-minute basis. One arterial baroreflex is mediated by stretch-sensitive sensory nerve endings in the carotid sinuses and the aortic arch. The rate of firing of these baroreceptors increases with arterial pressure, and the net effect is a decrease in sympathetic outflow, resulting in decreases in arterial pressure and heart rate. This is a primary mechanism for rapid buffering of acute fluctuations of arterial pressure that may occur during postural changes, behavioral or physiologic stress, and changes in blood volume. However, the activity of the baroreflex declines or adapts to sustained increases in arterial pressure such that the baroreceptors are reset to higher pressures. Baroreflex control of blood pressure deteriorates with advancing age, hypertension, and atherosclerosis. The consequences are increased blood pressure variability and an increased incidence of orthostatic hypotension. Patients with autonomic neuropathy and impaired baroreflex function may have extremely labile blood pressures with difficult-to-control episodic blood pressure spikes associated with tachycardia.

In both normal-weight and obese individuals, hypertension often is associated with increased sympathetic outflow. Based on recordings of postganglionic muscle nerve activity (detected by a microelectrode inserted in a peroneal nerve in the leg), sympathetic outflow tends to be higher in hypertensive than in normotensive individuals. Sympathetic outflow is increased in obesity-related hypertension and in hypertension associated with obstructive sleep apnea. Baroreceptor activation via electrical stimulation of carotid sinus afferent nerves lowers blood pressure in patients with "resistant" hypertension. Drugs that block the sympathetic nervous system are potent antihypertensive agents, indicating that the sympathetic nervous system plays a permissive, although not necessarily a causative, role in the maintenance of increased arterial pressure.

Pheochromocytoma is the most blatant example of hypertension related to increased catecholamine production, in this instance by a tumor. Blood pressure can be reduced by surgical excision of the tumor or by pharmacologic treatment with an  $\alpha_1$  receptor antagonist or with an inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis.

### RENIN-ANGIOTENSIN-ALDOSTERONE

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Renin is an aspartyl protease that is synthesized as an enzymatically inactive precursor, prorenin. Most renin in the circulation is synthesized in the renal afferent renal arteriole. Prorenin may be secreted directly into the circulation or may be activated within secretory cells

and released as active renin. There are three primary stimuli for renin secretion: (1) decreased NaCl transport in the distal portion of the thick ascending limb of the loop of Henle that abuts the corresponding afferent arteriole (macula densa), (2) decreased pressure or stretch within the renal afferent arteriole (baroreceptor mechanism), and (3) sympathetic nervous system stimulation of renin-secreting cells via adrenoreceptors. Conversely, renin secretion is inhibited by increased NaCl transport in the thick ascending limb of the loop of Henle, by increased stretch within the renal afferent arteriole, and by  $\beta_1$  receptor blockade. In addition, angiotensin II directly inhibits renin secretion due to angiotensin II type 1 receptors on juxtaglomerular cells, and renin secretion increases in response to pharmacologic blockade of either the angiotensin-converting enzyme or angiotensin II receptors.

Once released into the circulation, active renin cleaves a substrate, angiotensinogen, to form an inactive decapeptide, angiotensin I (Fig. 277-2). A converting enzyme, located primarily but not exclusively in the pulmonary circulation, converts angiotensin I to the active octapeptide, angiotensin II, by releasing the C-terminal histidyl-leucine dipeptide. The same converting enzyme cleaves a number of other peptides, including and thereby inactivating the vasodilator bradykinin. Acting primarily through angiotensin II type 1 receptors ( $AT_1$ ) on cell membranes, angiotensin II is a potent pressor substance and is the primary trophic factor for the secretion of aldosterone by the adrenal zona glomerulosa. Utilizing various signal transduction cascades, the  $AT_1$ R is believed to mediate most functions of angiotensin II, resulting in hypertension, cardiovascular remodeling, and end-organ damage. The angiotensin II type 2 receptor ( $AT_2$ R) has the opposite functional effects of the  $AT_1$ R. The  $AT_2$ R induces vasodilation, sodium excretion, and inhibition of cell growth and matrix formation. The  $AT_2$ R may improve vascular remodeling by stimulating smooth muscle cell apoptosis and contributes to the regulation of glomerular filtration rate.  $AT_1$ R blockade induces an increase in  $AT_2$ R activity.

Renin-secreting tumors are clear examples of renin-dependent hypertension. In the kidney, these tumors include benign hemangiopericytomas of the juxtaglomerular apparatus and, infrequently, renal carcinomas, including Wilms' tumors. Renin-producing carcinomas also have been described in lung, liver, pancreas, colon, and adrenals. Renovascular hypertension is another renin-mediated form of hypertension. Obstruction of the renal artery leads to decreased renal

perfusion pressure, thereby stimulating renin secretion. Over time, possibly as a consequence of secondary renal damage, this form of hypertension may become less renin-dependent.

Angiotensinogen, renin, and angiotensin II are also synthesized locally in many tissues, including the brain, pituitary, aorta, arteries, heart, adrenal glands, kidneys, adipocytes, leukocytes, ovaries, testes, uterus, spleen, and skin. Angiotensin II in tissues may be formed by the enzymatic activity of renin or by other proteases, e.g., tonin, chymase, and cathepsins. In addition to regulating local blood flow, tissue angiotensin II is a mitogen that stimulates growth and contributes to modeling and repair. Excess tissue angiotensin II may contribute to atherosclerosis, cardiac hypertrophy, and renal failure and, consequently, may be a target for pharmacologic therapy to prevent target organ damage.

Angiotensin II is the primary trophic factor regulating the synthesis and secretion of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone synthesis is also dependent on potassium, and aldosterone secretion may be decreased in potassium-depleted individuals. Although acute elevations of adrenocorticotrophic hormone (ACTH) levels also increase aldosterone secretion, ACTH is not an important trophic factor for the chronic regulation of aldosterone.

Aldosterone is a potent mineralocorticoid that increases sodium reabsorption by amiloride-sensitive epithelial sodium channels (ENaC) on the apical surface of the principal cells of the renal cortical collecting duct (Chap. 309). Electric neutrality is maintained by exchanging sodium for potassium and hydrogen ions. Consequently, increased aldosterone secretion may result in hypokalemia and alkalosis. Cortisol also binds to the mineralocorticoid receptor but normally functions as a less potent mineralocorticoid than aldosterone because cortisol is converted to cortisone by the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2. Cortisone has no affinity for the mineralocorticoid receptor. Primary aldosteronism is a compelling example of mineralocorticoid-mediated hypertension. In this disorder, adrenal aldosterone synthesis and release are independent of renin-angiotensin, and renin release is suppressed by the resulting volume expansion.

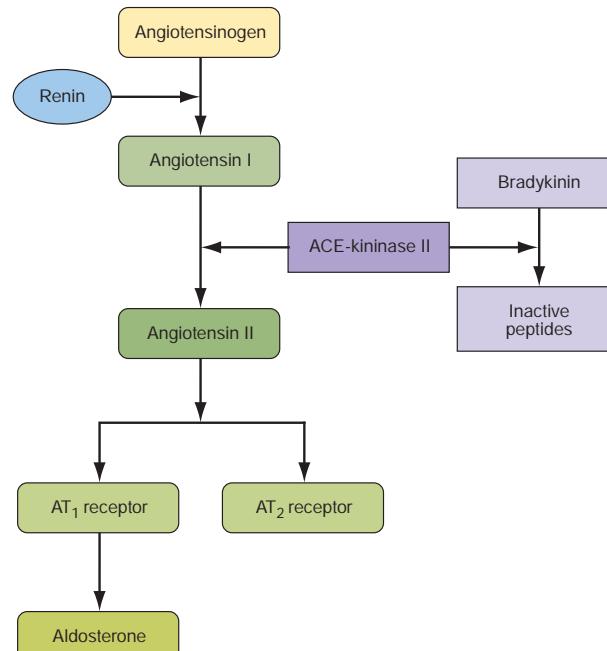
Mineralocorticoid receptors are expressed in a number of tissues in addition to the kidney, and mineralocorticoid receptor activation induces structural and functional alterations in the heart, kidney, and blood vessels, leading to myocardial fibrosis and left ventricular hypertrophy, nephrosclerosis, and vascular inflammation and remodeling, perhaps as a consequence of oxidative stress. These effects are amplified by a high salt intake. In animal models, spironolactone (an aldosterone antagonist) prevents aldosterone-induced myocardial fibrosis. In patients with CHF, low-dose spironolactone reduces the risk of progressive heart failure and sudden death from cardiac causes by 30%. Due to a renal hemodynamic effect, in patients with primary aldosteronism, high circulating levels of aldosterone also may cause glomerular hyperfiltration and albuminuria.

Increased activity of the renin-angiotensin-aldosterone axis is not invariably associated with hypertension. In response to a low-NaCl diet or to volume contraction, arterial pressure and volume homeostasis may be maintained by increased activity of the renin-angiotensin-aldosterone axis. Secondary aldosteronism (i.e., increased aldosterone secondary to increased renin-angiotensin), but not hypertension, also is observed in edematous states such as CHF and liver disease.

## VASCULAR MECHANISMS

Vascular radius and compliance of resistance arteries are important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and consequently, small decreases in lumen size significantly increase resistance. In hypertensive patients, structural, mechanical, or functional changes may reduce the lumen diameter of small arteries and arterioles. Remodeling refers to geometric alterations in the vessel wall without a change in vessel volume. Hypertrophic (increased cell size and increased deposition of intercellular matrix) or eutrophic vascular remodeling results in decreased lumen size and, hence, increased peripheral resistance. Apoptosis, low-grade inflammation, and vascular fibrosis also contribute to remodeling. Lumen diameter also is related to elasticity of

**FIGURE 277-2** Renin-angiotensin-aldosterone axis. ACE, angiotensin-converting enzyme.



the vessel. Vessels with a high degree of elasticity can accommodate an increase of volume with relatively little change in pressure, whereas in a semi-rigid vascular system, a small increment in volume induces a relatively large increment of pressure.

An association between arterial stiffness and hypertension is well established. A stiffened vasculature is less able to buffer short-term alterations in flow. Although it has been assumed that arterial stiffness is a manifestation of hypertension, recent evidence suggests that vascular stiffness may also contribute to elevated arterial pressure. Clinically, noninvasive determination of elevated pulse wave velocity between the carotid and femoral arteries is often interpreted as an indicator of arterial stiffness. Due to arterial stiffness, central blood pressures (aortic, carotid) may not correspond to brachial artery pressures. Ejection of blood into the aorta elicits a pressure wave that is propagated at a given velocity. The forward traveling wave generates a reflected wave that travels backward toward the ascending aorta. Although mean arterial pressure is determined by cardiac output and peripheral resistance, pulse pressure is related to the functional properties of large arteries and the amplitude and timing of the incident and reflected waves. Increased arterial stiffness results in increased pulse wave velocity of both incident and reflected waves. The consequence is augmentation of aortic systolic pressure and a reduction of aortic diastolic pressure, i.e., an increase in pulse pressure. The aortic augmentation index, a surrogate index of arterial stiffening, is calculated as the ratio of central arterial pressure to pulse pressure. However, wave reflections are also influenced by left ventricular structure and function. Central blood pressure may be measured directly by placing a sensor in the aorta or noninvasively by radial tonometry. Central blood pressure and the aortic augmentation index are independent predictors of cardiovascular disease and all-cause mortality. Central blood pressure also appears to be more strongly associated with preclinical organ damage than brachial blood pressure.

Ion transport by vascular smooth muscle cells may contribute to hypertension-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH ( $\text{pH}_i$ ). Three ion transport mechanisms participate in the regulation of  $\text{pH}_i$ : (1)  $\text{Na}^+/\text{H}^+$  exchange, (2)  $\text{Na}^+$ -dependent  $\text{HCO}_3^-/\text{Cl}^-$  exchange, and (3) cation-independent  $\text{HCO}_3^-/\text{Cl}^-$  exchange. Based on measurements in cell types that are more accessible than vascular smooth muscle (e.g., leukocytes, erythrocytes, platelets, skeletal muscle), activity of the  $\text{Na}^+/\text{H}^+$  exchanger is increased in hypertension, and this may result in increased vascular tone by two mechanisms. First, increased sodium entry may lead to increased vascular tone by activating  $\text{Na}^+/\text{Ca}^{2+}$  exchange and thereby increasing intracellular calcium. Second, increased  $\text{pH}_i$  enhances calcium sensitivity of the contractile apparatus, leading to an increase in contractility for a given intracellular calcium concentration. Additionally, increased  $\text{Na}^+/\text{H}^+$  exchange may stimulate growth of vascular smooth muscle cells by enhancing sensitivity to mitogens.

Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesizes and releases several vasoactive substances, including nitric oxide, a potent vasodilator. Endothelium-dependent vasodilation is impaired in hypertensive patients. This impairment often is assessed with high-resolution ultrasonography before and after the hyperemic phase of reperfusion that follows 5 min of forearm ischemia. Alternatively, endothelium-dependent vasodilation may be assessed in response to an intra-arterially infused endothelium-dependent vasodilator, e.g., acetylcholine. Endothelin is a vasoconstrictor peptide produced by the endothelium, and orally active endothelin antagonists may lower blood pressure in patients with resistant hypertension.

### IMMUNE MECHANISMS, INFLAMMATION, AND OXIDATIVE STRESS

Low-grade inflammation and uncontrolled activation of the immune system have been implicated in the pathogenesis of vascular injury and hypertension for at least four decades. Both thymus-derived cells (T cells) and bone marrow– or bursa-derived cells (B cells) are involved. Activation has been attributed to increased sympathetic nervous system activity, mechanical forces in the vascular wall, interstitial sodium

concentration, and a high salt intake. Inflammatory cytokines and free radicals secreted by activated immune cells may contribute to vascular and target organ injury. Inflammation and exudative injury are closely coupled. Inflammation, vascular stretch, angiotensin II, and salt have all been shown to result in the generation of reactive oxygen species (ROS), which modify T-cell function and further enhance inflammation. ROS also attenuate the effects of endogenous small-molecule vasodilators. Preliminary evidence suggests that hypertension is blunted and vascular endothelial function is preserved in experimental models that lack both T cells and B cells. In animal models of salt-sensitive hypertension, salt-related increases in renal perfusion pressure induce the infiltration of immune cells into the kidney. The infiltrating cells release cytokines and free radicals that may contribute to renal injury. Additionally, ROS within the renal medulla may disrupt pressure-natriuresis and thereby potentiate the development of hypertension.

Clinically, patients with primary hypertension have increased circulating levels of autoantibodies, and markers of oxidative stress have been described in both hypertensive and prehypertensive individuals. Increased numbers of activated immune cells (either in the circulation or tissue biopsies) and the inflammatory cytokines they produce also occur in patients with preeclampsia, resistant hypertension, malignant hypertension, and renal allograft rejection.

### PATHOLOGIC CONSEQUENCES OF HYPERTENSION

#### HEART

Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, increased atrial size, CHF, atherosclerotic coronary artery disease, microvascular disease, and cardiac arrhythmias, including atrial fibrillation. Independent of blood pressure, individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death. Control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease. Coronary artery calcium score provides a noninvasive estimate of target organ injury and is associated with cardiovascular events. However, there is currently relatively little information regarding the impact of improvement of this subclinical marker on prognosis.

CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two. Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in hypertensive patients. Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia. Cardiac catheterization provides the most accurate assessment of diastolic function. Alternatively, diastolic function can be evaluated by several noninvasive methods, including echocardiography and radionuclide angiography.

#### BRAIN

Stroke is the second most frequent cause of death in the world; it accounts for 5 million deaths each year, with an additional 15 million persons having nonfatal strokes. Elevated blood pressure is the strongest risk factor for stroke. Approximately 85% of strokes are due to infarction, and the remainder are due to either intracerebral or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals aged >65 years. Treatment of hypertension decreases the incidence of both ischemic and hemorrhagic strokes.

Hypertension is also associated with impaired cognition in an aging population, and longitudinal studies support an association between midlife hypertension and late-life cognitive decline. Vascular dementia and Alzheimer's disease often coexist. Hypertension is associated with beta amyloid deposition, a major pathologic factor in dementia. In addition to actual blood pressure level, arterial stiffness and visit-to-visit

blood pressure variability may be independently related to subclinical small vessel disease and subsequent cognitive decline. Hypertension-related cognitive impairment and dementia may also be a consequence of a single infarct due to occlusion of a "strategic" larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function.

Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50–150 mmHg) through a process termed *autoregulation* of blood flow. In patients with the clinical syndrome of malignant hypertension, encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Signs and symptoms of hypertensive encephalopathy may include severe headache, nausea and vomiting (often of a projectile nature), focal neurologic signs, and alterations in mental status. Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours. It is important to distinguish hypertensive encephalopathy from other neurologic syndromes that may be associated with hypertension, e.g., cerebral ischemia, hemorrhagic or thrombotic stroke, seizure disorder, mass lesions, pseudotumor cerebri, delirium tremens, meningitis, acute intermittent porphyria, traumatic or chemical injury to the brain, and uremic encephalopathy.

## KIDNEY

Hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the distribution of blood pressure above optimal pressure. Renal risk appears to be more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at every level of blood pressure.

Atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular injury also may be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. With progressive renal injury, there is a loss of autoregulation of renal blood flow, resulting in a lower blood pressure threshold for renal damage and a steeper slope between blood pressure and renal damage. The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration, and further renal damage. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft.

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio >300 mg/g) and microalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/g) are early markers of renal injury. They are also risk factors for renal disease progression and cardiovascular disease.

## PERIPHERAL ARTERIES

Blood vessels are a target organ atherosclerotic disease secondary to long-standing elevated blood pressure. Independent of blood pressure, arterial stiffness (measured as carotid-femoral pulse wave velocity or carotid pulse pressure) is associated with target organ disease, including stroke, heart disease, and renal failure. Hypertensive patients with arterial disease of the lower extremities are also at increased risk of future cardiovascular disease. Clinically, PAD may be recognized by the symptom of claudication. The ankle-brachial index (ratio of ankle to brachial systolic blood pressure) is a useful approach for evaluating peripheral arterial disease. An ankle-brachial index <0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. An ankle-brachial index <0.80 is associated with elevated blood pressure, particularly systolic blood pressure.

Whether arterial stiffness and vascular remodeling are primary alterations or secondary consequences of elevated arterial pressure remains to be established. Limited evidence suggests that vascular compliance and endothelium-dependent vasodilation may be

improved by aerobic exercise, weight loss, and antihypertensive agents. It remains to be determined whether these interventions affect arterial structure and stiffness via a blood pressure-independent mechanism and whether different classes of antihypertensive agents preferentially affect vascular structure and function.

## DEFINING HYPERTENSION

From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. In adults, there is a continuous, incremental risk of cardiovascular disease, stroke, and renal disease across levels of both systolic and diastolic blood pressure. The Multiple Risk Factor Intervention Trial (MRFIT), which included >350,000 male participants, demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality, extending down to systolic blood pressures of 120 mmHg. Similarly, results of a meta-analysis involving almost 1 million participants indicate that ischemic heart disease mortality, stroke mortality, and mortality from other vascular causes are directly related to the height of the blood pressure, beginning at 115/75 mmHg, without evidence of a threshold. Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic pressure. Among older individuals, systolic blood pressure and pulse pressure are more powerful predictors of cardiovascular disease than is diastolic blood pressure.

Clinically, hypertension may be defined as that level of blood pressure at which the institution of therapy reduces blood pressure-related morbidity and mortality. Clinical criteria for defining hypertension generally have been based on the average of two or more seated blood pressure readings during each of two or more outpatient visits. One recent classification recommends hypertension be defined as systolic blood pressure 130 mmHg or diastolic blood pressure 80 mmHg (**Table 277-1**). In contrast, previous guidelines defined hypertension as systolic blood pressure 140 mmHg or diastolic blood pressure

90 mmHg. Compared to the earlier definition, based on the new definition, the prevalence of hypertension among U.S. adults is substantially higher (46 vs 32%). In children and adolescents, hypertension is generally defined as systolic and/or diastolic blood pressure consistently >95th percentile for age, sex, and height. Blood pressures between the 90th and 95th percentiles are considered prehypertensive and are an indication for lifestyle interventions.

Out-of-office measurement of blood pressure can be helpful for confirmation and management of hypertension. Ambulatory monitors are usually programmed to obtain blood pressure readings every 15–30 min throughout the day and every 15–60 min during the night. Although ambulatory monitoring is generally accepted as the best out-of-office measurement, home blood pressure monitoring with less frequent measures is a more practical approach. Because ambulatory blood pressure recordings yield multiple readings throughout the day and night, they provide a more comprehensive assessment of the vascular burden of hypertension than do a limited number of office readings. Home blood pressures, including 24-h blood pressure recordings, more reliably predict target organ damage than do usual office blood pressures. Nighttime blood pressures are generally 10–20% lower than daytime blood pressures, and an attenuated nighttime blood pressure "dip" is associated with increased cardiovascular disease risk. Less well

**TABLE 277-1** Blood Pressure Classification in Adults

BLOOD PRESSURE CATEGORY	SYSTOLIC (mmHg)		DIASTOLIC (mmHg)
Normal	<120	and	<80
Elevated	120–129	and	<80
<b>Hypertension</b>			
Stage 1	130–139	or	80–89
Stage 2	140	or	>90

Source: Reproduced with permission from PK Whelton et al: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. Hypertension 71:1269, 2018.

**TABLE 277-2 Systolic Hypertension with Wide Pulse Pressure**

1. Decreased vascular compliance (arteriosclerosis)
2. Increased cardiac output
  - a. Aortic regurgitation
  - b. Thyrotoxicosis
  - c. Hyperkinetic heart syndrome
  - d. Fever
  - e. Arteriovenous fistula
  - f. Patent ductus arteriosus

established, the rate of rise of blood pressure in the early morning (blood pressure "surge") may also predict a higher risk of cardiovascular events.

Home blood pressure and average 24-h ambulatory blood pressure measurements are generally lower than clinic blood pressures. Recent guidelines provide values of home and ambulatory blood pressure monitoring that correspond to office-measured blood pressures. Approximately 15–20% of patients with elevated office blood pressures have normal ambulatory readings, a phenomenon termed "white coat hypertension." Long-term outcomes of individuals with white coat hypertension are more similar to normotensive individuals than to individuals with sustained hypertension (elevation of both office and out-of-office blood pressures). In contrast, "masked hypertension" (normal office blood pressure and elevated out-of-office blood pressure) is associated with a risk of cardiovascular disease and all-cause mortality twice that of normotensive individuals, with a risk range similar to that of patients with sustained hypertension. In population-based surveys, the prevalence of masked hypertension varies from 10 to 30%.

## CLINICAL DISORDERS OF HYPERTENSION

Depending on methods of patient ascertainment, ~80–95% of hypertensive patients are diagnosed as having primary, or "essential," hypertension (inclusive of patients with obesity and the metabolic syndrome). In the remaining 5–20% of hypertensive patients, an underlying disorder causing the elevation of blood pressure can be identified (**Tables 277-2 and 277-3**). In individuals with "secondary"

hypertension, a specific mechanism for the blood pressure elevation is often more apparent. Clues to secondary hypertension include characteristic clinical features, severe or drug-resistant hypertension, recent onset of hypertension, disproportionate target organ damage, and younger age.

## PRIMARY HYPERTENSION

Primary hypertension tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. The prevalence of primary hypertension increases with age, and individuals with relatively high blood pressures at younger ages are at increased risk for the subsequent development of hypertension. It is likely that primary hypertension represents a spectrum of disorders with different underlying pathophysiologies. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal. When plasma renin activity (PRA) is plotted against 24-h sodium excretion, ~10–15% of hypertensive patients have high PRA, and 25% have low PRA. High-renin patients may have a vasoconstrictor form of hypertension, whereas low-renin patients may have volume-dependent hypertension. Compared to other U.S. populations, African Americans have a high prevalence of hypertension and hypertension-related cardiovascular disease and renal morbidity and mortality. Hypertensive African Americans tend to have low plasma renin and volume-dependent hypertension.

## OBESITY AND THE METABOLIC SYNDROME

(See also **Chap. 408**) Sixty percent of hypertensive adults are >20% overweight, and there is a well-documented association between obesity (body mass index >30 kg/m<sup>2</sup>) and hypertension. Cross-sectional studies document a direct linear correlation between body weight (or body mass index) and blood pressure. Centrally located body fat is a more important determinant of blood pressure elevation than is peripheral body fat.

Hypertension and dyslipidemia frequently occur together and in association with resistance to insulin-stimulated glucose uptake. This clustering of risk factors is often, but not invariably, associated with obesity, particularly abdominal obesity. Insulin resistance also is associated with an unfavorable imbalance in the endothelial production of mediators that regulate platelet aggregation, coagulation, fibrinolysis, and vessel tone. When these risk factors cluster, the risks for CHD, stroke, diabetes, and cardiovascular disease mortality are increased further.

Depending on the populations studied and the methodologies for defining insulin resistance, ~25–50% of nonobese, nondiabetic hypertensive persons are insulin resistant. The constellation of insulin resistance, abdominal obesity, hypertension, and dyslipidemia has been designated as the *metabolic syndrome*. First-degree relatives of patients with primary hypertension are also insulin resistant, and hyperinsulinemia (a surrogate marker of insulin resistance) may predict the eventual development of hypertension and cardiovascular disease. An antinatriuretic effect of insulin may contribute to the development of hypertension. Although the metabolic syndrome may in part be heritable as a polygenic condition, the expression of the syndrome is modified by environmental factors, such as degree of physical activity and diet. Insulin sensitivity increases and blood pressure decreases in response to weight loss. The recognition that cardiovascular disease risk factors tend to cluster within individuals has important implications for the evaluation and treatment of hypertension. Evaluation of both hypertensive patients and individuals at risk for developing hypertension should include assessment of overall cardiovascular disease risk. Similarly, introduction of lifestyle modification strategies and drug therapies should address overall risk and not focus exclusively on hypertension.

## RENAL PARENCHYMAL DISEASES

Virtually all disorders of the kidney may cause hypertension, and renal disease is the most common cause of secondary hypertension.

**TABLE 277-3 Secondary Causes of Systolic and Diastolic Hypertension**

Renal	Parenchymal diseases, renal cysts (including polycystic kidney disease), renal tumors (including renin-secreting tumors), obstructive uropathy
Renovascular	Arteriosclerotic, fibromuscular dysplasia
Adrenal	Primary aldosteronism, Cushing's syndrome, 17 $\alpha$ -hydroxylase deficiency, 11 $\beta$ -hydroxylase deficiency, 11-hydroxysteroid dehydrogenase deficiency (licorice), pheochromocytoma
Aortic coarctation	
Obstructive sleep apnea	
Preeclampsia/eclampsia	
Neurogenic	Psychogenic, diencephalic syndrome, familial dysautonomia, polyneuritis (acute porphyria, lead poisoning), acute increased intracranial pressure, acute spinal cord section
Miscellaneous endocrine	Hypothyroidism, hyperthyroidism, hypercalcemia, acromegaly
Medications	High-dose estrogens, adrenal steroids, decongestants, appetite suppressants, amphetamines, cyclosporine, tricyclic antidepressants, atypical antipsychotics, monoamine oxidase inhibitors, erythropoietin, nonsteroidal anti-inflammatory agents, alcohol, herbal supplements, cocaine, others
Mendelian forms of hypertension	See Table 277-4

Hypertension is present in >80% of patients with chronic renal failure. In general, hypertension is more severe in glomerular diseases than in interstitial diseases such as chronic pyelonephritis. Conversely, hypertension may cause nephrosclerosis, and in some instances, it may be difficult to determine whether hypertension or renal disease was the initial disorder. Proteinuria >1000 mg/d and an active urine sediment are indicative of primary renal disease. In either instance, the goals are to control blood pressure and retard the rate of progression of renal dysfunction.

### RENOVASCULAR HYPERTENSION

Hypertension due to an occlusive lesion of a renal artery, renovascular hypertension, is a potentially curable form of hypertension. Two groups of patients are at risk for this disorder: older arteriosclerotic patients who have a plaque obstructing the renal artery, frequently at its origin, and patients with fibromuscular dysplasia. Atherosclerosis accounts for the large majority of patients with renovascular hypertension. Although fibromuscular dysplasia may occur at any age, it has a strong predilection for young white women. The lesions of fibromuscular dysplasia are frequently bilateral and, in contrast to atherosclerotic renovascular disease, tend to affect more distal portions of the renal artery.

Renovascular hypertension should be considered in patients with other evidence of atherosclerotic vascular disease. Severe or refractory hypertension, recent loss of hypertension control or recent onset of moderately severe hypertension, carotid or femoral artery bruits, flash pulmonary edema, and unexplained deterioration of renal function or deterioration of renal function associated with an angiotensin-converting enzyme inhibitor (ACEI) should raise the possibility of renovascular hypertension. Approximately 50% of patients with renovascular hypertension have an abdominal or flank bruit, and the bruit is more likely to be hemodynamically significant if it lateralizes or extends throughout systole into diastole.

If renal artery stenosis is suspected and if the clinical condition warrants an intervention such as percutaneous transluminal renal angioplasty (PTRA), placement of a vascular endoprosthesis (stent), or surgical renal revascularization, imaging studies should be the next step in the evaluation. Doppler ultrasound of the renal arteries produces reliable estimates of renal blood flow and offers the opportunity to track a lesion over time. Positive studies usually are confirmed at angiography, whereas false-negative results occur frequently, particularly in obese patients. Gadolinium-contrast magnetic resonance angiography offers clear images of the proximal renal artery but may miss distal lesions. An advantage is the opportunity to image the renal arteries with an agent that is not nephrotoxic. Contrast arteriography remains the "gold standard" for evaluation and identification of renal artery lesions.

Some degree of renal artery obstruction may be observed in almost 50% of patients with atherosclerotic disease, and there are several approaches for evaluating the functional significance of such a lesion to predict the effect of vascular repair on blood pressure control and renal function. Functionally significant lesions generally occlude >70% of the lumen of the affected renal artery. On angiography, the presence of collateral vessels to the ischemic kidney suggests a functionally significant lesion. A lateralizing renal vein renin ratio (ratio >1.5 of affected side/contralateral side) has a 90% predictive value for a lesion that would respond to vascular repair; however, the false-negative rate for blood pressure control is 50–60%.

A decision concerning vascular repair versus medical therapy and the type of repair procedure should be individualized. Several randomized clinical trials have found that PTCA with stent placement in patients with arteriosclerotic renal artery stenosis offers no advantages to medical therapy in controlling blood pressure, reducing cardiovascular events and mortality, or preserving kidney function. If blood pressure is adequately controlled with medical therapy and renal function remains stable, there may be little impetus to pursue an extensive evaluation for renal artery stenosis. Patients with long-standing hypertension, advanced renal insufficiency, or diabetes mellitus are less likely to benefit from renal vascular repair. Patients with fibromuscular disease

have more favorable outcomes with vascular repair than do patients with atherosclerotic lesions, presumably owing to their younger age, shorter duration of hypertension, and less systemic disease. The most effective medical therapies for renovascular hypertension include an ACE inhibitor or an angiotensin II receptor blocker; however, these agents decrease glomerular filtration rate in a stenotic kidney owing to efferent renal arteriolar dilation. In the presence of bilateral renal artery stenosis or renal artery stenosis to a solitary kidney, progressive renal insufficiency may result from the use of these agents. Importantly, the renal insufficiency is generally reversible after discontinuation of the offending drug.

### PRIMARY ALDOSTERONISM

Excess aldosterone production due to primary aldosteronism is a potentially curable form of hypertension. In patients with primary aldosteronism, increased aldosterone production is independent of the renin-angiotensin system, and the consequences are sodium retention, hypertension, hypokalemia, low PRA, cardiovascular disease, and kidney damage. The reported prevalence of this disorder varies from <2 to ~15% of hypertensive individuals. In part, this variation is related to the intensity of screening and the criteria for establishing the diagnosis.

History and physical examination provide little information about the diagnosis. The age at the time of diagnosis is generally the third through fifth decade. Hypertension is usually mild to moderate but occasionally may be severe; primary aldosteronism should be considered in all patients with refractory hypertension. Most patients are asymptomatic; however, infrequently, polyuria, polydipsia, paresthesias, or muscle weakness may be present as a consequence of hypokalemic alkalosis. Although serum K<sup>+</sup> is an insensitive screening test, in hypertensive patients with unprovoked hypokalemia (i.e., unrelated to diuretics, vomiting, or diarrhea), the prevalence of primary aldosteronism approaches 40–50%. In patients on diuretics, serum potassium <3.1 mmol/L (<3.1 meq/L) also raises the possibility of primary aldosteronism.

The ratio of plasma aldosterone (PA) to PRA (PA/PRA) is a useful screening test. These measurements preferably are obtained in ambulatory patients in the morning. A ratio >30:1 in conjunction with a PA concentration >555 pmol/L (>20 ng/dL) reportedly has a sensitivity of 90% and a specificity of 91% for an aldosterone-producing adenoma. In a Mayo Clinic series, an aldosterone-producing adenoma subsequently was confirmed surgically in >90% of hypertensive patients with a PA/PRA ratio >20 and a PA concentration 415 pmol/L (>15 ng/dL). There are, however, several caveats to interpreting the ratio. The cutoff for a "high" ratio is laboratory- and assay-dependent. Some antihypertensive agents may affect the ratio (e.g., aldosterone antagonists, angiotensin receptor blockers [ARBs], and ACEIs may increase renin; aldosterone antagonists may increase aldosterone). Current recommendations are to withdraw aldosterone antagonists for at least 4–6 weeks before obtaining these measurements. Because aldosterone biosynthesis is potassium-dependent, hypokalemia should be corrected with oral potassium supplements prior to screening. A high ratio in the absence of an elevated PA level is considerably less specific for primary aldosteronism. In patients with renal insufficiency, the ratio may also be elevated because of decreased aldosterone clearance. In patients with an elevated PA/PRA ratio, the diagnosis of primary aldosteronism can be confirmed by demonstrating failure to suppress PA to any one of four suppression tests: oral sodium loading, saline infusion, fludrocortisone, or captopril.

Several sporadic and familial adrenal abnormalities may culminate in the syndrome of primary aldosteronism, and appropriate therapy depends on the specific etiology. The two most common causes of sporadic primary aldosteronism are an aldosterone-producing adenoma and bilateral adrenal hyperplasia. Together, they account for >90% of all patients with primary aldosteronism. The tumor is most often unilateral and measures <3 cm in diameter. Most of the remainder of these patients have bilateral adrenocortical hyperplasia (idiopathic hyperaldosteronism). An increasing number of somatic mutations, including mutations in aldosterone-regulating genes, has been identified in adenomas and in idiopathic hyperaldosteronism. Rarely,

primary aldosteronism may be caused by an adrenal carcinoma or an ectopic malignancy, e.g., ovarian arrhenoblastoma. Functional differences in hormone secretion may assist in the diagnosis of adenoma versus hyperplasia. Aldosterone biosynthesis is more responsive to ACTH in patients with adenoma and more responsive to angiotensin in patients with hyperplasia. Consequently, patients with adenoma tend to have higher PA in the early morning that decreases during the day, reflecting the diurnal rhythm of ACTH, whereas PA tends to increase with upright posture in patients with hyperplasia, reflecting the normal postural response of the renin-angiotensin-aldosterone axis. However, there is overlap in the ability of these measurements to discriminate between adenoma and hyperplasia. Rare familial forms of primary aldosteronism include glucocorticoid-remediable primary aldosteronism and familial aldosteronism types II and III. Familial primary aldosteronism reflects a variety of germline mutations, and genetic testing may assist in the diagnosis of these disorders.

Adrenal computed tomography (CT) should be carried out in all patients diagnosed with primary aldosteronism. High-resolution CT may identify tumors as small as 0.3 cm and is positive for an adrenal tumor 90% of the time. If the CT is not diagnostic, an adenoma may be detected by adrenal scintigraphy with  $6\text{-}[I^{131}]$  iodomethyl-19-norcholesterol after dexamethasone suppression (0.5 mg every 6 h for 7 days); however, this technique has decreased sensitivity for adenomas <1.5 cm.

When carried out by an experienced radiologist, bilateral adrenal venous sampling for measurement of PA is the most accurate means of differentiating unilateral from bilateral forms of primary aldosteronism. A major difference in the aldosterone/cortisol ratio is indicative of unilateral disease. The sensitivity and specificity of adrenal venous sampling (95 and 100%, respectively) for detecting unilateral aldosterone hypersecretion are superior to those of adrenal CT; success rates are 90–96%, and complication rates are <2.5%. One frequently used protocol involves sampling for aldosterone and cortisol levels in response to ACTH stimulation. An ipsilateral/contralateral aldosterone ratio >4, with symmetric ACTH-stimulated cortisol levels, is indicative of unilateral aldosterone production.

Hypertension generally is responsive to surgery in patients with adenoma but not in patients with bilateral adrenal hyperplasia. For patients with a unilateral adenoma, surgical treatment is generally more effective than medical therapy. Unilateral adrenalectomy, often done via a laparoscopic approach, is curative in 40–70% of patients with an adenoma. Transient hypoadrenosteronism may occur up to 3 months postoperatively, resulting in hypokalemia, which should be treated with potassium-wasting diuretics and with fludrocortisone, if needed. Patients with bilateral hyperplasia should be treated medically. The drug regimen for these patients, as well as for patients with an adenoma who are poor surgical candidates, should include an aldosterone antagonist and, if necessary, other potassium-sparing diuretics.

Glucocorticoid-remediable hyperaldosteronism is a rare, monogenic autosomal dominant disorder characterized by moderate to severe hypertension, often occurring at an early age. These patients may have a family history of hemorrhagic stroke at a young age. Hypokalemia is usually mild or absent. Normally, angiotensin II stimulates aldosterone production by the adrenal zona glomerulosa, whereas ACTH stimulates cortisol production in the zona fasciculata. Owing to a chimeric gene on chromosome 8, ACTH also regulates aldosterone secretion by the zona fasciculata in patients with glucocorticoid-remediable hyperaldosteronism. The consequence is overproduction in the zona fasciculata of both aldosterone and hybrid steroids (18-hydroxycortisol and 18-oxocortisol) due to oxidation of cortisol. The diagnosis may be established by urine excretion rates of these hybrid steroids that are 20–30 times normal or by direct genetic testing. Therapeutically, suppression of ACTH with low-dose glucocorticoids corrects the hyperaldosteronism, hypertension, and hypokalemia. Aldosterone antagonists are also therapeutic options. Patients with familial aldosteronism types II and III are treated with aldosterone antagonists or adrenalectomy.

### CUSHING'S SYNDROME

(See also Chap. 386) Cushing's syndrome is related to excess cortisol production due either to excess ACTH secretion (from a pituitary

tumor or an ectopic tumor) or to ACTH-independent adrenal production of cortisol. Hypertension occurs in 75–80% of patients with Cushing's syndrome. The mechanism of hypertension may be related to stimulation of mineralocorticoid receptors by cortisol and increased secretion of other adrenal steroids. If clinically suspected based on phenotypic characteristics, in patients not taking exogenous glucocorticoids, laboratory screening may be carried out with measurement of 24-h excretion rates of urine-free cortisol or an overnight dexamethasone-suppression test. Late night salivary cortisol is also a sensitive and convenient screening test. Further endocrine and radiologic evaluation is required to confirm the diagnosis and identify the specific etiology of Cushing's syndrome. Appropriate therapy depends on the etiology.

### PHEOCHROMOCYTOMA

(See also Chap. 387) Catecholamine-secreting tumors are located in the adrenal medulla (pheochromocytoma) or in extra-adrenal paraganglion tissue (paraganglioma) and account for hypertension in ~0.05% of patients. If unrecognized, pheochromocytoma may result in lethal cardiovascular consequences. Clinical manifestations, including hypertension, are primarily related to increased circulating catecholamines, although some of these tumors may secrete a number of other vasoactive substances. In a small percentage of patients, epinephrine is the predominant catecholamine secreted by the tumor, and these patients may present with hypotension rather than hypertension. The initial suspicion of the diagnosis is based on symptoms and/or the association of pheochromocytoma with other disorders (Table 277-4). Approximately 20% of pheochromocytomas are familial with autosomal dominant inheritance. Inherited pheochromocytomas may be associated with multiple endocrine neoplasia (MEN) type 2A and type 2B, von Hippel-Lindau disease, and neurofibromatosis. Each of these syndromes is related to specific germline mutations. Mutations of succinate dehydrogenase genes are associated with paraganglioma syndromes, generally characterized by head and neck paragangliomas. Laboratory testing consists of measuring catecholamines in either urine or plasma, e.g., 24-h urine fractionated metanephrine excretion or plasma-free metanephrenes under standardized conditions. The urine measurement is less sensitive but more specific. The next step would involve imaging of the abdomen and pelvis (CT or magnetic resonance imaging). Genetic screening is available for evaluating patients and relatives suspected of harboring a pheochromocytoma associated with a familial syndrome. Peripheral adrenergic antagonists may be used to control blood pressure. Surgical excision is the definitive treatment of pheochromocytoma and results in cure in ~90% of patients.

