Valvular Heart Disease

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8

Chapter Outline

This chapter describes the pathophysiologic abnormalities in patients with common valvular heart diseases. Each condition is discussed separately because unifying principles do not govern the behavior of all stenotic or regurgitant valves. Effective patient management requires accurate identification of the valve lesion, a determination of its severity, and a clear understanding of the pathophysiologic consequences and natural history of the condition.

The evaluation of a patient with suspected valvular disease begins at the bedside with a careful history and physical examination from which the trained clinician can usually identify the type of abnormality present. Definitive diagnosis is most often achieved with transthoracic echocardiography (TTE), which allows for staging of disease severity. In selected patients, additional investigation with exercise testing or cardiac catheterization may be necessary to fully define the significance of the condition and guide therapy.

Management of patients with heart valve disease often involves serial clinical and echocardiographic assessments. Pharmacologic therapy is sometimes prescribed for symptomatic improvement, but recognition of timely indications for valve repair or replacement is essential, as will be described for each valve lesion.

MITRAL VALVE DISEASE

Mitral Stenosis

Etiology

By far, the most common underlying cause of mitral stenosis (MS) is prior rheumatic fever (see Box 8-1). Approximately 50% to 70% of patients with symptomatic MS provide a history of acute rheumatic fever occurring, on average, 20 years before presentation. Other rare etiologies of MS include calcification of the mitral annulus that extends onto the leaf ets, infective

BOX 8-1 Rheumatic Fever

Acute rheumatic fever (ARF) is an inf ammatory condition that primarily affects the heart, skin, and connective tissues. Its incidence has waned greatly in the past century in industrialized societies, where it is now rare, but it remains a major burden in developing countries. ARF arises as a complication of pharyngitis caused by group A beta-hemolytic streptococci and mainly aff icts children and young adults. During prior epidemics, approximately 3% of patients with acute streptococcal pharyngitis developed ARF 2 to 3 weeks after the initial throat infection. Common presenting symptoms are chills, fever, fatigue, and migratory arthritis. The cardinal clinical manifestations that establish the diagnosis are known as **Jones criteria** (see Table below).

Involvement of the heart is thought to result from autoimmune cross-reactivity between bacterial and cardiac antigens. Pathologically, carditis (cardiac inf ammation) aff icts all layers of the heart (pericardium, myocardium, and endocardium). Histopathologic examination may demonstrate **Aschoff bodies**, areas of focal fibrinoid necrosis surrounded by inf ammatory cells (see Figure) that later resolve to form fibrous scar tissue. During the acute episode, carditis may cause tachycardia, impaired ventricular contractility, a pericardial friction rub, and transient heart murmurs that ref ect turbulent f ow across inf amed valve leaf ets. Treatment of the acute episode includes high-dose aspirin to reduce inf ammation and penicillin to eliminate residual streptococcal infection.

The most important sequela of ARF is chronic rheumatic heart disease (RHD) characterized by permanent deformity and impairment of one or more cardiac valves. Symptoms of valvular dysfunction, however, do not manifest until 10 to 30 years after ARF has subsided. This latency period may be shorter with more aggressive disease sometimes observed in developing countries. RHD affects the mitral valve in almost all cases, the aortic valve in 20% to 30%, and rarely the tricuspid valve as well. Stenosis and/or regurgitation of each valve can result.

Management of RHD includes prophylaxis against recurrent streptococcal infection and treatment of the chronic valve lesions. Recurrences of ARF can incite further cardiac damage, so individuals with ARF should receive preventive low-dose penicillin prophylaxis at least until early adulthood, by which time exposure and susceptibility to streptococcal infections have diminished.

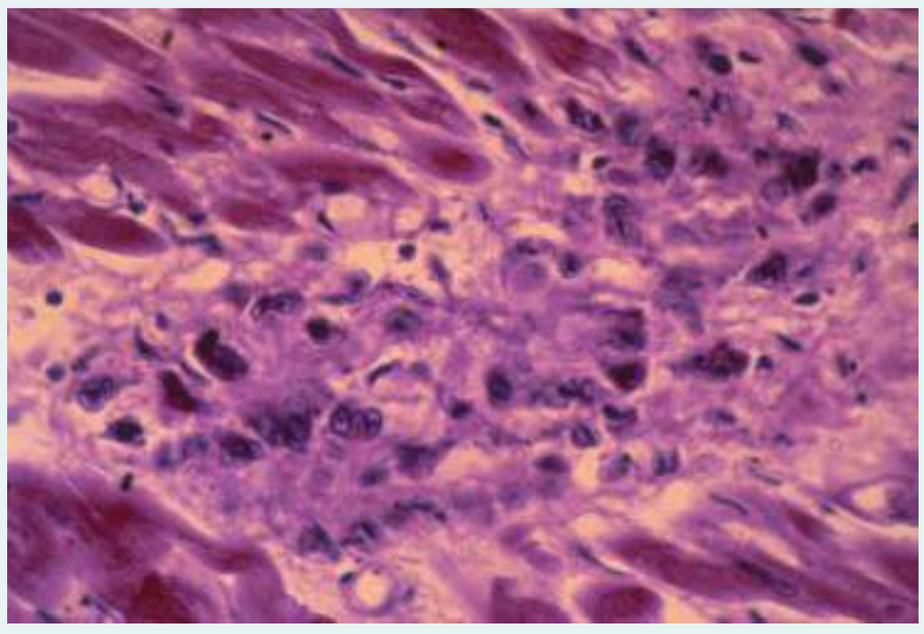

Figure. Histopathology of an Aschoff body in acute rheumatic carditis. Mononuclear inf ammatory cells surround a center of focal necrosis. (Courtesy of Dr. Frederick J. Schoen, Brigham and Women's Hospital, Boston.)

