many tissues, and certain channelopathies are also associated with skeletal muscle disorders and diabetes. Nevertheless, the most common channelopathies are isolated disorders of the heart, and their most feared consequence is sudden cardiac death (discussed in the next section).

Sudden Cardiac Death

SCD is most commonly defined as unexpected death from cardiac causes, either without symptoms or within 1 to 24 hours of symptom onset (different authors use different criteria); this happens in some 180,000 to 450,000 individuals each year in the United States alone. **The mechanism of SCD is most often a lethal arrhythmia (e.g., asystole or ventricular fibrillation).** Although ischemic injury (and other pathologies) can directly affect the major components of the conduction system, most cases of fatal arrhythmia are triggered by electrical irritability of myocardium distant from the major elements of the conduction system.

CAD is the leading cause of SCD, responsible for the majority of cases; unfortunately, SCD can be the first manifestation of IHD. In such cases, there is typically only chronic severe atherosclerotic disease with fixed critical stenoses; acute plaque disruption is found in only 10% to 20% of cases, and 80% to 90% of patients who suffer SCD but are successfully resuscitated do not show any enzymatic or ECG evidence of myocardial necrosis. Healed remote MIs are present in about 40%, and subendocardial myocyte vacuolization indicative of severe chronic ischemia is a common feature. With the decrease of prevalence of IHD in high income countries, SCD is increasingly being seen in individuals with hearts that are hypertrophic and fibrotic (from hypertension, obesity, substance abuse, etc.) without IHD.

With younger victims, nonatherosclerotic causes are more common etiologies for SCD:

- *Cardiac conduction abnormalities,* hereditary or acquired
- *Dilated* or *hypertrophic cardiomyopathy*
- *Congenital coronary arterial abnormalities*
- *Myocarditis*
- *Mitral valve prolapse*
- *Pulmonary hypertension*
- *Other miscellaneous causes,* such as pericardial tamponade, pulmonary embolism, systemic metabolic and hemodynamic alterations, catecholamines, and drugs of abuse, particularly cocaine and methamphetamine.

The prognosis of patients vulnerable to SCD is markedly improved by pharmaceutical intervention, and particularly by implantation of automatic cardioverter defibrillators that can sense and electrically counteract episodes of ventricular fibrillation.

KEY CONCEPTS

ARRHYTHMIAS

- Arrhythmias can be caused by ischemic or structural changes in the conduction system or by intrinsic myocyte electrical instability. In structurally normal hearts, arrhythmias are often due to mutations in ion channels that cause aberrant repolarization or depolarization.
- SCD typically results from ventricular fibrillation and is most frequently a consequence of CAD. Myocardial irritability typically results from nonlethal ischemia or from preexisting fibrosis from previous myocardial injury. SCD is less often due to acute plaque rupture with thrombosis that induces a rapidly fatal arrhythmia.

HYPERTENSIVE HEART DISEASE

Hypertensive heart disease (HHD) is a consequence of the increased demands placed on the heart by hypertension, causing pressure overload and ventricular hypertrophy. Although most commonly seen in the left heart as the result of systemic hypertension, pulmonary hypertension can cause right-sided HHD, or cor pulmonale.

Systemic (Left-Sided) Hypertensive Heart Disease

Hypertrophy of the heart is an adaptive response to the pressure overload of chronic hypertension. However, such compensatory changes may be ultimately maladaptive and can lead to myocardial dysfunction, myocardial "demand" ischemia, cardiac dilation, CHF, and in some cases sudden death.

The minimal pathologic criteria for the diagnosis of systemic HHD are the following: (1) left ventricular hypertrophy (usually concentric) in the absence of other cardiovascular pathology and (2) a clinical history or pathologic evidence of hypertension in other organs (e.g., kidney). The Framingham Study established unequivocally that even mild hypertension (levels only slightly above 140/90 mm Hg)—if sufficiently prolonged—induces left ventricular hypertrophy; some 30% of the population of the United States suffers from hypertension of at least this degree. More recently, the criteria for diagnosing hypertension were changed; according to the newest guidelines, diastolic pressures above 80 mm Hg, or systolic pressures above 120 mm Hg constitute clinically significant elevations in blood pressure. On that basis, almost one-half of individuals in the general population (!!) are hypertensive. The pathogenesis of hypertension is discussed in Chapter 11.