### MISCELLANEOUS CAUSES OF HYPERTENSION

Hypertension occurs in >50% of individuals with *obstructive sleep apnea*. Hypertension appears to be due to sympathetic activation caused by intermittent hypoxia and fragmented sleep. The severity of hypertension correlates with the severity of sleep apnea. Approximately 70% of patients with obstructive sleep apnea are obese. Hypertension related to obstructive sleep apnea also should be considered in patients with drug-resistant hypertension and patients with a history of snoring. The diagnosis can be confirmed by polysomnography. In obese patients, weight loss may alleviate or cure sleep apnea and related hypertension. Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) administered during sleep are effective therapies for obstructive sleep apnea. Although CPAP and BiPAP generally have only a modest effect on blood pressure, their use may improve blood pressure responsiveness to antihypertensive agents. Increasing evidence links other sleep-related disorders to hypertension, including restless legs syndrome and sleep-related bruxism.

*Coarctation of the aorta* is the most common congenital cardiovascular cause of hypertension (Chap. 269). The incidence is 1–8 per 1000 live births. It is usually sporadic but occurs in 35% of children with Turner's syndrome. Even when the anatomic lesion is surgically corrected in infancy, up to 30% of patients develop subsequent hypertension and are at risk of accelerated coronary artery disease and cerebrovascular events. Patients with less severe lesions may not be diagnosed until young adulthood. Physical findings include diminished

TABLE 277-4 Rare Mendelian Forms of Hypertension

DISEASE	PHENOTYPE	GENETIC CAUSE
Glucocorticoid-remediable hyperaldosteronism	Autosomal dominant Absent or mild hypokalemia	Chimeric 11 $\beta$ -hydroxylase/aldosterone gene on chromosome 8
17 $\alpha$ -Hydroxylase deficiency	Autosomal recessive Males: pseudohermaphroditism Females: primary amenorrhea, absent secondary sexual characteristics	Random mutations of the CYP17 gene on chromosome 10
11 $\beta$ -Hydroxylase deficiency	Autosomal recessive Masculinization	Mutations of the CYP11B1 gene on chromosome 8q21-q22
11 $\beta$ -Hydroxysteroid dehydrogenase deficiency (apparent mineralocorticoid excess syndrome)	Autosomal recessive Hypokalemia, low renin, low aldosterone	Mutations in the 11 $\beta$ -hydroxysteroid dehydrogenase gene
Liddle's syndrome	Autosomal dominant Hypokalemia, low renin, low aldosterone	Mutation subunits of the epithelial sodium channel SCNN1B and SCNN1C genes
Pseudohypoaldosteronism type II (Gordon's syndrome)	Autosomal dominant Hyperkalemia, normal glomerular filtration rate	Linkage to chromosomes 1q31-q42 and 17p11-q21
Hypertension exacerbated in pregnancy	Autosomal dominant Severe hypertension in early pregnancy	Missense mutation with substitution of leucine for serine at codon 810 (MR <sub>L810</sub> )
Polycystic kidney disease	Autosomal dominant Large cystic kidneys, renal failure, liver cysts, cerebral aneurysms, valvular heart disease	Mutations in the PKD1 gene on chromosome 16 and PKD2 gene on chromosome 4
Pheochromocytoma	Autosomal dominant (a) Multiple endocrine neoplasia, type 2A Medullary thyroid carcinoma, hyperparathyroidism (b) Multiple endocrine neoplasia, type 2B Medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, alimentary ganglioneuromatoses, marfanoid habitus (c) von Hippel-Lindau disease Retinal angiomas, hemangioblastomas of the cerebellum and spinal cord, renal cell carcinoma (d) Neurofibromatosis type 1 Multiple neurofibromas, café-au-lait spots	(a) Mutations in the RET protooncogene (b) Mutations in the RET protooncogene (c) Mutations in the VHL tumor-suppressor gene (d) Mutations in the NF1 tumor-suppressor gene

and delayed femoral pulses and a systolic pressure gradient between the right arm and the legs and, depending on the location of the coarctation, between the right and left arms. A blowing systolic murmur may be heard in the posterior left interscapular areas. The diagnosis may be confirmed by thoracic and abdominal CT, angiogram, and transesophageal echocardiography. Therapeutic options include surgical repair and balloon angioplasty, with or without placement of an intravascular stent. Subsequently, many patients do not have a normal life expectancy but may have persistent hypertension, with death due to ischemic heart disease, cerebral hemorrhage, or aortic aneurysm.

Several additional endocrine disorders, including *thyroid diseases* and *acromegaly*, cause hypertension. Mild diastolic hypertension may be a consequence of hypothyroidism, whereas hyperthyroidism may result in systolic hypertension. *Hypercalcemia* of any etiology, the most common being primary hyperparathyroidism, may result in hypertension. *Preeclampsia*, a hypertensive disorder of pregnancy that commonly presents after 20 weeks of gestation, may be a risk factor for subsequent cardiovascular disease and stroke. Hypertension also may be related to a number of prescribed or over-the-counter *medications and other substances*.

## MONOGENIC HYPERTENSION

In addition to glucocorticoid-remediable primary aldosteronism, a number of rare forms of monogenic hypertension have been identified (Table 277-4). These disorders may be recognized by their characteristic phenotypes, and in many instances, the diagnosis may be confirmed by genetic analysis. Several inherited defects in adrenal steroid biosynthesis and metabolism result in mineralocorticoid-induced hypertension and hypokalemia. In patients with a 17 $\alpha$ -hydroxylase deficiency, synthesis of sex hormones and cortisol is decreased (Fig. 277-3). Consequently, these individuals do not mature

sexually; males may present with pseudohermaphroditism and females with primary amenorrhea and absent secondary sexual characteristics. Because cortisol-induced negative feedback on pituitary ACTH production is diminished, ACTH-stimulated adrenal steroid synthesis proximal to the enzymatic block is increased. Hypertension and hypokalemia are consequences of increased synthesis of mineralocorticoids proximal to the enzymatic block, particularly desoxycorticosterone. Increased steroid production and, hence, hypertension may be treated with low-dose glucocorticoids. An 11 $\beta$ -hydroxylase deficiency results in a salt-retaining adrenogenital syndrome that occurs in 1 in 100,000 live births. This enzymatic defect results in decreased cortisol synthesis, increased synthesis of mineralocorticoids (e.g., desoxycorticosterone), and shunting of steroid biosynthesis into the androgen pathway. In the severe form, the syndrome may present early in life, including the newborn period, with virilization and ambiguous genitalia in females and penile enlargement in males, or in older children as precocious puberty and short stature. Acne, hirsutism, and menstrual irregularities may be the presenting features when the disorder is first recognized in adolescence or early adulthood. Hypertension is less common in the late-onset forms. Patients with an 11 $\beta$ -hydroxysteroid dehydrogenase deficiency have an impaired capacity to metabolize cortisol to its inactive metabolite, cortisone, and hypertension is related to activation of mineralocorticoid receptors by cortisol. This defect may be inherited or acquired, due to licorice-containing glycyrrhizin acid. The same substance is present in the paste of several brands of chewing tobacco. The defect in Liddle's syndrome (Chaps. 53 and 386) results from constitutive activation of amiloride-sensitive ENaC on the distal renal tubule, resulting in excess sodium reabsorption; the syndrome is ameliorated by amiloride. Hypertension exacerbated in pregnancy (Chap. 479) may be due to activation of the mineralocorticoid receptor by progesterone.

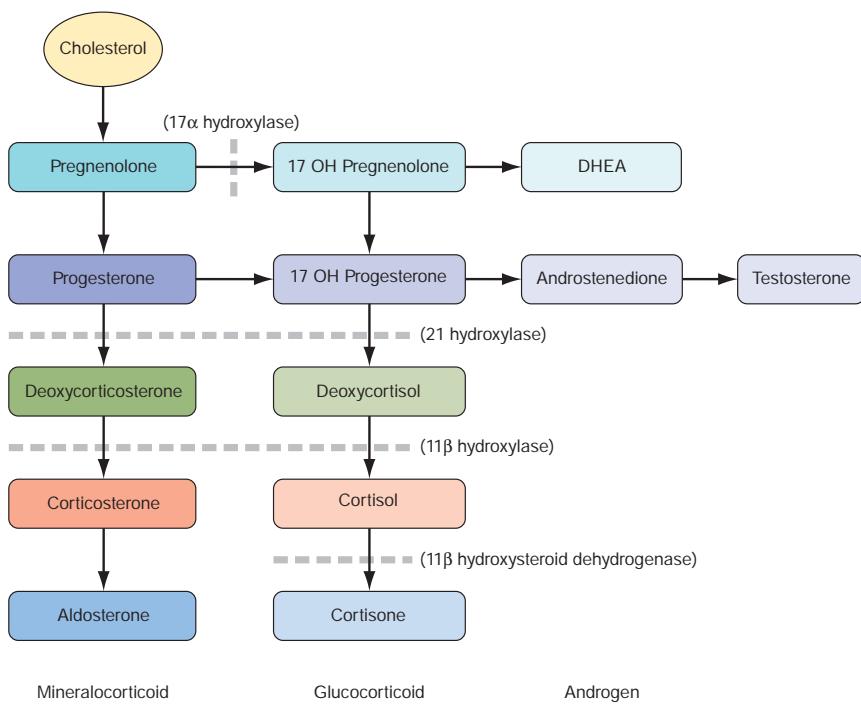


FIGURE 277-3 Adrenal enzymatic defects. DHEA, dehydroepiandrosterone.

## APPROACH TO THE PATIENT

### Hypertension

#### HISTORY AND PHYSICAL

The initial assessment of a hypertensive patient should include a complete history and physical examination to confirm a diagnosis of hypertension, screen for other cardiovascular disease risk factors, screen for secondary causes of hypertension, identify cardiovascular consequences of hypertension and other comorbidities, assess blood pressure-related lifestyles, and determine the potential for intervention. Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. **Table 277-5** lists salient features of the history and physical examination of the hypertensive patient.

Reliable measurements of blood pressure depend on attention to the details of the technique and conditions of the measurement. Proper training of observers, positioning of the patient, and selection of cuff size are essential. At the first visit, blood pressure should be measured in both arms, and the arm with higher readings should be used for subsequent measurements. An average of two to three measurements obtained on two to three separate occasions will provide a more accurate estimation of blood pressure than a single casual measurement. Rarely, in older patients, pseudohypertension may be related to the inability to measure blood pressure accurately in severely sclerotic arteries. This condition is suggested if the radial pulse remains palpable despite occlusion of the brachial artery by the cuff (Osler maneuver). The actual blood pressure can be determined by direct intra-arterial measurement. Owing to recent regulations preventing the use of mercury because of concerns about its potential toxicity, most office measurements are made with aneroid sphygmomanometers or with oscillometric devices. These instruments should be calibrated periodically, and their accuracy confirmed.

#### LABORATORY TESTING

**Table 277-6** lists recommended laboratory tests in the initial evaluation of hypertensive patients. Repeat measurements of renal

function, serum electrolytes, fasting glucose, and lipids may be obtained after the introduction of a new antihypertensive agent and then annually or more frequently if clinically indicated. More extensive laboratory testing is appropriate for patients with apparent drug-resistant hypertension or when the clinical evaluation suggests a secondary form of hypertension.

TABLE 277-5 Relevant History and Physical

#### History

Duration of hypertension  
Previous therapies: responses and side effects  
Family history of hypertension and cardiovascular disease  
Dietary and psychosocial history  
Alcohol consumption  
Other risk factors: weight change, dyslipidemia, smoking, diabetes, physical inactivity  
Evidence of secondary hypertension: history of renal disease; change in appearance; muscle weakness; spells of sweating, palpitations, tremor; erratic sleep, snoring, daytime somnolence; symptoms of hypo- or hyperthyroidism; use of agents that may increase blood pressure  
Evidence of target organ damage: history of TIA, stroke, transient blindness; angina, myocardial infarction, congestive heart failure; sexual function  
Other comorbidities

#### Physical

Body habitus  
Blood pressure in both arms  
Supine and standing blood pressures  
Funduscopic examination of retina  
Quality of femoral and pedal pulses  
Vascular and abdominal bruits  
Cardiac rate and rhythm  
Signs of congestive heart failure  
Characteristics of secondary hypertension

Abbreviation: TIA, transient ischemic attack.

**TABLE 277-6 Basic Laboratory Tests for Initial Evaluation**

SYSTEM	TEST
Renal	Microscopic urinalysis, albumin excretion, serum BUN and creatinine (compute eGFR)
Endocrine	Serum sodium, potassium, calcium, TSH
Metabolic	Fasting blood glucose, total cholesterol, HDL and LDL (often computed) cholesterol, triglycerides
Other	CBC, electrocardiogram

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

## TREATMENT

### Hypertension

Lowering systolic blood pressure by 10–12 mmHg and diastolic blood pressure by 5–6 mmHg confers relative risk reductions of 35–40% for stroke and 12–16% for CHD within 5 years of the initiation of treatment. The risk of heart failure is reduced by >50%; although the benefit of blood pressure lowering on progression of renal failure is less apparent, hypertension control is the single most effective intervention for slowing the rate of progression of hypertension-related kidney disease. There are more potentially preventable cardiovascular disease events attributed to elevated blood pressure in individuals at higher than at lower risk of cardiovascular disease and in older rather than younger adults.

#### LIFESTYLE INTERVENTIONS

Implementation of lifestyles that favorably affect blood pressure has implications for both the prevention and the treatment of hypertension. Health-promoting lifestyle modifications are recommended for individuals with “elevated” blood pressure and as an adjunct to drug therapy in hypertensive individuals (Table 277-7). These interventions should address overall cardiovascular disease risk. Although the impact of lifestyle interventions on blood pressure is more pronounced in persons with hypertension, in short-term trials, weight loss and reduction of dietary NaCl have been shown to prevent the development of hypertension. In hypertensive individuals, even if these interventions do not produce a sufficient reduction in blood pressure to avoid drug therapy, the number of medications or doses required for blood pressure control may be reduced.

Prevention and treatment of obesity are important for reducing blood pressure and cardiovascular disease risk. In short-term trials, even modest weight loss can lead to a reduction of blood pressure and an increase in insulin sensitivity. In longitudinal studies, a direct correlation exists between change in weight and change in blood pressure over time. Average blood pressure reductions of 6.3/3.1 mmHg have been observed with a reduction in mean body weight of 9.2 kg. Regular physical activity facilitates weight loss, decreases blood pressure, and reduces the overall risk of

**TABLE 277-7 Lifestyle Modifications to Manage Hypertension**

Weight reduction	Attain and maintain BMI <25 kg/m <sup>2</sup>
Dietary salt reduction	<6 g NaCl/d
Adapt DASH-type dietary plan	Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat. Diet is also rich in potassium, calcium, and magnesium.
Moderation of alcohol consumption	For those who drink alcohol, consume 2 drinks/d in men and 1 drink/d in women
Physical activity	Regular aerobic activity, e.g., brisk walking for 30 min/d

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension (trial).

cardiovascular disease. Blood pressure may be lowered by 30 min of moderately intense physical activity, such as brisk walking, 6–7 days a week, or by more intense, less frequent workouts.

There is individual variability in the sensitivity of blood pressure to NaCl, and this variability may have a genetic basis. Several genetic loci have been associated with NaCl sensitivity. Based on results of meta-analyses, lowering of blood pressure by limiting daily NaCl intake to 4.4–7.4 g (75–125 meq) results in blood pressure reductions of 3.7–4.9/0.9–2.9 mmHg in hypertensive individuals and lesser reductions in normotensive individuals. Salt sensitivity is especially common in blacks, older adults, and those with higher levels of blood pressure. Independent of its effect on blood pressure, excessive consumption of NaCl is associated with an increased risk of stroke and cardiovascular disease. Potassium and calcium supplementation have inconsistent modest antihypertensive effects, and, independent of blood pressure, potassium supplementation may be associated with reduced stroke mortality. Additionally, consuming three or more alcoholic drinks per day (a standard drink contains ~14 g ethanol) is associated with higher blood pressures, and a reduction of alcohol consumption is associated with a reduction of blood pressure. The Dietary Approaches to Stop Hypertension (DASH) trial convincingly demonstrated that over an 8-week period a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure in individuals with high-normal blood pressures or mild hypertension. Reduction of daily NaCl intake to <6 g (100 meq) augmented the effect of this diet on blood pressure. Fruits and vegetables are enriched sources of potassium, magnesium, and fiber, and dairy products are an important source of calcium.

#### PHARMACOLOGIC THERAPY

According to 2017 guidelines developed by the American College of Cardiology (ACC)/American Heart Association (AHA), atherosclerotic cardiovascular disease (ASCVD) risk estimation guides the threshold for initiation of blood pressure-lowering medications (Table 277-8). A risk calculator may be used to estimate risk of ASCVD, e.g., ACC/AHA Pooled Cohort Equations (<http://tools.acc.org/ASCVD-Risk-Estimator>).

There is considerable variation in individual responses to different classes of antihypertensive agents, and the magnitude of response to any single agent may be limited by activation of counter-regulatory mechanisms. To achieve goal blood pressure, most patients will require at least two antihypertensive agents. More often than not, combinations of agents, with complementary antihypertensive mechanisms, are required to achieve goal blood pressure reductions. Selection of antihypertensive agents and combinations of agents should be individualized, taking into account

**TABLE 277-8 ACC/AHA Guidelines for Hypertension Management**

#### Indications for Use of Blood Pressure-Lowering Medications

Secondary prevention of recurrent CVD events in patients with clinical CVD (defined as CHD, CHF, stroke) and SBP ≥130 mmHg or DBP ≥80 mmHg

Primary prevention in patients with an estimated 10-year ASCVD risk ≥10% and SBP ≥130 mmHg or DBP ≥80 mmHg

Primary prevention of CVD and low CVD risk in patients with SBP ≥140 mmHg or DBP ≥90 mmHg

#### Blood Pressure Goal for Patients with Hypertension

For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk ≥10%, a BP target <130/80 mmHg

#### Possible Exceptions to Therapeutic Target of <130/80 mmHg

Patients >80 years of age

Patients previously untreated for hypertension who experience an ischemic stroke or TIA and have blood pressure >140/90 mmHg

Acute therapy of most hypertensive urgencies and emergencies

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

age, severity of hypertension, other cardiovascular disease risk factors, comorbid conditions, and practical considerations related to cost, side effects, and frequency of dosing. The primary classes of drugs used to treat hypertension are listed in **Table 277-9**.

**Diuretics** Low-dose thiazide diuretics may be used alone or in combination with other antihypertensive drugs. Thiazides inhibit the  $\text{Na}^+/\text{Cl}^-$  pump in the distal convoluted tubule and hence increase sodium excretion. In the long term, they also may act as

**TABLE 277-9 Examples of Oral Drugs Used in Treatment of Hypertension**

DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE <sup>a</sup> (DOSING FREQUENCY/DAY)	OTHER INDICATIONS	CONTRAINdications/CAUTIONS
Diuretics				
Thiazides	Hydrochlorothiazide	6.25–50 mg (1–2)		Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
	Chlorthalidone	25–50 mg (1)		
Loop diuretics	Furosemide	40–80 mg (2–3)	CHF due to systolic dysfunction, CHF with preserved ejection fraction, renal failure	Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
	Ethacrynic acid	50–100 mg (2–3)		
Aldosterone antagonists	Spironolactone	25–100 mg (1–2)	CHF, primary aldosteronism, resistant hypertension	Renal failure, hyperkalemia
	Eplerenone	50–100 mg (1–2)		
K <sup>+</sup> retaining	Amiloride	5–10 mg (1–2)	Liddle's syndrome	Renal failure, hyperkalemia
	Triamterene	50–100 mg (1–2)		
Beta blockers				
Cardioselective	Atenolol	25–100 mg (1)	Angina, CHF, post-MI, sinus tachycardia, ventricular tachyarrhythmias, thoracic aortic disease	Asthma, COPD, second- or third-degree heart block, sick-sinus syndrome
	Metoprolol	25–100 mg (1–2)		
Nonselective	Propranolol	40–160 mg (2)		
	Propranolol LA	60–180 (1)		
Combined alpha/beta	Labetalol	200–800 mg (2)		
	Carvedilol	12.5–50 mg (2)		
Alpha antagonists				
Selective	Prazosin	2–20 mg (2–3)	Prostatism	
	Doxazosin	1–16 mg (1)		
Nonselective	Terazosin	1–10 mg (1–2)		
	Phenoxybenzamine	20–120 mg (2–3)	Pheochromocytoma	
Sympatholytics				
Central	Clonidine	0.1–0.6 mg (2)		
	Clonidine patch	0.1–0.3 mg (1/week)		
	Methyldopa	250–1000 mg (2)		
	Reserpine	0.05–0.25 mg (1)		
	Guanfacine	0.5–2 mg (1)		
ACE inhibitors	Captopril	25–200 mg (2)	Post-MI, coronary syndromes, CHF, nephropathy	Acute renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
	Lisinopril	10–40 mg (1)		
	Ramipril	2.5–20 mg (1–2)		
Angiotensin II antagonists	Losartan	25–100 mg (1–2)	CHF, nephropathy, ACE inhibitor cough	Renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
	Valsartan	80–320 mg (1)		
	Candesartan	2–32 mg (1–2)		
Renin inhibitors	Aliskiren	150–300 mg (1)	Diabetic nephropathy	Pregnancy
Calcium antagonists				
Dihydropyridines	Nifedipine (long-acting)	30–60 mg (1)		
	Verapamil (long-acting)	120–360 mg (1–2)	Post-MI, supraventricular tachycardias, angina	Second- or third-degree heart block
Nondihydropyridines	Diltiazem (long-acting)	180–420 mg (1)		
Direct vasodilators	Hydralazine	25–100 mg (2)		Severe coronary artery disease
	Minoxidil	2.5–80 mg (1–2)		

<sup>a</sup>At the initiation of therapy, lower doses may be preferable for elderly patients and for select combinations of antihypertensive agents.

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

vasodilators. Thiazides are safe, efficacious, inexpensive, and reduce clinical events. They provide additive blood pressure-lowering effects when combined with beta blockers, ACEIs, or ARBs. In contrast, addition of a diuretic to a calcium channel blocker is less effective. Usual doses of hydrochlorothiazide range from 6.25 to 50 mg/d. Owing to an increased incidence of metabolic side effects (hypokalemia, insulin resistance, increased cholesterol), higher doses generally are not recommended. Chlorthalidone is a diuretic structurally similar to hydrochlorothiazide, and like hydrochlorothiazide, it blocks sodium-chloride cotransport in the early distal tubule. However, chlorthalidone has a longer half-life (40–60 h vs 9–15 h) and an antihypertensive potency ~1.5–2.0 times that of hydrochlorothiazide. Potassium loss is also greater with chlorthalidone. Two potassium-sparing diuretics, amiloride and triamterene, act by inhibiting ENaC in the distal nephron. These agents are weak antihypertensive agents but may be used in combination with a thiazide to protect against hypokalemia. The main pharmacologic target for loop diuretics is the  $\text{Na}^+ \text{-K}^+ \text{-}2\text{Cl}^-$  cotransporter in the thick ascending limb of the loop of Henle. Loop diuretics generally are reserved for hypertensive patients with reduced glomerular filtration rates (reflected in serum creatinine >220  $\mu\text{mol/L}$  [ $>2.5 \text{ mg/dL}$ ]), CHF, or sodium retention and edema for some other reason, such as treatment with a potent vasodilator, e.g., minoxidil.

**Blockers of the Renin-Angiotensin System** ACEIs decrease the production of angiotensin II, increase bradykinin levels, and reduce sympathetic nervous system activity. ARBs provide selective blockade of  $\text{AT}_1$ Rs, and the effect of angiotensin II on unblocked  $\text{AT}_2$ Rs may augment their hypotensive effect. Both classes of agents are effective antihypertensive agents that may be used as monotherapy or in combination with diuretics, calcium antagonists, and alpha-blocking agents. ACEIs and ARBs improve insulin action and ameliorate the adverse effects of diuretics on glucose metabolism. Although the overall impact on the incidence of diabetes is modest, compared with amlodipine (a calcium antagonist), valsartan (an ARB) has been shown to reduce the risk of developing diabetes in high-risk hypertensive patients. ACEI/ARB combinations are less effective in lowering blood pressure than is the case when either class of these agents is used in combination with other classes of agents. In patients with vascular disease or a high risk of diabetes, combination ACEI/ARB therapy has been associated with more adverse events (e.g., cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure) without increases in benefit.

Side effects of ACEIs and ARBs include functional renal insufficiency due to efferent renal arteriolar dilation in a kidney with a stenotic lesion of the renal artery. Additional predisposing conditions to renal insufficiency induced by these agents include dehydration, CHF, and use of nonsteroidal anti-inflammatory drugs. Dry cough occurs in ~15% of patients, and angioedema occurs in <1% of patients taking ACEIs. Angioedema occurs most commonly in individuals of Asian origin and more commonly in African Americans than in whites. Hyperkalemia due to hypaldosteronism is an occasional side effect of both ACEIs and ARBs.

An alternative approach to blocking the renin-angiotensin system has recently been introduced into clinical practice for the treatment of hypertension: direct renin inhibitors. Blockade of the renin-angiotensin system is more complete with renin inhibitors than with ACEIs or ARBs. Aliskiren is the first of a class of oral, nonpeptide competitive inhibitors of the enzymatic activity of renin. Monotherapy with aliskiren seems to be as effective as an ACEI or ARB for lowering blood pressure, but not more effective. Further blood reductions may be achieved when aliskiren is used in combination with a thiazide diuretic or a calcium antagonist. Currently, aliskiren is not considered a first-line antihypertensive agent.

**Aldosterone Antagonists** Spironolactone is a nonselective aldosterone antagonist that may be used alone or in combination with a thiazide diuretic. It may be a particularly effective agent in

patients with low-renin primary hypertension, resistant hypertension, and primary aldosteronism. In patients with CHF, low-dose spironolactone reduces mortality and hospitalizations for heart failure when given in addition to conventional therapy with ACEIs, digoxin, and loop diuretics. Because spironolactone binds to progesterone and androgen receptors, side effects may include gynecomastia, impotence, and menstrual abnormalities. These side effects are circumvented by a newer agent, eplerenone, which is a selective aldosterone antagonist.

**Calcium Channel Blockers** Calcium antagonists reduce vascular resistance through L-channel blockade, which reduces intracellular calcium and blunts vasoconstriction. This is a heterogeneous group of agents that includes drugs in the following three classes: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and 1,4-dihydropyridines (nifedipine-like). Used alone and in combination with other agents (ACEIs, beta blockers,  $\alpha_1$ -adrenergic blockers), calcium antagonists effectively lower blood pressure; however, it is unclear if adding a diuretic to a calcium blocker results in a further lowering of blood pressure. Side effects of flushing, headache, and edema with dihydropyridine use are related to their potencies as arteriolar dilators; edema is due to an increase in transcapillary pressure gradients, not to net salt and water retention.

**Beta Blockers**  $\beta$ -Adrenergic receptor blockers lower blood pressure by decreasing cardiac output owing to a reduction of heart rate and contractility. Other proposed mechanisms by which beta blockers lower blood pressure include a central nervous system effect and inhibition of renin release. Beta blockers are particularly effective in hypertensive patients with tachycardia, and their hypotensive potency is enhanced by co-administration with a diuretic. In lower doses, some beta blockers selectively inhibit cardiac  $\beta_1$  receptors and have less influence on  $\beta_2$  receptors on bronchial and vascular smooth muscle cells; however, there seems to be no difference in the antihypertensive potencies of cardioselective and nonselective beta blockers. Some beta blockers have intrinsic sympathomimetic activity, although it is uncertain whether this constitutes an overall advantage or disadvantage in cardiac therapy. Beta blockers without intrinsic sympathomimetic activity decrease the rate of sudden death, overall mortality, and recurrent myocardial infarction. In patients with CHF, beta blockers reduce the risks of hospitalization and mortality. Carvedilol and labetalol block both  $\alpha_1$  receptors and peripheral  $\beta$ -adrenergic receptors. The potential advantages of combined  $\beta$ - and  $\alpha$ -adrenergic blockade in treating hypertension remain to be determined. Nebivolol represents another class of cardioselective beta blockers that has additional vasodilator actions related to enhancement of nitric oxide activity. Whether this confers greater clinical effectiveness remains to be determined.

**$\alpha$ -Adrenergic Blockers** Postsynaptic, selective  $\alpha$ -adrenoreceptor antagonists lower blood pressure by decreasing peripheral vascular resistance. They are effective antihypertensive agents used either as monotherapy or in combination with other agents. However, in clinical trials of hypertensive patients, alpha blockade has not been shown to reduce cardiovascular morbidity and mortality or to provide as much protection against CHF as other classes of antihypertensive agents. These agents are also effective in treating lower urinary tract symptoms in men with prostatic hypertrophy. Non-selective  $\alpha$ -adrenoreceptor antagonists bind to postsynaptic and presynaptic receptors and are used primarily for the management of patients with pheochromocytoma.

**Sympatholytic Agents** Centrally acting  $\alpha_2$  sympathetic agonists decrease peripheral resistance by inhibiting sympathetic outflow. They may be particularly useful in patients with autonomic neuropathy who have wide variations in blood pressure due to baroreceptor denervation. Drawbacks include somnolence, dry mouth, and rebound hypertension on withdrawal. Peripheral sympatholytics decrease peripheral resistance and venous constriction by depleting nerve terminal norepinephrine. Although they are potentially

effective antihypertensive agents, their usefulness is limited by orthostatic hypotension, sexual dysfunction, and numerous drug-drug interactions. Rebound hypertension is another concern with abrupt cessation of drugs with a short half-life.

**Direct Vasodilators** Direct vasodilators decrease peripheral resistance and concomitantly activate mechanisms that defend arterial pressure, notably the sympathetic nervous system, the renin-angiotensin-aldosterone system, and sodium retention. Usually, they are not considered first-line agents but are most effective when added to a combination that includes a diuretic and a beta blocker. Hydralazine is a direct vasodilator that has antioxidant and nitric oxide-enhancing actions. Minoxidil is a particularly potent vasodilator and is used most frequently in patients with renal insufficiency who are refractory to all other drugs. Hydralazine may induce a lupus-like syndrome, and side effects of minoxidil include hypertrichosis and pericardial effusion. Intravenous nitroprusside can be used to treat malignant hypertension and life-threatening left ventricular heart failure associated with elevated arterial pressure.

### COMPARISONS OF ANTIHYPERTENSIVES

Meta-analyses of pooled clinical trials suggest essentially equivalent blood pressure-lowering effects of the following six major classes of antihypertensive agents when used as monotherapy: thiazide diuretics, beta blockers, ACEIs, ARBs, calcium antagonists, and

blockers. On average, standard doses of most antihypertensive agents reduce blood pressure by 8–10/4–7 mmHg; however, there may be subgroup differences in responsiveness. Younger patients may be more responsive to beta blockers and ACEIs, whereas patients aged >50 years may be more responsive to diuretics and calcium antagonists. There is a limited relationship between plasma renin and blood pressure response. Patients with high-renin hypertension may be more responsive to ACEIs and ARBs than to other classes of agents, whereas patients with low-renin hypertension are more responsive to diuretics and calcium antagonists. Hypertensive African Americans tend to have low renin and may require higher doses of ACEIs and ARBs than whites for optimal blood pressure control, although this difference is abolished when these agents are combined with a diuretic. Beta blockers also appear to be less effective than thiazide diuretics in African Americans than in non-African Americans. Early pharmacogenetic studies, utilizing a candidate gene approach, genome-wide scans, or integrated metabolomic and genetic profiles, have shown associations of gene polymorphisms with blood pressure responsiveness to specific antihypertensive drugs. However, the reported effects have generally been too small to affect clinical decisions, and associated polymorphisms remain to be confirmed.

A meta-analysis of >30 randomized trials of blood pressure-lowering therapy indicates that for a given reduction in blood pressure, with several notable exceptions, the major drug classes produce similar overall net effects on total cardiovascular events. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that the occurrence of fatal CHD and nonfatal myocardial infarction was virtually identical in hypertensive patients treated with an ACEI (lisinopril), a diuretic (chlorthalidone), or a calcium antagonist (amlodipine). However, one arm of ALLHAT involving therapy with a peripherally acting antagonist (doxazosin) was terminated prematurely because the incidence of heart failure, stroke, and combined cardiovascular disease events was higher in doxazosin-treated than in chlorthalidone-treated patients. Increasing evidence suggests that beta blockers are inferior to other classes of agents for prevention of cardiovascular events, stroke, renal failure, and all-cause mortality. Some beta blockers have less effect on central aortic pressure than other classes of antihypertensive agents. However, beta blockers remain appropriate therapy for hypertensive patients with concomitant heart disease and related comorbidities. Calcium channel blockers may be inferior and diuretics superior to other classes of agents for the prevention of heart failure.

In specific patient groups, ACEIs may have particular advantages, beyond that of blood pressure control, in reducing cardiovascular and renal outcomes. ACEIs and ARBs decrease intraglomerular pressure and proteinuria and may retard the rate of progression of renal insufficiency, not totally accounted for by their hypotensive effects, in both diabetic and nondiabetic renal diseases. In patients with type 2 diabetes, treatment with an ACEI, an ARB, or aliskiren decreases proteinuria and delays the progression of renal disease. In experimental models of hypertension and diabetes, renal protection with aliskiren is comparable to that with ACEIs and ARBs. However, in patients with type 2 diabetes, addition of aliskiren to an ACEI provides no additional protection against cardiovascular or renal disease and may be associated with more adverse outcomes. Among African Americans with hypertension-related renal disease, ACEIs appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing, although not preventing, the decline of glomerular filtration rate. The renoprotective effect of these renin-angiotensin blockers, compared with other antihypertensive drugs, is less obvious at lower blood pressures.

In most patients with hypertension and heart failure due to systolic and/or diastolic dysfunction, diuretics, ACEIs or ARBs, and beta blockers improve survival. Independent of blood pressure, in both hypertensive and normotensive individuals, ACEIs attenuate the development of left ventricular hypertrophy, improve symptomatology and risk of death from CHF, and reduce morbidity and mortality rates in post-myocardial infarction patients. Similar benefits in cardiovascular morbidity and mortality rates in patients with CHF have been observed with the use of ARBs. ACEIs provide better coronary protection than do calcium channel blockers, whereas calcium channel blockers provide more stroke protection than do either ACEIs or beta blockers. Results of a large, double-blind, prospective clinical trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH] Trial) indicated that combination treatment with an ACEI (benazepril) plus a calcium antagonist (amlodipine) was superior to treatment with the ACEI plus a diuretic (hydrochlorothiazide) in reducing the risk of cardiovascular events and death among high-risk patients with hypertension. However, the combination of an ACEI and a diuretic has recently been shown to produce major reductions in morbidity and mortality in the very elderly. After a stroke, combination therapy with an ACEI and a diuretic, but not with an ARB, has been reported to reduce the rate of recurrent stroke.

There has been a recent resurgence of interest in two non-pharmacologic antihypertensive therapies that interrupt sympathetic outflow: (1) device-based carotid baroreflex activation by electrical stimulation of the carotid sinus; and (2) endovascular radiofrequency ablation of the renal sympathetic nerves. Both have been suggested as potential options for treatment of resistant hypertension. Whereas renal denervation is a minimally invasive procedure, carotid baroreceptor stimulation is a surgical procedure, usually performed under general anesthesia, that involves implanting electrodes on both the right and left carotid arteries. Clinical experience with baroreflex activation is limited. Enthusiasm for renal denervation has been questioned by the results of Simplicity HTN-3, a randomized, prospective clinical trial comparing bilateral renal denervation with a sham procedure in 535 patients with resistant hypertension. At the end of 6 months, there was no benefit of renal artery denervation on both office and ambulatory systolic blood pressures, the trial's primary endpoints. Subsequent clinical trials have demonstrated substantial blood pressure variability in responses to both of these interventions. It remains to be seen whether these interventions will be adopted into clinical practice.

### BLOOD PRESSURE GOALS OF ANTIHYPERTENSIVE THERAPY

Based on clinical trial data, the maximum protection against combined cardiovascular endpoints is achieved with pressures

<135–140 mmHg for systolic blood pressure and <80–85 mmHg for diastolic blood pressure; however, treatment has not reduced cardiovascular disease risk to the level in nonhypertensive individuals. According to a recent meta-analysis, the magnitude of the proportional reduction of cardiovascular events is broadly consistent regardless of baseline comorbidity, although the absolute benefit of blood pressure reduction is greater among individuals with the highest risk for cardiovascular events.

The degree of benefit derived from antihypertensive agents is related to the magnitude of the blood pressure reduction. An intensive blood pressure–lowering strategy is superior to a less intensive strategy for prevention of stroke and myocardial infarction. For example, the SPRINT trial studied 9361 subjects aged >50 years at increased risk for cardiovascular events. Intensive blood pressure control (systolic blood pressure <120 mmHg) reduced the risk of cardiovascular events and mortality by 25% compared with less intensive control (systolic blood pressure 135–139 mmHg). In patients with chronic renal insufficiency, a small, nonprogressive increase in the serum creatinine concentration may occur with intensive blood pressure lowering. This generally reflects a hemodynamic response, not structural renal injury, indicating that intraglomerular pressure has been reduced. Blood pressure control should not be allowed to deteriorate in order to prevent the modest creatinine rise.

In diabetic patients, effective blood pressure control reduces the risk of cardiovascular events and death as well as the risk for microvascular disease (nephropathy, retinopathy). Various guidelines have been recommended for hypertension control in patients with type 2 diabetes (e.g., <140/90, <140/85, or <130/80 mmHg). One widely cited study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial, failed to find superiority of intensive blood pressure lowering (<120 mmHg) over standard blood pressure control (<140 mmHg) in reducing the risk of the study's primary outcome (a composite endpoint of myocardial infarction, stroke, and cardiovascular death) in diabetic patients. However, that trial did demonstrate a significant reduction of stroke and left ventricular hypertrophy with more intensive therapy.

Guidelines establishing blood pressure targets for hypertension control continue to evolve. According to 2017 guidelines developed by the ACC/AHA, the recommended goal of blood pressure control for the primary and secondary prevention of cardiovascular disease is a blood pressure <130/80 mmHg, including patients with diabetes mellitus and chronic kidney diseases (Table 277-8). However, in hypertensive patients without elevated ASCVD risk, the clinical trial evidence is strongest for a target blood pressure of 140/90 mmHg. In contrast to other ACC/AHA recommendations that are based on randomized clinical trials, this guideline is primarily based on observational studies. Among older patients with isolated systolic hypertension, further lowering of diastolic blood pressure does not result in harm. Relatively little information is available concerning the risk-versus-benefit ratio of intensive antihypertensive therapy in individuals >80 years of age, and in this population, gradual blood pressure reduction to a less aggressive target level of control may be appropriate (e.g., 130–150 mmHg). More intensive control may be associated with a higher incidence of adverse events (e.g., syncope, electrolyte abnormalities, deterioration of renal function). Additionally, the <130/80 mmHg target blood pressure may not be acceptable or implementable in low- and middle-income countries because of the lack of supporting resources. In the final analysis, all patients need to be carefully monitored, and clinical decision-making should be individualized.

To achieve recommended blood pressure goals, the majority of individuals with hypertension will require treatment with more than one drug. Three or more drugs frequently are needed in patients with diabetes and renal insufficiency. For most agents, reduction of blood pressure at half-standard doses is only ~20% less than at standard doses. Appropriate combinations of agents at these lower doses may have additive or almost additive effects on

blood pressure with a lower incidence of side effects. Hypertension control rates are <20% worldwide and <50% in the United States. These low control rates reflect patient nonadherence and lack of implementation of recommended guidelines.

The term *resistant hypertension* refers to patients with blood pressures persistently >140/90 mmHg despite taking three or more antihypertensive agents, including a diuretic. Resistant or difficult-to-control hypertension is more common in patients aged >60 years than in younger patients. Resistant hypertension may be related to nonadherence to therapy, identifiable causes of hypertension (including obesity, primary aldosteronism, and excessive alcohol intake), and the use of any of a number of nonprescription and prescription drugs (Table 277-3). Evaluation of patients with resistant hypertension might include home blood pressure monitoring to determine if office blood pressures are representative of the usual blood pressure. A more extensive evaluation for a secondary form of hypertension should be undertaken if no other explanation for hypertension resistance becomes apparent. In the absence of a specific identifiable cause, mineralocorticoid receptor antagonists, especially spironolactone, have been demonstrated to be the most effective add-on drugs for the treatment of resistant hypertension. Additionally, resistant hypertension is often associated with increased sympathetic nervous activity, raising the possibility that electrical stimulation of the carotid baroreceptor or renal denervation may have a role in the treatment of these patients. However, that remains to be determined.