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BOX 8-1 Rheumatic Fever (continued)

Criteria for Diagnosis of Rheumatic Fever[a]

Major criteria
Carditis (inflammation of all three heart layers)
Migratory arthritis (mainly large joints)
Sydenham chorea (involuntary movements)
Erythema marginatum (skin rash with advancing edge and clearing center)
Subcutaneous nodules
Minor criteria
Arthralgias
Fever
Elevated acute-phase reactants (ESR, CRP)
Prolonged PR interval on electrocardiogram
Evidence of group A streptococcal infection
Antistreptolysin O antibodies
Positive throat culture or rapid antigen test

[a]Diagnosis requires evidence of streptococcal infection and either: two major criteria or one major plus two minor criteria.

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

endocarditis with large vegetations that obstruct the valve orifice, and rare congenital stenosis of the valve.

Pathology

Acute and recurrent inflammation produces the typical pathologic features of MS due to rheumatic heart disease. These include fibrous thickening and calcification of the valve leaflets, fusion of the commissures (the borders where the leaflets meet), and thickening and shortening of the chordae tendineae.

Pathophysiology

In early diastole in the normal heart, the mitral valve opens and blood flows freely from the left atrium (LA) into the left ventricle (LV), such that there is a negligible pressure difference between the two chambers. In MS, however, there is obstruction to blood flow across the valve such that emptying of the LA is impeded and there is an abnormal pressure gradient between the LA and LV (Figs. 8-1 and 8-2). As a result, the left atrial pressure increases. Hemodynamic changes become apparent when the cross-sectional area of the valve, normally 4 to 6 cm^2, is reduced to less than 2 cm^2.

The high left atrial pressure in MS is transmitted retrograde to the pulmonary circulation, resulting in increased pulmonary venous and capillary pressures (see Fig. 8-1). This elevation of hydrostatic pressure in the pulmonary vasculature may cause transudation of plasma into the lung interstitium and alveoli. The patient may therefore experience dyspnea and other symptoms of heart failure (as described in Chapter 9). In severe cases, significant elevation of pulmonary venous pressure leads to the opening of collateral channels between the pulmonary and bronchial veins. Subsequently, an engorged bronchial vein may rupture into a bronchus, resulting in hemoptysis (coughing up blood).