MORPHOLOGY

Hypertension induces left ventricular pressure overload hypertrophy, initially without ventricular dilation. As a result, the left ventricular wall thickening increases the weight of the heart disproportionately to the increase in overall cardiac size (Fig. 12.19A). The heart weight may exceed 500 g, and the left ventricular wall thickness may exceed 2.0 cm. Over time, the increased thickness of the left ventricular wall, associated with increased interstitial connective tissue, imparts a stiffness that impairs diastolic filling, often leading to left atrial enlargement.

Microscopically, the earliest change of systemic HHD is an increase in the transverse diameter of myocytes, which may be difficult to appreciate on routine microscopy. At a more advanced stage, variable degrees of cellular and nuclear enlargement become apparent, often accompanied by perivascular and interstitial fibrosis.

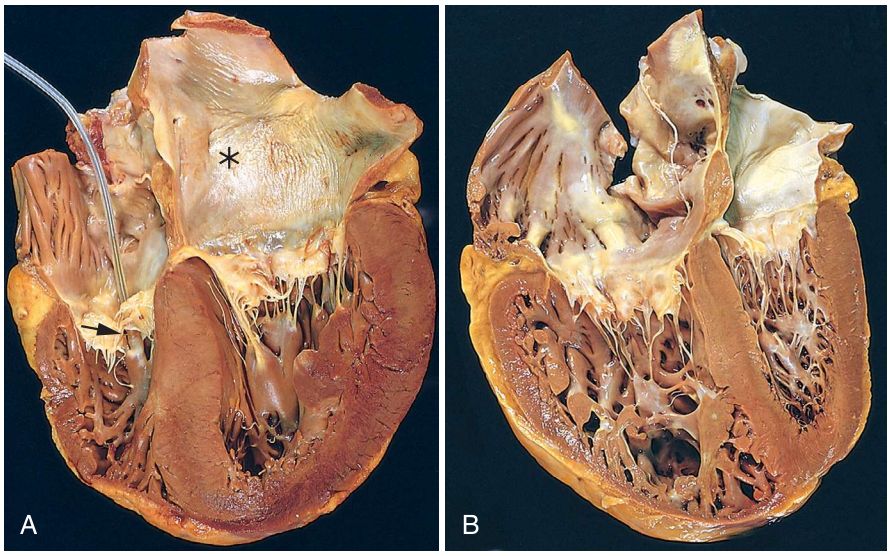

Figure 12.19 Hypertensive heart disease, systemic and pulmonary. (A) Systemic (left-sided) hypertensive heart disease. There is marked concentric thickening of the left ventricular wall causing reduction in lumen size. The left ventricle and left atrium *(asterisk)* are on the *right* in this apical four-chamber view of the heart. A pacemaker is present in the right ventricle *(arrow)*. (B) Pulmonary (right-sided) hypertensive heart disease (cor pulmonale). The right ventricle is markedly dilated and has a thickened free wall and hypertrophied trabeculae (apical four-chamber view of heart, right ventricle on left). The shape of the left ventricle *(to the right)* has been distorted by the enlarged right ventricle.

Compensated systemic HHD may be asymptomatic, producing only electrocardiographic or echocardiographic evidence of left ventricular enlargement. In many patients, systemic HHD comes to attention because of new atrial fibrillation induced by left atrial enlargement, or by progressive CHF. Depending on the severity, duration, and underlying basis of the hypertension, and on the adequacy of therapeutic control, the patient may (1) enjoy normal longevity and die of unrelated causes, (2) develop IHD due to both the potentiating effects of hypertension on coronary atherosclerosis and the ischemia induced by increased oxygen demand from the hypertrophic muscle, (3) suffer renal damage or cerebrovascular stroke as direct effects of hypertension, or (4) experience progressive heart failure or SCD. Effective control of hypertension can prevent cardiac hypertrophy and can even lead to its regression; with normalization of blood pressure, the associated risks of HHD are diminished.