### HYPERTENSIVE EMERGENCIES

Probably due to the widespread availability of antihypertensive therapy, in the United States, there has been a decline in the numbers of patients presenting with hypertensive urgencies and emergencies. Severe asymptomatic hypertension (systolic blood pressure

180 mmHg or diastolic blood pressure 120 mmHg) is considered a hypertensive “urgency,” but when accompanied by acute target damage, it is considered a hypertensive “emergency.” Most patients who present with severe hypertension are chronically hypertensive, and there are inherent risks to overly aggressive initial antihypertensive therapy. In hypertensive individuals, the upper and lower limits of autoregulation of cerebral blood flow are shifted to higher levels of arterial pressure, and rapid lowering of blood pressure to below the lower limit of autoregulation may precipitate cerebral ischemia or infarction as a consequence of decreased cerebral blood flow. Renal and coronary blood flows also may decrease with overly aggressive acute therapy. Consequently, the rapidity with which blood pressure should be lowered is dependent on the presence of new or worsening target organ damage and the presence or absence of cardiovascular disease complications. In patients with a hypertensive urgency, except for those with acute aortic dissections or hemorrhagic strokes, blood pressure is generally gradually lowered over 24 h to ~25% of the initial value. **Tables 277-10 and 277-11** list a number of hypertension-related emergencies and recommended therapies.

The syndrome of *malignant hypertension* is an example of a hypertensive emergency that is associated with an abrupt increase of blood pressure in a patient with underlying hypertension or related to the sudden onset of hypertension in a previously normotensive individual. The absolute level of blood pressure is not as important as its rate of rise. Pathologically, the syndrome is associated with diffuse necrotizing vasculitis, arteriolar thrombi, and fibrin deposition in arteriolar walls. Fibrinoid necrosis has been observed in arterioles of kidney, brain, retina, and other organs. Clinically, the syndrome is recognized by progressive retinopathy (arteriolar spasm, hemorrhages, exudates, and papilledema), deteriorating renal function with proteinuria, microangiopathic hemolytic anemia, and encephalopathy. Historic inquiry should include questions about the use of monoamine oxidase inhibitors and recreational drugs (e.g., cocaine, amphetamines). In patients with encephalopathy, the initial goal of therapy is to reduce mean

**TABLE 277-10 Preferred Parenteral Drugs for Selected Hypertensive Emergencies**

Hypertensive encephalopathy	Nitroprusside, nicardipine, labetalol
Malignant hypertension (when IV therapy is indicated)	Labetalol, nicardipine, nitroprusside, enalaprilat
Stroke	Nicardipine, labetalol, nitroprusside
Myocardial infarction/unstable angina	Nitroglycerin, nicardipine, labetalol, esmolol
Acute left ventricular failure	Nitroglycerin, enalaprilat, loop diuretics
Aortic dissection	Nitroprusside, esmolol, labetalol
Adrenergic crisis	Phentolamine, nitroprusside
Postoperative hypertension	Nitroglycerin, nitroprusside, labetalol, nicardipine
Preeclampsia/eclampsia of pregnancy	Hydralazine, labetalol, nicardipine

Source: Reproduced with permission from DG Vist, in S Oparil, MA Weber (eds): *Hypertension*, 2nd ed. Philadelphia, Elsevier Saunders, 2005.

arterial blood pressure by no more than 25% within minutes to 2 h or to a blood pressure in the range of 160/100–110 mmHg. This may be accomplished with IV nitroprusside, a short-acting vasodilator with a rapid onset of action that allows for minute-to-minute control of blood pressure. Parenteral labetalol and nicardipine are also effective agents for the treatment of hypertensive encephalopathy. In the absence of encephalopathy or another catastrophic event, it is preferable to reduce blood pressure over hours or longer rather than minutes. This goal may effectively be achieved initially with frequent dosing of short-acting oral agents such as captopril, clonidine, and labetalol.

Acute, transient blood pressure elevations that last days to weeks frequently occur after thrombotic and hemorrhagic strokes. Autoregulation of cerebral blood flow is impaired in ischemic cerebral tissue, and higher arterial pressures may be required to maintain cerebral blood flow. Aggressive reductions of blood pressure should be avoided. With the increasing availability of improved CT technology for the noninvasive measurement of cerebral blood flow, studies are in progress to evaluate the effects of different classes of antihypertensive agents on both blood pressure and cerebral blood flow after an acute stroke. To prevent recurrence of cerebrovascular events, reduction of blood pressure appears to be more important

than the choice of specific agents. In the absence of comorbid conditions requiring acute therapy, for patients with a systolic blood pressure  $>220$  mmHg or a diastolic blood pressure  $>120$  mmHg, who are not candidates for thrombolytic therapy or endovascular treatment, the benefit of instituting antihypertensive therapy within the first 48–72 h is uncertain. One suggestion for these patients is to lower blood pressure by 15% during the first 24 h after onset of the stroke. For patients with less severe hypertension, acute reduction of blood pressure is not effective in preventing death or dependency. If thrombolytic therapy or endovascular treatment is to be used, the recommended goal is to reduce blood pressure to  $<185$  mmHg systolic pressure and  $<110$  mmHg diastolic pressure before thrombolytic therapy is initiated. For neurologically stable patients with blood pressure  $>140/90$  mmHg, starting or restarting antihypertensive therapy after the first 24 h to improve long-term blood pressure control is reasonable. In patients with hemorrhagic stroke, who have systolic blood pressure  $>220$  mmHg, it is reasonable to use continuous intravenous drug infusion to lower blood pressure. However, there is no consistent evidence that acute reductions of systolic blood pressure to a more aggressive target than 140–179 mmHg improve functional outcome. The management of hypertension after subarachnoid hemorrhage is controversial. Cautious reduction of blood pressure is indicated if mean arterial pressure is  $>130$  mmHg.

In addition to pheochromocytoma, an adrenergic crisis due to catecholamine excess may be related to cocaine or amphetamine overdose, clonidine withdrawal, acute spinal cord injuries, and an interaction of tyramine-containing compounds with monoamine oxidase inhibitors. These patients may be treated with phentolamine or nitroprusside.

Treatment of hypertension in patients with acute aortic dissection is discussed in Chap. 280, and treatment of hypertension in pregnancy is discussed in Chap. 479.

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**TABLE 277-11 Usual Intravenous Doses of Antihypertensive Agents Used in Hypertensive Emergencies<sup>a</sup>**

ANTIHYPERTENSIVE AGENT	INTRAVENOUS DOSE
Nitroprusside	Initial 0.3 ( $\mu\text{g}/\text{kg}$ )/min; usual 2–4 ( $\mu\text{g}/\text{kg}$ )/min; maximum 10 ( $\mu\text{g}/\text{kg}$ )/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg or 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 $\mu\text{g}/\text{kg}$ over 1 min, then 50–300 ( $\mu\text{g}/\text{kg}$ )/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 $\mu\text{g}/\text{min}$ , then titrate by 5 $\mu\text{g}/\text{min}$ at 3–5-min intervals; if no response is seen at 20 $\mu\text{g}/\text{min}$ , incremental increases of 10–20 $\mu\text{g}/\text{min}$ may be used
Hydralazine	10–50 mg at 30-min intervals

<sup>a</sup>Constant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.



The renal vasculature is unusually complex with rich arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels deliver less blood and, with high oxygen consumption, leave the deeper medullary regions at the margin of hypoxemia. Vascular disorders that commonly threaten the blood supply of the kidney include large-vessel atherosclerosis, fibromuscular diseases, and embolic disorders. **Microvascular injury, including inflammatory and primary hematologic disorders, is described in Chap. 317.**

## MECHANISMS OF VASCULAR INJURY AND HYPERTENSION

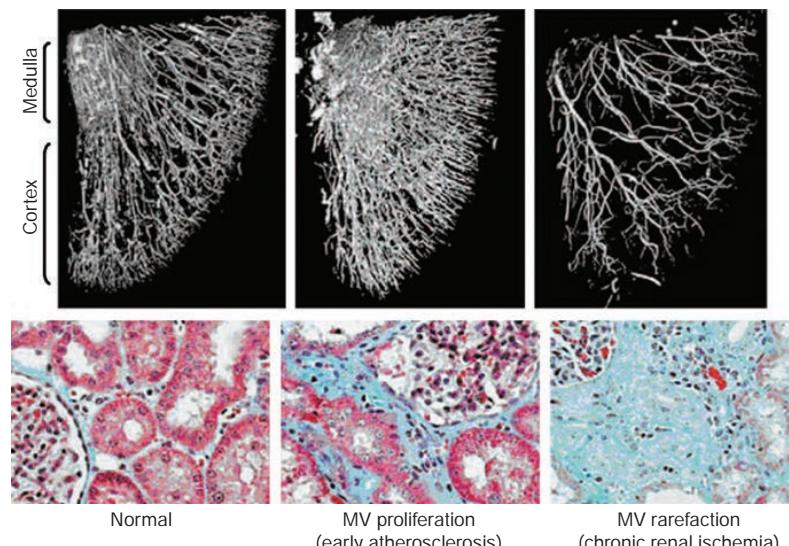
The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territories. Endothelial injury can be manifest by urinary albumin excretion (UAE), which is predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. UAE and the risk of cardiovascular events are both reduced with pharmacologic therapy such as antihypertensive drugs and statins. Experimental studies demonstrate functional changes and rarefaction of renal microvessels under conditions of accelerated atherosclerosis and/or compromise of proximal perfusion pressures with large-vessel disease (Fig. 278-1).

Large-vessel renal artery occlusive disease can result from extrinsic compression of the vessel, intimal dissection, aortic stent graft placement, fibromuscular dysplasia (FMD), or, most commonly, atherosclerotic disease. Any disorder that reduces perfusion pressure to the kidney can activate mechanisms that tend to restore renal pressures at the expense of developing systemic hypertension. Because restoration of perfusion pressures can reverse these pathways, renal artery stenosis is considered a specifically treatable "secondary" cause of hypertension.

Renal artery stenosis is common and often has only minor hemodynamic effects. FMD is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlusion and can be associated with renal artery aneurysms. Atherosclerotic renal artery stenosis (ARAS) is common in the general population (6.8% of a community-based sample above age 65). The prevalence increases with age and for patients with other vascular conditions such as coronary artery disease (18–23%) and/or peripheral aortic or lower extremity disease (>30%). If untreated, ARAS progresses in nearly 50% of cases over a 5-year period, sometimes to total occlusion. Intensive treatment of arterial blood pressure and statin therapy can slow these rates and improve clinical outcomes.

Critical levels of stenosis lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure (BP) rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. It can also be treated with restoration of renal blood flow by either endovascular or surgical revascularization. Most patients require continued antihypertensive drug therapy due to preexisting hypertension and because revascularization alone rarely lowers BP to normal.

ARAS and systemic hypertension tend to affect both the poststenotic and contralateral kidneys, reducing overall glomerular filtration rate (GFR) in ARAS. When kidney function is threatened by large-vessel disease primarily, it has been labeled ischemic nephropathy. Moderately reduced blood flow that develops gradually is associated with reduced GFR and limited oxygen consumption with preserved tissue oxygenation. Hence, kidney function often remains stable during medical therapy, sometimes for years. With more advanced disease, reductions in cortical perfusion and overt tissue hypoxia develop. Unlike FMD, ARAS develops in patients with other risk factors for atherosclerosis and is commonly superimposed upon preexisting small-vessel disease in the kidney resulting from hypertension, aging, and diabetes. Nearly 85% of patients considered for renal revascularization have



**FIGURE 278-1** Examples of micro-CT images from vessels defined by radiopaque casts injected into the renal vasculature. These illustrate the complex, dense cortical capillary network supplying the kidney cortex that can either proliferate or succumb to rarefaction under the influence of atherosclerosis and/or occlusive disease. Changes in blood supply are followed by tubulointerstitial fibrosis and loss of kidney function. MV, microvascular. (Reproduced with permission from LO Lerman, AR Chade. *Angiogenesis in the kidney: A new therapeutic target?*. *Curr Opin Nephrol Hypertens* 18:160, 2009.)

**TABLE 278-1 Summary of Imaging Modalities for Evaluating the Kidney Vasculature****Vascular Studies to Evaluate the Renal Arteries**

Duplex ultrasonography	Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis	Inexpensive; widely available, suitable for follow-up studies	Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries
Computed tomographic angiography	Shows the renal arteries and perirenal aorta	Provides excellent images; stents do not cause artifacts	Expensive, moderate volume of contrast required
Magnetic resonance angiography	Shows the renal arteries and perirenal aorta	Not nephrotoxic, but concerns for gadolinium toxicity exclude use in GFR <30 mL/min per 1.73 m <sup>2</sup> ; provides excellent images	Expensive; gadolinium excluded in renal failure, unable to visualize stented vessels
Intraarterial angiography	Shows location and severity of vascular lesion	Considered "gold standard" for diagnosis of large-vessel disease, usually performed simultaneous with planned intervention	Expensive, associated hazard of atheroemboli, contrast toxicity, procedure-related complications, e.g., dissection

**Perfusion Studies to Assess Differential Renal Blood Flow**

Captopril renography with technetium <sup>99m</sup> Tc mertiatide ( <sup>99m</sup> Tc MAG3)	Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion	Normal study excludes renovascular hypertension	Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dL (177 μmol/L)
---------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------	-------------------------------------------------	------------------------------------------------------------------------------------------------------

Abbreviation: GFR, glomerular filtration rate.

stage 3–5 chronic kidney disease (CKD) with GFR <60 mL/min per 1.73 m<sup>2</sup>. The presence of ARAS is a strong predictor of morbidity- and mortality-related cardiovascular events, independent of whether renal revascularization is undertaken.

## DIAGNOSIS OF RENOVASCULAR DISEASE

Diagnostic approaches to renal artery stenosis depend partly on the specific clinical questions to be addressed. Noninvasive characterization of the renal vasculature may be achieved by several techniques, summarized in **Table 278-1**. Although activation of the renin-angiotensin system is a key step in developing renovascular hypertension, it is transient. Levels of renin activity are therefore subject to timing, the effects of drugs, and sodium intake, and do not reliably predict the response to vascular therapy. Peak systolic renal artery velocities by Doppler ultrasound >200 cm/s generally predict hemodynamically important lesions (>60% vessel lumen occlusion), although some treatment trials have required velocity >300 cm/s to avoid false positives. The renal resistive index has predictive value regarding the viability of the kidney. It remains operator- and institution-dependent, however. Contrast-enhanced computed tomography (CT) with vascular reconstruction provides excellent vascular images and functional assessment, but carries a small risk of contrast toxicity. It provides a more reliable evaluation of accessory vessels and the distal vasculature than duplex or magnetic resonance imaging (MRI). Magnetic resonance angiography (MRA) is now less often used, as gadolinium contrast has been associated with nephrogenic systemic fibrosis particularly in patients with reduced GFR. Captopril-enhanced renography has a strong negative predictive value when entirely normal.

## TREATMENT

### Renal Artery Stenosis

While restoring renal blood flow and perfusion seems intuitively beneficial for high-grade occlusive lesions, revascularization procedures also pose hazards and expense. Patients with FMD are commonly younger females with otherwise normal vessels and a long life expectancy. These patients often respond well to percutaneous renal artery angioplasty. If BP can be controlled to goal levels and kidney function remains stable in patients with ARAS, it may be argued that medical therapy with follow-up for disease progression is equally effective over periods of 3–5 years. Multiple prospective randomized controlled trials have failed to identify compelling benefits for interventional revascularization procedures regarding short-term results of BP and renal function. Studies of

cardiovascular outcomes, including stroke, congestive heart failure, myocardial infarction, and end-stage renal failure, suggest a small mortality benefit for stented patients without proteinuria. Medical therapy should include blockade of the renin-angiotensin system, attainment of goal BPs, cessation of tobacco, statins, and aspirin. Follow-up requires surveillance for progressive occlusion manifest by worsening renal function and/or loss of BP control. Renal revascularization is now often reserved for patients failing medical therapy or developing additional complications.

Techniques of renal revascularization are improving. With experienced operators, major complications occur in <5% of cases, including renal artery dissection, capsular perforation, hemorrhage, and occasional atheroembolic disease. Although not common, atheroembolic disease can be catastrophic and accelerate both hypertension and kidney failure, precisely the events that revascularization is intended to prevent. Although renal blood flow usually can be restored by endovascular stenting, recovery of renal function is limited to ~25% of cases, with no change in 50% and some deterioration evident in others. Patients with rapid loss of kidney function, sometimes associated with antihypertensive drug therapy, or with vascular disease affecting the entire functioning kidney mass are more likely to recover function after restoring blood flow. When hypertension is refractory to effective therapy, revascularization offers real benefits. **Table 278-2** summarizes currently accepted guidelines for considering renal revascularization in addition to optimal medical therapy.

## ATHEROEMBOLIC RENAL DISEASE

Emboli to the kidneys arise most frequently as a result of cholesterol crystals breaking free of atherosclerotic vascular plaque and lodging in downstream microvessels. Most clinical atheroembolic events follow angiographic procedures, often of the coronary vessels. It has been argued that nearly all vascular interventional procedures lead to plaque fracture and release of microemboli, but clinical manifestations develop only in a fraction of these. The incidence of clinical atheroemboli has been increasing with more vascular procedures and longer life spans. Atheroembolic renal disease is suspected in >3% of elderly subjects with end-stage renal disease (ESRD) and is likely underdiagnosed. It is more frequent in males with a history of diabetes, hypertension, and ischemic cardiac disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinically evident cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome

**TABLE 278-2 Clinical Factors That Determine the Role of Revascularization in Addition to Medical Therapy for Renal Artery Stenosis****Factors Favoring Medical Therapy with Revascularization for Renal Artery Stenosis**

- Progressive decline in GFR during treatment of systemic hypertension
- Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure)
- Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
- Decline in the GFR during therapy with ACE inhibitors or ARBs
- Recurrent congestive heart failure in a patient in whom left ventricular dysfunction does not fully explain the cause

**Factors Favoring Medical Therapy and Surveillance of Renal Artery Disease**

- Controlled blood pressure with stable renal function (e.g., stable renal insufficiency)
- Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound)
- Advanced age and/or limited life expectancy
- Extensive comorbidity that make revascularization too risky
- High risk for or previous experience with atheroembolic disease
- Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., interstitial nephritis, diabetic nephropathy), particularly with proteinuria

**Abbreviations:** ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate.

commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common, sometimes reaching a malignant phase. Progressive renal failure can occur and require dialytic support. These cases often develop after a stuttering onset over many weeks and have an ominous prognosis. Mortality rate after 1 year exceeds 38%, and although some may eventually recover sufficiently to no longer require dialysis, many do not.

Beyond the clinical manifestations above, laboratory findings include rising creatinine, transient eosinophilia (60–80%), elevated sedimentation rate, and hypocomplementemia (15%). Establishing this diagnosis can be difficult and is often by exclusion. Definitive diagnosis depends on kidney biopsy demonstrating microvessel occlusion with cholesterol crystals that leave a “cleft” in the vessel. Biopsies obtained from patients undergoing surgical revascularization of the kidney indicate that silent cholesterol emboli are frequently present before any further manipulation is performed.

No effective therapy is available for atheroembolic disease once it has developed. Withdrawal of anticoagulation is recommended. Late recovery of kidney function after supportive measures sometimes occurs, and statin therapy may improve outcome. The role of embolic protection devices in the renal circulation during angiography is unclear, but a few prospective trials have failed to demonstrate major benefits. The effect of such devices is limited to distal protection during the endovascular procedure, and they offer no protection from embolic debris developing after removal.

## THROMBOEMBOLIC RENAL DISEASE

Thrombotic occlusion of renal vessels or branch arteries can lead to declining renal function and hypertension. It is difficult to diagnose and is often overlooked, especially in elderly patients. Thrombosis can develop as a result of local vessel abnormalities, such as local dissection, trauma, or inflammatory vasculitis. Local microdissections sometimes lead to patchy, transient areas of infarctions labeled “segmental arteriolar mediolysis.” Although hypercoagulability conditions sometimes present as renal artery thrombosis, this is rare. It can also

derive from distant embolic events, e.g., the left atrium in patients with atrial fibrillation or from fat emboli originating from traumatized tissue, most commonly large bone fractures. Cardiac sources include vegetations from subacute bacterial endocarditis. Systemic emboli to the kidneys may also arise from the venous circulation if right-to-left shunting occurs, e.g., through a patent foramen ovale.

Clinical manifestations vary depending on the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase (LDH) rise transiently to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sudden release of renin from ischemic tissue can develop rapidly, as long as some viable tissue in the “peri-infarct” border zone remains. If the infarct zone demarcates precisely, the rise in BP and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with CT angiography, MRI, or arteriography (Fig. 278-2).

## MANAGEMENT OF ARTERIAL THROMBOSIS OF THE KIDNEY

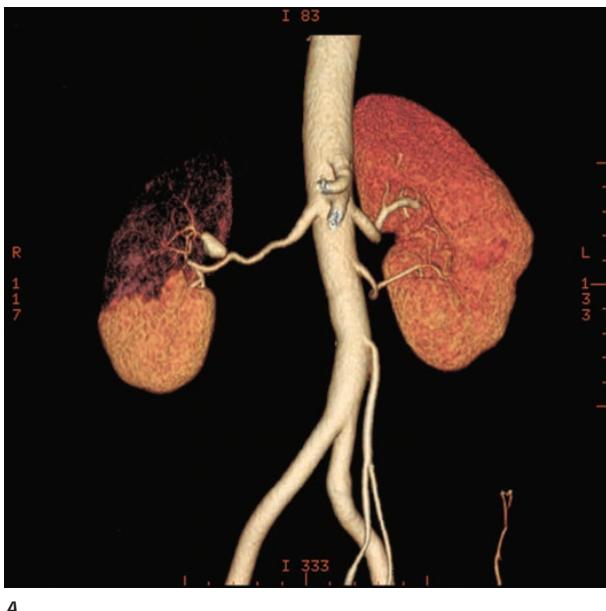
Options for interventions of newly detected arterial occlusion include surgical reconstruction, anticoagulation, thrombolytic therapy, endovascular procedures, and supportive care, particularly antihypertensive drug therapy. Application of these methods depends on the patient's overall condition, the precipitating factors (e.g., local trauma or systemic illness), the magnitude of renal tissue and function at risk, and the likelihood of recurrent events in the future. For unilateral disease, for example, arterial dissection with thrombosis and supportive care with anticoagulation may suffice. Acute, bilateral occlusion is potentially catastrophic, producing anuric renal failure. Depending on the precipitating event, surgical or thrombolytic therapies can sometimes restore kidney viability if undertaken early in the course of the acute event.

## MICROVASCULAR INJURY ASSOCIATED WITH HYPERTENSION

### ARTERIOLONEPHROSCLEROSIS

**“Malignant” Hypertension** Although BP rises with age, it has long been recognized that some individuals develop rapidly progressive BP elevations with target organ injury including retinal hemorrhages, encephalopathy, and declining kidney function. Placebo arms during the early controlled trials of hypertension therapy identified progression to severe levels in 20% of subjects over 5 years. If untreated, patients with target organ injury including papilledema and declining kidney function suffered mortality rates in excess of 50% over 6–12 months, hence the designation “malignant.” Postmortem studies of such patients identified vascular lesions, designated “fibrinoid necrosis,” with breakdown of the vessel wall, deposition of eosinophilic material including fibrin, and a perivascular cellular infiltrate. A separate lesion was identified in the larger interlobular arteries in many patients with hyperplastic proliferation of the vascular wall cellular elements, deposition of collagen, and separation of layers, designated the “onionskin” lesion. For many of these patients, fibrinoid necrosis led to obliteration of glomeruli and loss of tubular structures. Progressive kidney failure ensued and, without dialysis support, led to early mortality in untreated malignant-phase hypertension. These vascular changes could develop with pressure-related injury from a variety of hypertensive pathways, including but not limited to activation of the renin-angiotensin system and severe vasospasm associated with catecholamine release. Occasionally, endothelial injury is sufficient to induce microangiopathic hemolysis, as discussed below.

Antihypertensive therapy is the mainstay of therapy for malignant hypertension. With effective BP reduction, manifestations of vascular injury, including microangiopathic hemolysis and renal dysfunction, can improve over time. Whereas prior reports before the era of drug therapy suggested that 1-year mortality rates exceeded 90%, current survival over 5 years exceeds 50%.

**A****B**

**FIGURE 278-2** **A.** CT angiogram illustrating loss of circulation to the upper pole of the right kidney in a patient with fibromuscular disease and a renal artery aneurysm. Activation of the renin-angiotensin system produced rapidly developing hypertension. **B.** Angiogram illustrating high-grade renal artery stenosis affecting the left kidney. This lesion is often part of widespread atherosclerosis and sometimes is an extension of aortic plaque. This lesion develops in older individuals with preexisting atherosclerotic risk factors.

Malignant hypertension is less common in Western countries, although it persists in parts of the world where medical care and antihypertensive drug therapy are less available. It most commonly develops in patients with treated hypertension who neglect to take medications or who may use vasospastic drugs, such as cocaine. Renal abnormalities typically include rising serum creatinine and occasionally hematuria and proteinuria. Biochemical findings may include evidence of hemolysis (anemia, schistocytes, and reticulocytosis) and changes associated with kidney failure. African-American males are more likely to develop rapidly progressive hypertension and kidney failure than are whites in the United States. Genetic polymorphisms for *APOL1* that are common in the African-American population predispose to focal sclerosing glomerular disease, with severe hypertension developing at younger ages secondary to renal disease in this instance.

**Hypertensive Nephrosclerosis** Based on experience with malignant hypertension and epidemiologic evidence linking BP with long-term risks of kidney failure, it has long been assumed that lesser degrees of hypertension induce less severe, but prevalent, changes in kidney vessels and loss of kidney function. As a result, a large portion of patients reaching ESRD without a specific etiologic diagnosis are assigned the designation “hypertensive nephrosclerosis.” Pathologic examination commonly identifies afferent arteriolar thickening with deposition of homogeneous eosinophilic material (hyaline arteriolosclerosis) associated with narrowing of vascular lumina. Clinical manifestations include retinal vessel changes associated with hypertension (arteriolar narrowing, arteriovenous crossing changes), left ventricular hypertrophy, and elevated BP. The role of these vascular changes in kidney function is unclear. Postmortem and biopsy samples from normotensive kidney donors demonstrate similar vessel changes associated with aging, dyslipidemia, and glucose intolerance. Although BP reduction does slow progression of proteinuric kidney diseases and is warranted to reduce the excessive cardiovascular risks associated with CKD, antihypertensive therapy does not alter the course of kidney dysfunction identified specifically as hypertensive nephrosclerosis.

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**279**

## Deep-Venous Thrombosis and Pulmonary Thromboembolism

Samuel Z. Goldhaber

### EPIDEMIOLOGY

Venous thromboembolism (VTE) encompasses deep-venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death, chronic disability, and emotional distress. In the United States, there are an estimated 100,000–180,000 deaths attributed annually to PE.

Beginning in 2015, the life expectancy in the United States has decreased, primarily due to more deaths among young and middle-aged adults of all racial groups. Drug overdoses, alcoholic liver disease, and suicides have garnered the most attention for this increase in midlife

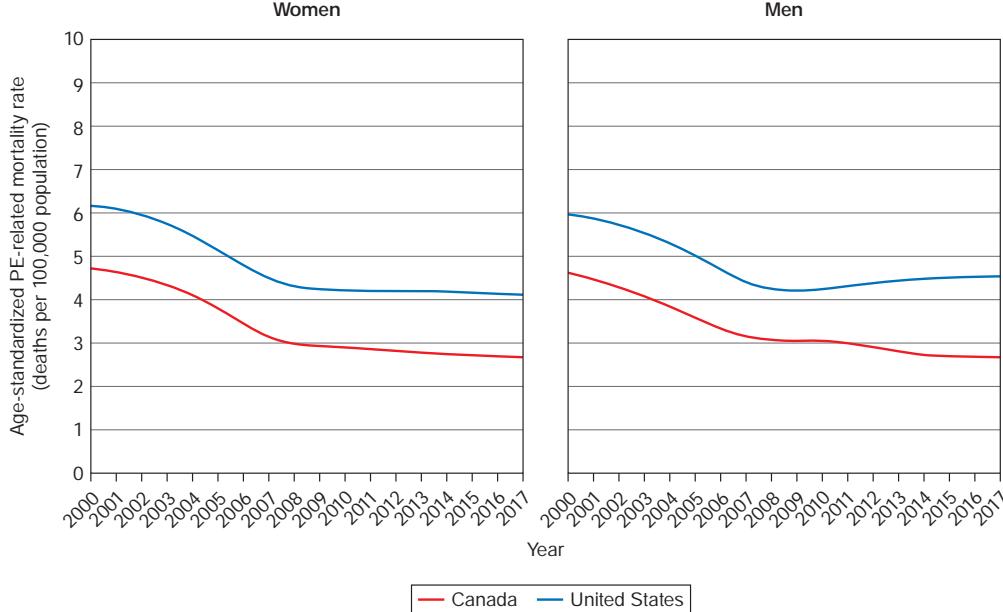


FIGURE 279-1 Time trends in pulmonary embolism (PE)-related age-standardized mortality in women and men in the United States and Canada from 2000 to 2017.

mortality; however, increasing deaths from heart and lung diseases, as well as hypertension, stroke, and diabetes mellitus, help account for this unwanted trend. The annual PE-related age-standardized mortality rate has been increasing among young and middle-aged adults since 2007 (Fig. 279-1). Among the elderly, the rate of decrease of PE-related mortality has slowed. PE patients residing in zip codes with lower socioeconomic status have increased in-hospital mortality. In contrast, Canada's and Denmark's annual age-standardized mortality rate with PE as the underlying cause of death has decreased across all age groups. Europe's age-standardized annual PE-related mortality rate has decreased linearly since year 2000.

In 2020, COVID-19 erupted and caused a global pandemic. The most notable clinical feature is a life-threatening acute respiratory syndrome requiring prolonged mechanical ventilation and causing a high case-fatality rate. This viral illness also causes extensive DVT and PE, even when patients receive standard pharmacologic prophylaxis as soon as they are hospitalized. At autopsy, about one-fourth of patients have both macrovascular and microvascular PE. Arterial thrombosis also occurs and causes myocardial infarction and stroke. The contributing etiologies of this widespread thrombosis are excessive inflammation with cytokine storm, platelet activation, endothelial dysfunction, and stasis (Fig. 279-2).

In the United States, Medicare fee-for-service beneficiaries with acute PE have a high 14% readmission rate within 30 days of hospital discharge. The reasons are uncertain, but the high rate suggests that we need to improve the transition of care from inpatient to outpatient. In addition to survival after PE, we now focus more attention on the quality of life after PE. About half of PE patients report persistent dyspnea, fatigue, and reduced exercise capacity, and about one-quarter have persistent right ventricular dysfunction on echocardiogram following the diagnosis of PE. This constellation of findings is being recognized more frequently and is called the “post-PE syndrome.” These patients may subsequently develop chronic thromboembolic pulmonary hypertension.

Chronic thromboembolic pulmonary hypertension causes breathlessness, especially with exertion. Postthrombotic syndrome (also known as *chronic venous insufficiency*) damages the venous valves of the leg and worsens the quality of life by causing ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes deep skin ulceration (Fig. 279-3).

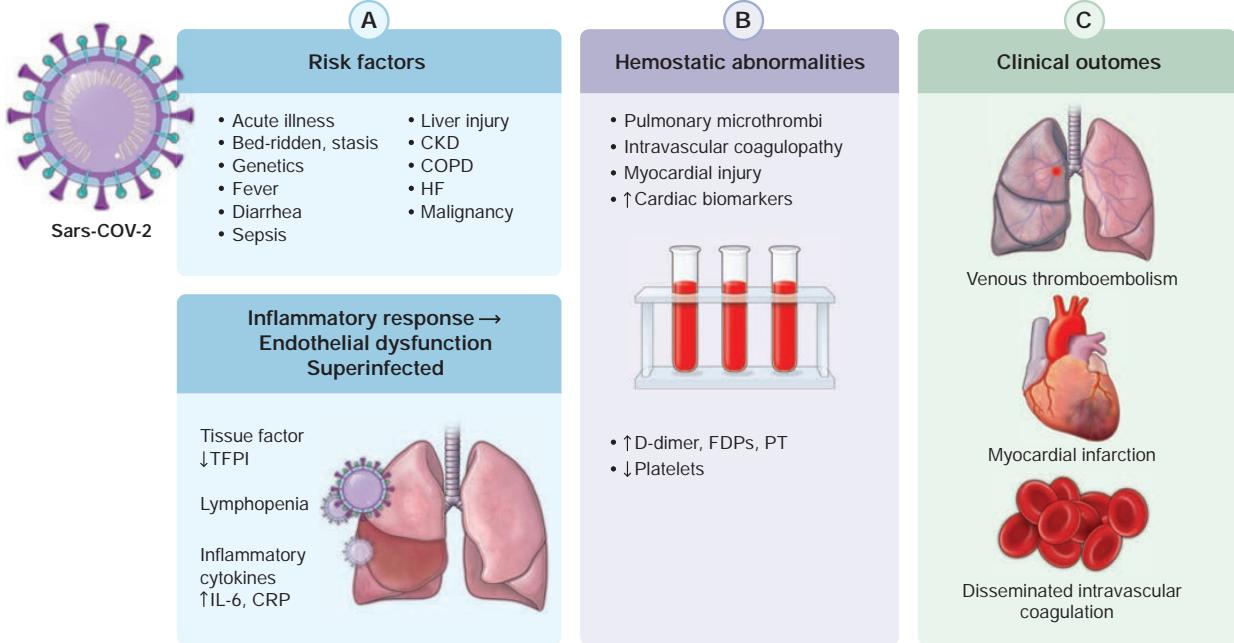
## PATHOPHYSIOLOGY

**Inflammation** Inflammation takes center stage as a trigger of acute PE and DVT. Inflammation-related risk factors and medical illnesses are now linked as precipitants of VTE (Table 279-1).

**Prothrombotic States** The two most common autosomal dominant genetic mutations are (1) factor V Leiden, which causes resistance to the endogenous anticoagulant activated protein C (which inactivates clotting factors V and VIII), and (2) the prothrombin gene mutation, which increases the plasma prothrombin concentration (Chaps. 65 and 117). Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors are associated with VTE but are rare. Antiphospholipid antibody syndrome is an acquired (not genetic) thrombophilic disorder that predisposes to both venous and arterial thrombosis. Counterintuitively, the presence of genetic mutations such as heterozygous factor V Leiden and prothrombin gene mutation does not appear to increase the risk of recurrent VTE. However, patients with antiphospholipid antibody syndrome may warrant indefinite-duration anticoagulation, even if the initial VTE was provoked by trauma or surgery.

**Clinical Risk Factors** Common comorbidities include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, long-haul air travel, air pollution, estrogen-containing contraceptives, pregnancy, postmenopausal hormone replacement, surgery, and trauma. Sedentary lifestyle is increasingly prevalent. A Japanese study found that each 2 h per day increment of television watching is associated with a 40% increased likelihood of fatal PE.

**Activated Platelets** Virchow's triad of venous stasis, hypercoagulability, and endothelial injury leads to recruitment of activated platelets, which release microparticles. These microparticles contain proinflammatory mediators that bind neutrophils, stimulating them to release their nuclear material and form web-like extracellular networks called neutrophil extracellular traps. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet-dependent thrombin generation. Venous thrombi form and flourish in an environment of stasis, low oxygen tension, and upregulation of proinflammatory genes.



**FIGURE 279-2** Postulated mechanisms of coagulopathy and pathogenesis of thrombosis in COVID-19. **A.** Sars-CoV-2 infection activates an inflammatory response, leading to release of inflammatory mediators. Endothelial and hemostatic activation ensues, with decreased levels of TFPI and increased tissue factor. The inflammatory response to severe infection is marked by lymphopenia and thrombocytopenia. Liver injury may lead to decreased coagulation and antithrombin formation. **B.** COVID-19 may be associated with hemostatic derangement and elevated troponin. **C.** Increased thromboembolic state results in venous thromboembolism, myocardial infarction, or, in case of further hemostatic derangement, disseminated intravascular coagulation. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FDP, fibrin degradation product; HF, heart failure; TFPI, tissue factor pathway inhibitor; IL, interleukin; LDH, lactate dehydrogenase; PT, prothrombin time. (This article was published in *Journal of the American College of Cardiology*; 75, B Bikdeli et al: COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review; 2950-2973. Copyright Elsevier 2020. Reproduced with permission from Elsevier.)

**Interaction between Venous Thromboembolism and Atherothrombosis** Carotid artery plaque doubles the risk of VTE. This observation led to discovery of the broad interaction among VTE,



**FIGURE 279-3** Skin ulceration in the lateral malleolus from postthrombotic syndrome of the leg.

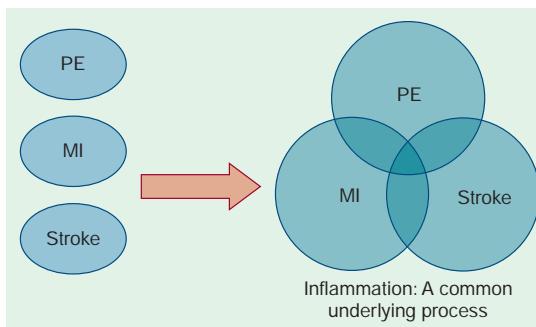
acute coronary syndrome, and acute stroke (Fig. 279-4). These three conditions share similar risk factors and similar pathophysiology: inflammation, hypercoagulability, and endothelial injury. Patients who suffer VTE are more than twice as likely to have a future myocardial infarction or stroke. Conversely, patients with myocardial infarction or stroke are more than twice as likely to suffer a future VTE.

**Embolization** When deep-venous thrombi (Fig. 279-5) detach from their site of formation, they embolize to the vena cava, right atrium, and right ventricle, and lodge in the pulmonary arterial circulation, thereby causing acute PE. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale

**TABLE 279-1** Inflammation-Linked Conditions That Can Trigger PE or DVT

Ulcerative colitis
Crohn's disease
Rheumatoid arthritis
Psoriasis
Diabetes mellitus, type 2
Obesity/metabolic syndrome
Hypercholesterolemia, especially elevated LDL cholesterol
Lipoprotein(a)
Pneumonia
Acute coronary syndrome
Acute stroke
Cigarette smoking
Sepsis/septic shock
Erythropoiesis-stimulating agents
Blood transfusion
Cancer

**Abbreviations:** DVT, deep-venous thrombosis; LDL, low-density lipoprotein; PE, pulmonary embolism.



**FIGURE 279-4** Broad interaction between venous thromboembolism and atherosclerosis. MI, myocardial infarction; PE, pulmonary embolism.

or atrial septal defect. Many patients with PE have no evidence of DVT because the clot has already embolized to the lungs.

**Physiology** The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial  $O_2$  tension gradient, which represents the inefficiency of  $O_2$  transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries (Fig. 279-6).

Other pathophysiologic abnormalities include the following:

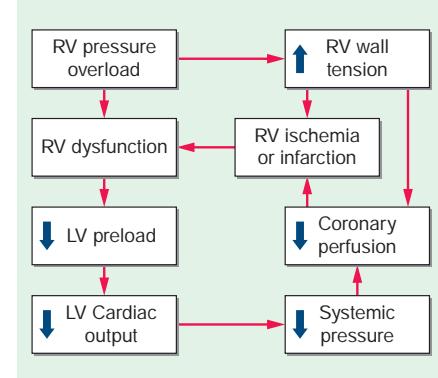
1. *Increased pulmonary vascular resistance* due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial  $O_2$  gradient.
2. *Impaired gas exchange* due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, or impaired carbon monoxide transfer due to loss of gas exchange surface.
3. *Alveolar hyperventilation* due to reflex stimulation of irritant receptors.
4. *Increased airway resistance* due to constriction of airways distal to the bronchi.
5. *Decreased pulmonary compliance* due to lung edema, lung hemorrhage, or loss of surfactant.

#### Pulmonary Hypertension, Right Ventricular (RV) Dysfunction, and RV Microinfarction

Pulmonary artery obstruction and



**FIGURE 279-5** Deep-venous thrombosis at autopsy.



**FIGURE 279-6** Pathophysiology of pulmonary embolism (PE). LV, left ventricular; RV, right ventricular.

neurohumoral mediators cause a rise in pulmonary artery pressure and in pulmonary vascular resistance. When RV wall tension rises, RV dilation and dysfunction ensue, with release of the cardiac biomarker, brain natriuretic peptide, due to abnormal RV stretch. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV dysfunction reduces LV distensibility and impairs LV filling. Increased RV wall tension also compresses the right coronary artery, limits myocardial oxygen supply, and precipitates right coronary artery ischemia and RV microinfarction, with release of cardiac biomarkers such as troponin. Underfilling of the LV may lead to a fall in LV cardiac output and systemic arterial pressure, with consequent circulatory collapse and death (Fig. 279-6).

#### CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP-VENOUS THROMBOSIS

**Pulmonary Embolism** **Massive (high-risk)** PE accounts for 5–10% of cases and is usually characterized by systemic arterial hypotension and extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure. **Submassive (intermediate-risk)** PE accounts for 20–25% of patients and is characterized by RV dysfunction despite normal systemic arterial pressure. The combination of right heart failure and release of cardiac biomarkers such as troponin indicates a high risk of clinical deterioration. **Low-risk PE** constitutes about 65–75% of cases. These patients have an excellent prognosis.