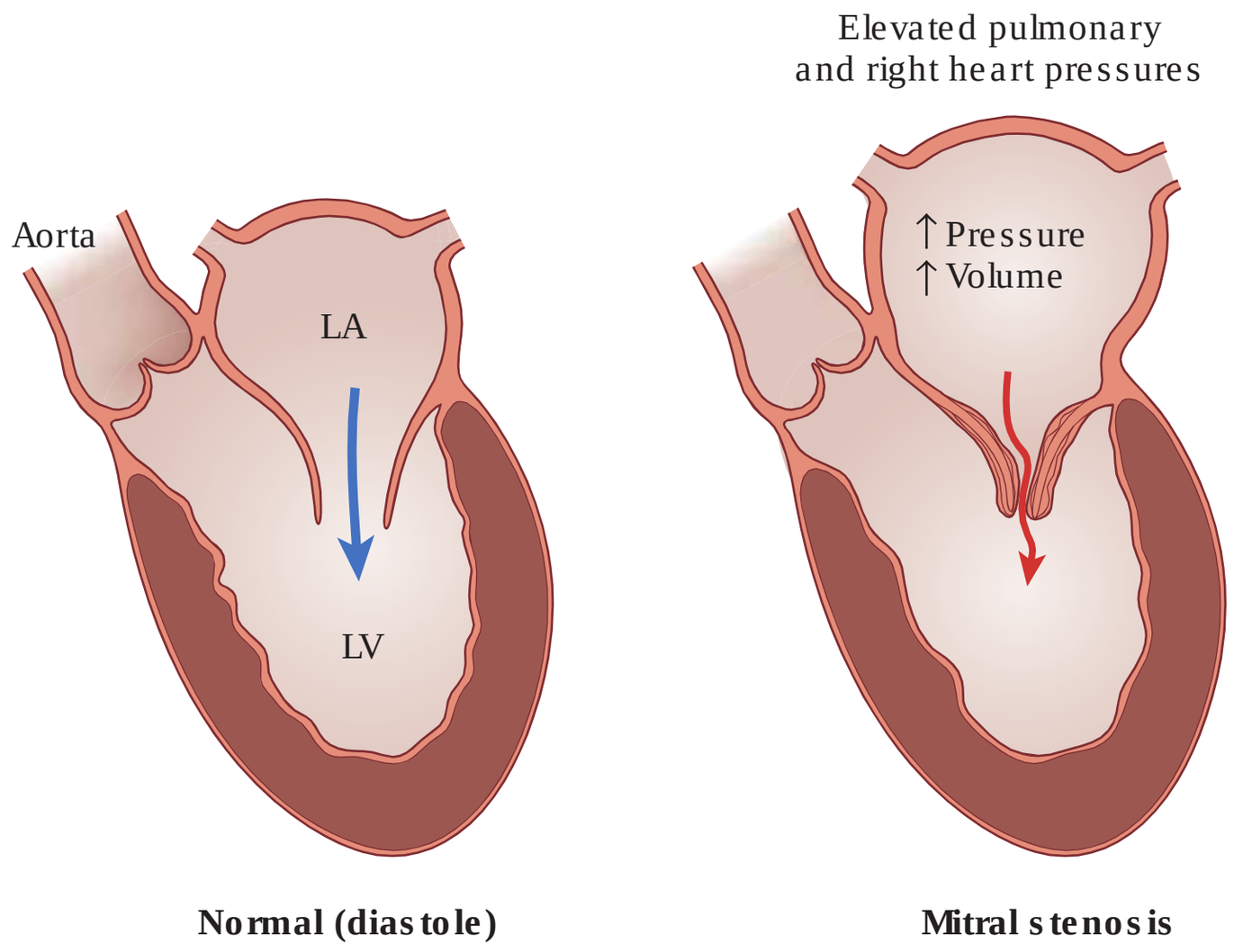


FIGURE 8-1. Pathophysiology of mitral stenosis. In the normal heart, blood flows freely from the left atrium (LA) into the left ventricle (LV) during diastole (blue arrow). In mitral stenosis, there is obstruction to LA emptying (red arrow). Thus, the LA pressure increases, which in turn elevates pulmonary and right heart pressures.

The elevation of left atrial pressure in MS can result in two distinct forms of pulmonary hypertension: passive and reactive. Most patients with MS exhibit passive pulmonary hypertension, related to the backward transmission of the elevated LA pressure into the pulmonary vasculature as described in the previous paragraph. This actually represents an "obligatory" increase in pulmonary artery pressure that preserves forward flow in the setting of increased left atrial and pulmonary venous pressures. Additionally, approximately 40% of patients with MS demonstrate reactive pulmonary hypertension with medial hypertrophy and intimal fibrosis of the pulmonary arterioles. Reactive pulmonary hypertension initially serves a "beneficial" role because the increased arteriolar resistance impedes blood flow into the engorged pulmonary capillary bed and thus reduces capillary hydrostatic pressure (thereby "protecting" the pulmonary capillaries from even higher pressures). However, this benefit is at the cost of decreased blood flow through the pulmonary vasculature and elevation of the right-sided heart pressures, as the right ventricle pumps against the increased resistance. Chronic