Pulmonary (Right-Sided) Hypertensive Heart Disease (Cor Pulmonale)

Normally, because the pulmonary vasculature is the low-pressure side of the circulation, the right ventricle has a thinner and more compliant wall than the left ventricle. Isolated pulmonary HHD, or cor pulmonale, stems from right ventricular pressure overload. Chronic cor pulmonale is characterized by right ventricular hypertrophy, dilation, and potentially right-sided failure. Typical causes of chronic cor pulmonale are disorders of the lungs, especially chronic parenchymal diseases such as emphysema, and primary pulmonary hypertension (Table 12.7; see also Chapter 15). Acute cor pulmonale can follow massive pulmonary embolism. Nevertheless, it should also be remembered that pulmonary hypertension most commonly occurs as a complication of left-sided heart disease.

MORPHOLOGY

In acute cor pulmonale there is marked dilation of the right ventricle without hypertrophy. On cross-section, the normal crescent shape of the right ventricle chamber is transformed to a dilated ovoid. In chronic cor pulmonale, the right ventricular wall thickens, sometimes up to 1.0 cm or more (see Fig. 12.19B). More subtle right ventricular hypertrophy may take the form of thickening of the muscle bundles in the outflow tract, immediately

Table 12.7 Disorders Predisposing to Cor Pulmonale

Diseases of the Pulmonary Parenchyma
Chronic obstructive pulmonary disease
Diffuse pulmonary interstitial fibrosis
Pneumoconioses
Cystic fibrosis
Bronchiectasis
Diseases of the Pulmonary Vessels
Recurrent pulmonary thromboembolism
Primary pulmonary hypertension
Extensive pulmonary arteritis (e.g., granulomatosis with polyangiitis)
Drug-, toxin-, or radiation-induced vascular obstruction
Extensive pulmonary tumor microembolism
Disorders Affecting Chest Movement
Kyphoscoliosis
Marked obesity (sleep apnea, pickwickian syndrome)
Neuromuscular diseases
Disorders Inducing Pulmonary Arterial Constriction
Metabolic acidosis
Hypoxemia
Chronic altitude sickness
Obstruction of major airways
Idiopathic alveolar hypoventilation

below the pulmonary valve, or thickening of the moderator band, the muscle bundle that connects the ventricular septum to the anterior right ventricular papillary muscle. Sometimes, the hypertrophied right ventricle compresses the left ventricular chamber or leads to regurgitation and fibrous thickening of the tricuspid valve.

KEY CONCEPTS

HYPERTENSIVE HEART DISEASE

- HHD can affect either the left ventricle or the right ventricle; the latter is called cor pulmonale. Elevated pressures induce myocyte hypertrophy and interstitial fibrosis that increases wall thickness and myocardial stiffness.
- The chronic pressure overload of systemic hypertension causes left ventricular concentric hypertrophy, often associated with left atrial dilation due to impaired diastolic filling of the ventricle. Persistently elevated pressure overload can cause ventricular failure with dilation.
- Cor pulmonale results from pulmonary hypertension due to primary lung parenchymal or vascular disorders. There is commonly right ventricular and right atrial hypertrophy; right ventricular and atrial dilation can occur.

VALVULAR HEART DISEASE

Valvular disease can come to clinical attention due to stenosis, insufficiency (synonyms: regurgitation or incompetence), or both.