**Deep-Venous Thrombosis** Lower extremity DVT usually begins in the calf and can propagate proximally to the popliteal, femoral, and iliac veins. Leg DVT is ~10 times more common than **upper extremity DVT**, which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase. **Superficial venous thrombosis** usually presents with erythema, tenderness, and a “palpable cord.” Patients are at risk for extension of the superficial vein thrombosis to the deep-venous system.

#### DIAGNOSIS

**Clinical Evaluation** PE is known as “the Great Masquerader.” Diagnosis is difficult because symptoms and signs are nonspecific. In the United States, there appears to be excessive ordering of computed tomography (CT) pulmonary angiograms in patients suspected of PE. In a study of 27 emergency departments in Indiana and Dallas-Fort Worth, where 1.8 million patient encounters were logged, 5% of patients underwent CT pulmonary angiography. Increased d-dimer correlated with an increased diagnostic yield rate, varying from 1.3% in Indiana to 4.8% in Dallas-Fort Worth.

The standard upper of limit of a d-dimer is 500 ng/mL. However, guidelines now recommend use of an age-adjusted d-dimer when ruling out acute PE. The age-adjusted d-dimer applies to patients older than 50 years of age with low or intermediate clinical probability of PE. To calculate the upper limit of normal d-dimer in these patients, multiply the age by 10. For example, a 70-year-old patient suspected of PE would have 700 ng/mL as the upper limit of normal. The age-adjusted d-dimer does not apply to patients suspected of acute DVT. In validation studies, implementing routine use of the age-adjusted d-dimer may reduce the number of CT pulmonary angiograms that are ordered by about one-third.

The most common symptom of PE is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to ensue despite standard medical treatment of the concomitant illness. This scenario presents a clinical clue to the possible coexistence of PE.

With DVT, the most common symptom is a cramp or “charley horse” in the lower calf that persists and intensifies over several days. Wells Point Score criteria help estimate the clinical likelihood of DVT and PE (Table 279-2). Patients with a low likelihood of DVT or a low-to-moderate likelihood of PE should undergo initial diagnostic evaluation with d-dimer testing alone (see “Blood Tests”) without obligatory imaging tests if the d-dimer test result is negative (Fig. 279-7). However, patients with a high clinical likelihood of VTE should skip d-dimer testing and undergo imaging as the next step in the diagnostic algorithm.

**Clinical Pearls** Not all leg pain is due to DVT, and not all dyspnea is due to PE (Table 279-3). Sudden, severe calf discomfort suggests a ruptured Baker’s cyst. Fever and chills usually herald cellulitis rather than DVT. Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. Recurrent left thigh edema especially in young women raises the possibility of May-Thurner syndrome, with right proximal iliac artery compression of the left proximal iliac vein. If a leg is diffusely edematous, DVT is unlikely. More probable is an acute exacerbation of venous insufficiency due to postthrombotic syndrome. Upper extremity venous thrombosis may present with asymmetry in the supravacuicular fossa or in the circumference of the upper arms.

**TABLE 279-2 Clinical Decision Rules**

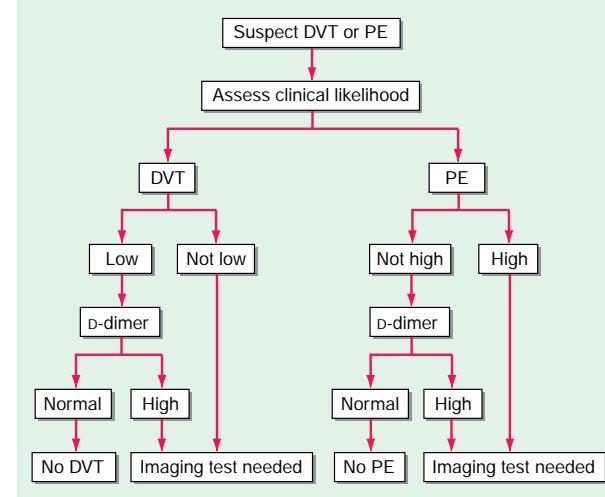
Low Clinical Likelihood of DVT if Point Score Is Zero or Less; Moderate Likelihood if Score Is 1 to 2; High Likelihood if Score Is 3 or Greater

CLINICAL VARIABLE	DVT SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	-2

High Clinical Likelihood of PE if Point Score Exceeds 4

CLINICAL VARIABLE	PE SCORE
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Abbreviations: DVT, deep-venous thrombosis; PE, pulmonary embolism.



**FIGURE 279-7** How to decide whether diagnostic imaging is needed. For assessment of clinical likelihood, see Table 279-2. DVT, deep-venous thrombosis; PE, pulmonary embolism.

**Pulmonary infarction** usually indicates a small PE. This condition is exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves. *Nonthrombotic PE* etiologies include fat embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that can embolize, such as hair, talc, and cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin.

**Nonimaging Diagnostic Modalities • BLOOD TESTS** The quantitative plasma d-dimer enzyme-linked immunosorbent assay (ELISA) rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin. Elevation of d-dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of the d-dimer is >80% for DVT (including isolated calf DVT) and >95% for PE. The d-dimer is less sensitive for DVT than for PE because the DVT thrombus size is smaller. A normal d-dimer is a useful “rule out” test for PE. However, the d-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, the postoperative state, and those in the second or third trimester of pregnancy. Therefore, d-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.

**TABLE 279-3 Differential Diagnosis of DVT and PE**

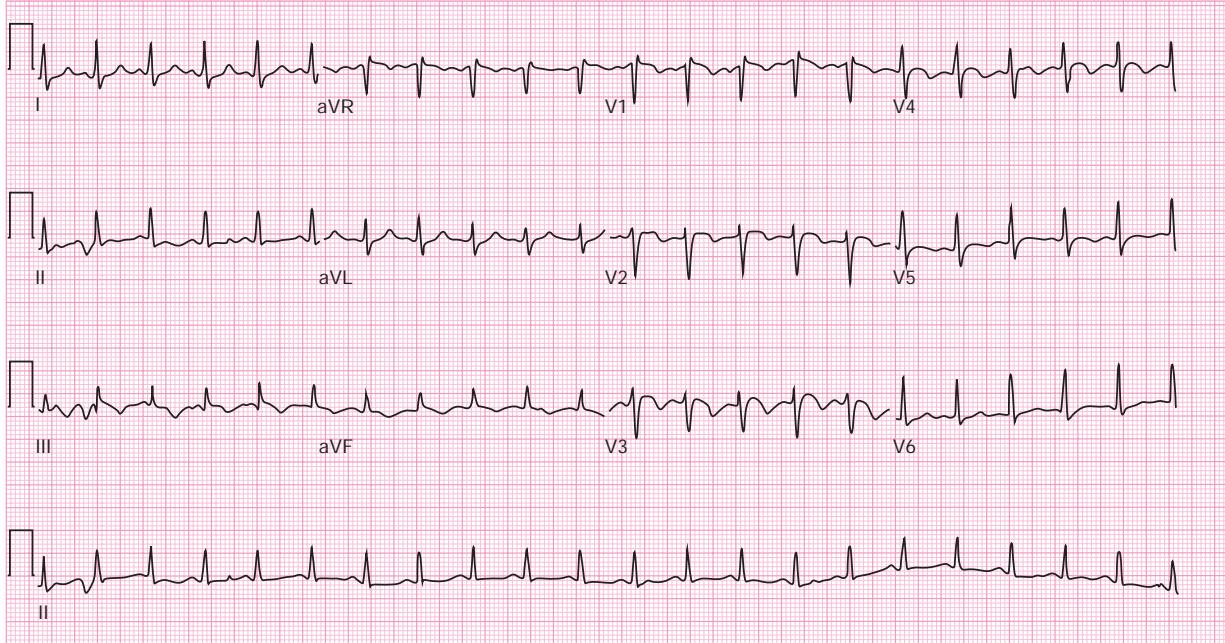
#### DVT

- Ruptured Baker’s cyst
- Muscle strain/injury
- Cellulitis
- Acute postthrombotic syndrome/venous insufficiency

#### PE

- Pneumonia, asthma, chronic obstructive pulmonary disease
- Congestive heart failure
- Pericarditis
- Pleurisy: “viral syndrome,” costochondritis, musculoskeletal discomfort
- Rib fracture, pneumothorax
- Acute coronary syndrome
- Anxiety
- Vasovagal syncope

Abbreviations: DVT, deep-venous thrombosis; PE, pulmonary embolism.



**FIGURE 279-8** Electrocardiogram with both the S1Q3T3 sign and T-wave inversions in leads V<sub>1</sub>-V<sub>4</sub>—typical of an anatomically large pulmonary embolism. This patient's CT pulmonary angiogram is shown as Figures 279-10A and B.

**ELEVATED CARDIAC BIOMARKERS** Serum troponin and plasma heart-type fatty acid-binding protein levels increase because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

**ELECTROCARDIOGRAM** The most frequently cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III (**Chap. 240**). This finding is relatively specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V<sub>1</sub> to V<sub>4</sub> (**Fig. 279-8**).

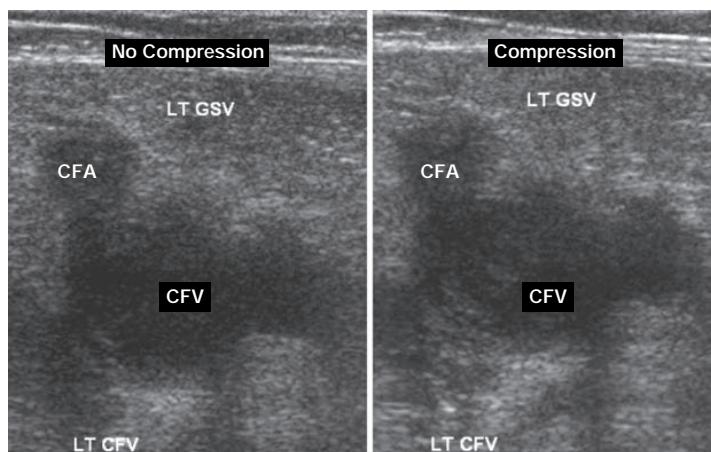
**Noninvasive Imaging Modalities • VENOUS ULTRASONOGRAPHY** Ultrasonography of the deep-venous system relies on loss of vein compressibility as the primary diagnostic criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure on the ultrasound transducer. This creates the illusion of a “wink.” With acute DVT, the vein loses its compressibility because of passive distention by acute thrombus. The diagnosis of acute DVT is even

more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity (**Fig. 279-9**). The vein itself often appears mildly dilated, and collateral channels may be absent.

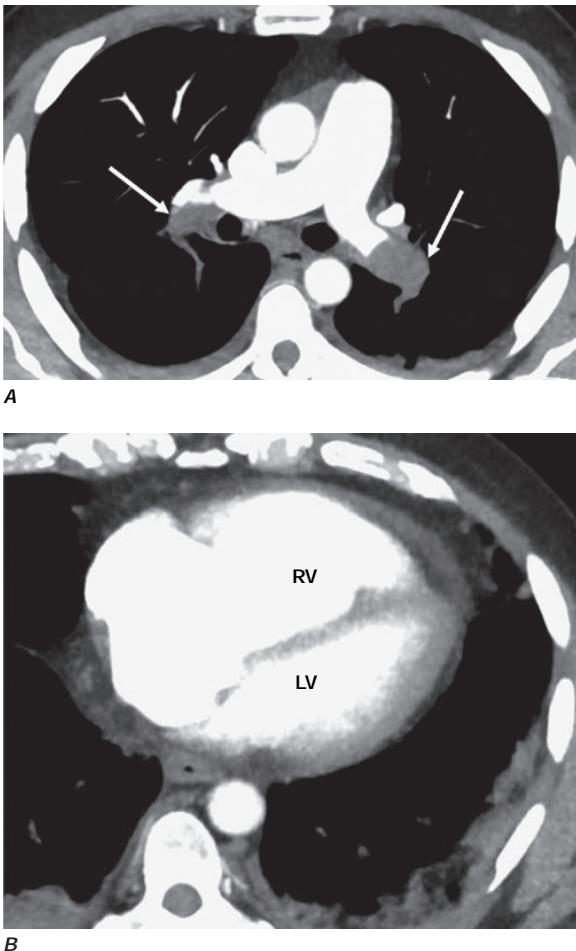
Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing DVT or by any obstructive process within the pelvis. For patients with a technically poor or nondiagnostic venous ultrasound, one should consider alternative imaging modalities for DVT, such as CT and magnetic resonance imaging.

**CHEST ROENTGENOGRAPHY** A normal or nearly normal chest x-ray often occurs in PE. Well-established abnormalities include focal oligemia (Westermark's sign), a peripheral wedge-shaped density usually located at the pleural base (Hampton's hump), and an enlarged right descending pulmonary artery (Palla's sign).

**CHEST CT** CT of the chest with intravenous contrast is the principal imaging test for the diagnosis of PE (**Fig. 279-10A**). Thin-cut chest CT



**FIGURE 279-9** Venous ultrasound, with and without compression of the leg veins. CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; LT, left.



**FIGURE 279-10** **A.** Massive bilateral proximal pulmonary embolism on an axial chest CT image in a 53-year-old man (whose electrocardiogram is shown in Fig. 279-8) with filling defects in the right and left main pulmonary arteries (white arrows). **B.** Four-chamber view in the same patient showing the right ventricle (RV) larger than the left ventricle (LV).

images can provide exquisite detail, with 1 mm of resolution during a short breath hold. Sixth-order branches can be visualized with resolution superior to that of conventional invasive contrast pulmonary angiography. The CT scan also provides an excellent four-chamber view of the heart (**Fig. 279-10B**). RV enlargement on chest CT indicates an increased likelihood of death within the next 30 days compared with PE patients who have normal RV size. In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs, such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, and aortic pathology.

**LUNG SCANNING** Lung scanning has become a second-line diagnostic test for PE, used mostly for patients who cannot tolerate intravenous contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and are trapped in the pulmonary capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans, obtained with a radiolabeled inhaled gas such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung, thereby providing possible explanations for perfusion defects other than acute PE, such as asthma and chronic obstructive pulmonary disease. A high-probability scan for PE is defined as two or more

segmental perfusion defects in the presence of normal ventilation. The diagnosis of PE is very unlikely in patients with normal and nearly normal scans and, in contrast, is ~90% certain in patients with high-probability scans.

**MAGNETIC RESONANCE (MR) (CONTRAST-ENHANCED) IMAGING** When ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE but is not reliable for smaller segmental and subsegmental PE.

**ECHOCARDIOGRAPHY** Echocardiography is *not* a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is a very useful diagnostic tool for detecting conditions that may mimic PE, such as acute myocardial infarction, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly. The best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesis of the RV free wall with normal or hyperkinetic motion of the RV apex. One should consider transesophageal echocardiography when CT scanning facilities are not available or when a patient has renal failure or severe contrast allergy that precludes administration of contrast despite premedication with high-dose steroids. This imaging modality can identify saddle, right main, or left main PE.

**Invasive Diagnostic Modalities • PULMONARY ANGIOGRAPHY** Chest CT with contrast (see above) has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis is planned. A definitive diagnosis of PE requires visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion ("cut-off") of vessels, segmental oligemia or avascularity, and a prolonged arterial phase with slow filling, and tortuous, tapering peripheral vessels.

**CONTRAST PHLEBOGRAPHY** Venous ultrasonography has virtually replaced contrast phlebography as the principal diagnostic test for suspected DVT. However, contrast phlebography is used when an interventional procedure is planned.

**Integrated Diagnostic Approach** An integrated diagnostic approach streamlines the workup of suspected DVT and PE (**Fig. 279-11**).

## TREATMENT

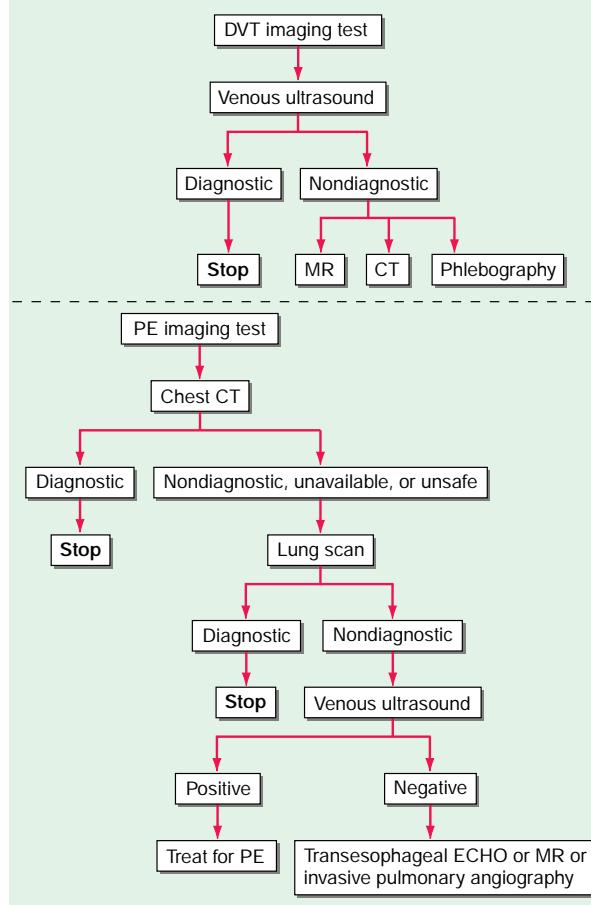
### Deep-Venous Thrombosis

#### PRIMARY THERAPY

*Primary therapy* consists of clot dissolution with pharmacomechanical therapy using low-dose catheter-directed thrombolysis. The open vein hypothesis postulates that patients who receive primary therapy will sustain less long-term damage to venous valves, with consequent lower rates of postthrombotic syndrome. However, the ATTRACT trial randomized 692 patients with femoral or iliofemoral DVT to catheter-directed thrombolysis versus usual care with anticoagulation alone. After 2 years of follow-up, there was no overall reduction in postthrombotic syndrome in the thrombolysis group. Nevertheless, there was a trend toward less postthrombotic syndrome 2 years after randomization among patients with iliofemoral DVT (compared with only femoral DVT) who received catheter-directed thrombolysis compared with anticoagulation alone.

**Asymptomatic DVT** In the primary prevention APEX trial sub-study of patients with asymptomatic DVT, 299 patients with asymptomatic DVT were compared with 5898 patients with no DVT. Those with asymptomatic DVT had a threefold higher mortality rate.

**Upper Extremity DVT** As peripherally inserted central catheter (PICC) use has increased, so has the rate of upper extremity DVT.



**FIGURE 279-11** Imaging tests to diagnose deep-venous thrombosis (DVT) and pulmonary embolism (PE). ECHO, echocardiography; MR, magnetic resonance.

This rate can be decreased by more judicious selection of patients who require a PICC, use of single-lumen rather than double- or triple-lumen PICCs, and use of the smallest possible lumen size, ideally 4 French rather than 5 or 6 French.

**Isolated Calf DVT** The GARFIELD-VTE Registry recruited 2145 patients with isolated calf DVT and 3846 patients with proximal DVT with or without calf DVT. Isolated calf DVT patients were more likely to have either undergone surgery or have experienced leg trauma, and they were less likely to have active cancer or a prior history of VTE. Almost all isolated calf DVT patients received anticoagulation, and nearly half were anticoagulated for at least 1 year. In a smaller study of 871 patients with leg DVT, the 10-year mortality was the same in patients with isolated calf DVT compared to those with proximal leg DVT. Cancer-associated isolated calf DVT had as high a recurrence rate as cancer-associated proximal leg DVT.

#### SECONDARY PREVENTION

Anticoagulation or placement of an inferior vena cava (IVC) filter constitutes *secondary prevention* of VTE. IVC filters are indicated in patients with an absolute contraindication to anticoagulation and for those who have suffered recurrent VTE while receiving therapeutic doses of anticoagulation. Under most circumstances, IVC filters are not indicated for primary prevention of VTE. The IVC filter should be retrieved if the clinician judges that the patient no longer requires it.

For patients with swelling of the legs when acute DVT is diagnosed, below-knee graduated compression stockings may be prescribed, usually 30–40 mmHg or 20–30 mmHg, to lessen patient

discomfort. They should be replaced every 3 months because they lose their elasticity. However, prescription of vascular compression stockings in asymptomatic newly diagnosed acute DVT patients does not prevent the development of postthrombotic syndrome.

## TREATMENT

### Pulmonary Embolism

#### RISK STRATIFICATION

Hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, and elevation of the troponin level due to RV microinfarction portend a high risk of an adverse clinical outcome despite anticoagulation. When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone (Fig. 279-12).

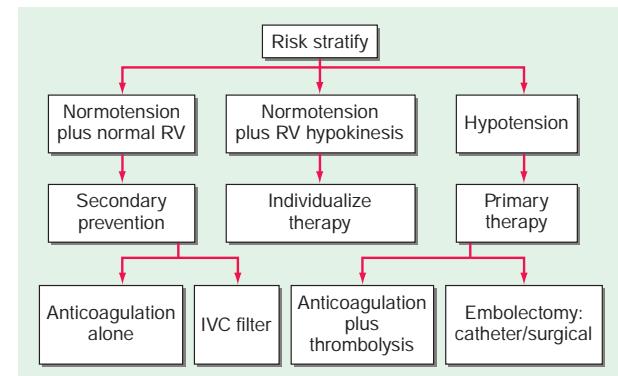
#### ANTICOAGULATION

Effective anticoagulation is the foundation for successful treatment of DVT and PE. There are three major strategies: (1) the classical but waning strategy of parenteral anticoagulation with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux “bridged” to warfarin; (2) parenteral therapy, switched after 5 days to a novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent); or (3) oral anticoagulation monotherapy with rivaroxaban or apixaban (both are anti-Xa agents) with a 3-week or 1-week loading dose, respectively, followed by a maintenance dose. For patients with VTE in the setting of suspected or proven heparin-induced thrombocytopenia, one can choose between two parenteral direct thrombin inhibitors: argatroban and bivalirudin (Table 279-4).

**Unfractionated Heparin** UFH binds to and accelerates the activity of antithrombin, thus preventing additional thrombus formation. UFH is dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s. Use an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg per h in patients with normal liver function. The short half-life of UFH is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired. Heparin also has pleiotropic effects that may decrease systemic and local inflammation.

**Low-Molecular-Weight Heparins** These fragments of UFH exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than does UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

**Fondaparinux** Fondaparinux, an anti-Xa pentasaccharide, is essentially an ultra-low-molecular-weight heparin. It is administered as



**FIGURE 279-12** Acute management of pulmonary thromboembolism. IVC, inferior vena cava; PE, pulmonary embolism; RV, right ventricular.

**TABLE 279-4 Anticoagulation of VTE****Non-Warfarin Anticoagulation**

- Unfractionated heparin, bolus and continuous infusion, to achieve aPTT 2–3 times the upper limit of the laboratory normal, or
- Enoxaparin 1 mg/kg twice daily with normal renal function, or
- Dalteparin 200 U/kg once daily or 100 U/kg twice daily, with normal renal function, or
- Tinzaparin 175 U/kg once daily with normal renal function, or
- Fondaparinux weight-based once daily: adjust for impaired renal function
- Direct thrombin inhibitors: argatroban or bivalirudin (with suspected or proven heparin-induced thrombocytopenia)
- Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily with the dinner meal thereafter
- Apixaban 10 mg twice daily for 1 week, followed by 5 mg twice daily thereafter
- Dabigatran: 5 days of unfractionated heparin, LMWH, or fondaparinux followed by dabigatran 150 mg twice daily
- Edoxaban: 5 days of unfractionated heparin, LMWH, or fondaparinux followed by edoxaban 60 mg once daily with normal renal function, weight >60 kg, in the absence of potent P-glycoprotein inhibitors

**Warfarin Anticoagulation**

Requires 5–10 days of administration to achieve effectiveness as monotherapy

Use full-dose unfractionated heparin, LMWH, or fondaparinux as “bridging agents” when initiating warfarin. Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, achieve the target INR range.

Usual start dose is 5 mg

Titrate to INR, target 2.0–3.0

**Abbreviations:** aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin.

a weight-based once-daily subcutaneous injection in a prefilled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. The dose must be adjusted downward for patients with renal dysfunction.

**Warfarin** This vitamin K antagonist prevents carboxylation-dependent activation of coagulation factors II, VII, IX, and X (**Chapter 65**). The full effect of warfarin requires daily therapy for at least 5 days. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin. The dose of warfarin is usually targeted to achieve a target international normalized ratio (INR) of 2.5, with a range of 2.0–3.0. Hundreds of drug-drug and drug-food interactions affect warfarin metabolism. Warfarin can cause major hemorrhage, including intracranial hemorrhage, even when the INR remains within the desired therapeutic range. Warfarin can also cause “off-target” side effects such as alopecia or arterial vascular calcification. Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Some patients can self-monitor their INR with a home point-of-care fingerstick machine, and a few can be taught to self-dose their warfarin.

**Novel Oral Anticoagulants** Novel oral anticoagulants (NOACs) are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, require no laboratory coagulation monitoring and no restriction on eating green leafy vegetables, and have few drug-drug interactions.

**Management of Bleeding from Anticoagulants** For life-threatening or intracranial hemorrhage due to heparin or LMWH, administer protamine sulfate. The dabigatran antibody idarucizumab is an effective, rapidly acting antidote for dabigatran. Andexanet reverses the bleeding complications from the anti-Xa anticoagulants. Major bleeding from warfarin is best managed with prothrombin complex concentrate. With less serious bleeding, fresh-frozen plasma or intravenous vitamin K can be used. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absence of bleeding.

**TABLE 279-5 Take-Home Points from the European Society of Cardiology 2019 Pulmonary Embolism Guidelines**

- Terminology such as “provoked” versus “unprovoked” PE/DVT is no longer supported by the Guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation.
- Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and:
  - No identifiable risk factor
  - A persistent risk factor
  - A minor transient or reversible risk factor

**Abbreviations:** PE, pulmonary embolism; VTE, venous thromboembolism.

**Cancer and Venous Thromboembolism** For patients with cancer and VTE, prescribe LMWH as monotherapy or a NOAC in the absence of a gastrointestinal cancer, and continue extended-duration anticoagulation until the patient is declared cancer-free.

**Duration of Anticoagulation** Based on contemporary observational and randomized trials, data-driven guidelines have changed fundamentally our conceptual approach to determining the optimal duration of anticoagulation. We should no longer try to classify a VTE as “provoked” or “unprovoked.” The reason is that many types of provoked VTE lead to as great a risk of recurrence after anticoagulation is discontinued as unprovoked VTE. The European Society of Cardiology (ESC) Pulmonary Embolism Guidelines, rewritten in 2019, are instructive in this regard (**Tables 279-5 and 279-6**).

**INFERIOR VENA CAVA FILTERS**

The two principal indications for insertion of an IVC filter are (1) active bleeding that precludes anticoagulation and (2) recurrent venous thrombosis despite intensive anticoagulation. Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis and prophylaxis of extremely high-risk patients are “softer” indications for filter placement. The filter itself may fail by permitting the passage of small- to medium-size clots via collateral veins that develop. Paradoxically, by providing a nidus for clot formation, filters increase the DVT rate, even though they usually prevent PE. Consider placing retrievable rather than permanent filters. The retrievable filters can be removed many months after insertion, unless thrombus forms and is trapped within the filter.

**MANAGEMENT OF MASSIVE PE**

For patients with massive PE and hypotension, replete volume with 500 mL of normal saline. Additional fluid should be infused with extreme caution because excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Norepinephrine and dobutamine are first-line vasopressor and inotropic agents, respectively, for treatment of PE-related shock. Norepinephrine increases RV inotropy and systemic arterial pressure. It also restores the coronary perfusion

**TABLE 279-6 Risk of Recurrent Venous Thromboembolism after Discontinuing Anticoagulation (European Society of Cardiology 2019 Pulmonary Embolism Guidelines)**

RISK OF RECURRENT	EXAMPLES
Low risk (<3% per year)	Major surgery or trauma
Intermediate risk (3–8% per year)	Minor surgery Hospitalized with acute medical illness Pregnancy/estrogens Long-haul flight Inflammatory bowel disease Autoimmune disease No identifiable risk factor (formerly called “unprovoked”)
High risk (>8% per year)	Active cancer Antiphospholipid syndrome

gradient. Dobutamine increases RV inotropy and lowers filling pressures. It may worsen systemic arterial hypotension unless used in combination with a vasopressor. Maintain a low threshold for initiating these pressors. If heroic measures are warranted, consider veno-arterial extracorporeal membrane oxygenation (ECMO). This strategy should only be employed when ECMO is being used as a "bridge" to definitive treatment with thrombolysis or embolectomy.

### FIBRINOLYSIS

Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by (1) dissolving much of the anatomically obstructing pulmonary arterial thrombus, (2) preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension, and (3) lysing much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE.

The U.S. Food and Drug Administration (FDA)-approved systemically administered fibrinolytic regimen is 100 mg of recombinant tissue plasminogen activator (tPA) prescribed as a continuous peripheral intravenous infusion over 2 h. The sooner thrombolysis is administered, the more effective it is. However, this approach can be used for at least 14 days after the PE has occurred. A popular off-label dosing regimen is 50 mg of TPA administered over 2 h. This lower dose may be associated with fewer bleeding complications.

Contraindications to fibrinolysis include intracranial disease, recent surgery, and trauma. The overall major bleeding rate is ~10%, including a 2–3% risk of intracranial hemorrhage. Careful screening of patients for contraindications to fibrinolytic therapy (*Chap. 275*) is the best way to minimize bleeding risk.

For patients with submassive PE who have preserved systolic blood pressure but moderate or severe RV dysfunction, use of fibrinolysis remains controversial. A 2019 American Heart Association Scientific Statement suggests considering advanced therapy with thrombolysis or embolectomy in patients with lack of improvement, clinical deterioration, severe physical distress with anticoagulation alone, clot in transit, severe or persistent RV strain, signs of low cardiac output, low bleeding risk, and good life expectancy.

### PHARMACOMECHANICAL CATHETER-DIRECTED THERAPY

Pharmacomechanical catheter-directed therapy usually combines physical fragmentation or pulverization of thrombus with catheter-directed low-dose thrombolysis. Mechanical techniques include catheter maceration and intentional embolization of clot more distally, suction thrombectomy, rheolytic hydrolysis, and low-energy ultrasound-facilitated thrombolysis. With pharmacomechanical catheter-directed therapy, the dose of alteplase can be markedly reduced, usually to a range of 20–25 mg, instead of the peripheral intravenous systemic dose of 100 mg. In 2014, the FDA approved ultrasound-facilitated catheter-directed thrombolysis for acute massive and submassive PE. Using a total tPA dose of 24 mg administered over 12 h, this approach decreased RV dilation, reduced pulmonary hypertension, decreased anatomic thrombus burden, and minimized intracranial hemorrhage. Lower doses and shorter durations of TPA are currently being studied.

### PULMONARY EMBOLECTOMY

The risk of major hemorrhage with systemically administered fibrinolysis has prompted a renaissance of interest in surgical embolectomy, an operation that had almost become extinct. More rapid referral before the onset of irreversible multisystem organ failure and improved surgical technique have resulted in a high survival rate.

### PULMONARY THROMBOENDARTERECTOMY

Chronic thromboembolic pulmonary hypertension develops in 2–4% of acute PE patients. Therefore, PE patients who have initial pulmonary hypertension (usually diagnosed with Doppler echocardiography) should be followed up at about 6 weeks and, if necessary, at 6 months, with repeat echocardiograms to determine whether pulmonary arterial pressure has normalized. Patients impaired by

dyspnea due to chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy, which, when successful, can markedly reduce, and sometimes even cure, pulmonary hypertension (*Chap. 283*). The operation requires median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest. The mortality rate at experienced centers is ~5%. Inoperable patients should be managed with pulmonary vasodilator therapy and balloon angioplasty of pulmonary arterial webs.

### EMOTIONAL SUPPORT

Patients with VTE may feel overwhelmed when they learn that they are suffering from PE or DVT. Some have never previously encountered serious cardiovascular illness. They fear they will not be able to adapt to the new limitations imposed by anticoagulation. They worry about the health of their families and the genetic implications of their illness. Those who are advised to discontinue anticoagulation may feel especially vulnerable about the potential for suffering recurrent VTE. At Brigham and Women's Hospital, a physician-nurse-facilitated PE support group was initiated to address these concerns and has met monthly for >30 years. The nonprofit organization North American Thrombosis Forum ([www.NATFonline.org](http://www.NATFonline.org)) has initiated monthly online support groups that garner worldwide participation.

### PREVENTION OF VTE

Prevention of DVT and PE (*Table 279-7*) is of paramount importance because VTE is difficult to detect and poses a profound medical and economic burden. Low-dose UFH or LMWH is the most common form of in-hospital prophylaxis. Computerized reminder systems can

**TABLE 279-7 Prevention of Venous Thromboembolism Among Hospitalized Patients**

CONDITION	PROPHYLAXIS STRATEGY
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Medical oncology	Enoxaparin or dalteparin Rivaroxaban or apixaban
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Warfarin (target INR 2.0–3.0) Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily Rivaroxaban 10 mg daily, beginning 6–10 h postoperatively Aspirin 81–325 mg daily Dabigatran 110 mg first day, then 20 mg daily Apixaban 2.5 mg bid, beginning 12–24 h postoperatively
Medically ill patients, especially if immobilized, with a history of prior VTE, with an indwelling central venous catheter, or with cancer (but without active gastroduodenal ulcer, major bleeding within 3 months, or platelet count <50,000)	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Medically ill patients about to be discharged from hospital	Rivaroxaban
Anticoagulation contraindicated	Intermittent pneumatic compression devices (but whether graduated compression stockings are effective in medical patients remains uncertain)

Abbreviations: INR, international normalized ratio; VTE, venous thromboembolism.

increase the use of preventive measures and, at Brigham and Women's Hospital, have reduced the symptomatic VTE rate by >40%. Audits of hospitals to ensure that prophylaxis protocols are followed correctly will also increase utilization of preventive measures.

Duration of in-hospital prophylaxis is short because the length of stay for hospitalization due to medical illnesses such as pneumonia is short. The FDA has approved extended-duration VTE prophylaxis continuing after hospital discharge with the anti-Xa agent rivaroxaban.

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and shear stress, the aorta is particularly prone to injury and disease resulting from mechanical trauma. The aorta is also more prone to rupture than is any other vessel, especially with the development of aneurysmal dilation, since its wall tension, as governed by Laplace's law (i.e., proportional to the product of pressure and radius), will be increased.

## CONGENITAL ANOMALIES OF THE AORTA

Congenital anomalies of the aorta usually involve the aortic arch and its branches. Symptoms such as dysphagia, stridor, and cough may occur if an anomaly causes a ring around or otherwise compresses the esophagus or trachea. Anomalies associated with symptoms include double aortic arch, origin of the right subclavian artery distal to the left subclavian artery, and right-sided aortic arch with an aberrant left subclavian artery. A Kommerell's diverticulum is an anatomic remnant of a right aortic arch. Most congenital anomalies of the aorta do not cause symptoms and are detected during catheter-based procedures. The diagnosis of suspected congenital anomalies of the aorta typically is confirmed by computed tomographic (CT) or magnetic resonance (MR) angiography. Surgery is used to treat symptomatic anomalies.

Coarctation of the aorta (Chap. 269) typically occurs near the insertion of the ligamentum arteriosum, adjacent to the left subclavian artery. It may be associated with a bicuspid aortic valve, aortic arch hypoplasia, other congenital heart defects, and intracranial aneurysms. A pulse delay or pressure differential between the upper and lower extremities should raise suspicion of aortic coarctation. Imaging modalities, including echocardiography, CT, and MR angiography are used to confirm the diagnosis. If untreated, hypertension develops in the arteries proximal to the coarctation. Treatment of hemodynamically significant aortic coarctation includes endovascular stent implantation if feasible or surgical repair.

## AORTIC ANEURYSM

An aneurysm is defined as a pathologic dilation of a segment of a blood vessel. A *true aneurysm* involves all three layers of the vessel wall and is distinguished from a *pseudoaneurysm*, in which the intimal and medial layers are disrupted and the dilated segment of the aorta is lined by adventitia only and, at times, by perivascular clot. Aneurysms also may be classified according to their gross appearance. A *fusiform aneurysm* affects the entire circumference of a segment of the vessel, resulting in a diffusely dilated artery. In contrast, a *saccular aneurysm* involves only a portion of the circumference, resulting in an outpouching of the vessel wall. Aortic aneurysms also are classified according to location, i.e., abdominal versus thoracic. Aneurysms of the descending thoracic aorta are usually contiguous with infradiaphragmatic aneurysms and are referred to as *thoracoabdominal aortic aneurysms*.

### ETIOLOGY

Aortic aneurysms result from conditions that cause degradation or abnormal production of the structural components of the aortic wall: elastin and collagen. The causes of aortic aneurysms may be broadly categorized as degenerative disorders, genetic or developmental diseases, vasculitis, infections, and trauma (Table 280-1). Inflammation, oxidative stress, proteolysis, and biomechanical wall stress contribute to the degenerative processes that characterize most aneurysms of the abdominal and descending thoracic aorta. These are mediated by B-cell and T-cell lymphocytes, macrophages, inflammatory cytokines, and matrix metalloproteinases that degrade elastin and collagen and alter the tensile strength and ability of the aorta to accommodate pulsatile stretch. The associated histopathology demonstrates destruction of elastin and collagen, decreased vascular smooth muscle, in-growth of new blood vessels, and inflammation. Factors associated with degenerative aortic aneurysms include aging, cigarette smoking, hypercholesterolemia, hypertension, and male sex.

The most common pathologic condition associated with degenerative aortic aneurysms is *atherosclerosis*. Many patients with aortic aneurysms have coexisting risk factors for atherosclerosis, as well as atherosclerosis in other blood vessels.

The pathologic condition of aortic aneurysms associated with genetic or developmental diseases is medial degeneration, a histopathologic

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## Diseases of the Aorta

Mark A. Creager, Joseph Loscalzo



The aorta is the conduit through which blood ejected from the left ventricle is delivered to the systemic arterial bed. In adults, its diameter is ~3 cm at the origin and in the ascending portion, 2.5 cm in the descending portion in the thorax, and 1.8–2 cm in the abdomen. The aortic wall consists of a thin intima composed of endothelium, subendothelial connective tissue, and an internal elastic lamina; a thick tunica media composed of smooth muscle cells and extracellular matrix; and an adventitia composed primarily of connective tissue enclosing the vasa vasorum and nervi vascularis. In addition to the conduit function of the aorta, its viscoelastic and compliant properties serve a buffering function. The aorta is distended during systole to allow a portion of the stroke volume and elastic energy to be stored, and it recoils during diastole so that blood continues to flow to the periphery. Owing to its continuous exposure to high pulsatile pressure

**TABLE 280-1 Diseases of the Aorta: Etiology and Associated Factors**

Aortic aneurysm
Degenerative
Aging
Cigarette smoking
Hypercholesterolemia
Hypertension
Atherosclerosis
Genetic or developmental
Marfan's syndrome
Loeys-Dietz syndrome
Ehlers-Danlos syndrome type IV
Aneurysm-osteoarthritis syndrome
Bicuspid aortic valve
Turner's syndrome
Familial
Fibromuscular dysplasia
Chronic aortic dissection
Aortitis (see below)
Infective (see below)
Trauma
Acute aortic syndromes (aortic dissection, acute intramural hematoma, penetrating atherosclerotic ulcer)
Degenerative disorders (see above)
Genetic/developmental disorders (see above)
Hypertension
Aortitis (see below)
Pregnancy
Trauma
Aortic occlusion
Atherosclerosis
Thromboembolism
Aortitis
Vasculitis
Takayasu's arteritis
Giant cell arteritis
Rheumatic
Rheumatoid aortitis
HLA-B27-associated spondyloarthropathies
Behçet's syndrome
Cogan's syndrome
IgG4-related systemic disease
Idiopathic aortitis
Infective
Syphilis
Tuberculosis
Mycotic ( <i>Salmonella</i> , staphylococcal, streptococcal, fungal)

term used to describe the degeneration of collagen and elastic fibers in the tunica media of the aorta as well as the loss of medial cells that are replaced by multiple clefts of mucoid material, such as proteoglycans. Medial degeneration characteristically affects the proximal aorta, results in circumferential weakness and dilation, and leads to the development of fusiform aneurysms involving the ascending aorta and the sinuses of Valsalva. Found in patients with Marfan's syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type IV (Chap. 413), hypertension, bicuspid aortic valves, Turner's syndrome, and familial thoracic aortic aneurysm syndromes, it sometimes appears as an isolated condition in patients without any other apparent disease. Thoracic and abdominal aortic aneurysms also occur in patients with

fibromuscular dysplasia, although the nature of the aortic pathology is not established.