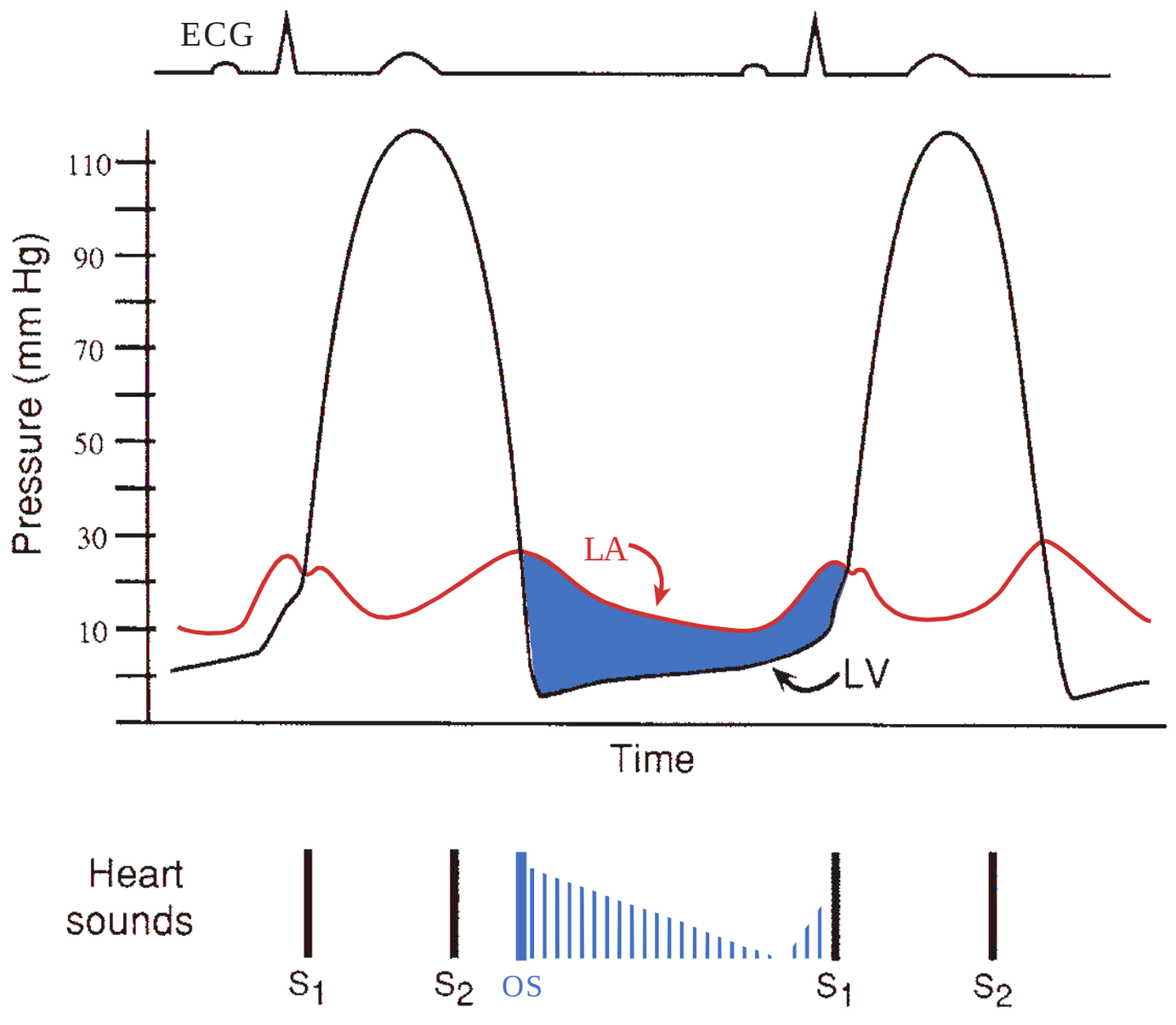


FIGURE 8-2. Hemodynamic profile of mitral stenosis. The left atrial (LA) pressure is elevated, and there is a pressure gradient (shaded area) between the LA and left ventricle (LV) during diastole. Compare with schematic of normal tracing (see Fig. 2-1). Abnormal heart sounds are present: there is a diastolic opening snap (OS) that corresponds to the opening of the mitral valve, followed by a decrescendo murmur. There is an accentuation of the murmur just before S_1 owing to the increased pressure gradient when the LA contracts in patients in sinus rhythm (presystolic accentuation).

elevation of right ventricular pressure leads to hypertrophy and dilatation of that chamber and ultimately to right-sided heart failure.

Chronic pressure overload of the LA in MS leads to left atrial enlargement. Left atrial dilatation stretches the atrial conduction fibers and may disrupt the integrity of the cardiac conduction system, resulting in atrial f brillation (a rapid irregular heart rhythm; see Chapter 12). Atrial fibrillation contributes to a decline in cardiac output in MS because the increased heart rate shortens diastole. This reduces the time available for blood to f ow across the obstructed mitral valve to fill the LV, and, at the same time, further augments the elevated left atrial pressure. In addition, with atrial fibrillation, there is a loss of the late diastolic atrial contraction that normally contributes to LV filling.

The relative stagnation of blood f ow in the dilated LA in MS, especially when combined with the development of atrial fibrillation, predisposes to intra-atrial thrombus formation. Thromboemboli to the brain and other organs may follow, leading to devastating complications such as cerebrovascular occlusion (stroke). Thus, MS patients who develop atrial fibrillation require chronic anticoagulation therapy.

The consequences of MS primarily affect the left atrium and the pulmonary vasculature, as described above. Left ventricular pressures are usually normal, but impaired filling of the chamber through the stenotic valve may reduce LV stroke volume and cardiac output.

Clinical Manifestations and Evaluation

Presentation

The natural history of MS is variable. Survival exceeds 80% in asymptomatic or minimally symptomatic patients at 10 years. However, the 10-year survival of untreated patients after onset of symptoms is only 50-60%. Longevity is much more limited for patients with advanced symptoms and is dismal for those who develop significant pulmonary hypertension, with a mean survival of less than 3 years.

The clinical presentation of MS depends largely on the degree of reduction of the valve area. The more severe the stenosis, the greater the symptoms related to elevation of left atrial and pulmonary venous pressures. The earliest manifestations are those of dyspnea and reduced exercise capacity. In mild MS, dyspnea may be absent at rest; however, it develops on exertion as LA pressure rises with the exercise-induced increase in blood f ow through the heart and faster heart rate (i.e., decreased diastolic filling time). Other conditions and activities that augment heart rate and cardiac blood f ow and precipitate or exacerbate symptoms of MS include fever, anemia, hyperthyroidism, pregnancy, rapid arrhythmias such as atrial fibrillation, emotional stress, and sexual intercourse.

With more severe MS (i.e., a smaller valve area), dyspnea occurs even at rest. Increasing fatigue and more severe signs of pulmonary congestion, such as orthopnea and paroxysmal nocturnal dyspnea (described in Chapter 9), occur. With advanced MS and pulmonary hypertension, signs of right-sided heart failure ensue, including jugular venous distention, hepatomegaly, ascites, and peripheral edema. Compression of the recurrent laryngeal nerve by an enlarged pulmonary artery or LA may cause hoarseness (known as Ortner syndrome).

Less often, the diagnosis of MS is heralded by one of its complications: atrial fibrillation, thromboembolism, infective endocarditis, or hemoptysis, as described in the earlier section on Pathophysiology.

Examination

On examination, there are several typical findings of MS. Palpation of the chest may reveal a right ventricular “tap” in patients with increased right ventricular pressure. Auscultation discloses a loud S_1 (the first heart sound, which is associated with mitral valve closure) in the early stages of the disease. The increased S_1 results from the high pressure gradient between

the atrium and ventricle, which keeps the mobile portions of the mitral valve leaflets widely separated throughout diastole; at the onset of systole, ventricular contraction abruptly slams the leaflets together from a relatively wide position, causing the closure sound to be more prominent (see Chapter 2). In late stages of the disease, the intensity of S_1 may normalize or become reduced as the valve leaflets thicken, calcify, and become less mobile.

A main feature of auscultation in MS is a high-pitched "opening snap" (OS) that follows S_2. The OS is thought to result from the sudden tensing of the chordae tendineae and stenotic leaflets on opening of the abnormal valve. The interval between S_2 and the OS relates inversely to the severity of MS. That is, the more severe the MS, the higher the LA pressure and the earlier the valve is forced open in diastole. The OS is followed by a low-frequency decrescendo murmur (termed diastolic rumble) caused by turbulent flow across the stenotic valve during diastole (see Fig. 8-2). The duration, but not the intensity, of the diastolic murmur relates to the severity of MS. The more severe the stenosis, the longer it takes for the LA to empty and for the gradient between the LA and LV to dissipate. Near the end of diastole, contraction of the LA in patients in sinus rhythm causes the pressure gradient between the LA and LV to rise again (see Fig. 8-2); therefore, the murmur briefly becomes louder at that time (termed presystolic accentuation). This final accentuation of the murmur does not occur if atrial fibrillation has developed because there is no effective atrial contraction in that situation.