- *Stenosis* is the failure of a valve to open completely, obstructing forward flow. Acquired valvular stenosis is almost always due to a primary leaflet abnormality and is virtually always a chronic process (e.g., calcification or valve scarring).
- *Insufficiency* results from failure of a valve to close completely, thereby allowing regurgitation (backflow) of blood. Valvular insufficiency can result from either intrinsic disease of the valve leaflets (e.g., endocarditis) or disruption of the supporting structures (e.g., the aorta, mitral annulus, tendinous cords, papillary muscles, or ventricular free wall) without primary leaflet injury. It can appear abruptly, as with chordal rupture, or insidiously as a consequence of leaflet scarring and retraction.

Stenosis or insufficiency can occur alone or together in the same valve. Valvular disease can involve only one valve (the mitral valve being the most common target) or more than one valve. Abnormal flow through diseased valves typically produces abnormal heart sounds called murmurs; severe lesions can even be externally palpated as thrills. Depending on the valve involved, murmurs are best heard at different locations on the chest wall; moreover, the nature (regurgitation versus stenosis) and severity of the valvular disease determines the quality and timing of the murmur (e.g., harsh systolic or soft diastolic murmurs).

The clinical consequences of valve dysfunction vary depending on the valve involved, the degree of impairment, the tempo of disease onset, and the rate and quality of compensatory mechanisms. For example, sudden destruction of an aortic valve cusp by infection (infectious endocarditis; see later) can cause acute, massive, and rapidly fatal aortic regurgitation. In contrast, rheumatic mitral stenosis typically develops indolently over years, and its clinical effects can be well tolerated for extended periods. Certain conditions can complicate valvular heart disease by increasing the demands on the heart; for example, the increased output demands of pregnancy can exacerbate valve disease and lead to unfavorable maternal or fetal outcomes. Valvular stenosis or insufficiency often produces secondary changes, both proximal and distal to the affected valve, particularly in the myocardium. Generally, valvular stenosis leads to pressure overload cardiac hypertrophy, whereas valvular insufficiency leads to volume overload; both situations can culminate in heart failure. In addition, the ejection of blood through narrowed stenotic valves can produce high speed "jets" of blood that injure the endothelium or endocardium where they impact.

Valvular abnormalities can be congenital (discussed earlier) or acquired. Acquired valvular stenosis is almost always a consequence of a remote or chronic injury of the valve leaflets that declares itself clinically only after many years. In contrast, acquired valvular insufficiency can result from intrinsic disease of the valve leaflets or damage to or distortion of the supporting structures (e.g., the aorta, mitral annulus, tendinous cords, papillary muscles, ventricular free wall).

The causes of acquired heart valve diseases are summarized in Table 12.8. The most frequent causes of the major valvular lesions are as follows:

- *Aortic stenosis:* calcification and sclerosis of anatomically normal or congenitally bicuspid aortic valves
- *Aortic insufficiency:* dilation of the ascending aorta, often secondary to hypertension and/or aging
- *Mitral stenosis:* rheumatic heart disease (RHD)
- *Mitral insufficiency:* myxomatous degeneration (MVP), or left ventricular dilation due to ischemic or nonischemic heart failure

Calcific Valvular Degeneration

Heart valves are subjected to high levels of repetitive mechanical stress, particularly at the hinge points of the leaflets; this is a consequence of (1) millions of cardiac contractions per year, (2) substantial tissue deformations during each contraction, and (3) transvalvular pressure gradients in the closed phase of each contraction of approximately 120 mm Hg for the mitral and 80 mm Hg for the aortic valve. It is therefore not surprising that these delicate structures can suffer cumulative damage and calcification that lead to clinically important dysfunction.

Calcific Aortic Stenosis

The most common of all valvular abnormalities, calcific aortic stenosis is usually the consequence of age-associated "wear and tear" of either anatomically normal valves or congenitally bicuspid valves (found in approximately 1% of the population). The prevalence of aortic stenosis is estimated at 2% and is increasing as the general population ages. Aortic stenosis of previously normal valves (termed degenerative calcific aortic stenosis) usually comes to clinical attention in the seventh to ninth decades of life, whereas