Familial clusterings of aortic aneurysms occur in 20% of patients, suggesting a hereditary basis for the disease. Mutations of the gene that encodes fibrillin-1 are present in patients with Marfan's syndrome. Fibrillin-1 is an important component of extracellular microfibrils, which support the architecture of elastic fibers and other connective tissue. Deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by transforming growth factor (TGF-). Loeys-Dietz syndrome is caused by mutations in the genes that encode TGF- receptors 1 (*TGFR1*) and 2 (*TGFR2*). Increased signaling by TGF- and mutations of *TGFR1*, *TGFR2*, *TGFR3*, as well as *TGFB2* and *TGFB3*, may cause thoracic aortic aneurysms. Mutations of *SMAD3*, which encodes a downstream signaling protein involved with TGF binding to its receptors, have been described in a syndrome of thoracic aortic aneurysm; craniofacial, skeletal, and cutaneous anomalies; and osteoarthritis. Thoracic aortic aneurysm is associated with autosomal dominant polycystic kidney disease, which is caused by mutations in *PKD1*. Mutations of the genes encoding the smooth muscle-specific alpha-actin (*ACTA2*), smooth muscle cell-specific myosin heavy chain 11 (*MHC11*), myosin light chain kinase (*MYLK*), and type I cGMP-dependent protein kinase (*PRKG1*) and mutations of *TGFR2* and *SMAD3* have been reported in some patients with nonsyndromic familial thoracic aortic aneurysms. Mutations in type III procollagen (*COL3A1*) have been implicated in Ehlers-Danlos type IV syndrome.

The infectious causes of aortic aneurysms include syphilis, tuberculosis, and other bacterial infections. *Syphilis* (Chap. 182) is a relatively uncommon cause of aortic aneurysm. Syphilitic periaortitis and mesoaoartitis damage elastic fibers, resulting in thickening and weakening of the aortic wall. Approximately 90% of syphilitic aneurysms are located in the ascending aorta or aortic arch. *Tuberculous aneurysms* (Chap. 178) typically affect the thoracic aorta and result from direct extension of infection from hilar lymph nodes or contiguous abscesses as well as from bacterial seeding. Loss of aortic wall elasticity results from granulomatous destruction of the medial layer. A *mycotic aneurysm* is a rare condition that develops as a result of staphylococcal, streptococcal, *Salmonella*, or other bacterial or fungal infections of the aorta, usually at an atherosclerotic plaque. These aneurysms are usually saccular. Blood cultures are often positive and reveal the nature of the infective agent.

Vasculitides associated with aortic aneurysm include Takayasu's arteritis and giant cell arteritis, which may cause aneurysms of the aortic arch and descending thoracic aorta. Spondyloarthropathies such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, relapsing polychondritis, and reactive arthritis are associated with dilation of the ascending aorta. Aortic aneurysms occur in patients with Behçet's syndrome (Chap. 364), Cogan's syndrome, and IgG4-related systemic disease. Aortic aneurysms also result from idiopathic aortitis. *Traumatic aneurysms* may occur after penetrating or nonpenetrating chest trauma and most commonly affect the descending thoracic aorta just beyond the site of insertion of the ligamentum arteriosum. Chronic aortic dissections are associated with weakening of the aortic wall that may lead to the development of aneurysmal dilatation.

## THORACIC AORTIC ANEURYSMS

The clinical manifestations and natural history of thoracic aortic aneurysms depend on their location. Medial degeneration is the most common pathology associated with ascending aortic aneurysms, whereas atherosclerosis is the condition most frequently associated with aneurysms of the descending thoracic aorta. The average growth rate of thoracic aneurysms is 0.1–0.2 cm per year. Thoracic aortic aneurysms associated with Marfan's syndrome or aortic dissection may expand at a greater rate. The risk of rupture is related to the size of the aneurysm and the presence of symptoms, ranging approximately from 2–3% per year for thoracic aortic aneurysms <4.0 cm in diameter to 7% per year for those >6 cm in diameter. Most thoracic aortic aneurysms are asymptomatic; however, compression or erosion of adjacent tissue by aneurysms may cause symptoms such as chest pain, shortness of breath, cough, hoarseness, and dysphagia. Aneurysmal dilation of the



**FIGURE 280-1** A chest x-ray of a patient with a thoracic aortic aneurysm.

ascending aorta may cause congestive heart failure as a consequence of aortic regurgitation, and compression of the superior vena cava may produce congestion of the head, neck, and upper extremities.

A chest x-ray may be the first test that suggests the diagnosis of a thoracic aortic aneurysm (**Fig. 280-1**). Findings include widening of the mediastinal shadow and displacement or compression of the trachea or left main stem bronchus. Echocardiography, particularly transesophageal echocardiography, can be used to assess the proximal ascending aorta and descending thoracic aorta. Contrast-enhanced CT, magnetic resonance imaging (MRI), and conventional invasive aortography are sensitive and specific tests for assessment of aneurysms of the thoracic aorta and involvement of branch vessels (**Fig. 280-2**). In asymptomatic patients whose aneurysms are too small to justify surgery, noninvasive testing with either contrast-enhanced CT or MRI should be performed at least every 6–12 months to monitor expansion.



**FIGURE 280-2** A magnetic resonance angiogram demonstrating a fusiform aneurysm of the ascending thoracic aorta. (Courtesy of Dr. Michael Steigner, Brigham and Women's Hospital, Boston, MA, with permission.)

## TREATMENT

### Thoracic Aortic Aneurysms

-Adrenergic blockers currently are recommended for patients with thoracic aortic aneurysms, particularly those with Marfan's syndrome, who have evidence of aortic root dilatation to reduce the rate of further expansion. Additional medical therapy should be given as necessary to control hypertension. Angiotensin receptor antagonists may reduce the rate of aortic dilation in patients with Marfan's syndrome by blocking TGF- signaling. Clinical outcome trials have found that the rate of aortic root enlargement in patients with Marfan's syndrome was similar with atenolol and losartan. Operative repair with placement of a prosthetic graft is indicated in patients with symptomatic ascending thoracic aortic aneurysms, and for most asymptomatic aneurysms, including those associated with bicuspid aortic valves when the aortic root or ascending aortic diameter is  $>5.5$  cm, or when the growth rate is  $>0.5$  cm per year. Replacement of the ascending aorta  $>4.5$  cm is reasonable in patients with bicuspid aortic valves undergoing aortic valve replacement because of severe aortic stenosis or aortic regurgitation. In patients with Marfan's syndrome, ascending thoracic aortic aneurysms of 4–5 cm should be considered for surgery. Operative repair is indicated for patients with degenerative descending thoracic aortic aneurysms when the diameter is  $>6$  cm, and endovascular repair should be considered if feasible when the diameter is  $>5.5$  cm. Repair is also recommended when the diameter of a descending thoracic aortic aneurysm has increased  $>1$  cm per year.

### ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms occur more frequently in males than in females, and the incidence increases with age. Cigarette smoking is a potent modifiable risk factor. Abdominal aortic aneurysms  $>4.0$  cm may affect 1–2% men aged  $>50$  years. At least 90% of all abdominal aortic aneurysms  $>4.0$  cm are related to atherosclerotic disease, and most of these aneurysms are below the level of the renal arteries. Prognosis is related to both the size of the aneurysm and the severity of coexisting coronary artery and cerebrovascular disease. The risk of rupture increases with the size of the aneurysm: the 5-year risk for aneurysms  $<5$  cm is 1–2%, whereas it is 20–40% for aneurysms  $>5$  cm in diameter. The formation of mural thrombi within aneurysms may predispose to peripheral embolization.

An abdominal aortic aneurysm commonly produces no symptoms. It usually is detected on routine examination as a palpable, pulsatile, expansile, and nontender mass, or it is an incidental finding observed on an abdominal imaging study performed for other reasons. As abdominal aortic aneurysms expand, however, they may become painful. Some patients complain of strong pulsations in the abdomen; others experience pain in the chest, lower back, or scrotum. Aneurysmal pain is usually a harbinger of rupture and represents a medical emergency. More often, acute rupture occurs without any prior warning, and this complication is always life-threatening. Rarely, there is leakage of the aneurysm with severe pain and tenderness. Acute pain and hypotension occur with rupture of the aneurysm, which requires an emergency operation or endovascular repair.

Abdominal radiography may demonstrate the calcified outline of the aneurysm; however, ~25% of aneurysms are not calcified and cannot be visualized by x-ray imaging. An abdominal ultrasound can delineate the transverse and longitudinal dimensions of an abdominal aortic aneurysm and may detect mural thrombus. Abdominal ultrasound is useful for serial documentation of aneurysm size and can be used to screen patients at risk for developing an aortic aneurysm. In one large study, ultrasound screening of men aged 65–74 years was associated with a risk reduction in aneurysm-related death of 42%. In a meta-analysis of population-based randomized clinical trials, ultrasound screening of men aged 65 years or older was associated with a 35% risk reduction in aneurysm-related death over 12–15 years. Screening by ultrasonography is recommended for men aged 65–75 years who have ever smoked. The benefits of screening women aged



**FIGURE 280-3** A computed tomographic angiogram depicting a fusiform abdominal aortic aneurysm before (left) and after (right) treatment with a bifurcated stent graft. (Courtesy of Drs. Elizabeth George and Frank Rybicki, Brigham and Women's Hospital, Boston, MA, with permission.)

65–75 years who have ever smoked is not established. In addition, male and female siblings or offspring of persons with abdominal aortic aneurysms, as well as individuals with thoracic aortic or peripheral arterial aneurysms, should be considered for screening for abdominal aortic aneurysms. CT with contrast and MRI are accurate noninvasive tests to determine the location and size of abdominal aortic aneurysms and to plan endovascular or open surgical repair (Fig. 280-3). Contrast aortography may be used for the evaluation of patients with aneurysms, but the procedure carries a small risk of complications such as bleeding, allergic reactions, and atheroembolism. Since the presence of mural thrombi may reduce the luminal size, aortography may underestimate the diameter of an aneurysm.

## TREATMENT

### Abdominal Aortic Aneurysms

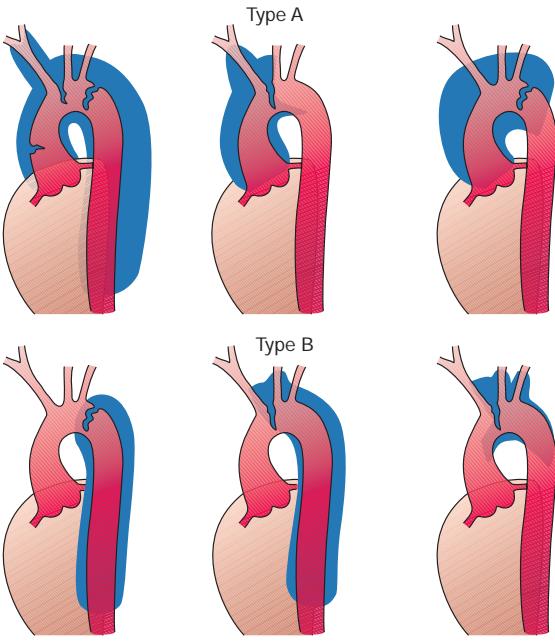
Statins are indicated to reduce the risk of cardiovascular events related to atherosclerosis. Medical therapies, such as  $\beta$ -adrenergic blockers and renin-angiotensin inhibitors, have not proven effective in reducing the rate of aneurysm growth. Operative repair of the aneurysm with insertion of a prosthetic graft or endovascular placement of an aortic stent graft (Fig. 274-3) is indicated for abdominal aortic aneurysms of any size that are expanding rapidly or are associated with symptoms. For asymptomatic aneurysms, abdominal aortic aneurysm repair is indicated if the diameter is  $>5.5$  cm. In randomized trials of patients with abdominal aortic aneurysms  $<5.5$  cm, there was no difference in the long-term ( $>8$ -year) mortality rate between those followed with ultrasound surveillance and those undergoing elective endovascular or surgical repair. Thus, serial noninvasive follow-up of smaller aneurysms ( $<5.5$  cm) is an alternative to immediate repair. The decision to perform an open surgical operation or endovascular repair is based in part on the vascular anatomy and comorbid conditions. Endovascular repair of abdominal aortic aneurysms has a lower short-term morbidity rate, but a comparable long-term mortality rate with open surgical reconstruction. Long-term surveillance with CT or MR aortography is indicated after endovascular repair to detect leaks and possible aneurysm expansion.

In surgical candidates, careful preoperative cardiac and general medical evaluations (followed by appropriate therapy for complicating conditions) are essential. Preexisting coronary artery disease, congestive heart failure, pulmonary disease, diabetes mellitus, and advanced age add to the risk of surgery. With careful preoperative cardiac evaluation and postoperative care, the operative mortality rate approximates 1–2%. After acute rupture, the mortality rate of emergent operation is 45–50%. Endovascular repair with stent placement is an alternative approach to treat ruptured aneurysms and may be associated with a lower mortality rate.

## ACUTE AORTIC SYNDROMES

The four major acute aortic syndromes are aortic rupture (discussed earlier), aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. Aortic dissection is caused by a circumferential or, less frequently, transverse tear of the intima. It often occurs along the right lateral wall of the ascending aorta where the hydraulic shear stress is high. Another common site is the descending thoracic aorta just below the ligamentum arteriosum. The initiating event is either a primary intimal tear with secondary dissection into the media or a medial hemorrhage that dissects into and disrupts the intima. The pulsatile aortic flow then dissects along the elastic lamellar plates of the aorta and creates a false lumen. The dissection usually propagates distally down the descending aorta and into its major branches, but it may propagate proximally. Distal propagation may be limited by atherosclerotic plaque. In some cases, a secondary distal intimal disruption occurs, resulting in the reentry of blood from the false to the true lumen.

There are at least two important pathologic and radiologic variants of aortic dissection: intramural hematoma without an intimal flap and penetrating atherosclerotic ulcer. Acute intramural hematomas may progress to dissection and rupture. Penetrating atherosclerotic ulcers are caused by erosion of a plaque into the aortic media, are usually localized, and are not associated with extensive propagation. They are found primarily in the middle and distal portions of the descending thoracic aorta and are associated with extensive atherosclerotic disease. The ulcer can



**FIGURE 280-4 Classification of aortic dissections.** Stanford classification: Type A dissections (*top*) involve the ascending aorta independent of site of tear and distal extension; type B dissections (*bottom*) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending or descending aorta (*top left*); type II dissection is limited to ascending or transverse aorta, without descending aorta (*top center + top right*); type III dissection involves descending aorta only (*bottom left*). (*Reproduced with permission from DC Miller, in RM Doroghazi, EE Slater [eds]: Aortic Dissection. New York, McGraw-Hill, 1983.*)

erode beyond the internal elastic lamina, leading to medial hematoma, and may progress to false aneurysm formation or rupture.

Several classification schemes have been developed for thoracic aortic dissections. DeBakey and colleagues initially classified aortic dissections as type I, in which an intimal tear occurs in the ascending aorta but the dissection may propagate to the aortic arch, the descending thoracic aorta, and even the abdominal aorta; type II, in which the dissection is limited to the ascending aorta; and type III, in which the intimal tear is located in the descending aorta with distal propagation of the dissection (Fig. 280-4). Another classification (Stanford) is that of type A, in which the dissection involves the ascending aorta (proximal dissection), and type B, in which it is limited to the arch and/or descending aorta (distal dissection). From a management standpoint, classification of aortic dissections and intramural hematomas into type A or B is more practical and useful, since DeBakey types I and II are managed in a similar manner.

The factors that predispose to aortic dissection include those associated with medial degeneration and others that increase aortic wall stress (Table 280-1). Systemic hypertension is a coexisting condition in 70% of patients. Aortic dissection is the major cause of morbidity and mortality in patients with Marfan's syndrome (Chap. 413) or Loeys-Dietz syndrome, and similarly may affect patients with Ehlers-Danlos syndrome. The incidence also is increased in patients with inflammatory aortitis (i.e., Takayasu's arteritis, giant cell arteritis), congenital aortic valve anomalies (e.g., bicuspid valve), coarctation of the aorta, and a history of aortic trauma. In addition, the risk of dissection is increased in otherwise normal women during the third trimester of pregnancy. Aortic dissection also may occur as a consequence of weight lifting, cocaine use, or deceleration injury.

## CLINICAL MANIFESTATIONS

The peak incidence of aortic dissection is in the sixth and seventh decades. Men are more affected than women by a ratio of 2:1. The presentations of aortic dissection and its variants are the consequences

of intimal tear, dissecting hematoma, occlusion of involved arteries, and compression of adjacent tissues. Acute aortic dissection presents with the sudden onset of pain (Chap. 14), which often is described as very severe and tearing and is associated with diaphoresis. The pain may be localized to the front or back of the chest, often the interscapular region, and typically migrates with propagation of the dissection. Other symptoms include syncope, dyspnea, and weakness. Physical findings may include hypertension or hypotension, loss of pulses, aortic regurgitation, pulmonary edema, and neurologic findings due to carotid artery obstruction (hemiplegia, hemianesthesia) or spinal cord ischemia (paraplegia). Bowel ischemia, hematuria, and myocardial ischemia all may occur. These clinical manifestations reflect complications resulting from the dissection occluding the major arteries. Furthermore, clinical manifestations may result from the compression of adjacent structures (e.g., superior cervical ganglia, superior vena cava, bronchus, esophagus) by the expanding dissection causing aneurysmal dilation and include Horner's syndrome, superior vena cava syndrome, hoarseness, dysphagia, and airway compromise. Hemopericardium and cardiac tamponade may complicate a type A lesion with retrograde dissection. Acute aortic regurgitation is an important and common (>50%) complication of proximal dissection. It is the outcome of either a circumferential tear that widens the aortic root or a disruption of the annulus by a dissecting hematoma that tears a leaflet(s) or displaces it, inferior to the line of closure. Signs of aortic regurgitation include bounding pulses, a wide pulse pressure, a diastolic murmur often radiating along the right sternal border, and evidence of congestive heart failure. The clinical manifestations depend on the severity of the regurgitation.

In dissections involving the ascending aorta, the chest x-ray often reveals a widened superior mediastinum. A pleural effusion (usually left-sided) also may be present. This effusion is typically serosanguineous and not indicative of rupture unless accompanied by hypotension and falling hematocrit. In dissections of the descending thoracic aorta, a widened mediastinum may be observed on chest x-ray. In addition, the descending aorta may appear to be wider than the ascending portion. An electrocardiogram that shows no evidence of myocardial ischemia is helpful in distinguishing aortic dissection from myocardial infarction among patients who present with chest pain. Rarely, the dissection involves the right or, less commonly, left coronary ostium and causes acute myocardial infarction.

The diagnosis of aortic dissection can be established by noninvasive techniques such as echocardiography, CT, and MRI. Aortography is used less commonly because of the accuracy of these noninvasive techniques. Transthoracic echocardiography can be performed simply and rapidly and has an overall sensitivity of 60–85% for aortic dissection. For diagnosing proximal ascending aortic dissections, its sensitivity exceeds 80%; it is less useful for detecting dissection of the arch and descending thoracic aorta. Transesophageal echocardiography requires greater skill and patient cooperation but is very accurate in identifying dissections of the ascending and descending thoracic aorta but not the arch, achieving 98% sensitivity and ~90% specificity. Echocardiography also provides important information regarding the presence and severity of aortic regurgitation and pericardial effusion. CT and MRI are both highly accurate in identifying the intimal flap and the extent of the dissection and involvement of major arteries; each has a sensitivity and specificity >90%. They are useful in recognizing intramural hemorrhage and penetrating ulcers. The relative utility of transesophageal echocardiography, CT, and MRI depends on the availability and expertise in individual institutions as well as on the hemodynamic stability of the patient, with CT and MRI obviously less suitable for unstable patients.

## TREATMENT

### Aortic Dissection

Medical therapy should be initiated as soon as the diagnosis is considered. The patient should be admitted to an intensive care unit for hemodynamic monitoring. Unless hypotension is present, therapy

should be aimed at reducing cardiac contractility and systemic arterial pressure, and thus shear stress. For acute dissection, unless contraindicated,  $\beta$ -adrenergic blockers should be administered parenterally, using intravenous propranolol, metoprolol, or the short-acting esmolol to achieve a heart rate of  $\sim 60$  beats/min. This should be accompanied by sodium nitroprusside infusion to lower systolic blood pressure to 120 mmHg. Labetalol (**Chap. 277**), a drug with both  $\alpha$ - and  $\beta$ -adrenergic blocking properties, also may be used as a parenteral agent in acute therapy for dissection.

The calcium channel antagonists verapamil and diltiazem may be used intravenously if nitroprusside or  $\beta$ -adrenergic blockers cannot be employed. The addition of a parenteral angiotensin-converting enzyme (ACE) inhibitor such as enalaprilat to a  $\beta$ -adrenergic blocker also may be considered. Isolated use of a direct vasodilator such as hydralazine is contraindicated because these agents can increase hydraulic shear and may propagate the dissection.

Emergent or urgent surgical correction is the preferred treatment for acute ascending aortic dissections and intramural hematomas (type A). Surgery involves excision of the intimal flap, obliteration of the false lumen, and placement of an interposition graft. Aortic valve repair or a composite valve-graft conduit is used if the aortic valve is disrupted. The overall in-hospital mortality rate after surgical treatment of patients with aortic dissection is reported to be 15–25%. The major causes of perioperative mortality and morbidity include myocardial infarction, paraplegia, renal failure, tamponade, hemorrhage, and sepsis. Thoracic endovascular aortic repair with an endoluminal stent graft is indicated for complicated type B dissections, including those characterized by propagation, compromise of major aortic branches, impending rupture, or continued pain. Other transcatheter techniques, such as fenestration of the intimal flaps and stenting of narrowed branch vessels to increase flow to compromised organs, are used in selected patients. Surgical correction is indicated for complicated type B dissections, particularly if endovascular repair is not feasible. Hybrid procedures consisting of both surgery and endovascular repair may be used when the dissection involves both the aortic arch and the descending thoracic aorta. For uncomplicated and stable distal dissections and intramural hematomas (type B), medical therapy is the preferred treatment. The in-hospital mortality rate of medically treated patients with type B dissection is  $\sim 12\%$ . Long-term therapy for patients with aortic dissection and intramural hematomas (with or without surgery) consists of control of hypertension and reduction of cardiac contractility with the use of  $\beta$ -adrenergic blockers plus other antihypertensive agents, such as ACE inhibitors or calcium antagonists. Patients with chronic type B dissection and intramural hematomas should be followed on an outpatient basis every 6–12 months with contrast-enhanced CT or MRI to detect propagation or expansion. Patients with Marfan's syndrome are at high risk for postdissection complications. The long-term prognosis following hospital discharge for patients with treated dissections is generally good with careful follow-up; the 10-year survival rate is  $\sim 60\%$ .

## CHRONIC ATHEROSCLEROTIC OCCLUSIVE DISEASE

Atherosclerosis may affect the thoracic and abdominal aorta. Occlusive aortic disease caused by atherosclerosis usually is confined to the distal abdominal aorta below the renal arteries. Frequently the disease extends to the iliac arteries (**Chap. 281**). Claudication characteristically involves the buttocks, thighs, and calves and may be associated with impotence in males (Leriche's syndrome). The severity of the symptoms depends on the adequacy of collaterals. With sufficient collateral blood flow, a complete occlusion of the abdominal aorta may occur without the development of ischemic symptoms. The physical findings include the absence of femoral and other distal pulses bilaterally and the detection of an audible bruit over the abdomen (usually at or below the umbilicus) and the common femoral arteries. Atrophic skin, loss of hair, and coolness of the lower extremities usually are observed. In advanced ischemia, rubor on dependency and pallor on elevation can be seen.

The diagnosis usually is established by physical examination and noninvasive testing, including leg pressure measurements, Doppler velocity analysis, pulse volume recordings, and duplex ultrasonography. The anatomy may be defined by MR, CT, or conventional contrast angiography, typically performed when one is considering revascularization. Catheter-based endovascular or operative treatment is indicated in patients with lifestyle-limiting or debilitating symptoms of claudication and patients with critical limb ischemia.

## ACUTE AORTIC OCCLUSION

Acute occlusion in the distal abdominal aorta constitutes a medical emergency because it threatens the viability of the lower extremities; it usually results from an occlusive (saddle) embolus that almost always originates from the heart. Rarely, acute occlusion may occur as the result of *in situ* thrombosis in a preexisting severely narrowed segment of the aorta.

The clinical picture is one of acute ischemia of the lower extremities. Severe rest pain, coolness, and pallor of the lower extremities and the absence of distal pulses bilaterally are the usual manifestations. Diagnosis should be established rapidly by MRI, CT, or aortography. Emergency thrombectomy or revascularization is indicated.

## AORTITIS

Aortitis, a term referring to inflammatory disease of the aorta, may be caused by large vessel vasculitides such as Takayasu's arteritis and giant cell arteritis, rheumatic and HLA-B27-associated spondyloarthropathies, Behcet's syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, Cogan's syndrome, Erdheim-Chester disease, IgG4-related systemic disease, and infections such as syphilis, tuberculosis, and *Salmonella*, or it may be associated with retroperitoneal fibrosis. Aortitis may result in aneurysmal dilation and aortic regurgitation, occlusion of the aorta and its branch vessels, or acute aortic syndromes.

## TAKAYASU'S ARTERITIS

(See also **Chap. 363**) This inflammatory disease often affects the ascending aorta and aortic arch, causing obstruction of the aorta and its major arteries. Takayasu's arteritis is also termed *pulseless disease* because of the frequent occlusion of the large arteries originating from the aorta. It also may involve the descending thoracic and abdominal aorta and occlude large branches such as the renal arteries. Aortic aneurysms also may occur. The pathology is a panarteritis characterized by mononuclear cells and occasionally giant cells, with marked intimal hyperplasia, medial and adventitial thickening, and, in the chronic form, fibrotic occlusion. The disease is most prevalent in young females of Asian descent but does occur in women of other geographic and ethnic origins and also in young men. During the acute stage, fever, malaise, weight loss, and other systemic symptoms may be evident. Elevations of the erythrocyte sedimentation rate and C-reactive protein are common. The chronic stages of the disease, which is intermittently active, present with symptoms related to large artery occlusion, such as upper extremity claudication, cerebral ischemia, and syncope. The process is progressive, and there is no definitive therapy. Glucocorticoids are effective in most patients during the acute phase. Other immunosuppressive agents, such as methotrexate, azathioprine, leflunomide, or mycophenolate, are prescribed to some patients to lower glucocorticoid requirements and treat relapses. Biologically targeted agents are also used, but efficacy has not been established in randomized clinical trials. Surgical bypass or endovascular intervention of a critically stenotic artery may be necessary.

## GIANT CELL ARTERITIS

(See also **Chap. 363**) This vasculitis occurs in older individuals and affects women more often than men. Primarily large and medium-size arteries are affected. The pathology is that of focal granulomatous lesions involving the entire arterial wall; it frequently is associated with polymyalgia rheumatica. Obstruction of medium-size arteries (e.g., temporal and ophthalmic arteries) and major branches of the aorta

and the development of aortitis and aortic regurgitation are important complications of the disease. High-dose glucocorticoid therapy should be administered early and then gradually tapered. Immunosuppressive therapy with methotrexate may allow reduction in steroid dosage and reduce the risk of relapse. Tocilizumab, an interleukin-6 antagonist, demonstrated efficacy in several randomized trials. Other biologically targeted therapies are under investigation.

### RHEUMATIC AORTITIS

Rheumatoid arthritis (**Chap. 358**), ankylosing spondylitis (**Chap. 362**), psoriatic arthritis (**Chap. 362**), reactive arthritis (formerly known as Reiter's syndrome) (**Chap. 362**), relapsing polychondritis, and inflammatory bowel disorders may all be associated with aortitis involving the ascending aorta. The inflammatory lesions usually involve the ascending aorta and may extend to the sinuses of Valsalva, the mitral valve leaflets, and adjacent myocardium. The clinical manifestations are aneurysm, aortic regurgitation, and involvement of the cardiac conduction system.

### IDIOPATHIC AORTITIS

Idiopathic abdominal aortitis is characterized by adventitial and periaortic inflammation with thickening of the aortic wall. It is associated with abdominal aortic aneurysms and idiopathic retroperitoneal fibrosis. Affected individuals may present with vague constitutional symptoms, fever, and abdominal pain. Retroperitoneal fibrosis can cause ureteral obstruction and hydronephrosis. Glucocorticoids and immunosuppressive agents may reduce the inflammation.

### INFECTIVE AORTITIS

Infective aortitis may result from direct invasion of the aortic wall by bacterial pathogens such as *Staphylococcus*, *Streptococcus*, and *Salmonella* or by fungi. These bacteria cause aortitis by infecting the aorta at sites of atherosclerotic plaque. Bacterial proteases lead to degradation of collagen, and the ensuing destruction of the aortic wall leads to the formation of a saccular aneurysm referred to as a mycotic aneurysm. Mycotic aneurysms have a predilection for the suprarenal abdominal aorta. The pathologic characteristics of the aortic wall include acute and chronic inflammation, abscesses, hemorrhage, and necrosis. Mycotic aneurysms typically affect the elderly and occur in men three times more frequently than in women. Patients may present with fever, sepsis, and chest, back, or abdominal pain; there may have been a preceding diarrheal illness. Blood cultures are positive in the majority of patients. Both CT and MRI are useful to diagnose mycotic aneurysms. Treatment includes antibiotic therapy and surgical removal of the affected part of the aorta and revascularization of the lower extremities with grafts placed in uninfected tissue.

Syphilitic aortitis is a late manifestation of luetic infection (**Chap. 182**) that usually affects the proximal ascending aorta, particularly the aortic root, resulting in aortic dilation and aneurysm formation. Syphilitic aortitis occasionally may involve the aortic arch or the descending aorta. The aneurysms may be saccular or fusiform and are usually asymptomatic, but compression of and erosion into adjacent structures may result in symptoms; rupture also may occur.

The initial lesion is an obliterative endarteritis of the vasa vasorum, especially in the adventitia. This is an inflammatory response to the invasion of the adventitia by the spirochetes. Destruction of the aortic media occurs as the spirochetes spread into this layer, usually via the lymphatics accompanying the vasa vasorum. Destruction of collagen and elastic tissues leads to dilation of the aorta, scar formation, and calcification. These changes account for the characteristic radiographic appearance of linear calcification of the ascending aorta.

The disease typically presents as an incidental chest radiographic finding 15–30 years after initial infection. Symptoms may result from aortic regurgitation, narrowing of coronary ostia due to syphilitic aortitis, compression of adjacent structures (e.g., esophagus), or rupture. Diagnosis is established by a positive serologic test, i.e., rapid plasmin reagent (RPR) or fluorescent treponemal antibody. Treatment includes penicillin and surgical excision and repair.

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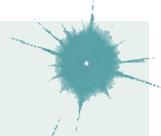
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## Arterial Diseases of the Extremities

Mark A. Creager, Joseph Loscalzo



### PERIPHERAL ARTERY DISEASE

Peripheral artery disease (PAD) is defined as a clinical disorder in which there is a stenosis or occlusion in the aorta or the arteries of the limbs. Atherosclerosis is the leading cause of PAD in patients >40 years old. Other causes include thrombosis, embolism, vasculitis, fibromuscular dysplasia, entrapment, cystic adventitial disease, and trauma. The highest prevalence of atherosclerotic PAD occurs in the sixth and seventh decades of life. As in patients with atherosclerosis of the coronary and cerebral vasculature, there is an increased risk of developing PAD in cigarette smokers and in persons with diabetes mellitus, hypercholesterolemia, hypertension, or renal insufficiency.

**Pathology** Segmental lesions that cause stenosis or occlusion are usually localized to large and medium-size vessels. The pathology of the lesions includes atherosclerotic plaques with calcium deposition, thinning of the media, patchy destruction of muscle and elastic fibers, fragmentation of the internal elastic lamina, and thrombi composed of platelets and fibrin. The primary sites of involvement are the abdominal aorta and iliac arteries (30% of symptomatic patients), the femoral and popliteal arteries (80–90% of patients), and the more distal vessels, including the tibial and peroneal arteries (40–50% of patients). Atherosclerotic lesions occur preferentially at arterial branch points, which are sites of increased turbulence, altered shear stress, and intimal injury.

**2108** Involvement of the distal vasculature is most common in elderly individuals and patients with diabetes mellitus.

**Clinical Evaluation** Fewer than 50% of patients with PAD are symptomatic, although many have a slow or impaired gait. The most typical symptom is intermittent claudication, which is defined as a pain, ache, cramp, numbness, or a sense of fatigue in the muscles; it occurs during exercise and is relieved by rest. The site of claudication is distal to the location of the occlusive lesion. For example, buttock, hip, thigh, and calf discomfort occurs in patients with aortoiliac disease, whereas calf claudication develops in patients with femoral-popliteal disease. Symptoms are far more common in the lower than in the upper extremities because of the higher incidence of obstructive lesions in the former region. In patients with severe arterial occlusive disease in whom resting blood flow cannot accommodate basal nutritional needs of the tissues, critical limb ischemia may develop. Patients complain of rest pain or a feeling of cold or numbness in the foot and toes. Frequently, these symptoms occur at night when the legs are horizontal and improve when the legs are in a dependent position. With severe ischemia, rest pain may be persistent.

Important physical findings of PAD include decreased or absent pulses distal to the obstruction, the presence of bruits over the narrowed artery, and muscle atrophy. With more severe disease, hair loss, thickened nails, smooth and shiny skin, reduced skin temperature, and pallor or cyanosis are common physical signs. In patients with critical limb ischemia, ulcers or gangrene may occur. Elevation of the legs and repeated flexing of the calf muscles produce pallor of the soles of the feet, whereas rubor, secondary to reactive hyperemia, may develop when the legs are dependent. The time required for rubor to develop or for the veins in the foot to fill when the patient's legs are transferred from an elevated to a dependent position is related to the severity of the ischemia and the presence of collateral vessels. Patients with severe ischemia may develop peripheral edema because they keep their legs in a dependent position much of the time. Ischemic neuropathy can result in numbness and hyporeflexia.

**Noninvasive Testing** The history and physical examination are often sufficient to establish the diagnosis of PAD. An objective assessment of the presence and severity of disease is obtained by noninvasive techniques. Arterial pressure can be recorded noninvasively in the legs by placement of sphygmomanometric cuffs at the ankles and the use of a Doppler device to auscultate or record blood flow from the dorsalis

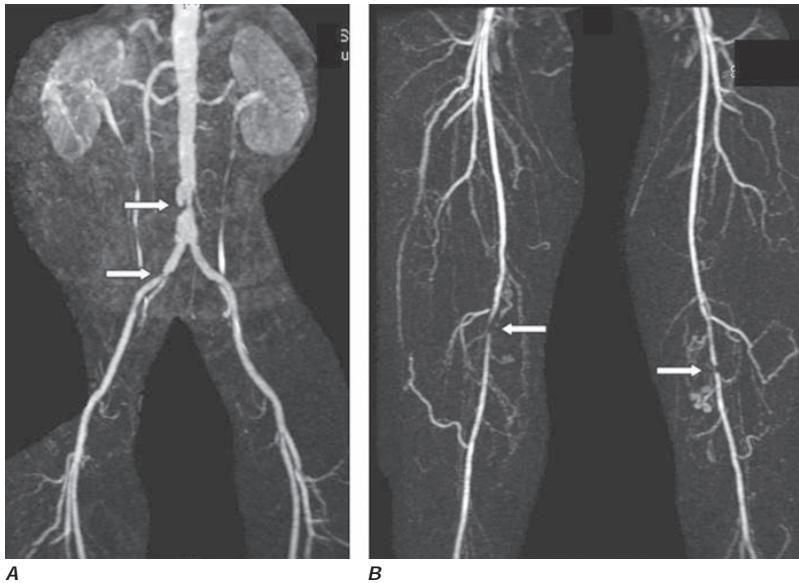
pedis and posterior tibial arteries. Normally, systolic blood pressure in the legs and arms is similar. Indeed, ankle pressure may be slightly higher than arm pressure due to pulse-wave amplification. In the presence of hemodynamically significant stenoses, the systolic blood pressure in the leg is decreased. Thus, the ratio of the ankle and brachial artery pressures (termed the *ankle-brachial index*, or ABI) is 1.00–1.40 in normal individuals. ABI values of 0.91–0.99 are considered “borderline,” and those <0.90 are abnormal and diagnostic of PAD. ABIs >1.40 indicate noncompressible arteries secondary to vascular calcification.

Other noninvasive tests include segmental pressure measurements, segmental pulse volume recordings, duplex ultrasonography (which combines B-mode imaging and Doppler flow velocity waveform analysis), transcutaneous oximetry, and stress testing (usually using a treadmill). Placement of pneumatic cuffs enables assessment of systolic pressure along the legs. The presence of pressure gradients between sequential cuffs provides evidence of the presence and location of hemodynamically significant stenoses. In addition, the amplitude of the pulse volume contour becomes blunted in the presence of significant PAD. Duplex ultrasonography is used to image and detect stenotic lesions in native arteries and bypass grafts.

Treadmill testing allows the physician to assess functional limitations objectively. Decline of the ABI immediately after exercise provides further support for the diagnosis of PAD in patients with equivocal symptoms and findings on examination.

Magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and conventional catheter-based angiography should not be used for routine diagnostic testing, but are performed before potential revascularization (Fig. 281-1). Each test is useful in defining the anatomy to assist planning for endovascular and surgical revascularization procedures.

**Prognosis** The natural history of patients with PAD is influenced primarily by the extent of coexisting coronary artery and cerebrovascular disease. Approximately one-third to one-half of patients with symptomatic PAD have evidence of coronary artery disease (CAD) based on clinical presentation and electrocardiogram, and over one-half have significant CAD by coronary angiography. Patients with PAD have a 15–25% 5-year mortality rate and a two- to fourfold increased risk of death from cardiovascular disease. Measurement of ABI is useful for detecting PAD and identifying persons at risk for adverse cardiovascular and limb events. Mortality rates are highest in those with the most



**FIGURE 281-1** Magnetic resonance angiography of a patient with intermittent claudication, showing stenoses of the distal abdominal aorta and right common iliac artery (**A**) and stenoses of the right and left superficial femoral arteries (**B**). (Courtesy of Dr. Edwin Gravereaux, with permission.)

severe PAD. The ABI worsens in almost 40% of patients, and symptoms progress in ~20–25% when assessed over a period of 5 years. Approximately 11% of patients with symptomatic PAD ultimately develop critical limb ischemia, and 25–30% of patients with critical limb ischemia undergo amputation within 1 year. The prognosis is worse in patients who continue to smoke cigarettes or have diabetes mellitus.

## TREATMENT

### Peripheral Artery Disease

Patients with PAD should receive therapies to reduce the risk of associated cardiovascular events, such as myocardial infarction and death, and to improve limb symptoms, prevent progression to critical limb ischemia, and preserve limb viability. Risk factor modification and antithrombotic therapy should be initiated to improve cardiovascular outcomes. The importance of discontinuing cigarette smoking cannot be overemphasized. The physician must assume a major role in this lifestyle modification. Counseling and adjunctive drug therapy with the nicotine patch, bupropion, or varenicline increase smoking cessation rates and reduce recidivism. It is important to control blood pressure in hypertensive patients. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may reduce the risk of cardiovascular events in patients with symptomatic PAD. -Adrenergic blockers do not worsen claudication and may be used to treat hypertension, especially in patients with coexistent CAD. Treatment of hypercholesterolemia with statins and, if needed, adjunctive lipid-lowering agents such as ezetimibe or a PCSK9 inhibitor, is advocated to reduce the risk of myocardial infarction, stroke, and death. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on the Management of Blood Cholesterol recommends high-intensity statin treatment in patients with atherosclerotic disorders, including PAD, with the aim of achieving a 50% or greater reduction in low-density lipoprotein cholesterol. Platelet inhibitors, including aspirin and the adenosine diphosphate (ADP) antagonist clopidogrel, reduce the risk of adverse cardiovascular events in patients with atherosclerosis and are recommended for patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia or prior lower extremity revascularization. Outcomes with ticagrelor are similar to those with clopidogrel. The benefit of dual antiplatelet therapy with both aspirin and clopidogrel compared with aspirin alone in reducing cardiovascular morbidity and mortality rates in patients with PAD is uncertain. When added to other antiplatelet therapy, vorapaxar, a protease activated receptor-1 antagonist that inhibits thrombin-mediated platelet activation, decreases the risk of adverse cardiovascular events in patients with atherosclerosis, including PAD. It also reduces the risk of acute limb ischemia and peripheral revascularization; however, it is associated with an increased rate of moderate bleeding. The anticoagulant warfarin is as effective as antiplatelet therapy in preventing adverse cardiovascular events but causes more major bleeding; therefore, it is not indicated to improve outcomes in patients with chronic PAD. The combination of a low dose of the oral factor Xa inhibitor rivaroxaban and aspirin improves cardiovascular and limb outcomes in patients with established atherosclerosis, including PAD, including those who have undergone peripheral revascularization, but is associated with increased risk of bleeding.