Murmurs caused by other valve lesions are often found concurrently in patients with MS. For example, mitral regurgitation (discussed later in this chapter) frequently coexists with MS. Additionally, right-sided heart failure caused by severe MS may induce tricuspid regurgitation as a result of right ventricular enlargement. A diastolic decrescendo murmur along the left sternal border may be present owing to coexistent aortic regurgitation (because of rheumatic involvement of the aortic leaflets) or pulmonic regurgitation (because of MS-induced pulmonary hypertension).

The electrocardiogram in MS routinely shows left atrial enlargement and, if pulmonary hypertension has developed, right ventricular hypertrophy. Atrial fibrillation may be present. The chest radiograph reveals left atrial enlargement, pulmonary vascular redistribution, interstitial edema, and Kerley B lines resulting from edema within the pulmonary septae (see Chapter 3). With the development of pulmonary hypertension, right ventricular enlargement and prominence of the pulmonary arteries appear.

Echocardiography is of major diagnostic value in MS. Structural findings include thickened mitral leaflets with abnormal fusion of their commissures and restricted separation during diastole. The degree of left atrial enlargement can be quantified, and if present, intra-atrial thrombus may be visualized. The mitral valve area can be measured directly on cross-sectional views or calculated from Doppler velocity measurements (a technique known as the "diastolic pressure half-time"). Patients can be stratified into stages of disease severity based partly on the mitral valve area. A normal mitral valve orifice measures between 4 and 6 cm^2. Current guidelines define clinically important "severe" MS as a valve area ≤ 1.5 cm^2, a state that is typically accompanied by LA enlargement and elevated pulmonary artery systolic pressure. A valve area ≤ 1.0 cm^2 is termed "very severe" MS. If the findings determined by echocardiography seem milder than the patient's history and examination suggest, an exercise test with accompanying Doppler assessment, or cardiac catheterization may be warranted to further define hemodynamic measurements.

Treatment

Salt intake restriction and diuretic therapy may improve symptoms due to vascular congestion. Heart rate slowing agents, such as β-blockers or nondihydropyridine calcium channel blockers (e.g., diltiazem or verapamil, see Chapter 17), increase diastolic LV filling time and therefore ease symptoms that occur during exercise. These drugs, or digoxin, are similarly useful to slow the ventricular rate in patients with accompanying rapid atrial fibrillation.

Anticoagulant therapy to prevent thromboembolism is recommended for MS patients with atrial fibrillation, or an identified atrial thrombus, or prior embolic events.

Percutaneous or surgical valve interventions are the only treatments that alter the natural history of MS and are indicated in patients with severe, symptomatic MS. Percutaneous balloon mitral valvuloplasty is the treatment of choice in appropriately selected patients (those without advanced anatomic deformity of the valve, mitral regurgitation, or left atrial thrombus). During this procedure, a balloon catheter is advanced from the femoral vein into the right atrium, across the atrial septum (by intentionally puncturing the interatrial septum), and through the narrowed mitral valve orifice. The balloon is then rapidly inf ated, thereby "cracking" open the fused commissures. The short- and long-term results of this procedure are typically excellent and compare favorably with those of surgical treatment in anatomically appropriate patients. In young adults with the most suitable anatomy for the procedure, the event-free survival rate approaches 80% to 90% over 3 to 7 years of follow-up. Approximately 5% of patients undergoing balloon mitral valvuloplasty are left with a residual atrial septal defect due to the transseptal puncture. Less frequent complications include cerebral emboli at the time of valvuloplasty, cardiac perforation by the catheter, or the unintentional creation of substantial mitral regurgitation.

Open mitral valve commissurotomy (an operation in which the stenotic commissures are separated under direct visualization) may be undertaken in patients for whom percutaneous balloon valvuloplasty is not feasible or successful. It is effective in relieving obstruction, and restenosis occurs in fewer than 20% of patients over 10 to 20 years of follow-up. Perioperative mortality rates are low (2%). Mitral valve replacement is considered in patients who are not appropriate candidates for balloon valvuloplasty or open commissurotomy.

Mitral Regurgitation

Etiology

The mitral valve apparatus is a complex structure composed of an annulus, two leaf ets, chordae tendineae, and papillary muscles, supported by the adjacent myocardium to which the annulus and papillary muscles are attached (Fig. 8-3). Disruption to the structural integrity of any of these components or their coordinated action can result in abnormal closure of the valve during systole, with ensuing mitral regurgitation (MR). MR is categorized as