Therapies for intermittent claudication and critical limb ischemia include supportive measures, medications, exercise training, endovascular interventions, and surgery. Supportive measures include meticulous care of the feet, which should be kept clean and protected against excessive drying with moisturizing creams. Well-fitting and protective shoes are advised to reduce trauma. Elastic support hose should be avoided, as it reduces blood flow to the skin. In patients with critical limb ischemia, shock blocks under the head of the bed together with a canopy over the feet may improve perfusion pressure and ameliorate some of the rest pain.

Patients with claudication should be encouraged to exercise regularly and at progressively more strenuous levels. Supervised exercise training programs for 30- to 45-min sessions, at least three per week for 12 weeks, prolong walking distance. The beneficial effect of supervised exercise training on walking performance in patients with claudication often is similar to or greater than that realized after a revascularization procedure. Structured home and community-based exercise programs are also effective. Pharmacologic treatment of PAD has not been as successful as the medical treatment of CAD (**Chap. 273**). In particular, vasodilators as a class have not proved to be beneficial. During exercise, peripheral vasodilation occurs distal to sites of significant arterial stenoses. As a result, perfusion pressure falls, often to levels lower than those generated in the interstitial tissue by the exercising muscle. Drugs such as -adrenergic blocking agents, calcium channel antagonists, and other vasodilators have not been shown to be effective in patients with PAD.

Cilostazol, a phosphodiesterase inhibitor with vasodilator and antiplatelet properties, increases claudication distance by 40–60% and improves measures of quality of life. The mechanism of action accounting for its beneficial effects is not known. Pentoxyphilline, a substituted xanthine derivative, increases blood flow to the microcirculation and enhances tissue oxygenation. Although several placebo-controlled studies have found that pentoxyphilline modestly increases the duration of exercise, its efficacy has not been confirmed in other clinical trials. Statins appeared effective for treatment of intermittent claudication in initial clinical trials, but more studies are needed to confirm the efficacy of this class of drugs.

There is no definitive medical therapy for critical limb ischemia. Vasodilator prostaglandins are not effective in relieving symptoms or preventing limb loss. Enthusiasm for therapy with angiogenic growth factors abated when clinical trials of intramuscular gene transfer of DNA encoding vascular endothelial growth factor, fibroblast growth factor, hepatocyte growth factor, or hypoxia-inducible factor 1 failed to demonstrate improvement in symptoms or outcomes in patients with intermittent claudication or critical limb ischemia. Most clinical trials of bone marrow-derived vascular progenitor cells to promote angiogenesis and preserve limb viability in patients with critical limb ischemia have failed to demonstrate benefit, although a meta-analysis of these trials suggested a modest reduction in the risk of amputation.

### REVASCULARIZATION

Revascularization procedures, including catheter-based and surgical interventions, are usually indicated for patients with disabling, progressive, or severe symptoms of intermittent claudication despite medical therapy in order to improve walking distance and functional capacity. These are also indicated in patients with critical limb ischemia to relieve pain and prevent limb loss. MRA, CTA, or conventional angiography should be performed to assess vascular anatomy in patients who are being considered for revascularization. Endovascular interventions include percutaneous transluminal balloon angioplasty (PTA) (including drug-coated balloons), stent placement (including drug-eluting stents), stent grafts, and atherectomy (**Chap. 276**). When endovascular intervention is performed in conjunction with a supervised exercise program, walking distance improves more than with exercise training alone.

PTA and stenting of the iliac artery are associated with higher success rates than are PTA and stenting of the femoral and popliteal arteries. Approximately 90–95% of iliac PTAs are initially successful, and the 3-year patency rate is >75%. Patency rates may be higher if a stent is placed in the iliac artery. The initial success rate for femoral-popliteal PTA and stenting approximate 90% with 60% 3-year patency rates. Several clinical trials have found lower femoral-popliteal restenosis rates with drug-coated balloons than with PTA, and with drug-eluting stents compared with bare metal stents. Recent meta-analyses have raised concerns about increased mortality in patients treated with paclitaxel drug-coated balloons and drug-eluting stents, but conclusive evidence of this adverse

outcome from prospective randomized trials is lacking. Endovascular interventions of the infrapopliteal, tibial, and peroneal arteries, often in conjunction with treatment of more proximal lesions, can be undertaken to treat critical limb ischemia and prevent limb loss.

Several operative procedures are available for treating patients with PAD. The preferred operative procedure depends on the location and extent of the obstruction(s) and the general medical condition of the patient. Operative procedures for aortoiliac disease include aortobifemoral bypass, axillofemoral bypass, femorofemoral bypass, and aortoiliac endarterectomy. The most frequently used procedure is the aortobifemoral bypass using knitted Dacron grafts. Immediate graft patency approaches 99%, and 5- and 10-year graft patency rates in survivors are >90% and 80%, respectively. Operative complications include myocardial infarction and stroke, infection of the graft, peripheral embolization, and sexual dysfunction from interruption of autonomic nerves in the pelvis. The operative mortality rate ranges from 1 to 3%, mostly due to ischemic heart disease.

Operative therapy for femoral-popliteal and tibioperoneal artery disease includes *in situ* and reverse autogenous saphenous vein bypass grafts, placement of polytetrafluoroethylene (PTFE) or other synthetic grafts, and thromboendarterectomy. The operative mortality rate ranges from 1 to 3%. The long-term patency rate depends on the type of graft used, the location of the distal anastomosis, and the patency of runoff vessels beyond the anastomosis. Patency rates of femoral-popliteal saphenous vein bypass grafts approach 90% at 1 year and 70–80% at 5 years. Five-year patency rates of infrapopliteal saphenous vein bypass grafts are 60–70%. In contrast, 5-year patency rates of infrapopliteal PTFE grafts are <30%.

Preoperative cardiac risk assessment may identify individuals who are especially likely to experience an adverse cardiac event during the perioperative period. Patients with angina, prior myocardial infarction, heart failure, diabetes, or renal insufficiency are among those at increased risk. Stress testing with treadmill exercise (if feasible), radionuclide myocardial perfusion imaging, or echocardiography permits further stratification of risk in these patients, particularly those with poor or unknown functional capacity ([Chap. 276](#)). Patients with abnormal test results require close supervision and adjunctive management with anti-ischemic medications. Coronary angiography and coronary artery revascularization compared with optimal medical therapy do not improve outcomes in most patients undergoing peripheral vascular surgery, but cardiac catheterization should be considered in patients with unstable angina and angina refractory to medical therapy as well as those suspected of having left main or three-vessel CAD.

## FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia is a hyperplastic disorder that typically affects medium-size and small arteries, but it can also affect larger arteries. It occurs predominantly in females and usually involves the renal and carotid/vertebral arteries but can involve coronary and mesenteric arteries, as well as extremity vessels such as the iliac and subclavian arteries. Fibromuscular dysplasia may cause stenosis, dissection, aneurysm, or thrombosis in affected arteries.

The histologic classification includes intimal fibroplasia, medial dysplasia, and adventitial hyperplasia. Medial dysplasia is subdivided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Medial fibroplasia is the most common type and is characterized by alternating areas of thinned media and fibromuscular ridges. The internal elastic lamina usually is preserved. A contemporary classification based on the angiographic appearance divides fibromuscular dysplasia into two types: multifocal (analogous to medial dysplasia) and focal (intimal fibroplasia).

The iliac arteries are the limb arteries most likely to be affected by fibromuscular dysplasia. It is identified angiographically by a “string of beads” multifocal appearance caused by thickened fibromuscular ridges contiguous with thin, less-involved portions of the arterial wall, or less commonly, as a focal tubular stenosis. When limb vessels are

involved, clinical manifestations are similar to those for atherosclerosis, including claudication and rest pain. PTA and surgical reconstruction have been beneficial in patients with debilitating symptoms or threatened limbs.

## THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger's disease) is an inflammatory occlusive vascular disorder involving small and medium-size arteries and veins in the distal upper and lower extremities. Cerebral, visceral, and coronary vessels may be affected rarely. This disorder develops most frequently in men <40 years of age. The prevalence is higher in Asians and individuals of Eastern European descent. Although the cause of thromboangiitis obliterans is not known, there is a definite relationship to cigarette smoking in patients with this disorder.

In the initial stages of thromboangiitis obliterans, polymorphonuclear leukocytes infiltrate the walls of the small and medium-size arteries and veins. The internal elastic lamina is preserved, and a cellular, inflammatory thrombus develops in the vascular lumen. As the disease progresses, mononuclear cells, fibroblasts, and giant cells replace the neutrophils. Later stages are characterized by perivascular fibrosis, organized thrombus, and recanalization.

The clinical features of thromboangiitis obliterans often include a triad of claudication of the affected extremity, Raynaud's phenomenon, and migratory superficial vein thrombophlebitis. Claudication usually is confined to the calves and feet or the forearms and hands because this disorder primarily affects distal vessels. In the presence of severe digital ischemia, trophic nail changes, painful ulcerations, and gangrene may develop at the tips of the fingers or toes. The physical examination shows normal brachial and popliteal pulses but reduced or absent radial, ulnar, and/or tibial pulses. MRA, CTA, and conventional arteriography are helpful in making the diagnosis. Smooth, tapering segmental lesions in the distal vessels are characteristic, as are collateral vessels at sites of vascular occlusion. Proximal atherosclerotic disease is usually absent. The diagnosis can be confirmed by excisional biopsy and pathologic examination of an involved vessel.

There is no specific treatment except abstention from tobacco. The prognosis is worse in individuals who continue to smoke, but results are discouraging even in those who stop smoking. Arterial bypass of the larger vessels may be used in selected instances, as well as local debridement, depending on the symptoms and severity of ischemia. Antibiotics may be useful; anticoagulants and glucocorticoids are not helpful. If these measures fail, amputation may be required.

## VASCULITIS

Other vasculitides may affect the arteries that supply the upper and lower extremities. [Takayasu's arteritis and giant cell \(temporal\) arteritis are discussed in Chap. 363.](#)

## ACUTE LIMB ISCHEMIA

Acute limb ischemia occurs when arterial occlusion results in the sudden cessation of blood flow to an extremity. The severity of ischemia and the viability of the extremity depend on the location and extent of the occlusion and the presence and subsequent development of collateral blood vessels. Principal causes of acute arterial occlusion include embolism, thrombus *in situ*, arterial dissection, and trauma.

The most common sources of arterial emboli are the heart, aorta, and large arteries. Cardiac disorders that cause thromboembolism include atrial fibrillation; acute myocardial infarction; ventricular aneurysm; cardiomyopathy; infectious and marantic endocarditis; thrombi associated with prosthetic heart valves; and atrial myxoma. Emboli to the distal vessels may also originate from proximal sites of atherosclerosis and aneurysms of the aorta and large vessels. Less frequently, an arterial occlusion results paradoxically from a venous thrombus that has entered the systemic circulation via a patent foramen ovale or another septal defect. Arterial emboli tend to lodge at vessel bifurcations because the vessel caliber decreases at those sites; in the lower extremities, emboli lodge most frequently in the femoral artery, followed by the iliac artery, aorta, and popliteal and tibioperoneal arteries.

Acute arterial thrombosis *in situ* occurs most frequently in atherosclerotic vessels at the site of an atherosclerotic plaque or aneurysm and in arterial bypass grafts. Trauma to an artery may disrupt continuity of blood flow and cause acute limb ischemia via formation of an acute arterial thrombus or by disruption of an artery's integrity and extravasation of blood. Arterial occlusion may complicate arterial punctures and placement of catheters; it also may result from arterial dissection if the intimal flap obstructs the artery. Less common causes include thoracic outlet compression syndrome, which causes subclavian artery occlusion, and entrapment of the popliteal artery by abnormal placement of the medial head of the gastrocnemius muscle. Polycythemia and hypercoagulable disorders (Chaps. 103 and 116) are also associated with acute arterial thrombosis.

### CLINICAL FEATURES

The symptoms of an acute arterial occlusion depend on the location, duration, and severity of the obstruction. Often severe pain, paresthesia, numbness, and coldness develop in the involved extremity within 1 h. Paralysis may occur with severe and persistent ischemia. Physical findings include loss of pulses distal to the occlusion, cyanosis or pallor, mottling, decreased skin temperature, muscle stiffening, loss of sensation, weakness, and/or absent deep tendon reflexes. If acute arterial occlusion occurs in the presence of an adequate collateral circulation, as is often the case in acute graft occlusion, the symptoms and findings may be less severe. In this situation, the patient complains about an abrupt decrease in the distance walked before claudication occurs or of modest pain and paresthesia. Pallor and coolness are evident, but sensory and motor functions generally are preserved. The clinical evaluation includes Doppler assessment of peripheral blood flow. The diagnosis of acute limb ischemia is usually apparent from the clinical presentation. In most circumstances, MRA, CTA, or catheter-based arteriography is used to confirm the diagnosis and demonstrate the location and extent of arterial occlusion.

### TREATMENT

#### Acute Limb Ischemia

Once the diagnosis is made, the patient should be anticoagulated with intravenous heparin to prevent propagation of the clot and recurrent embolism. In cases of severe ischemia of recent onset, particularly when limb viability is jeopardized, immediate intervention to ensure reperfusion is indicated. Catheter-directed thrombolysis/thrombectomy, surgical thromboembolectomy, and arterial bypass procedures are used to restore blood flow to the ischemic extremity promptly, particularly when a large proximal vessel is occluded.

Intraarterial thrombolytic therapy with recombinant tissue plasminogen activator, reteplase, or tenecteplase is most effective when acute arterial occlusion is recent (<2 weeks) and caused by a thrombus in an atherosclerotic vessel, arterial bypass graft, or occluded stent. Thrombolytic therapy is also indicated when the patient's overall condition contraindicates surgical intervention or when smaller distal vessels are occluded, thus preventing surgical access. Meticulous observation for hemorrhagic complications is required during intraarterial thrombolytic therapy. Ultrasound-emitting catheters may accelerate reperfusion by improving thrombus permeability to thrombolytic agents. Another endovascular approach to thrombus removal is percutaneous mechanical thrombectomy using devices that employ hydrodynamic forces or rotating baskets to fragment and remove the clot. These treatments may be used alone but usually are used in conjunction with pharmacologic thrombolysis. Surgical revascularization is preferred when restoration of blood flow must occur within 24 h to prevent limb loss or when symptoms of occlusion have been present for >2 weeks. Amputation is performed when the limb is not viable, as characterized by loss of sensation, paralysis, and the absence of Doppler-detected blood flow in both arteries and veins.

Long-term anticoagulation is indicated when acute limb ischemia is caused by cardiac thromboembolism. Emboli resulting from

infective endocarditis, the presence of prosthetic heart valves, or atrial myxoma often require surgical intervention to remove the cause.

### ATHEROEMBOLISM

Atheroembolism is another cause of limb ischemia. In this condition, multiple small deposits of fibrin, platelets, and cholesterol debris embolize from proximal atherosclerotic lesions or aneurysmal sites. Large protruding aortic atherosomas are a source of emboli that may lead to limb ischemia, as well as stroke and renal insufficiency. Atheroembolism may occur after intraarterial procedures. Since atheroemboli to limbs tend to lodge in the small vessels of the muscle and skin and may not occlude the large vessels, distal pulses usually remain palpable. Patients complain of acute pain and tenderness at the site of embolization. Digital vascular occlusion may result in ischemia and the "blue toe" syndrome; digital necrosis and gangrene may develop (Fig. 281-2). Localized areas of tenderness, pallor, and livedo reticularis (see below) occur at sites of emboli. Skin or muscle biopsy may demonstrate cholesterol crystals.

Ischemia resulting from atheroemboli is notoriously difficult to treat. Local foot care and occasionally amputation may be needed to treat necrotic areas. Analgesics are indicated for pain relief. Usually neither surgical revascularization procedures nor thrombolytic therapy is helpful because of the multiplicity, composition, and distal location of the emboli. Therapy with antiplatelet drugs and statins improves cardiovascular outcome in patients with atherosclerosis, but it is not established whether either class of drugs prevents recurrent atheroembolism. Similarly, it is not known whether anticoagulant therapy is effective. Endovascular or surgical intervention to exclude or bypass the atherosclerotic vessel or aneurysm that causes the recurrent atheroemboli may be necessary.

### THORACIC OUTLET COMPRESSION SYNDROME

This is a symptom complex resulting from compression of the neurovascular bundle (artery, vein, or nerves) at the thoracic outlet as it courses through the neck and shoulder. Cervical ribs, abnormalities of the scalenus anticus muscle, proximity of the clavicle to the first rib, or abnormal insertion of the pectoralis minor muscle may compress the subclavian artery, subclavian vein, and brachial plexus as these structures pass from the thorax to the arm. Depending on the structures affected, thoracic outlet compression syndrome is divided into arterial, venous, and neurogenic forms. Patients with neurogenic thoracic outlet compression may develop shoulder and arm pain, weakness, and paresthesias. Patients with arterial compression may experience claudication, Raynaud's phenomenon, and even ischemic tissue loss and gangrene. Venous compression may cause thrombosis of the subclavian



**FIGURE 281-2 Atheroembolism** causing cyanotic discoloration and impending necrosis of the toes ("blue toe" syndrome).

## APPROACH TO THE PATIENT

### Thoracic Outlet Compression Syndrome

Examination of a patient with arterial thoracic outlet compression syndrome is often normal unless provocative maneuvers are performed. Occasionally, distal pulses are decreased or absent and digital cyanosis and ischemia may be evident.

Several maneuvers that support the diagnosis of arterial thoracic outlet compression syndrome may be used to precipitate symptoms, cause a subclavian artery bruit, and diminish arm pulses. These maneuvers include the abduction and external rotation test, in which the affected arm is abducted by 90° and the shoulder is externally rotated; the scalene maneuver (extension of the neck and rotation of the head to the side of the symptoms); the costoclavicular maneuver (posterior rotation of shoulders); and the hyperabduction maneuver (raising the arm 180°). A chest x-ray will indicate the presence of cervical ribs. Duplex ultrasonography, MRA, and contrast angiography can be performed during provocative maneuvers to demonstrate thoracic outlet compression of the subclavian artery. Neurophysiologic tests such as the electromyogram, nerve conduction studies, and somatosensory evoked potentials may be abnormal if the brachial plexus is involved, but the diagnosis of neurogenic thoracic outlet syndrome is not necessarily excluded if these tests are normal owing to their low sensitivity.

Most patients can be managed conservatively. They should be advised to avoid the positions that cause symptoms. Many patients benefit from shoulder girdle exercises. Surgical procedures such as removal of the first rib and resection of the scalenus anticus muscle are necessary occasionally for relief of symptoms or treatment of ischemia.

### POPLITEAL ARTERY ENTRAPMENT

Popliteal artery entrapment typically affects young athletic men and women when the gastrocnemius or popliteus muscle compresses the popliteal artery and causes intermittent claudication. Thrombosis, embolism, or popliteal artery aneurysm may occur. The pulse examination may be normal unless provocative maneuvers such as ankle dorsiflexion and plantar flexion are performed. The diagnosis is confirmed by duplex ultrasound, CTA, MRA, or conventional angiography. Treatment involves surgical release of the popliteal artery or vascular reconstruction.

### POPLITEAL ARTERY ANEURYSM

Popliteal artery aneurysms are the most common peripheral artery aneurysms. Approximately 50% are bilateral. Patients with popliteal artery aneurysms often have aneurysms of other arteries, especially the aorta. The most common clinical presentation is limb ischemia secondary to thrombosis or embolism. Rupture occurs less frequently. Other complications include compression of the adjacent popliteal vein or peroneal nerve. Popliteal artery aneurysm can be detected by palpation and confirmed by duplex ultrasonography. Repair is indicated for symptomatic aneurysms or when the diameter exceeds 2–3 cm, owing to the risk of thrombosis, embolism, or rupture.

### ARTERIOVENOUS FISTULA

Abnormal communications between an artery and a vein, bypassing the capillary bed, may be congenital or acquired. Congenital arteriovenous fistulas are a result of persistent embryonic vessels that fail to differentiate into arteries and veins; they may be associated with birthmarks, can be located in almost any organ of the body, and frequently occur in the extremities. Acquired arteriovenous fistulas either are created to provide vascular access for hemodialysis or occur as a result of a penetrating injury such as a gunshot or knife wound or as complications of arterial catheterization or surgical dissection. An uncommon cause of arteriovenous fistula is rupture of an arterial aneurysm into a vein.

The clinical features depend on the location and size of the fistula. Frequently, a pulsatile mass is palpable, and a thrill and a bruit lasting throughout systole and diastole are present over the fistula. With long-standing fistulas, clinical manifestations of chronic venous insufficiency, including peripheral edema; large, tortuous varicose veins; and stasis pigmentation become apparent because of the high venous pressure. Evidence of ischemia may occur in the distal portion of the extremity. Skin temperature is higher over the arteriovenous fistula. Large arteriovenous fistulas may result in an increased cardiac output with consequent cardiomegaly and high-output heart failure ([Chap. 257](#)).

The diagnosis is often evident from the physical examination. Compression of a large arteriovenous fistula may cause reflex slowing of the heart rate (Nicoladoni-Branham sign). Duplex ultrasonography may detect an arteriovenous fistula, especially one that affects the femoral artery and vein at the site of catheter access. CTA and conventional angiography can confirm the diagnosis and are useful in demonstrating the site and size of the arteriovenous fistula.

Management of arteriovenous fistulas may involve surgery, radiotherapy, or embolization. Congenital arteriovenous fistulas are often difficult to treat because the communications may be numerous and extensive, and new communications frequently develop after ligation of the most obvious ones. Many of these lesions are best treated conservatively using elastic support hose to reduce the consequences of venous hypertension. Occasionally, embolization with autologous material, such as fat or muscle, or with hemostatic agents, such as gelatin sponges or silicon spheres, is used to obliterate the fistula. Acquired arteriovenous fistulas are usually amenable to surgical treatment that involves division or excision of the fistula. Occasionally, autogenous or synthetic grafting is necessary to reestablish continuity of the artery and vein.

### RAYNAUD'S PHENOMENON

Raynaud's phenomenon is characterized by episodic digital ischemia, manifested clinically by the sequential development of digital blanching, cyanosis, and rubor of the fingers or toes after cold exposure and subsequent rewarming. Emotional stress may also precipitate Raynaud's phenomenon. The color changes are usually well demarcated and are confined to the fingers or toes. Typically, one or more digits will appear white when the patient is exposed to a cold environment or touches a cold object ([Fig. 281-3A](#)). The blanching, or pallor, represents the ischemic phase of the phenomenon and results from vasospasm of digital arteries. During the ischemic phase, capillaries and venules dilate, and cyanosis results from the deoxygenated blood that is present in these vessels. A sensation of cold or numbness or paresthesia of the digits often accompanies the phases of pallor and cyanosis.

With rewarming, the digital vasospasm resolves, and blood flow into the dilated arterioles and capillaries increases dramatically. This "reactive hyperemia" imparts a bright red color to the digits. In addition to rubor and warmth, patients often experience a throbbing, painful sensation during the hyperemic phase. Although the triphasic color response is typical of Raynaud's phenomenon, some patients may develop only pallor and cyanosis; others may experience only cyanosis.

Raynaud's phenomenon is broadly separated into two categories: idiopathic, termed primary Raynaud's phenomenon, and secondary Raynaud's phenomenon, which is associated with other disease states or known causes of vasospasm ([Table 281-1](#)).

**Primary Raynaud's Phenomenon** This appellation is applied when the secondary causes of Raynaud's phenomenon have been excluded. Over 50% of patients with Raynaud's phenomenon have the primary form. Women are affected about five times more often than men, and the age of presentation is usually between 20 and 40 years. The fingers are involved more frequently than the toes. Initial episodes may involve only one or two fingertips, but subsequent attacks may involve the entire finger and may include all the fingers. The toes are affected in 40% of patients. Although vasospasm of the toes usually occurs in patients with symptoms in the fingers, it may happen alone. Rarely, the earlobes, the tip of the nose, tongue, nipple, or penis are involved. Raynaud's phenomenon occurs frequently in patients who also have migraine headaches or variant angina. These associations



**FIGURE 281-3** Vascular diseases associated with temperature: *A*, Raynaud's phenomenon; *B*, acrocyanosis; *C*, livedo reticularis; *D*, pernio; *E*, erythromelalgia; and *F*, frostbite.

suggest that there may be a common predisposing cause for the vasospasm.

Results of physical examination are often entirely normal; the radial, ulnar, and pedal pulses are normal. The fingers and toes may be cool between attacks and may perspire excessively. Nailfold capillaroscopy reveals normal superficial capillaries, which appear as regularly spaced hairpin loops. Thickening and tightening of the digital subcutaneous tissue (*sclerodactyly*) develop in 10% of patients. Angiography of the digits for diagnostic purposes is not indicated.

In general, patients with primary Raynaud's disease have milder clinical manifestations. Fewer than 1% of these patients lose a part of a digit. After the diagnosis is made, the disease improves spontaneously in ~15% of patients and progresses in ~30%.

**Secondary Causes of Raynaud's Phenomenon** Raynaud's phenomenon occurs in 80–90% of patients with systemic sclerosis (scleroderma) and is the presenting symptom in 30% (Chap. 360). It may be the only symptom of scleroderma for many years. Abnormalities of the digital vessels may contribute to the development of Raynaud's phenomenon in this disorder. Ischemic fingertip ulcers may develop and progress to gangrene and autoamputation. About 20% of patients with systemic lupus erythematosus (SLE) have Raynaud's phenomenon (Chap. 356). Occasionally, persistent digital ischemia develops and may result in ulcers or gangrene. In most severe cases, the small vessels are occluded by a proliferative endarteritis. Raynaud's phenomenon occurs in ~30% of patients with dermatomyositis or polymyositis (Chap. 365). It frequently develops in patients with rheumatoid arthritis and may be related to the intimal proliferation that occurs in the digital arteries.

Atherosclerosis of the extremities is a common cause of Raynaud's phenomenon in men aged >50 years. Thromboangiitis obliterans is an uncommon cause of Raynaud's phenomenon but should be considered

in young men, particularly those who are cigarette smokers. The development of cold-induced pallor in these disorders may be confined to one or two digits of the involved extremity. Occasionally, Raynaud's phenomenon may follow acute occlusion of large and medium-sized arteries by a thrombus or embolus. Embolization of atheroembolic debris may cause digital ischemia. The latter situation often involves one or two digits and should not be confused with Raynaud's phenomenon. In patients with thoracic outlet compression syndrome, Raynaud's phenomenon may result from diminished intravascular pressure, stimulation of sympathetic fibers in the brachial plexus, or a combination of both. Raynaud's phenomenon occurs in patients with

**TABLE 281-1 Classification of Raynaud's Phenomenon**

Primary or idiopathic Raynaud's phenomenon
Secondary Raynaud's phenomenon
Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis, mixed connective tissue disease, Sjögren's syndrome
Arterial occlusive diseases: atherosclerosis of the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome
Pulmonary hypertension
Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome, complex regional pain syndrome
Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, lymphoplasmacytic lymphoma
Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing
Drugs and toxins: ergot derivatives, methysergide, $\beta$ -adrenergic receptor blockers, bleomycin, vinblastine, cisplatin, gemcitabine, vinyl chloride

primary pulmonary hypertension (**Chap. 283**); this is more than coincidental and may reflect a neurohumoral abnormality that affects both the pulmonary and digital circulations.

A variety of blood dyscrasias may be associated with Raynaud's phenomenon. Cold-induced precipitation of plasma proteins, hyperviscosity, and aggregation of red cells and platelets may occur in patients with cold agglutinins, cryoglobulinemia, or cryofibrinogenemia. Hyperviscosity syndromes that accompany myeloproliferative disorders and lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia) should also be considered in the initial evaluation of patients with Raynaud's phenomenon.

Raynaud's phenomenon occurs often in patients whose vocations require the use of vibrating hand tools, such as chain saws or jackhammers. The frequency of Raynaud's phenomenon also seems to be increased in pianists and keyboard operators. Electric shock injury to the hands or frostbite may lead to the later development of Raynaud's phenomenon.

Several drugs have been causally implicated in Raynaud's phenomenon. They include ergot preparations, methysergide,  $\beta$ -adrenergic receptor antagonists, and the chemotherapeutic agents bleomycin, vinblastine, cisplatin, and gemcitabine.

## TREATMENT

### Raynaud's Phenomenon

Most patients with Raynaud's phenomenon experience only mild and infrequent episodes. These patients need reassurance and should be instructed to dress warmly and avoid unnecessary cold exposure. In addition to gloves and mittens, patients should protect the trunk, head, and feet with warm clothing to prevent cold-induced reflex vasoconstriction. Tobacco use is contraindicated.

Drug treatment should be reserved for severe cases. Dihydropyridine calcium channel antagonists such as nifedipine, isradipine, felodipine, and amlodipine decrease the frequency and severity of Raynaud's phenomenon. Diltiazem may be considered but is less effective. The postsynaptic  $\beta$ -adrenergic antagonist prazosin has been used with favorable responses; doxazosin and terazosin may also be effective. Phosphodiesterase type 5 inhibitors such as sildenafil, tadalafil, and vardenafil may improve symptoms in patients with secondary Raynaud's phenomenon, as occurs with systemic sclerosis. There is also evidence that topical nitroglycerin preparations are effective. Digital sympathectomy is helpful in some patients who are unresponsive to medical therapy. Injection of botulinum toxin into the perivascular tissue of the wrist or palm improved ischemic manifestations of severe Raynaud's phenomenon in case series, but controlled clinical trials are lacking.

### ACROCYANOSIS

In this condition, there is arterial vasoconstriction and secondary dilation of the capillaries and venules with resulting persistent cyanosis of the hands and, less frequently, the feet. Cyanosis may be intensified by exposure to a cold environment. Acrocyanosis may be categorized as primary or secondary to an underlying condition. In primary acrocyanosis, women are affected much more frequently than men, and the age of onset is usually  $<30$  years. Generally, patients are asymptomatic but seek medical attention because of the discoloration. The prognosis is favorable, and pain, ulcers, and gangrene do not occur. Examination reveals normal pulses, peripheral cyanosis, and moist palms (**Fig. 281-3B**). Trophic skin changes and ulcerations do *not* occur. The disorder can be distinguished from Raynaud's phenomenon because it is persistent and not episodic, the discoloration extends proximally from the digits, and blanching does not occur. Ischemia secondary to arterial occlusive disease can usually be excluded by the presence of normal pulses. Central cyanosis and decreased arterial oxygen saturation are not present. Patients should be reassured and advised to dress warmly and avoid cold exposure. Pharmacologic intervention is not indicated.

Secondary acrocyanosis may result from hypoxemia, vasoconstrictor medications, connective tissue diseases, atheroembolism,

antiphospholipid antibodies, cold agglutinins, or cryoglobulins and is associated with anorexia nervosa and postural orthostatic tachycardia syndrome. Treatment should be directed at the underlying disorder.

### LIVEDO RETICULARIS

In this condition, localized areas of the extremities develop a mottled or rete (netlike) appearance of reddish to blue discoloration (**Fig. 281-3C**). There are primary and secondary forms of livedo reticularis. The primary, or idiopathic, form of this disorder may be benign or associated with ulcerations. The benign form occurs more frequently in women than in men, and the most common age of onset is the third decade. The mottling typically is symmetric and uniform and may be more prominent after cold exposure and improve with warming. Patients with the benign form are usually asymptomatic and seek attention for cosmetic reasons. These patients should be reassured and advised to avoid cold environments. No drug treatment is indicated. Primary livedo reticularis with ulceration is also called *atrophie blanche en plaque*. The ulcers are painful and may take months to heal. Secondary livedo reticularis can occur with atheroembolism (see above), SLE and other vasculitides, antiphospholipid antibodies, hyperviscosity, cryoglobulinemia, and Sneddon's syndrome (ischemic stroke and livedo reticularis). Livedo racemosa is the term used to characterize secondary livedo reticularis, when the mottling is irregular and disrupted, and does not improve with warming. Rarely, skin ulcerations develop.

### PERNIO (CHILBLAINS)

Pernio is a vasculitic disorder associated with exposure to cold; acute forms have been described. Raised erythematous lesions develop most commonly on the toes or fingers in cold weather (**Fig. 281-3D**). They are associated with pruritus and a burning sensation, and they may blister and ulcerate. Pathologic examination demonstrates angiitis characterized by intimal proliferation and perivascular infiltration of mononuclear and polymorphonuclear leukocytes. Giant cells may be present in the subcutaneous tissue. Patients should avoid exposure to cold, and ulcers should be kept clean and protected with sterile dressings. Sympatholytic drugs and dihydropyridine calcium channel antagonists may be effective in some patients.

### ERYTHROMELALGIA

This disorder is characterized by burning pain and erythema of the extremities (**Fig. 281-3E**). The feet are involved more frequently than the hands, and males are affected more frequently than females. Erythromelalgia may occur at any age but is most common in middle age. It may be primary (also termed erythermalgia) or secondary. Mutations in the SCN9A gene, which encodes the Nav1.7 voltage-gated sodium channel expressed in sensory and sympathetic nerves, have been described in inherited forms of erythromelalgia. The most common causes of secondary erythromelalgia are myeloproliferative disorders such as polycythemia vera and essential thrombocythosis. Less common causes include drugs, such as calcium channel blockers, bromocriptine, and pergolide; neuropathies; connective tissue diseases such as SLE; and paraneoplastic syndromes. Patients complain of burning in the extremities that is precipitated by exposure to a warm environment and aggravated by a dependent position. The symptoms are relieved by exposing the affected area to cool air or water or by elevation. Erythromelalgia can be distinguished from ischemia secondary to peripheral arterial disorders because the peripheral pulses are present. There is no specific treatment; aspirin may produce relief in patients with erythromelalgia secondary to myeloproliferative disease. Topical anesthetics may be considered to relieve pain. Treatment of associated disorders in secondary erythromelalgia may be helpful.

### FROSTBITE

In this condition, tissue damage results from severe environmental cold exposure or from direct contact with a very cold object. Tissue injury results from both freezing and vasoconstriction. Frostbite usually affects the distal aspects of the extremities or exposed parts of the face, such as the ears, nose, chin, and cheeks. Superficial frostbite involves the skin and subcutaneous tissue. Patients experience pain or

paresthesia, and the skin appears white and waxy. After rewarming, there is cyanosis and erythema, wheal-and-flare formation, edema, and superficial blisters. Deep frostbite involves muscle, nerves, and deeper blood vessels. It may result in edema of the hand or foot, vesicles and bullae, tissue necrosis, and gangrene (**Fig. 281-3F**).

Initial treatment is rewarming, performed in an environment where reexposure to freezing conditions will not occur. Rewarming is accomplished by immersion of the affected part in a water bath at temperatures of 40°–44°C (104°–111°F). Massage, application of ice water, and extreme heat are contraindicated. The injured area should be cleansed with soap or antiseptic, and sterile dressings should be applied. Analgesics are often required during rewarming. Antibiotics are used if there is evidence of infection. The efficacy of sympathetic blocking drugs is not established. After recovery, the affected extremity may exhibit increased sensitivity to cold.

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### VENOUS ANATOMY

Veins in the extremities can be broadly classified as either superficial or deep. The superficial veins are located between the skin and deep fascia. In the legs, these include the great and small saphenous veins and their tributaries. The great saphenous vein is the longest vein in the body. It originates on the medial side of the foot and ascends anterior to the medial malleolus and then along the medial side of the calf and thigh, and drains into the common femoral vein. The small saphenous vein originates on the dorsolateral aspect of the foot, ascends posterior to the lateral malleolus and along the posterolateral aspect of the calf, and drains into the popliteal vein. The deep veins of the leg accompany the major arteries. There are usually paired peroneal, anterior tibial, and posterior tibial veins in the calf, which converge to form the popliteal vein. Soleal tributary veins drain into the posterior tibial or peroneal veins, and gastrocnemius tributary veins drain into the popliteal vein. The popliteal vein ascends in the thigh as the femoral vein. The confluence of the femoral vein and deep femoral vein form the common femoral vein, which ascends in the pelvis as the external iliac and then common iliac vein, which converges with the contralateral common iliac vein at the inferior vena cava. Perforating veins connect the superficial and deep systems in the legs at multiple locations, normally allowing blood to flow from the superficial to deep veins. In the arms, the superficial veins include the basilic, cephalic, and median cubital veins and their tributaries. The basilic and cephalic veins course along the medial and lateral aspects of the arm, respectively, and these are connected via the median cubital vein in the antecubital fossa. The deep veins of the arms accompany the major arteries and include the radial, ulnar, brachial, axillary, and subclavian veins. The subclavian vein converges with the internal jugular vein to form the brachiocephalic vein, which joins the contralateral brachiocephalic vein to form the superior vena cava. Bicuspid valves are present throughout the venous system to direct the flow of venous blood centrally.

**Pathophysiology of Chronic Venous Disease** Varicose veins are dilated, bulging, tortuous superficial veins, measuring at least 3 mm in diameter. The smaller and less tortuous reticular veins are dilated intradermal veins, which appear blue-green, measure 1–3 mm in diameter, and do not protrude from the skin surface. Telangiectasias, or spider veins, are small, dilated veins, <1 mm in diameter, located near the skin surface, and form blue, purple, or red linear, branching, or spider-web patterns.

Varicose veins can be categorized as primary or secondary. Primary varicose veins originate in the superficial system and result from defective structure and function of the valves of the saphenous veins, intrinsic weakness of the vein wall, and high intraluminal pressure. Approximately one-half of these patients have a family history of varicose veins. Other factors associated with primary varicose veins include aging, pregnancy, hormonal therapy, obesity, and prolonged standing. Secondary varicose veins result from venous hypertension, associated with deep-venous insufficiency or deep-venous obstruction, and incompetent perforating veins that cause enlargement of superficial veins. Arteriovenous fistulas also cause varicose veins in the affected limb.

**Chronic venous insufficiency** is a consequence of incompetent veins in which there is venous hypertension and extravasation of fluid and blood elements into the tissue of the limb. It may occur in patients with varicose veins but usually is caused by disease in the deep veins. It also is categorized as primary or secondary. Primary deep-venous insufficiency is a consequence of an intrinsic structural or functional abnormality in the vein wall or venous valves leading to valvular reflux. Secondary deep-venous insufficiency is caused by obstruction and/or valvular incompetence from previous deep-vein thrombosis (**Chap. 279**). Deep-venous insufficiency occurs following deep-vein thrombosis, as the delicate valve leaflets become thickened and contracted and can no longer prevent retrograde flow of blood and the vein itself becomes rigid and thick walled. Although most veins recanalize after an episode of thrombosis, the large proximal veins may remain occluded. Secondary incompetence develops in distal valves because high pressures distend the vein and separate the leaflets. Other causes of secondary

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## Chronic Venous Disease and Lymphedema

Mark A. Creager, Joseph Loscalzo

### CHRONIC VENOUS DISEASE

Chronic venous diseases range from telangiectasias and reticular veins, to varicose veins, to chronic venous insufficiency with edema, skin changes, and ulceration. This section of the chapter will focus on identification and treatment of varicose veins and chronic venous insufficiency, since these problems are encountered frequently by the internist. The estimated prevalence of varicose veins in the United States is ~15% in men and 30% in women. Chronic venous insufficiency with edema affects ~7.5% of men and 5% of women, and the prevalence increases with age ranging from 2% among those <50 years of age to 10% of those 70 years of age. Approximately 20% of patients with chronic venous insufficiency develop venous ulcers.

deep-venous insufficiency include May-Thurner syndrome, where the left iliac vein is occluded or stenosed by extrinsic compression from the overlapping right common iliac artery; extrinsic compression from tumor or retroperitoneal fibrosis; arteriovenous fistulas resulting in increased venous pressure; congenital deep-vein agenesis or hypoplasia; and venous malformations as may occur in Klippel-Trénaunay and Parkes-Weber syndromes.

**Clinical Presentation** Patients with venous varicosities are often asymptomatic but still concerned about the cosmetic appearance of their legs. Superficial venous thrombosis may be a recurring problem, and rarely, a varicosity ruptures and bleeds. Symptoms in patients with varicose veins or venous insufficiency, when they occur, include a dull ache, throbbing or heaviness, or pressure sensation in the legs typically after prolonged standing; these symptoms usually are relieved with leg elevation. Additional symptoms may include cramping, burning, pruritus, leg swelling, and skin ulceration.

The legs are examined in both the supine and standing positions. Visual inspection and palpation of the legs in the standing position confirm the presence of varicose veins. The location and extent of the varicose veins should be noted. Edema, stasis dermatitis, and skin ulceration near the ankle may be present if there is superficial venous insufficiency and venous hypertension. Findings of deep-venous insufficiency include increased leg circumference, venous varicosities, edema, and skin changes. The edema, which is usually pitting, may be confined to the ankles, extend above the ankles to the knees, or involve the thighs in severe cases. Over time, the edema may become less pitting and more indurated. Dermatologic findings associated with venous stasis include hyperpigmentation, erythema, eczema, lipodermatosclerosis, *atrophie blanche*, and a phlebectasia corona. Lipodermatosclerosis is the combination of induration, hemosiderin deposition, and inflammation, and typically occurs in the lower part of the leg just above the ankle. Atrophie blanche is a white patch of scar tissue, often with focal telangiectasias and a hyperpigmented border; it usually develops near the medial malleolus. A phlebectasia corona is a fan-shaped pattern of intradermal veins near the ankle or on the foot. Skin ulceration may occur near the medial and lateral malleoli. A venous ulcer is often shallow and characterized by an irregular border, a base of granulation tissue, and the presence of exudate (Fig. 282-1).