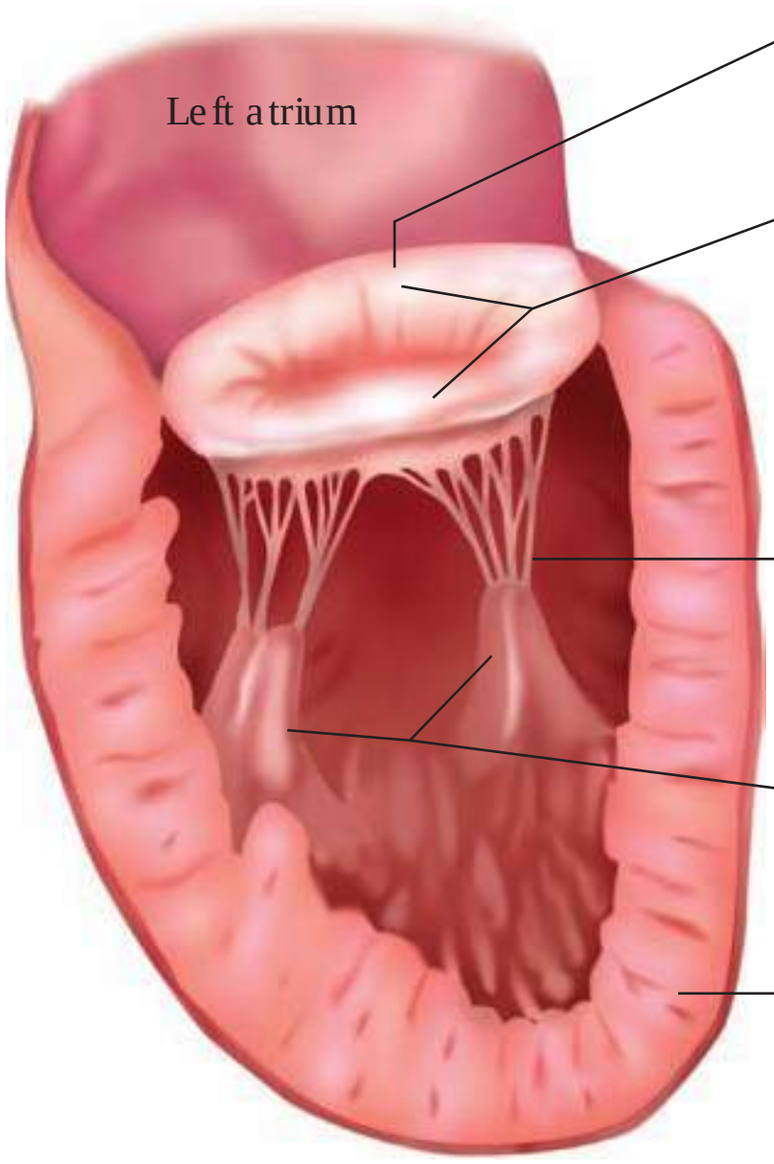


FIGURE 8-3. The mitral valve apparatus and associated common etiologies of mitral regurgitation. MVP, mitral valve prolapse; SAM, systolic anterior motion.

primary if it is due to a structural defect of one or more of the valve components, or secondary if the valve is structurally normal, but regurgitation instead results from left ventricular enlargement. In the latter case, MR arises from abnormal coaptation and closure of the mitral leaflets owing to dilatation of the mitral annulus by the enlarged LV, and/or spatial separation of the papillary muscles, which places traction of the chordae and attached leaflets. Furthermore, depending on the nature of the valvular insult, MR can present as an "acute" or "chronic" condition, with different pathophysiologic consequences.

Most cases of acute MR are primary in nature and result from sudden damage to components of the valve apparatus. For example, rupture of an infarcted papillary muscle can occur within days of an acute ST-segment elevation MI, often resulting in severe MR (see Chapter 7). Acute MR due to sudden rupture of chordae tendineae can result from infective endocarditis, blunt trauma to the chest, or from degeneration of the chordae owing to connective tissue disorders such as Marfan syndrome.

Chronic MR has multiple primary causes, including myxomatous degeneration of the valve, in which "floppy" leaflets allow regurgitation to occur by bowing excessively into the LA during systole (termed "mitral valve prolapse" and described in the next section). Other causes of chronic primary MR include rheumatic deformity of the valve, congenital valve defects, and extensive calcification of the mitral annulus, which prevents normal movement of the valve leaflets, thus interfering with valve closure.

Secondary (also termed "functional") chronic MR results from LV enlargement and/or dysfunction as described above, as may occur with prior myocardial infarction, chronic ischemic heart disease, or dilated cardiomyopathy (see Chapter 10).

Pathophysiology

In MR, a portion of the left ventricular stroke volume is ejected backward into the low-pressure LA during systole (Fig. 8-4). As a result, the forward cardiac output (into the aorta) is less than the LV's total output (forward flow plus backward leak). Therefore, the