FIGURE 282-1 Venous insufficiency with active venous ulcer near the medial malleolus. (Courtesy of Dr. Steven Dean, with permission.)

Bedside maneuvers can be used to distinguish primary varicose veins from secondary varicose veins caused by deep-venous insufficiency. With the contemporary use of venous ultrasound (see below), however, these maneuvers are employed infrequently. The Brodie-Trendelenburg test is used to determine whether varicose veins are secondary to deep-venous insufficiency. As the patient is lying supine, the leg is elevated and the veins allowed to empty. Then, a tourniquet is placed on the proximal part of the thigh and the patient is asked to stand. Filling of the varicose veins within 30 s indicates that the varicose veins are caused by deep-venous insufficiency and incompetent perforating veins. Primary varicose veins with superficial venous insufficiency are the likely diagnosis if venous refilling occurs promptly after tourniquet removal. The Perthes test assesses the possibility of deep-venous obstruction. A tourniquet is placed on the midthigh after the patient has stood, and the varicose veins are filled. The patient is then instructed to walk for 5 min. A patent deep-venous system and competent perforating veins enable the superficial veins below the tourniquet to collapse. Deep-venous obstruction is likely to be present if the superficial veins distend further with walking.

**Differential Diagnosis** The duration of leg edema helps to distinguish chronic venous insufficiency from acute deep-vein thrombosis. Lymphedema, as discussed later in this chapter, is often confused with chronic venous insufficiency, and both may occur together. Other disorders that cause leg swelling should be considered and excluded when evaluating a patient with presumed venous insufficiency. Bilateral leg swelling occurs in patients with congestive heart failure, hypoalbuminemia secondary to nephrotic syndrome or severe hepatic disease, or myxedema caused by hypothyroidism or pretibial myxedema associated with Graves' disease, and with drugs such as dihydropyridine calcium channel blockers and thiazolidinediones. Unilateral causes of leg swelling also include ruptured leg muscles, hematomas secondary to trauma, and popliteal cysts. Cellulitis may cause erythema and swelling of the affected limb. Leg ulcers may be caused by severe peripheral artery disease and critical limb ischemia; neuropathies, particularly those associated with diabetes; and less commonly, skin cancer, vasculitis, or rarely as a complication of hydroxyurea. The location and characteristics of venous ulcers help to differentiate these from other causes.

**Classification of Chronic Venous Disease** The CEAP (clinical, etiologic, anatomic, pathophysiologic) classification schema incorporates the range of symptoms and signs of chronic venous disease to characterize its severity. It also broadly categorizes the etiology as primary, secondary, or congenital; identifies the affected veins as superficial, deep, or perforating; and characterizes the pathophysiology as reflux, obstruction, both, or neither (Table 282-1).

**Diagnostic Testing** The principal diagnostic test to evaluate patients with chronic venous disease is venous duplex ultrasonography. A venous duplex ultrasound examination uses a combination of B-mode imaging and spectral Doppler to detect the presence of venous obstruction and venous reflux in superficial and deep veins. Color-assisted Doppler ultrasound is useful to visualize venous flow patterns. Obstruction may be diagnosed by the absence of flow, the presence of an echogenic thrombus within the vein, or failure of the vein to collapse when a compression maneuver is applied by the sonographer, the last implicating the presence of an intraluminal thrombus. Venous reflux is detected by prolonged reversal of venous flow direction during a Valsalva maneuver, particularly for the common femoral vein or saphenofemoral junction, or after compression and release of a cuff placed on the limb distal to the area being interrogated.

Some vascular laboratories use air or strange gauge plethysmography to assess the severity of venous reflux and complement findings from the venous ultrasound examination. Venous volume and venous refilling time are measured when the legs are placed in a dependent position and after calf exercise to quantify the severity of venous reflux and the efficiency of the calf muscle pump to affect venous return.

**TABLE 282-1 CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) Classification****Clinical Classification**

- C<sub>0</sub> No visible or palpable signs of venous disease
- C<sub>1</sub> Telangiectasias or reticular veins
- C<sub>2</sub> Varicose veins
  - C<sub>2x</sub> Recurrent varicose veins
- C<sub>3</sub> Edema
- C<sub>4</sub> Changes in skin and subcutaneous secondary to CVD
  - C<sub>4a</sub> Pigmentation or eczema
  - C<sub>4b</sub> Lipodermatosclerosis or atrophie blanche
  - C<sub>4c</sub> Corona phlebectatica
- C<sub>5</sub> Healed venous ulcer
- C<sub>6</sub> Active venous ulcer
  - C<sub>6x</sub> Recurrent active venous ulcer

**Etiologic Classification**

- E<sub>p</sub> Primary
- E<sub>s</sub> Secondary
  - E<sub>si</sub> Secondary – intravenous
  - E<sub>se</sub> Secondary – extravenous
- E<sub>c</sub> Congenital
- E<sub>n</sub> No cause identified

**Anatomic Classification**

- A<sub>s</sub> Superficial
- A<sub>p</sub> Perforator
- A<sub>d</sub> Deep
- A<sub>n</sub> No venous anatomic location identified

**Pathophysiologic Classification**

- P<sub>r</sub> Reflux
- P<sub>o</sub> Obstruction
- P<sub>ro</sub> Reflux and obstruction
- P<sub>n</sub> No pathophysiology identified

*Abbreviation:* CVD, chronic venous disease.

*Source:* Data from F Lurie et al: J Vasc Surg 8:342, 2020.

Magnetic resonance, computed tomographic, and conventional venography are rarely required to determine the cause and plan treatment for chronic venous insufficiency unless there is suspicion for pathology that might warrant intervention. These modalities are used to identify obstruction or stenosis of the inferior vena cava and iliofemoral veins, as may occur in patients with previous proximal deep-vein thrombosis; occlusion of inferior vena cava filters; extrinsic compression from tumors; and May-Thurner syndrome.

**TREATMENT****Chronic Venous Disease****SUPPORTIVE MEASURES**

Varicose veins usually are treated with conservative measures. Symptoms often decrease when the legs are elevated periodically, prolonged standing is avoided, and elastic support hose are worn. External compression with elastic stockings, multilayer elastic wraps, stretch bandages, or inelastic garments provides a counterbalance to the hydrostatic pressure in the veins. Although compression garments may improve symptoms, they do not prevent progression of varicose veins. Graduated compression stockings with pressures of 20–30 mmHg are suitable for most patients with simple varicose veins, although higher pressures may be required

for patients with varicose veins and manifestations of venous insufficiency such as edema and ulcers.

Patients with chronic venous insufficiency also should be advised to avoid prolonged standing or sitting; frequent leg elevation is helpful. Graded compression therapy consisting of stockings or multilayered compression bandages is the standard of care for advanced chronic venous insufficiency characterized by edema, skin changes, or venous ulcers defined as CEAP clinical class C3–C6. Graduated compression stockings of 30–40 mmHg are more effective than lesser grades for healing venous ulcers. The length of stocking depends on the distribution of edema. Calf-length stockings are tolerated better by most patients, particularly elderly patients; for patients with varicose veins or edema extending to the thigh, thigh-length stockings or panty hose should be considered. Exercise training, including leg muscle strengthening, may improve calf muscle pump function and antegrade venous flow, and reduce the severity of chronic venous insufficiency. Overweight and obese patients should be advised to lose weight via caloric restriction and exercise.

In addition to a compression bandage or stocking, patients with venous ulcers also may be treated with low-adherent absorbent dressings that take up exudates while maintaining a moist environment. Other types of dressings include hydrocolloid (an adhesive dressing composed of polymers such as carboxymethylcellulose that absorbs exudates by forming a gel), hydrogel (a nonabsorbent dressing comprising >80% water or glycerin that moisturizes wounds), foam (an absorbent dressing made with polymers such as polyurethane), and alginate (an absorbent, biodegradable dressing that is derived from seaweed), but there is little evidence that these are more effective than low-adherent absorbent dressings. The choice of specific dressing depends on the amount of drainage, presence of infection, and integrity of the skin surrounding the ulcer. Ulcers should be debrided of necrotic tissue. Antibiotics are not indicated unless the ulcer is infected. The multilayered compression bandage or graduated compression garment is then put over the dressing.

**MEDICAL THERAPIES**

There are no drugs approved by the U.S. Food and Drug Administration for the treatment of chronic venous insufficiency. Diuretics may reduce edema, but at the risk of volume depletion and compromise in renal function. Topical steroids may be used for a short period of time to treat inflammation associated with stasis dermatitis. Several herbal supplements, such as horse chestnut seed extract (aescin); flavonoids, including diosmin, hesperidin, or the two combined as micronized purified flavonoid fraction; and French maritime pine bark extract, are touted to have venoconstrictive and anti-inflammatory properties. Although meta-analyses have suggested that aescin reduces edema, pruritus, and pain and that micronized purified flavonoid fraction in conjunction with compression therapy facilitates venous ulcer healing, there is insufficient evidence to recommend the general use of these substances in patients with chronic venous insufficiency.

**INTERVENTIONAL AND SURGICAL THERAPIES**

Ablative procedures, including endovenous thermal and nonthermal ablation, sclerotherapy, and surgery, are used to treat varicose veins in selected patients who have persistent symptoms, great saphenous vein incompetency, and complications of venous insufficiency including dermatitis, edema, and ulcers. Ablative therapy may also be indicated for cosmetic reasons.

Endovenous thermal ablation procedures of the saphenous veins include endovenous laser therapy and radiofrequency ablation. To ablate the great saphenous vein, a catheter is placed percutaneously and advanced from the level of the knee to just below the saphenofemoral junction via ultrasound guidance. Thermal energy is then delivered as the catheter is pulled back. The heat injures the endothelium and media and promotes thrombosis and fibrosis,

resulting in venous occlusion. Average 1- and 5-year occlusion rates exceed 90% following endovenous laser therapy and are slightly less after radiofrequency ablation. Deep-vein thrombosis of the common femoral vein adjacent to the saphenofemoral junction is an uncommon but potential complication of endovenous thermal ablation. Other adverse effects of thermal ablation procedures include pain, paresthesias, bruising, hematoma, and hyperpigmentation.

Nonthermal ablation procedures of the saphenous veins include endovenous delivery of a cyanoacrylate tissue adhesive, which causes fibrosis, and mechanochemical ablation, which involves insertion of a rotating wire to injure the endothelium and infusion of a liquid sclerosant. One-year occlusion rates approximate or exceed 90%, respectively. Adverse effects of nonthermal ablation procedures include superficial thrombophlebitis, deep vein thrombosis, ecchymoses, hematomas, and hyperpigmentation.

Sclerotherapy involves the injection of a chemical into a vein to cause fibrosis and obstruction. Sclerosing agents approved by the U.S. Food and Drug Administration include sodium tetradecyl sulfate, polidocanol, sodium morrhuate, and glycerin. The sclerosing agent is administered as a liquid or mixed with air or CO<sub>2</sub>/O<sub>2</sub> to create a foam. It is first injected into the great saphenous vein or its affected tributaries, often with ultrasound guidance. Thereafter, smaller more distal veins and incompetent perforating veins are injected. Following completion of the procedure, elastic bandages are applied, or 30–40 mmHg compression stockings are worn for 1–2 weeks. Average 1- and 5-year occlusion rates are 81 and 74%, respectively, following sclerotherapy. Complications are uncommon and include deep-vein thrombosis, hematomas, damage to adjacent saphenous or sural nerves, and infection. Anaphylaxis is a very rare but severe complication.

Surgical therapy usually involves ligation and stripping of the great and small saphenous veins. The procedure is performed under general anesthesia. Incisions are made at the groin and the upper calf. The great saphenous vein is ligated below the saphenofemoral junction, and a wire is inserted into the great saphenous vein and advanced distally. The proximal part of the great saphenous vein is secured to the wire and retrieved, i.e., stripped, via the calf incision. Stripping of the great saphenous vein below the knee and stripping of the small saphenous vein usually are not performed because of the respective risks of saphenous and sural nerve injury. Complications of great saphenous vein ligation and stripping include deep-vein thrombosis, bleeding, hematoma, infection, and nerve injury. Recurrent varicose veins occur in up to 50% patients by 5 years, due to technical failures, deep-venous insufficiency, and incompetent perforating veins.

Stab phlebectomy is another surgical treatment for varicose veins. A small incision is made alongside the varicose vein, and it is avulsed by means of a forceps or hook. This procedure may be performed in conjunction with saphenous vein ligation and stripping or thermal ablation. Subfascial endoscopic perforator surgery (SEPS) uses endoscopy to identify and occlude incompetent perforating veins. It also may be performed along with other ablative procedures.

Endovascular interventions, surgical bypass, and reconstruction of the valves of the deep veins are performed when feasible to treat patients with advanced chronic venous insufficiency who have not responded to other therapies. Catheter-based interventions, usually involving placement of endovenous stents, may be considered to treat some patients with chronic occlusions of the iliac veins. Technical success rates exceed 85% in most series, and long-term patency is achieved in ~75% of these patients. Iliocaval bypass, femorooiliac venous bypass, and femorofemoral crossover venous bypass are procedures used occasionally to treat iliofemoral vein occlusion; saphenopopliteal vein bypass can be used to treat chronic femoropopliteal vein obstruction. Long-term patency rates for venous bypass procedures generally exceed 60% and are associated with improvement in symptoms. Surgical reconstruction of the valves of the deep veins and valve transfer procedures are used to treat valvular incompetence. Valvuloplasty involves tightening

the valve by commissural apposition. With valve transfer procedures, a segment of vein with a competent valve, such as a brachial or axillary vein, or adjacent saphenous or deep femoral vein, is inserted as an interposition graft in the incompetent vein. Both valvuloplasty and vein transfer operations result in ulcer healing in the majority of patients, although success rates are somewhat better with valvuloplasty.

**Lymphedema** Lymphedema is a chronic condition caused by impaired transport of lymph and characterized by swelling of one or more limbs and occasionally the trunk and genitalia. Fluid accumulates in interstitial tissues when there is an imbalance between lymph production and lymph absorption, a process governed in large part by Starling forces. Deficiency, reflux, or obstruction of lymph vessels perturbs the ability of the lymphatic system to reabsorb proteins that had been filtered by blood vessels, and the tissue osmotic load promotes interstitial accumulation of water. Persistent lymphedema leads to inflammatory and immune responses characterized by infiltration of mononuclear cells, fibroblasts, and adipocytes, leading to adipose and collagen deposition in the skin and subcutaneous tissues.

**Lymphatic Anatomy** Lymphatic capillaries are blind-ended tubes formed by a single layer of endothelial cells. The absent or widely fenestrated basement membrane of lymphatic capillaries allows access to interstitial proteins and particles. Lymphatic capillaries merge to form microlymphatic precollector vessels, which contain few smooth muscle cells. The precollector vessels drain into collecting lymphatic vessels, which comprise endothelial cells, a basement membrane, smooth muscle, and baffle valves. The collecting lymphatic vessels in turn merge to form larger lymphatic conduits. Analogous to venous anatomy, there are superficial and deep lymphatic vessels in the legs, which communicate at the popliteal and inguinal lymph nodes. Pelvic lymphatic vessels drain into the thoracic duct, which ascends from the abdomen to the thorax and connects with the left brachiocephalic vein. Lymph is propelled centrally by the phasic contractile activity of lymphatic smooth muscle and facilitated by the contractions of contiguous skeletal muscle. The presence of lymphatic valves ensures unidirectional flow.

**Etiology** Lymphedema may be categorized as primary or secondary (**Table 282-2**). The prevalence of primary lymphedema is ~1.15 per 100,000 persons <20 years of age. Females are affected more frequently than males. Primary lymphedema may be caused by agenesis, hypoplasia, hyperplasia, or obstruction of the lymphatic vessels. There are three clinical subtypes: congenital lymphedema, which appears shortly after birth; lymphedema praecox, which has its onset at the time of puberty; and lymphedema tarda, which usually begins after age 35. Familial forms of congenital lymphedema (Milroy's disease) and lymphedema praecox (Meige's disease) may be inherited in an autosomal dominant manner with variable penetrance; autosomal or sex-linked recessive forms are less common. At least 19 genes are associated with inherited forms of lymphedema. Mutations in genes expressing vascular endothelial growth factor receptor 3 (VEGFR3), which is a determinant of lymphangiogenesis, cause Milroy's disease; and a mutation of the gene encoding VEGF-C, a ligand for VEGFR3, may cause a Milroy's disease-like phenotype. A mutation of the LSC1 gene is associated with the cholestasis-lymphedema syndrome. Mutations in the FOXC2 gene, which encodes a transcription factor that interacts with a signaling pathway involved in the development of lymphatic vessels, cause the lymphedema-distichiasis syndrome, in which lymphedema praecox occurs in patients who also have a double row of eyelashes. A mutation of SOX18, a transcription factor upstream of lymphatic endothelial cell differentiation, has been described in patients with lymphedema, alopecia, and telangiectasias (hypotrichosis, lymphedema, telangiectasia syndrome). Mutations of the CCBE1 gene, which enhances the lymphangiogenic effects of VEGF-C, cause Hennekam's lymphangiectasia-lymphedema syndrome, and KIF11 gene mutations are associated with microcephaly-lymphedema syndrome. Mutations of the GATA2 gene, which is involved in the development of lymphatic valves, cause

**TABLE 282-2 Causes of Lymphedema****Primary**

Sporadic (no identified cause)

Genetic disorders

Milroy's disease (*VEGFR3, VEGF-C*)

Meige's disease (gene mutation not established)

Lymphedema-distichiasis syndrome (*FOXC2*)Cholestasis-lymphedema (*LSC1*)Hennekam's lymphangiectasia-lymphedema syndrome (*LCCBE1*)Emberger's syndrome-lymphedema and predisposition to AML (*GATA2*)Microcephaly-lymphedema syndrome (*KIF11*)Hypotrichosis-lymphedema-telangiectasia (*SOX18*)

Chromosomal aneuploidies

Turner's syndrome

Klinefelter's syndrome

Trisomy 13, 18, or 21

Other disorders associated with primary lymphedema

Noonan's syndrome

Klippel-Trenaunay syndrome

Parkes-Weber syndrome

Yellow nail syndrome

Intestinal lymphangiectasia syndrome

Lymphangiomyomatosis

Neurofibromatosis type 1

**Secondary**

Infection

Bacterial lymphangitis (*Streptococcus pyogenes, Staphylococcus aureus*)Lymphogranuloma venereum (*Chlamydia trachomatis*)Filariasis (*Wuchereria bancrofti, Brugia malayi, B. timori*)

Tuberculosis

Neoplastic infiltration of lymph nodes

Lymphoma

Prostate

Others

Surgery or irradiation of axillary or inguinal lymph nodes for treatment of cancer

Iatrogenic

Lymphatic division (during peripheral bypass surgery, varicose vein surgery, or harvesting of saphenous veins)

Miscellaneous

Contact dermatitis

Podoconiosis

Rheumatoid arthritis

Pregnancy

Factitious

lymphedema. Other infectious causes include lymphogranuloma venereum and tuberculosis. A common acquired cause of lymphedema in tropical countries is podoconiosis, which results from barefoot exposure and absorption of silicate particles in soil derived from volcanic rock. In developed countries, the most common secondary cause of lymphedema is surgical excision or irradiation of axillary and inguinal lymph nodes for treatment of cancers, such as breast, cervical, endometrial, and prostate cancer, sarcomas, and malignant melanoma. Lymphedema of the arm occurs in 13% of breast cancer patients after axillary node dissection and in 22% after both surgery and radiotherapy. Lymphedema of the leg affects ~15% of patients with cancer after inguinal lymph node dissection. Tumors, such as prostate cancer and lymphoma, also can infiltrate and obstruct lymphatic vessels. Less common causes include contact dermatitis, rheumatoid arthritis, pregnancy, and self-induced or factitious lymphedema after application of tourniquets.

**Clinical Presentation** Lymphedema is generally a painless condition, but patients may experience a chronic dull, heavy sensation in the leg, and most often, they are concerned about the appearance of the leg. Lymphedema of the lower extremity initially involves the foot and gradually progresses up the leg so that the entire limb becomes edematous (Fig. 282-2). In the early stages, the edema is soft and pits easily with pressure. Over time, subcutaneous adipose tissue accumulates, the limb enlarges further and loses its normal contour, and the toes appear square. Thickening of the skin is detected by Stemmer's sign, which is the inability to tent the skin at the base of the toes. *Peau d'orange* is a term used to describe dimpling of the skin, resembling that of an orange peel, caused by lymphedema. In the chronic stages, the edema no longer pits and the limb acquires a woody texture as the tissues become indurated and fibrotic. The International Society of Lymphology describes four clinical stages of lymphedema (Table 282-3).

**Differential Diagnosis** Lymphedema should be distinguished from other disorders that cause unilateral leg swelling, such as deep-vein thrombosis and chronic venous insufficiency. In the latter condition, the edema is softer, and there is often evidence of a stasis



**FIGURE 282-2** **A.** Lymphedema characterized by swelling of the leg, nonpitting edema, and squaring of the toes. (Courtesy of Dr. Marie Gerhard-Herman, with permission.) **B.** Advanced chronic stage of lymphedema illustrating the woody appearance of the leg with acanthosis and verrucous overgrowths. (Courtesy of Dr. Jeffrey Olin, with permission.)

lymphedema and a predisposition to acute myeloid leukemia. Patients with a chromosomal aneuploidy, such as Turner's syndrome, Klinefelter's syndrome, or trisomy 18, 13, or 21, may develop lymphedema. Syndromic vascular anomalies associated with lymphedema also include Klippel-Trenaunay syndrome and Parkes-Weber syndrome. Other disorders associated with lymphedema include Noonan's syndrome, yellow nail syndrome, intestinal lymphangiectasia syndrome, lymphangiomyomatosis, and neurofibromatosis type 1.

Secondary lymphedema is an acquired condition that results from damage to or obstruction of previously normal lymphatic channels. Recurrent episodes of bacterial lymphangitis, usually caused by streptococci, are a very common cause of lymphedema. The most common etiology of secondary lymphedema worldwide is lymphatic filariasis, affecting >120 million children and adults and causing lymphedema and elephantiasis in 14 million of these affected individuals (Chap. 233). Recurrent bacterial lymphangitis by *Streptococcus* may result in chronic

**TABLE 282-3 Stages of Lymphedema****Stage 0 (or Ia)**

A latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist for months or years before overt edema occurs.

**Stage I**

Early accumulation of fluid relatively high in protein content that subsides with limb elevation. Pitting may occur. An increase in proliferating cells may also be seen.

**Stage II**

Limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Late in stage II, the limb may or may not pit as excess fat and fibrosis supervene.

**Stage III**

Lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

*Source:* Adapted from The 2013 Consensus Document of the International Society of Lymphology: *Lymphology* 46:1, 2013.

dermatitis, hyperpigmentation, and superficial venous varicosities, as described earlier. Other causes of leg swelling that resemble lymphedema are myxedema and lipedema. Lipedema usually occurs in women and is caused by accumulation of adipose tissue in the leg from the thigh to the ankle with sparing of the feet.

**Diagnostic Testing** The evaluation of patients with lymphedema should include diagnostic studies to clarify the cause. Abdominal and pelvic ultrasound and computed tomography (CT) can be used to detect obstructing lesions such as neoplasms. Magnetic resonance imaging (MRI) of the affected limb may reveal a honeycomb pattern characteristic of lymphedema in the epifascial compartment and identify enlarged lymphatic channels and lymph nodes. MRI also is useful to distinguish lymphedema from lipedema. Lymphoscintigraphy and lymphangiography are rarely indicated, but either can be used to confirm the diagnosis or differentiate primary from secondary lymphedema. Lymphoscintigraphy involves the injection of radioactively labeled technetium-containing colloid into the distal subcutaneous tissue of the affected extremity, which is imaged with a scintigraphic camera to visualize lymphatic vessels and lymph nodes. Findings indicative of primary lymphedema include absent or delayed filling of the lymphatic vessels or dermal back flow caused by lymphatic reflux. Findings of secondary lymphedema include dilated lymphatic vessels distal to an area of obstruction. In lymphangiography, iodinated radiocontrast material is injected into a distal lymphatic vessel that has been isolated and cannulated. In primary lymphedema, lymphatic channels are absent, hypoplastic, or ectatic. In secondary lymphedema, lymphatic channels often appear dilated beneath the level of obstruction. The complexities of lymphatic cannulation and the risk of lymphangitis associated with the contrast agent limit the utility of lymphangiography. Optical imaging with a near-infrared fluorescence dye may enable quantitative imaging of lymph flow.

**TREATMENT****Lymphedema**

Patients with lymphedema of the lower extremities must be instructed to take meticulous care of their feet and legs to prevent cellulitis and lymphangitis. Skin hygiene is important, and emollients can be used to prevent drying. Prophylactic antibiotics are often helpful, and fungal infection should be treated aggressively. Patients should be encouraged to participate in physical activity; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or

depression related to body image, self-esteem, functional disability, and fear of limb loss.

Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage used in decongestive physiotherapy for lymphedema involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose. Occasionally, intermittent pneumatic compression devices can be applied at home to facilitate reduction of the edema. Diuretics are contraindicated and may cause depletion of intravascular volume and metabolic abnormalities.

Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy lymphedema. Other surgical interventions are rarely used and often not successful in ameliorating lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility.

Therapeutic lymphangiogenesis has been studied in rodent models of lymphedema. Overexpression of VEGF-C generates new lymphatic vessels and improves lymphedema in a murine model of primary lymphedema, and administration of recombinant VEGF-C or VEGF-D stimulated lymphatic growth in preclinical models of postsurgical lymphedema. There may be additional benefit when administered in conjunction with lymph node transfer. Clinical trials in patients with lymphedema are required to determine efficacy of gene transfer and cell-based therapies for lymphedema.

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Pulmonary hypertension (PH) is a heterogeneous disease involving pathogenic remodeling of the pulmonary vasculature, which increases pulmonary artery pressure and vascular resistance. The most common causes of PH are left heart or primary lung disease; PH is also observed in some patients as a late complication of luminal pulmonary embolism. Pulmonary arterial hypertension (PAH) is an uncommon, but distinct, PH subtype characterized by the interplay between molecular and genetic events that cause an obliterative arteriopathy and symptoms of dyspnea, chest pain, and syncope. If left untreated, PH carries a high mortality rate, largely owing to decompensated right heart failure.

There have been significant advances in the field with regard to understanding disease pathogenesis, diagnosis, and classification. For example, the mean pulmonary artery pressure (mPAP) used to diagnose PH has been lowered from 25 mmHg to >20 mmHg. This adjustment emphasizes earlier detection of PH, as a substantial delay in diagnosis of up to 2 years is common and has important implications for both quality of life and life span. Clinicians should be able to recognize the signs and symptoms of PH and complete a systematic evaluation in at-risk patients. In this way, prompt diagnosis, appropriate treatment, and optimized patient outcome are achievable.

### PATHOBIOLOGY

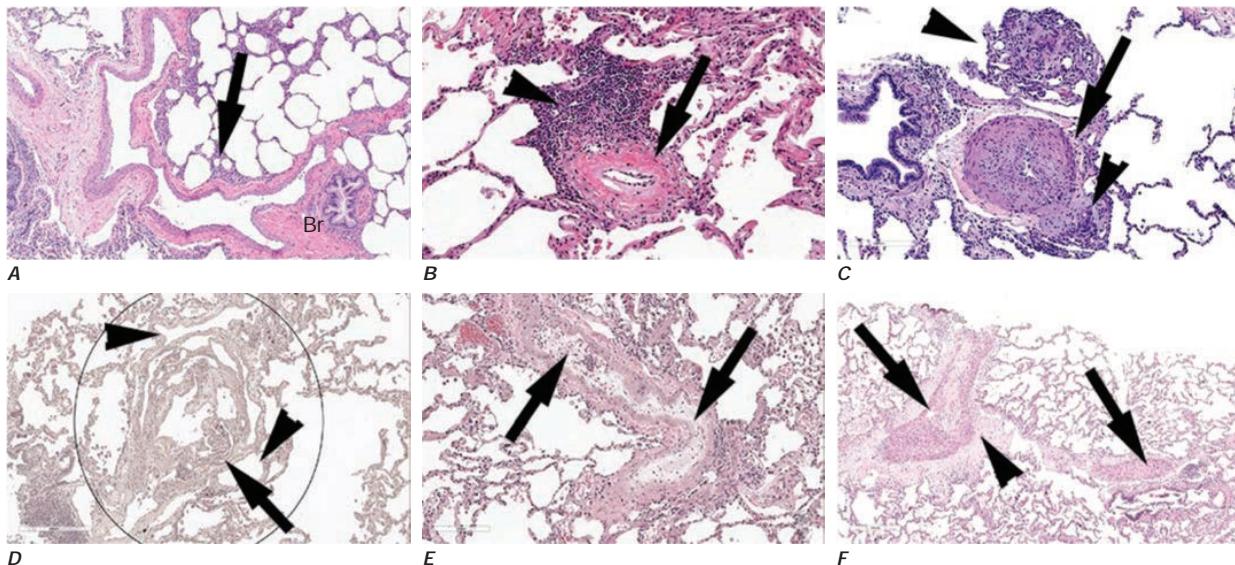
Apoptosis resistance, cell proliferation, dysregulated metabolism, and increased oxidant stress involving pulmonary vascular cells and adventitial fibroblasts underlie the pathogenesis of PAH. These events lead to

hypertrophic, fibrotic, and plexogenic remodeling of distal (small) pulmonary arterioles, which decreases vascular compliance and promotes *in situ* thrombosis (Fig. 283-1). A minority of patients appear to have a vasoconstriction-dominant phenotype, which, if present, requires a unique treatment strategy discussed in greater detail below.

Abnormalities in multiple molecular pathways and genes that regulate pulmonary vascular endothelial and smooth muscle cells have been identified (Table 283-1). These abnormalities include decreased expression of the voltage-regulated potassium channel, mutations in the bone morphogenetic protein receptor-2, increased tissue factor expression, overactivation of the serotonin transporter, hypoxia-induced activation of hypoxia-inducible factor-1 $\alpha$ , and activation of nuclear factor of activated T cells. Recently, overlap in the pathobiology of PAH with solid tumor cancers has been recognized, leading to the identification of pyruvate dehydrogenase kinase and neural precursor cell expressed developmentally downregulated 9 (NEDD9) as important in PAH. Thrombin deposition in the pulmonary vasculature that develops as an independent abnormality or as a result of endothelial dysfunction may amplify the obliterative arteriopathy.

### PATHOPHYSIOLOGY

In PAH, pathologic changes to pulmonary arterial compliance result in a progressive increase in total pulmonary vascular resistance (PVR). The resting PVR increases through the temporal progression of PAH, corresponding to a rise in mPAP. To preserve cardiac output (CO) in the face of elevated right ventricular afterload, right ventricular work must increase. A sustained (or progressive) increase in right ventricular work causes a shift in the efficiency of right ventricular systolic function by which maintaining pulmonary circulatory pressure depletes myocardial energy. These changes occur at the expense of energy normally reserved to maintain optimal blood perfusion through the alveolar-capillary



**FIGURE 283-1** Panels on the left show examples of plexogenic pulmonary arteriopathy. Representative images of a normal lung (A) and examples of pulmonary vascular remodeling in pulmonary arterial hypertension (B–F), including idiopathic pulmonary arterial hypertension (B–E) and pulmonary venoocclusive disease (F), are shown. A. Normal pulmonary artery (arrow) adjacent to a terminal bronchiole (Br). B. Marked media and intima thickening of small vessels (arrow), partly surrounded by lymphoid cells form a cluster reminiscent of a primary follicle (arrowhead). C. Idiopathic pulmonary hypertension lung with a markedly muscularized medium-sized pulmonary artery (arrow), which distally branches into a plexiform lesion (lower arrowhead) and an adjacent plexiform lesion (upper arrowhead). D. Complex vascular lesion (circle) with a combination of telangiectatic-like dilations of the pulmonary artery (arrowheads) and a plexiform lesion (arrow). E. Medium-sized pulmonary artery with complete lumen obliteration with a loose collagen, poorly cellular matrix (arrows). F. Interlobular septal, medium-sized vein (arrowhead) obliterated by loose connective tissue (arrows), likely the result of an organized thrombus, characteristic of venoocclusive disease. (These representative images were provided courtesy of Dr. Rubin Tudor. The samples were obtained through the evaluation of lungs collected by the Pulmonary Hypertension Breakthrough Initiative, with similar pulmonary vascular pathology spectrum as reported in reference E Stacher et al: Modern age pathology of pulmonary arterial hypertension. Am J Respir Crit Care Med 186:261, 2012.) Adapted with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved. Reproduced with permission from BA Maron et al: Pulmonary Arterial Hypertension: Diagnosis, Treatment, and Novel Advances. Am J Respir Crit Care Med 203:1472, 2021.

**TABLE 283-1 Molecular and Genetic Determinants of the Pathogenesis of Pulmonary Arterial Hypertension**

Alterations in regulators of proliferation

- Growth factors
  - PDGF
  - FGF
  - VEGF
  - EGF
- TGF- $\beta$
- BMP
- Transcription factors
- MMPs
- Cytokines
- Chemokines
- Mitochondria

Alterations in mediators of fibrosis

- TGF- $\beta$ 1
- NEDD9
- Programmed death-ligand 1
- ADAMTS8
- Galectin-3

Alterations in inflammatory mediators

- Altered T-cell subsets
- Monocytes and macrophages
- IL-1 $\beta$
- IL-6
- MCP-1
- RANTES
- Fractalkine

Alterations in vascular tone

- Endothelin
- Nitric oxide
- Serotonin
- Prostaglandin
- K<sup>+</sup> channels
- Ca<sup>2+</sup> channels

Hypoxia-induced remodeling

- HIF-1 $\alpha$
- ROS
- Mitochondria

Alterations in TGF- $\beta$  signaling pathways

- BMPR2
- ALK1
- Endoglin (ENG)
- SMAD9
- TGF- $\beta$ 1

Selected genetic risk factors

- BMPR2
- EIF2AK4
- SOX17
- AQP1
- SMAD9
- ENG
- KCNK3
- CAV1

**Abbreviations:** ADAMT, a disintegrin and metalloproteinase with thrombospondin motifs; ALK1, activin receptor-like kinase 1; AQP, aquaporin; BMP, bone morphogenic protein; CAV, caveolin; EGF, epidermal-derived growth factor; EIF2AK4, eukaryotic translation initiation factor 2 alpha kinase 4; FGF, fetal-derived growth factor; HIF-1 $\alpha$ , hypoxia-inducible factor-1; IL, interleukin; KCNK, Potassium two pore domain channel subfamily K member 3; MCP-1, monocyte chemoattractant protein-1; MMP, mucous membrane pemphigoid; NEDD9, neural precursor cell expressed, developmentally downregulated 9; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; SOX, SRY-box transcription factor 17; TGF- $\beta$ , transforming growth factor  $\beta$ ; VEGF, vascular endothelial-derived growth factor.

interface for blood oxygenation, a process termed right ventricular-pulmonary arterial uncoupling. In end-stage PAH, the CO declines, leading to a decrease in mPAP (**Fig. 283-2**), and extrapulmonary vascular manifestations are frequent; these include overactivation of neurohumoral signaling, renal failure, and volitional muscle atrophy, which is likely due to deconditioning (**Fig. 283-3**).

## DIAGNOSIS

The diagnosis of PH can be missed without a reasonable index of suspicion. Indeed, findings from clinical registries suggest that PH is often overlooked, even among patients with numerous risk factors. This shortcoming may be because PH symptoms are nonspecific, insidious, and overlap considerably with many common conditions, such as asthma or left heart failure. Additionally, there is a misconception that in patients with comorbid cardiopulmonary conditions (e.g., interstitial lung disease, mitral valve disease), PH is merely an extension of the underlying disease rather than a specific clinical entity.

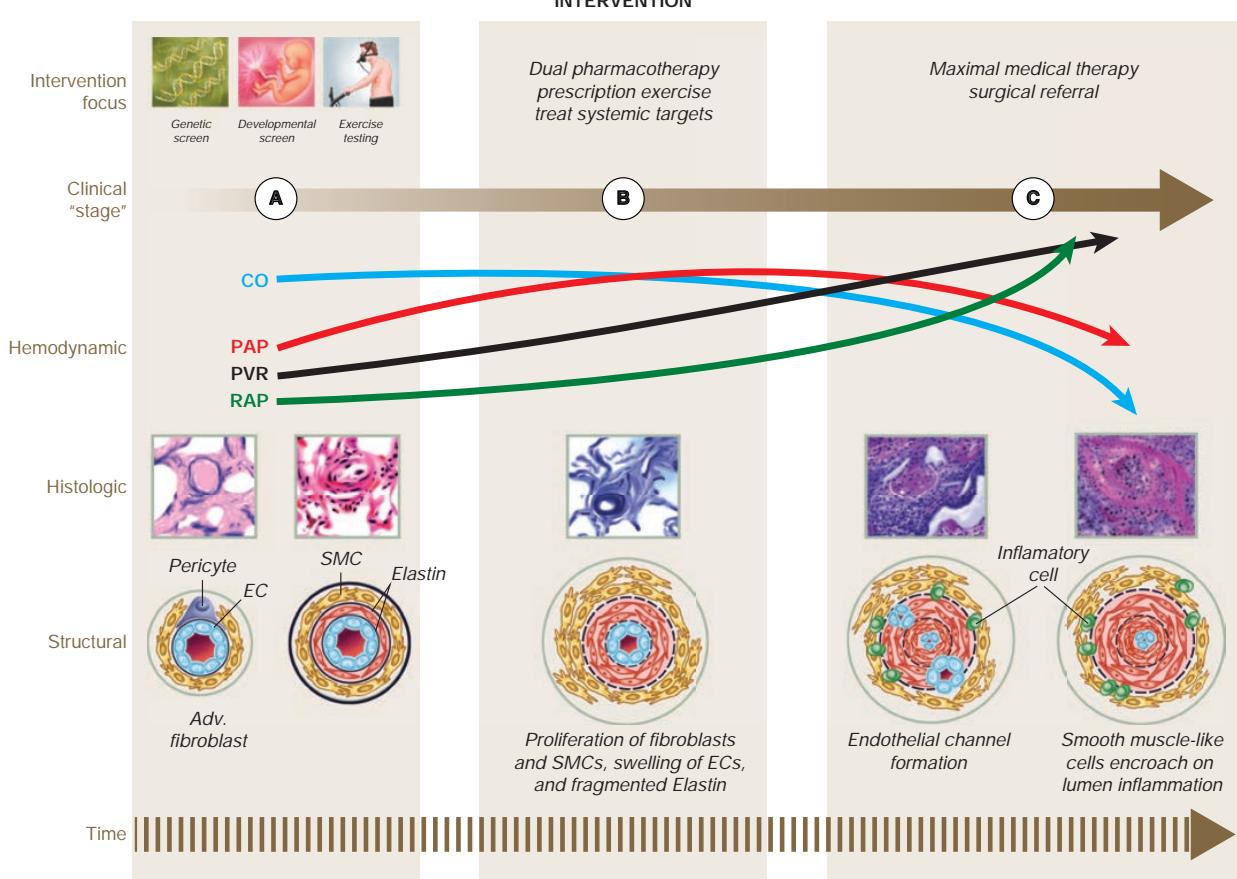
Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and syncope are less common and associated with more advanced disease. In early phases of PAH, the physical examination is often unrevealing. As the disease progresses, there may be evidence of right ventricular failure with elevated jugular venous pressure, lower extremity edema, and ascites. Additionally, the cardiovascular examination may reveal an accentuated P<sub>2</sub> component of the second heart sound, a right-sided S<sub>3</sub> or S<sub>4</sub>, and a holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are commonly concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma (or the limited cutaneous form, CREST [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia]), and crackles on examination of the lungs and systemic hypertension may be clues to left-sided systolic or diastolic heart failure.

**Overview of the Diagnostic Clinical Evaluation** Once clinical suspicion is raised, a systematic approach to diagnosis and assessment is essential. In advanced disease, electrocardiography may show right ventricular hypertrophy or strain, and enlargement of pulmonary arteries and obliteration of the retrosternal space is often observed on chest roentgenography (**Fig. 283-4**). In turn, echocardiography with agitated saline (bubble) study is the most important initial screening test. Elevated estimated pulmonary artery systolic pressure (>35 mmHg) or a hypertrophied or dilated right ventricle support the diagnosis of PH. Important additional information can be gleaned about specific etiologies of PH, such as valvular disease, left ventricular systolic and diastolic function, left atrial enlargement, and intracardiac shunt.