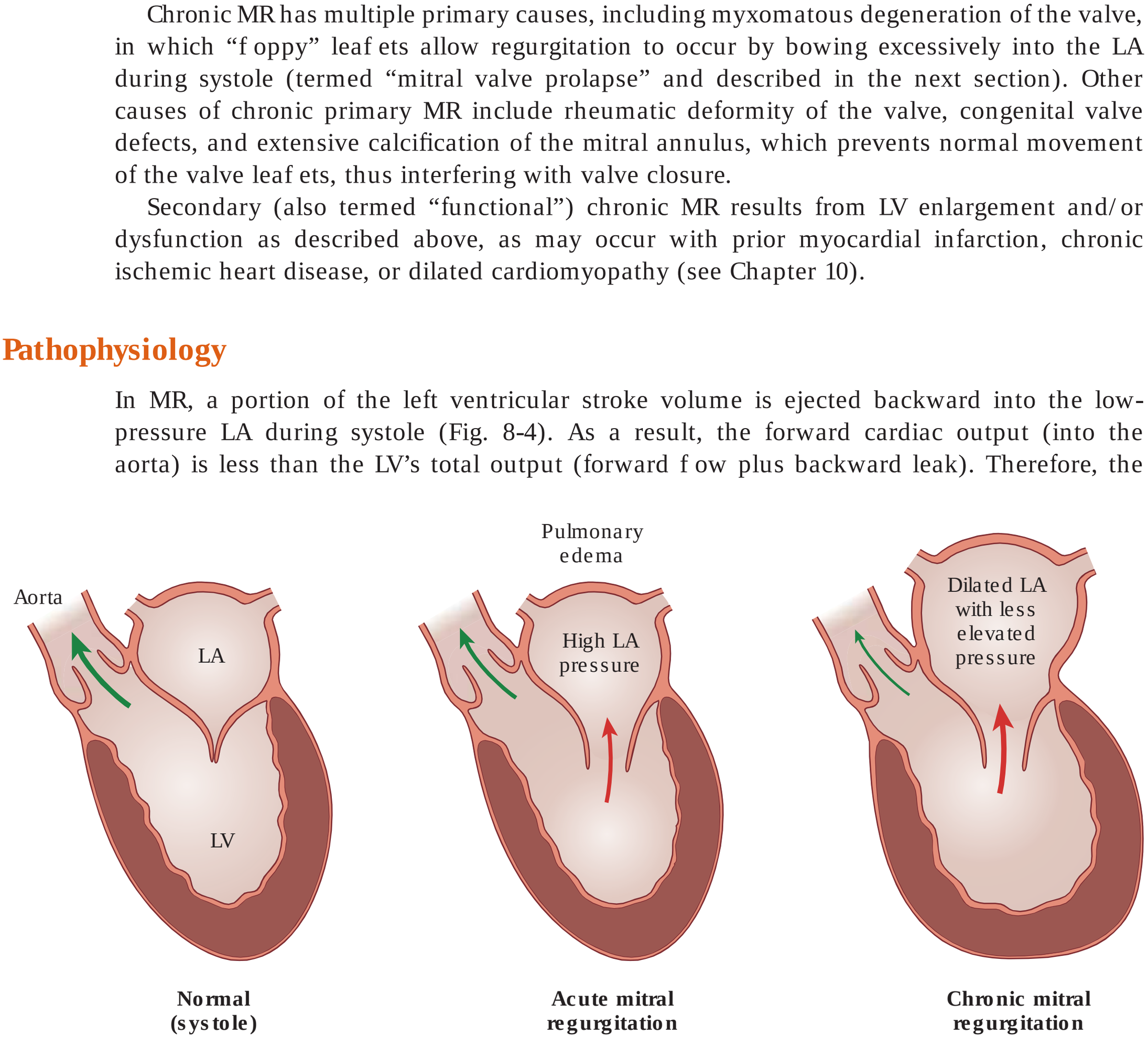


FIGURE 8-4. Pathophysiology of mitral regurgitation. In the normal heart, left ventricular (LV) contraction during systole forces blood exclusively through the aortic valve into the aorta (green arrow); the closed mitral valve prevents regurgitation into the left atrium (LA). In mitral regurgitation (MR), a portion of LV output is forced backward into the LA (red arrows), so that forward cardiac output into the aorta is reduced. In acute MR, the LA is of normal size and is relatively noncompliant, such that the LA pressure rises significantly and pulmonary edema may result. In chronic MR, the LA has enlarged and is more compliant, so that the LA pressure is less elevated and pulmonary congestive symptoms are less common. The LV enlargement and the eccentric hypertrophy result from the chronically elevated volume load.

direct consequences of MR include (1) an elevation of left atrial volume and pressure, (2) a reduction of forward cardiac output, and (3) a volume-related stress on the LV because the regurgitant volume returns to the LV in diastole along with the normal pulmonary venous return. To meet normal circulatory needs and to eject the additional volume, LV stroke volume must rise. This increase is accomplished by the Frank–Starling mechanism (see Chapter 9), whereby the elevated LV diastolic volume augments myofiber stretch and stroke volume. The hemodynamic consequences of MR vary depending on the degree of regurgitation and how long it has been present.

The severity of MR and the ratio of forward cardiac output to backward f ow are dictated by five factors: (1) the size of the mitral orifice during regurgitation, (2) the systolic pressure gradient between the LV and LA, (3) the systemic vascular resistance opposing forward LV blood f ow, (4) left atrial compliance, and (5) the duration of regurgitation with each systolic contraction.

The regurgitant fraction in MR is defined as follows:

$$\frac{\text{Volume of MR}}{\text{Total LV stroke volume}}$$

This ratio rises whenever the resistance to aortic outf ow is increased (i.e., blood follows the path of least resistance). For example, high systemic blood pressure or the presence of aortic stenosis will increase the regurgitant fraction. The extent to which left atrial pressure rises in response to the regurgitant volume is determined by the left atrial compliance. Compliance is a measure of the chamber's pressure–volume relationship, ref ecting the ease or difficulty with which the chamber can be filled (see Table 9.1).