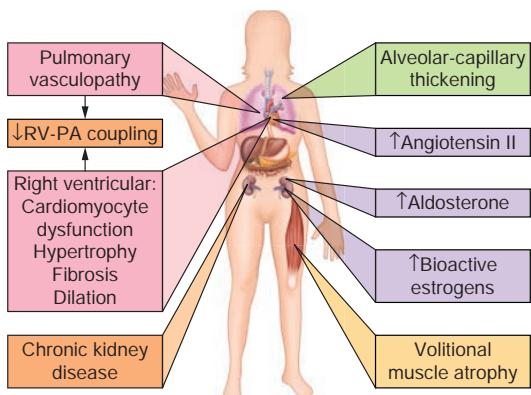
A high-quality echocardiogram that is absolutely normal may obviate the need for further PH evaluation. However, this is distinct from an echocardiogram in which tricuspid regurgitation is not detected. In this scenario, the information required to estimate pulmonary artery pressure is lacking, and PH is observed in one-third of such patients. Patients with evidence of PH on echocardiography or in whom unexplained dyspnea or hypoxemia is evident despite an unremarkable echocardiogram often require further assessment.

Additional tests focusing on functional capacity are useful for quantifying disease burden, such as a 6-minute walk distance (6-MWD) assessment, which also aids in assessing prognosis. Cardiopulmonary exercise testing (CPET) differentiates between cardiac and pulmonary causes of dyspnea and includes measuring peak volume of oxygen consumption, which is an integrated parameter of cardiopulmonary fitness and also useful in prognosticating PH. In patients with a normal CPET, further invasive testing is often unnecessary. One exception to this approach is in patients with reassuring CPET results but in whom a significant decrease in exercise tolerance from baseline is nonetheless reported, often observed in elite athletes or highly conditioned individuals with early-stage PH.

Invasive hemodynamic monitoring with right heart catheterization (RHC) is the gold standard for PH diagnosis and severity assessment. Interpretation of RHC data, however, is often optimized by information from diagnostic tests that support and frame the clinical context of pulmonary vascular disease.



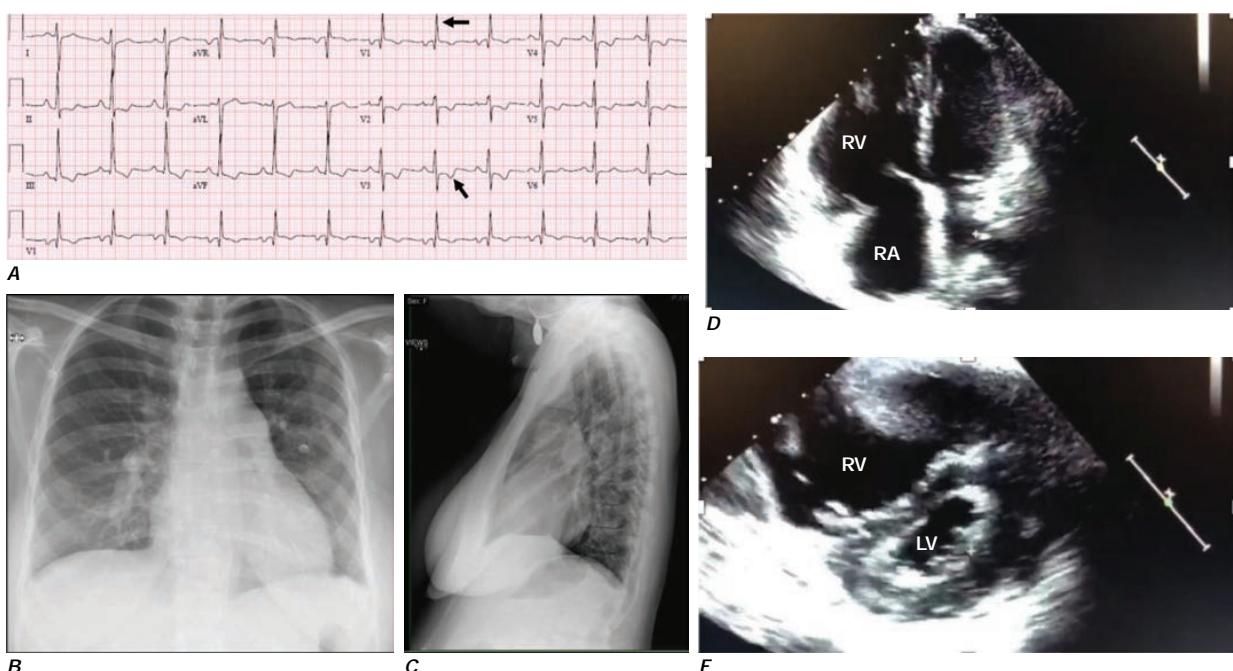
**FIGURE 283-2** An integrated overview of pulmonary arterial hypertension (PAH). In PAH, initial changes in the histopathophenotype of distal pulmonary arterioles precedes significant changes in hemodynamics or the development of symptoms in most patients (clinical stage A). As vascular remodeling progresses, there is an increase in pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP), and right atrial pressure (RAP). In clinical stage B, symptoms are evident and, when diagnosed, prompt early, aggressive treatment. Effacement of pulmonary arterioles results in severely increased PVR that promotes right heart failure, defined by a decrease in cardiac output (CO) and PAP. Patients in clinical stage C have severe symptoms and require full therapeutic intervention. Identifying clinical stage A patients remains challenging, although genetic risk factors or symptoms with exercise may be informative. EC, endothelial cell; SMC, smooth muscle cell. (Reprinted with permission of the American Thoracic Society. Copyright © 2022 American Thoracic Society. All rights reserved. BA Maron, SH Abman, 2017: Translational advances in the field of pulmonary hypertension: Focusing on Developmental Origins and Disease Inception for the Prevention of Pulmonary Hypertension. Am J Respir Crit Care Med 195:292, 2017.)



**FIGURE 283-3** Systemic manifestations of pulmonary arterial hypertension (PAH). In PAH, the vasculopathy is severe and increases pulmonary vascular resistance. This promotes right ventricular-pulmonary arterial uncoupling, which describes inefficient work and energy expenditure by the right ventricle. Systemic manifestations, which are likely secondary to changes in cardiopulmonary hemodynamics, include overactivation of neurohumoral signaling, chronic kidney disease, increased bioactive sex hormones, and volitional muscle atrophy. RV-PA, right ventricular-pulmonary arterial.

**Stepwise Approach to Diagnosing PH** One common PH diagnostic strategy is outlined below; however, the approach should be individualized in practice according to a particular patient's clinical and risk factor profile. For example, patients with a strong history of inhaled tobacco use may benefit from prioritizing diagnostic tests assessing pulmonary function and the lung parenchyma, whereas a myocardial ischemia evaluation should be considered early in the evaluation of patients with left-sided cardiomyopathy.

**PULMONARY FUNCTION AND LUNG IMAGING** Pulmonary function testing results may suggest restrictive or obstructive lung diseases as the cause of dyspnea or PH. In PAH, an isolated reduction in diffusing capacity of the lungs for carbon monoxide ( $Dl_{CO}$ ) is a classic finding. High-resolution computed tomography (CT) provides useful information, particularly enlargement of the main pulmonary artery, right ventricle, and atria, as well as peripheral pruning of small vessels; however, high-resolution CT may also reveal signs of venous congestion, including centrilobular ground glass infiltrate and thickened septa. In the absence of left heart disease, these findings suggest pulmonary venous disease, a rare cause of PAH that can be quite challenging to diagnose. CT is also critical for distinguishing co-morbid interstitial lung disease, emphysema, or overlap syndromes that include fibrosis and obstructive pulmonary disease.



**FIGURE 283-4** Electrocardiography, chest roentgenography, and two-dimensional echocardiography in advanced pulmonary arterial hypertension. **A.** Standard 12-lead electrocardiogram shows peaked R waves in lead  $V_1$  and ST-segment depression in leads  $V_2$ - $V_3$ , suggestive of right ventricular hypertrophy with strain (arrows). **B, C.** Anterior-posterior and lateral chest roentgenogram demonstrating enlargement of central pulmonary arteries and obliteration of the retrosternal space, indicative of right ventricular hypertrophy. **D, E.** Apical four-chamber and two-chamber short axis views acquired by transthoracic echocardiography demonstrate right ventricular (RV) and right atrial (RA) enlargement, as well as interventricular septal flattening in diastole consistent with pressure overload. LV, left ventricle.

**SLEEP STUDIES** Nocturnal desaturation is a common finding in PH, even in the absence of sleep-disordered breathing. Thus, all patients should undergo nocturnal oximetry screening, regardless of whether classic symptoms of obstructive sleep apnea or obesity-hypoventilation syndrome are present.

**ASSESSMENT OF PULMONARY ARTERIAL THROMBOSIS** Patients with prior luminal pulmonary embolism are at increased risk for chronic thromboembolic pulmonary hypertension (CTEPH), which is a specific PH subtype characterized by vascular fibrosis and arterial microthrombus. Although CTEPH is curable in many patients by surgical endarterectomy, it is also widely underdiagnosed. Ventilation-perfusion ( $V/Q$ ) scanning is the primary test used to screen and diagnose CTEPH, which should be considered in any patient with PH of unclear etiology. The role of CT angiography in the diagnosis and management of CTEPH continues to evolve. At present, CT angiography is commonly used to stage anatomic thromboembolic burden, which may be ultimately necessary to determine operative candidacy. The definitive diagnostic procedure remains pulmonary angiography since contrast enhancement in this study provides detailed information on webbing, stricture, and vascular tapering patterns pathognomonic for CTEPH.

**SEROLOGY** Laboratory data that are important for screening include a human immunodeficiency virus (HIV) test when clinically indicated. In addition, all patients should have antinuclear antibodies, rheumatoid factor, and anti-Scl-70 antibodies assessed to screen for the most common rheumatologic diseases associated with PH. Liver function and hepatitis serology tests are important to screen for underlying liver disease. Methamphetamine use is recognized increasingly as a cause of PAH, and screening should be considered in patients from endemic regions or in whom the cause of PAH is not otherwise established. Finally, brain natriuretic peptide (BNP) and the N-terminus of its pro-peptide (NT-proBNP) correlate with right ventricular (dys) function, hemodynamic severity, and functional status in PAH. Medical therapy also lowers NT-proBNP levels in PAH, and therefore this test may be used as a biomarker for assessing treatment response in clinical practice.

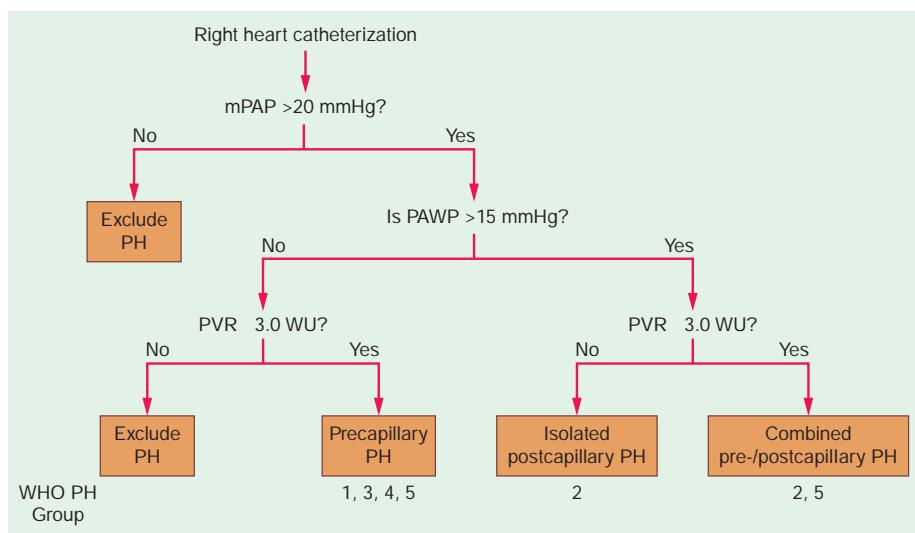
**INVASIVE CARDIOPULMONARY HEMODYNAMICS** The RHC remains the gold standard test to both establish the diagnosis of PH and guide selection of appropriate medical therapy. The hemodynamic criteria for diagnosing PH requires, first, an mPAP  $>20$  mmHg. Precapillary and postcapillary PH are then distinguished by virtue of a pulmonary artery wedge pressure (PAWP) (or left ventricular end-diastolic pressure [LVEDP])  $<15$  mmHg or  $>15$  mmHg, respectively. Isolated precapillary PH also requires a PVR  $>3.0$  Wood units (WU), whereas isolated postcapillary PH is defined by PVR  $<3.0$  WU. Increasingly, combined pre- and postcapillary PH is recognized, defined by elevated mPAP  $>20$  mmHg, PVR  $>3.0$  WU, and PAWP  $>15$  mmHg (Fig. 283-5).

These hemodynamic profiles inform PH clinical categorization. For example, isolated precapillary PH is most often due to primary lung disease, PAH, or CTEPH. Isolated postcapillary PH occurs in patients with mitral valvular disease, left ventricular systolic dysfunction, or heart failure with preserved ejection fraction. The same etiologies for isolated postcapillary PH also underlie combined pre- and postcapillary PH. When present, this indicates that chronic vascular congestion due to left atrial hypertension has resulted in substantial pulmonary vascular remodeling.

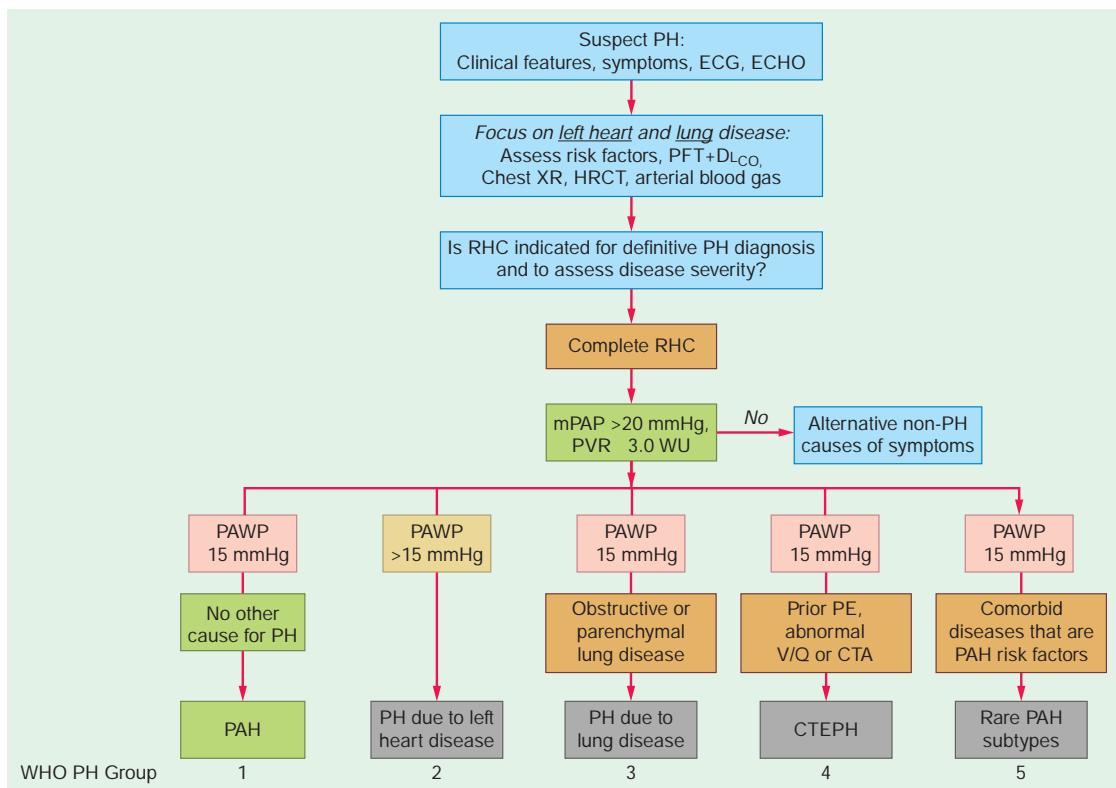
Vasoreactivity testing should be reserved mainly for patients with idiopathic or hereditary PAH. Vasodilators with a short duration of action, such as inhaled nitric oxide (NO $\cdot$ ) or inhaled epoprostenol, are preferred for testing. A decrease in mPAP by  $>10$  mmHg to an absolute level  $<40$  mmHg without a decrease in CO is defined as a positive pulmonary vasodilator response, and such responders are considered for long-term treatment with calcium channel blockers. Less than 5% of patients are deemed vasoreactive, although prognosis among these patients is particularly favorable.

### PULMONARY HYPERTENSION CLASSIFICATION

In 1998, a PH clinical classification schema was formulated, of which PAH (formerly *primary pulmonary hypertension*) is a subgroup, according to similarities in pathophysiologic mechanisms and clinical presentation. The categorization of PH at that time and currently exists for the purpose of facilitating novel treatments to be tested among different presentations (Fig. 283-6). Efforts are underway to define



**FIGURE 283-5** Hemodynamic classification of pulmonary hypertension (PH). Data from right heart catheterization (RHC) exclude PH or inform precapillary, postcapillary, or combined pre-/postcapillary PH phenotypes. These categories, in turn, correspond to World Health Organization (WHO) PH clinical groups as follows: group 1, pulmonary arterial hypertension; group 2, PH from left heart disease; group 3, PH from primary lung disease and sleep-disordered breathing; group 4, chronic thromboembolic pulmonary hypertension; group 5, selected (rare or miscellaneous) causes of PH. mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.



**FIGURE 283-6** Strategy for diagnosing pulmonary hypertension (PH) in clinical practice. A high index of clinical suspicion for PH is raised based on clinical features, symptoms, and findings on transthoracic echocardiography (ECHO). The prevalence of PH is elevated in primary lung or cardiovascular disease; therefore, an initial assessment should be geared toward diagnosing these comorbidities. This may include emphasis on cardiovascular risk factors, pulmonary function testing (PFT), and/or high-resolution computed tomography (HRCT) of the chest. The diagnosis of PH and assessment of disease severity are determined by findings on right heart catheterization (RHC). Classification of PH subtype hinges on hemodynamic parameters and clinical features. Group 2 PH may be evident with  $PVR < 3.0$  WU, as detailed in Fig. 283-5. CTA, computed tomographic angiography; CTEPH, chronic thromboembolic pulmonary hypertension;  $D_{LCO}$ , diffusing capacity of carbon monoxide; ECG, electrocardiogram; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PE, pulmonary embolism; PVR, pulmonary vascular resistance; V/Q, ventilation/perfusion nuclear scan; WHO, World Health Organization; XR, x-ray.

pulmonary vascular diseases based on molecular phenotyping that, in the future, may offer a guide for improved management decisions as precision medicine strategies continue to evolve.

The current classification system, last revised in 2018 during the Sixth World Symposium on Pulmonary Hypertension, recognizes five PH categories listed here sequentially as groups 1–5: PAH; PH due to left heart disease; PH due to chronic lung disease or sleep-disordered breathing; CTEPH; and a group of miscellaneous diseases that rarely (or inconsistently) cause PH.

**Pulmonary Arterial Hypertension** WHO group 1 PH, or PAH, involves marked pulmonary arterial precapillary remodeling, including intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and classic plexiform lesions. The hemodynamic criteria for PAH are sustained elevation in resting mPAP >20 mmHg, PVR 3.0 WU, and PAWP or LVEDP of 15 mmHg based on RHC. Idiopathic PAH (IPAH) is a progressive disease that leads to right heart failure and early mortality. From the original National Institutes of Health registry on IPAH in 1987, the average age at diagnosis was 36 years, with only 9% of patients with IPAH over the age of 60. However, contemporary data now inclusive of numerous international registries suggest a different clinical profile. The mean age of PAH patients is reported to be 54–68 years old across studies. This reflects, in part, rising awareness of this disease in the elderly. The prevalence of IPAH favors women to men by ~3.1-fold; however, the hemodynamics at diagnosis are more severe, and the prognosis is less favorable in men compared to women.

**Diseases Associated with PAH** Other forms of PAH that deserve specific consideration are those associated with congenital heart disease with intracardiac shunt, connective tissue disease, portal hypertension, and HIV.

**CONGENITAL HEART DISEASE** PAH in the setting of congenital heart disease is important to recognize since surgical correction may be indicated and when successful is associated with favorable prognosis. This is particular salient today, as more congenital heart disease patients live to adulthood and populate general medical practices. Still, referral to adult congenital heart disease centers should be considered for patients with suspected PAH, which in this population is subclassified into four groups: Eisenmenger's syndrome, systemic-to-pulmonary shunts, coincidental or small defects causing shunts, and postoperative/closed defects causing shunts. Surgical repair of congenital anatomic lesions may be indicated prior to elevation in PVR >3.0 WU to avoid the development of Eisenmenger's syndrome, a pathophysiologic consequence of progressive pulmonary vascular remodeling due to a large-volume left-to-right shunt that is associated with cyanosis, hyperviscosity, weakness, and shortened life span.

**CONNECTIVE TISSUE DISEASE** Patients with connective tissue disease-associated PAH are encountered relatively commonly in clinical practice. Although case series link rheumatoid arthritis and systemic lupus erythematosus with pulmonary vascular disease, the predominant clinical phenotype is systemic sclerosis-associated PAH. It is important to distinguish patients with limited cutaneous scleroderma from those with diffuse scleroderma because PH in the former is likely PAH and PH in the latter often occurs in the setting of interstitial lung disease. Although the average age of scleroderma onset is between 30 and 50 years old, patients who eventually develop scleroderma-associated PAH tend to be older at the time of scleroderma diagnosis. The development of PAH in scleroderma is particularly worrisome prognostically, although implementation of modern therapies improves outcome.

**PORTOPULMONARY HYPERTENSION** Among patients with established portal hypertension, 2–10% develop portopulmonary hypertension independent of the cause of liver disease. Furthermore, portopulmonary hypertension is observed in patients with nonhepatic etiologies of portal hypertension. A hyperdynamic circulatory state is common, as in most patients with advanced liver disease; however, the same pulmonary vascular remodeling observed in other forms of PAH is seen in the pulmonary vascular bed in portopulmonary hypertension.

It is important to distinguish this process from hepatopulmonary syndrome, which can also manifest with dyspnea and hypoxemia but is pathophysiologically distinct from portopulmonary hypertension in that abnormal vasodilation of the pulmonary vasculature leads to intrapulmonary shunting. Portopulmonary hypertension is an established marker of adverse outcome in the post-liver transplant period with 100% mortality reported in one study among patients with mPAP 50 mmHg.

**HIV-PAH** The true prevalence of HIV-PAH is not known; however, this PAH subtype is an important cause of mortality in the HIV-infected population, and prognosis in these patients is among the least favorable for all PH subgroups. There is no correlation between the stage of HIV infection and the development of PAH.

**Pulmonary Hypertension Associated with Left Heart Disease** Patients with PH due to left ventricular systolic dysfunction, aortic and mitral valve disease, and heart failure with preserved ejection fraction (HFpEF) are classified in WHO group 2. The hallmark of this PH phenotype is elevated left atrial pressure with resulting pulmonary venous hypertension. In left-sided systolic heart failure or HFpEF, even mildly elevated mPAP is associated with adverse clinical outcome. It should be noted that PH in the setting of mitral stenosis or regurgitation is an indication for surgical (or percutaneous) valve intervention.

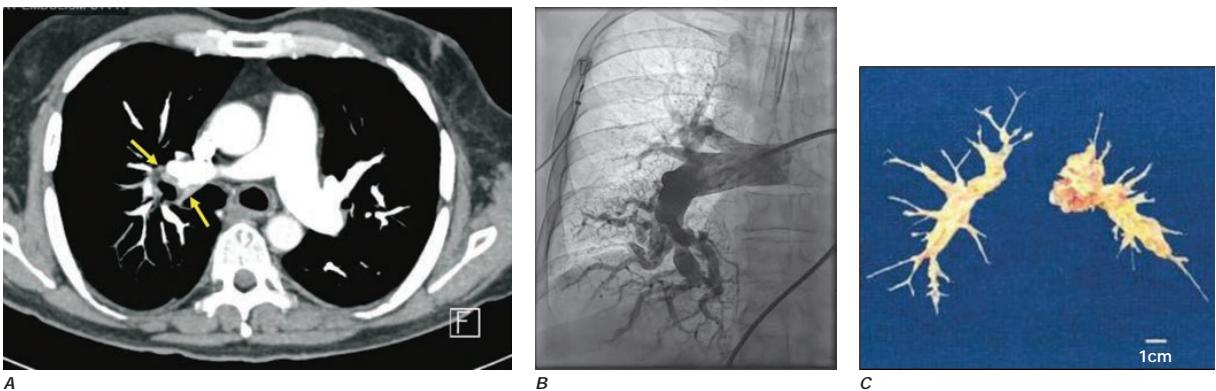
Regardless of the cause of elevated left atrial pressure, the increased pulmonary venous pressure indirectly leads to a rise in pulmonary arterial pressure. Chronic pulmonary venous hypertension leading to a reactive pulmonary arterial vasculopathy is considered in these patients when PVR is 3 WU. Pathologically, this process is marked by pulmonary arteriolar remodeling with intimal fibrosis and medial hyperplasia akin to that seen in PAH, as well as pulmonary venule sclerosis and thickening.

**Pulmonary Hypertension Associated with Lung Disease** Intrinsic lung disease is the second most common cause of PH and has been observed in both chronic obstructive pulmonary disease (COPD) and interstitial lung disease. Additionally, PH is also diagnosed in diseases of mixed obstructive/restrictive pathophysiology: bronchiectasis, cystic fibrosis, mixed obstructive-restrictive disease marked by fibrosis in the lower lung zones, and emphysema predominantly in the upper lung zones. When associated with chronic lung disease, PH is usually modest. For example, 90% of COPD patients have mPAP >20 mmHg, but an mPAP >35 mmHg is observed in only 5% of patients. Nonetheless, the subgroup of patients with primary lung disease and severe PH is challenging clinically, as extensive pulmonary arterial involvement, very low  $\text{DL}_{\text{CO}}$  on pulmonary function testing, and inhibition of normal vasoactivity are observed and are associated with poor outcome. Sleep-disordered syndromes generally result in mild PH.

**Pulmonary Hypertension Associated with Chronic Thromboembolic Disease** The development of PH after chronic thromboembolic obstruction of the pulmonary arteries, termed CTEPH, is well described. The incidence of CTEPH following a single pulmonary embolic event is difficult to determine accurately, but probably is between 3 and 7% of patients. Importantly, 25% of patients with CTEPH have no history of clinical venous thromboembolism, suggesting that CTEPH may develop following a subclinical pulmonary embolism or through a diverse range of mechanisms. Obstruction of the proximal pulmonary vasculature due to webbing, stricture, or focal fibrotic occlusion signifies proximal vessel involvement. Distal pulmonary arterioles remodel by luminal narrowing or obliteration. Approximately 10–15% of patients will develop a disease very similar clinically and pathologically to PAH after resection of the proximal thrombus (Fig. 283-7).

## OTHER DISORDERS AFFECTING THE PULMONARY VASCULATURE

**Sarcoidosis** Patients with sarcoidosis can develop PH as a result of lung involvement, and those who present with progressive dyspnea



**FIGURE 283-7** Chronic thromboembolic pulmonary hypertension (CTEPH) imaging findings and surgical endarterectomy specimen. **A.** Contrast-enhanced computed tomography of the chest shows an obstructive vascular pattern involving segmental pulmonary arteries (yellow arrows) in a 63-year-old man with exertional dyspnea and remote history of pulmonary embolism. **B.** Still image of a pulmonary angiography of the right lung (submaximal injection shown) shows pulmonary artery stricture, webbing, and severe dearborization that is classic for CTEPH. **C.** Fibrotic, chronic clot specimens resected during surgical pulmonary endarterectomy, which is curative in most CTEPH patients. (Panel C is reproduced with permission from IM Lang, M Madani: Update on chronic thromboembolic pulmonary hypertension. *Circulation* 130:508, 2014.)

and PH require a thorough evaluation. In sarcoidosis, PH develops mainly due to granulomatous inflammation of the pulmonary vessels, although mechanical compression of pulmonary arteries by enlarged lymph nodes is also reported.

**Sickle Cell Disease** Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease (and other hemoglobinopathies), including PH, which occurs in 6–10% of patients. The etiology is multifactorial, including hemolysis, hypoxemia, thromboembolism, chronically high CO, and chronic liver disease.

**Schistosomiasis** Globally, schistosomiasis is among the most common causes of PH. The development of PH occurs in the setting of hepatosplenic disease and portal hypertension. Studies suggest that inflammation from the infection triggers maladaptive pulmonary vascular changes. The diagnosis is confirmed by finding the parasite ova in the urine or stool of patients with symptoms, which can be difficult. The efficacy of therapies directed toward PH in these patients is unknown.

### PHARMACOLOGIC TREATMENT OF PAH

Prior to the availability of disease-specific therapy, the 1- and 3-year mortality rates for IPAH or hereditary PAH were 68 and 48%, respectively. In the current era, there are 14 U.S. Food and Drug Administration (FDA)-approved medical therapies for PAH, and standardized treatment strategies have been developed that emphasize early, aggressive pharmacotherapy initiated at a PH specialty clinical center. Among optimally treated patients, the 1- and 3-year survival rates have improved to 91 and 69%, respectively. All medical therapies target the prostacyclin, NO<sup>•</sup>, or endothelin receptor signaling pathways. Drug delivery methods now include oral, inhaled, subcutaneous (including via surgically implanted devices), and intravenous routes.

**Prostanoids** In PAH, endothelial dysfunction and platelet activation cause an imbalance of arachidonic acid metabolites with reduced prostacyclin levels and increased thromboxane A<sub>2</sub> production. Prostacyclin (PGI<sub>2</sub>) activates cyclic adenosine monophosphate (cAMP)-dependent pathways that mediate vasodilation. PGI<sub>2</sub> also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Protein levels of prostacyclin synthase are decreased in pulmonary arteries of patients with PAH. This imbalance of mediators is offset therapeutically by the administration of either exogenous prostacyclin (and analogues, termed prostanoids) or a prostacyclin receptor agonist.

Epoprostenol was the first prostanoid available for the management of PAH. Epoprostenol delivered as a continuous intravenous infusion improves functional capacity and survival in PAH. The efficacy of

epoprostenol in WHO Functional Class (FC) III and IV PAH patients was demonstrated in a clinical trial that showed improved quality of life, mPAP, PVR, 6-MWD, and mortality. Treprostinil has a longer half-life than epoprostenol (~4 h vs ~6 min), which allows for subcutaneous administration. Treprostinil has been shown to improve pulmonary hemodynamics, symptoms, exercise capacity, and survival in PAH. Inhaled prostacyclin provides the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects of infusion catheters (e.g., risk of infection and infusion site reactions). Both inhaled iloprost and treprostinil have been approved for patients with PAH and severe heart failure symptoms. Oral prostacyclin is also efficacious in clinical trials, but the maximal dose is modest and, therefore, generally reserved as a second-line therapy.

Selexipag is an oral nonprostanoid diphenylpyrazine derivative that binds the prostaglandin I<sub>2</sub> (IP) receptor with high affinity. The active metabolite of selexipag has a prolonged half-life in comparison with prostanoid analogues and permits twice-daily dosing. The efficacy of selexipag was evaluated in patients with PAH in New York Heart Association (NYHA) FC II to III on background therapy with either an endothelin-1 (ET-1) receptor antagonist or sildenafil, or both. This trial represents the largest randomized placebo-controlled trial among patients with PAH ever completed, enrolling 1156 patients treated for a median of 1.4 years. Selexipag reduced the risk of hospitalization and the risk of disease progression by 43% ( $p < .0001$ ) compared to those who received placebo. There were no significant differences in mortality between the two study groups, and the side effect profile was similar to that of prostacyclins.

**Endothelin Receptor Antagonists** Endothelin receptor antagonists (ERAs) inhibit the detrimental effects of ET-1, a potent endogenous vasoconstrictor and vascular smooth muscle mitogen. In PAH, ET-1 associates positively with PVR and mPAP, and inversely with CO and 6-MWD. The ET-1 signaling axis is complex and cell type-specific: ET type A (ET<sub>A</sub>) and type B (ET<sub>B</sub>) receptors expressed in pulmonary artery smooth muscle cells mediate vasoconstriction, whereas human pulmonary artery endothelial cells express ET<sub>B</sub> receptors that promote ET-1 clearance and vasodilation through endothelial nitric oxide synthase activation and prostacyclin release.

The three ERAs approved for use in the United States are the non-selective ET<sub>A/B</sub> receptor antagonists bosentan and macitentan and the selective ET<sub>A</sub> antagonist ambrisentan. Studies have shown that bosentan improves hemodynamics and exercise capacity and delays clinical worsening. The randomized, placebo-controlled, phase 3 Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 trial comparing bosentan to placebo demonstrated improved symptoms, 6-MWD, and WHO FC in patients treated with bosentan. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary

**2128** Arterial Hypertension Patients (EARLY) study comparing bosentan to placebo demonstrated improved PVR and 6-MWD in patients with WHO FC II.

Several studies, including the phase 3, placebo-controlled Ambrisentan in Pulmonary Arterial Hypertension, (ARIES)-1 trial, have demonstrated that ambrisentan improves exercise tolerance, WHO FC, hemodynamics, and quality of life in patients with PAH. More recently, the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial randomized 742 PAH patients to receive placebo or macitentan, which is an ET<sub>A/B</sub> antagonist with optimized receptor binding affinity. The majority of patients were on some form of background PAH therapy. Over an average treatment duration of 85 weeks, the hazard ratio for achieving the composite primary endpoint of PAH-related clinical worsening, which included death or disease progression, was decreased by 45% in the 10-mg dose arm.

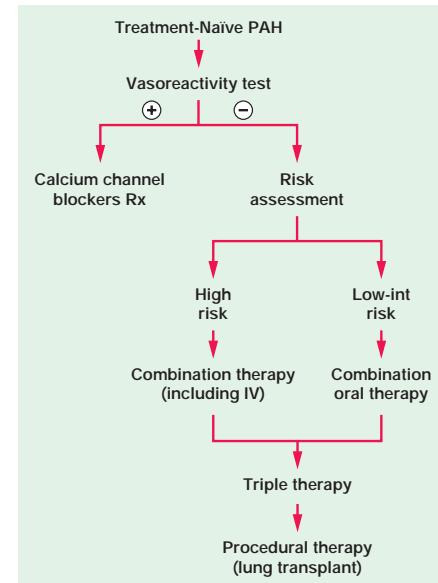
**Nitric Oxide Pathway Effectors** The gaseous, lipophilic molecule NO· is generated by endothelial nitric oxide synthase in endothelial cells and activates soluble guanylyl cyclase (sGC) to generate cGMP in vascular smooth muscle cells and platelets. The cyclic nucleotide cGMP is a second messenger that induces vasodilation through relaxation of arterial smooth muscle cells and inhibits platelet activation. Phosphodiesterase type 5 (PDE-5) enzymes are highly expressed in lung vascular tissue (and the corpus cavernosum of the penis). The PDE-5 inhibitors prevent hydrolysis (inactivation) of cGMP to maximize NO·-dependent vasodilation, serving as the basis for use of this drug class in the treatment of PH (and erectile dysfunction). The two PDE-5 inhibitors used for the treatment of PAH are sildenafil and tadalafil. Both agents have been shown to improve hemodynamics and 6-MWD.

Riociguat increases bioactive cGMP by (1) stabilizing the molecular interaction between NO· and sGC, and (2) directly stimulating sGC independent of NO· bioavailability. Riociguat significantly improved exercise capacity, pulmonary hemodynamics, WHO FC, and time to clinical worsening in patients with PAH and is the sole approved pharmacotherapy for CTEPH patients for whom surgical pulmonary endarterectomy is ineffective or contraindicated.

### APPROACH TO PAH TREATMENT

The approach to PAH treatment has evolved substantially from the prior era in which success was defined by delaying mortality in end-stage disease. Now, treatment aims to achieve a low clinical risk profile, defined as a 1-year mortality risk of <5%. Generally, this describes a patient with minimal symptoms, WHO FC I or II, 6-WMD >440 m, and cardiac index 2.5 L/min per m<sup>2</sup>. To accomplish this goal, most patients will ultimately require two or more PAH pharmacotherapies in addition to risk factor modification (such as a low-sodium diet), diuretic use, supplemental oxygen, and prescription (or supervised) exercise. Combination pharmacotherapy has a number of hypothetical advantages: as multiple pathogenic intermediaries are identified and the neoplastic nature of PAH is recognized increasingly, it is clear that targeting the diverse pathobiologic and pathophysiologic events involved in vascular remodeling is needed to optimize treatment. The concept of combination therapy in PAH is modeled after other complex diseases in which a similar approach has been effective, including HIV, cancer, and heart failure.

The role of early, aggressive therapy with combination oral treatments was addressed in the landmark Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION) trial. Treatment-naïve, incident PAH patients (n = 500) were randomized to a combination of ambrisentan and tadalafil, ambrisentan monotherapy, or tadalafil monotherapy. Up-front combination therapy with ambrisentan and tadalafil was associated with a 50% lower risk of clinical worsening (composite of death, lung transplantation, hospitalization for PAH worsening, and worsening PAH) when compared with the monotherapy groups. This difference was driven primarily by the delay in time to first hospitalization. Importantly, initial combination therapy was not associated with an increase in adverse events. Registry data suggest that patients on dual therapy with a PDE-5 inhibitor plus



**FIGURE 283-8** Treatment strategy overview for patients with newly diagnosed pulmonary arterial hypertension (PAH). Incident, treatment-naïve patients diagnosed with PAH should be assessed with vasoreactivity testing at the time of right heart catheterization. Patients with a positive vasoreactivity test indicating an acute and robust vasodilatory response following administration of nitric oxide (or other approved pulmonary vasodilator) are treated with high-dose oral calcium channel blocker therapy (Rx) and have a favorable prognosis, but compose a minority (<5%) of all PAH patients. Among patients with a negative vasoreactivity study, treatment selection is determined by clinical risk: high-risk patients, such as those with advanced heart failure or syncope, are treated with combination drug therapy, including intravenous prostacyclin therapy. Low- or intermediate (Int)-risk patients are initiated on combination oral therapy, which generally includes an endothelin receptor antagonist and phosphodiesterase type 5 inhibitor. Subsequent add-on therapy (i.e., triple therapy) is considered in patients who deteriorate clinically or fail to improve. Lung transplantation or other surgical strategies are considered in patients with severe PAH refractory to maximal medical treatment.

ERA combinations alternative to the drugs studied in AMBITION also have better outcomes compared to patients treated with monotherapy, suggesting that the attendant benefit from combination therapy may not be drug-specific (**Fig. 283-8**).

The paradigm shift toward early, aggressive pharmacotherapy in PAH is expanding to up-front triple combination therapy. Although limited currently to smaller prospective studies in highly selected patients, initiation of intravenous epoprostenol, bosentan, and sildenafil in one report was associated with sustained clinical and hemodynamic improvement and 100% survival at 3 years.

### UNMET AND FUTURE RESEARCH NEEDS IN PULMONARY HYPERTENSION

Despite substantial gains in quality of life and survival in PAH, elevated patient mortality and limited quality of life remain at unacceptable levels. Improved awareness among clinicians and patients could lead to more timely diagnosis that will affect the response to therapy and survival. Patients should also have the option of referral to a specialty center that focuses on treatment of patients with pulmonary vascular disease, which will ensure their access to state-of-the-art (multidisciplinary) care. Presently, only three classes of therapy exist for patients with PAH, and these do not reverse vascular remodeling sufficiently to provide a definitive long-term (>10 year) clinical benefit. In addition, the role of currently available drugs in early-stage disease is not known and requires further investigation (**Table 283-2**). Treatments that address fibrosis and metabolic changes in pulmonary vascular cells are needed. Finally, disease-specific treatments are lacking for PH due to left heart disease or lung disease. Therefore, developing therapeutics for these large and vulnerable populations is of paramount importance.

**TABLE 283-2 FDA-Approved Therapies for the Treatment of Pulmonary Arterial Hypertension (PAH)**

GENERIC NAME	ROUTE OF ADMINISTRATION	DRUG CLASS	INDICATION
Epoprostenol	IV	Prostacyclin derivative	Treatment of PAH to improve exercise capacity
Iloprost	Inhaled	Prostacyclin derivative	Treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA class), and lack of deterioration
Treprostinil	IV or SC	Prostacyclin derivative	Treatment of PAH to diminish symptoms associated with exercise
Treprostinil	Inhaled	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Treprostinil	Oral	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Selexipag	Oral	Selective IP receptor agonist	Treatment of PAH to improve a composite endpoint lack of clinical deterioration
Bosentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve a composite endpoint of delay of clinical worsening
Sildenafil	Oral or IV	PDE5 inhibitor	Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise ability
Riociguat	Oral	Soluble guanylyl cyclase stimulator	Treatment of PAH to improve exercise ability

Abbreviations: FDA, U.S. Food and Drug Administration; IV, intravenous; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase-5; SC, subcutaneous.

### Acknowledgement

Dr. Aaron Waxman contributed to this chapter in the 20th edition and some material from that chapter has been retained here.

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