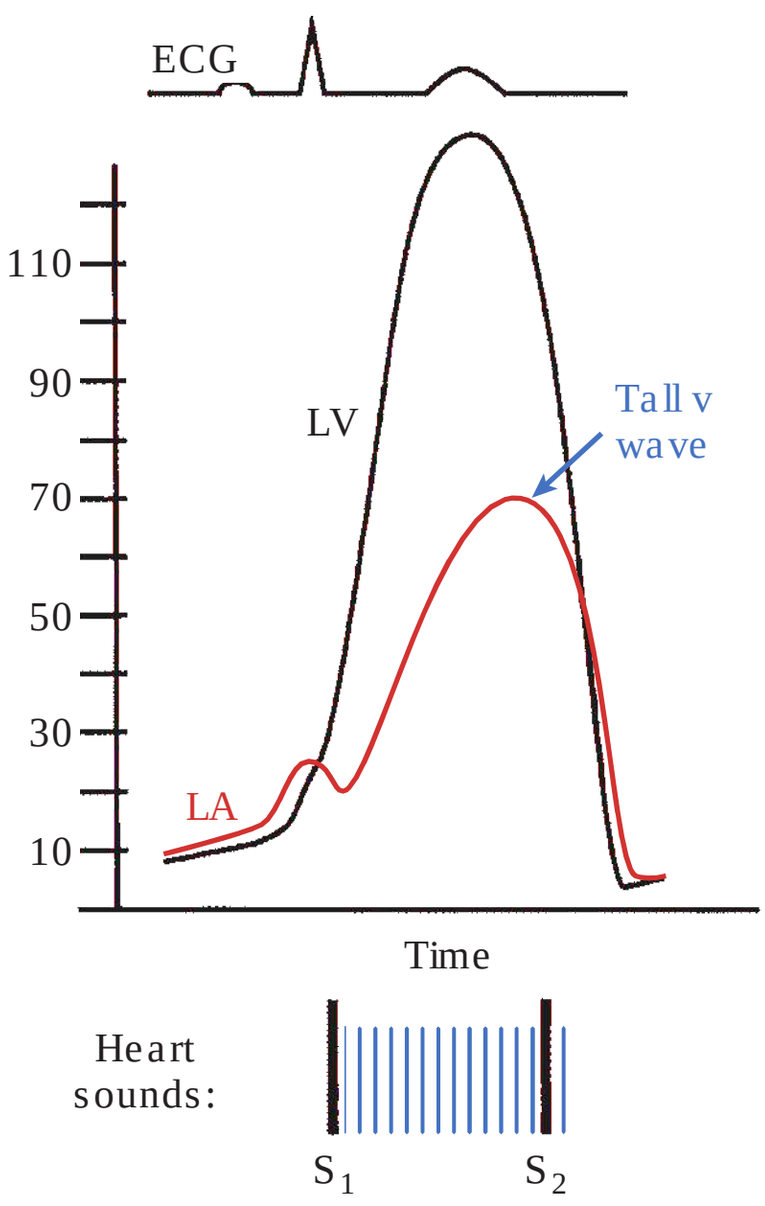


FIGURE 8-5. Hemodynamic prof le of mitral regurgitation (MR). A large systolic v wave is noted in the left atrial (LA) pressure tracing. A holosystolic murmur is present in chronic MR (as shown here), beginning at the first heart sound (S_1) and continuing through the second heart sound (S_2). In acute severe MR, the systolic murmur may actually have a decrescendo quality, ref ecting rapid equilibration of LV and LA pressures owing to the relatively low LA compliance. ECG, electrocardiogram; LV, left ventricle.

In acute MR, left atrial compliance undergoes little immediate change. Because the LA is a relatively stiff chamber, its pressure increases substantially when it is suddenly exposed to a regurgitant volume load (see Fig. 8-4). This elevated pressure is transmitted backward to the pulmonary circulation and can result in rapid pulmonary congestion and edema, a medical emergency.

In acute MR, the LA pressure, or the pulmonary capillary wedge pressure (an indirect measurement of LA pressure; see Chapter 3), demonstrates a prominent v wave (often referred to as a "cv" wave when it merges with the preceding c wave), ref ecting the increased LA filling during systole (Fig. 8-5). Additionally, as in MS, pulmonary artery and right-heart pressures passively rise.

In acute MR, the LV accommodates the increased volume load returning from the LA according to the Frank–Starling relationship. The result is a compensatory increase in the LV stroke volume and ejection fraction, such that at the end of each systolic contraction, LV volume remains normal in the nonfailing heart. Systolic emptying of the ventricle is facilitated in MR by the reduced total impedance to LV contraction (i.e., the afterload is lower than normal), since a portion of the LV output is directed into the relatively low-impedance LA, rather than into the higher-pressure aorta.

In contrast to the acute situation, the more gradual development of chronic MR permits the LA to undergo compensatory

changes that lessen the effects of regurgitation on the pulmonary circulation (see Fig. 8-4). In particular, the LA dilates and its compliance increases such that the chamber is able to accommodate a larger volume without a substantial increase in pressure. Left atrial dilatation is therefore adaptive in that it prevents significant increases in pulmonary vascular pressures. However, this adaptation occurs at the cost of reduced forward cardiac output, because the compliant LA becomes a preferred low-pressure "sink" for left ventricular ejection, compared with the aorta. Consequently, as progressively larger fractions of blood regurgitate into the LA, symptoms of chronic MR include those of low forward cardiac output (e.g., weakness and fatigue). In addition, chronic left atrial dilatation predisposes to the development of atrial fibrillation.

Thus, major pathophysiologic differences between acute and chronic MR relate to a great extent to left atrial size and compliance (see Fig. 8-4):

Acute MR: Normal LA size and compliance → High LA pressure → High pulmonary venous pressure → Pulmonary congestion and edema

Chronic MR: Increased LA size and compliance → Relatively normal LA and pulmonary venous pressures, but decreased forward cardiac output

In chronic MR, the LV also undergoes gradual compensatory dilatation in response to the volume load through eccentric hypertrophy (see Chapter 9). Compared with acute MR, the resulting increased ventricular compliance accommodates the augmented filling volume with relatively normal diastolic pressures. Forward output in chronic MR is preserved to near-normal levels for an extended period by maintaining a higher stroke volume via the Frank–Starling mechanism. Over years, however, chronic volume overload results in deterioration of systolic ventricular function, a decline in forward output, and symptoms of heart failure.

Clinical Manifestations and Evaluation

Presentation

As should be clear from the pathophysiology discussion, patients with acute MR usually present with symptoms of pulmonary edema (see Chapter 9). The symptoms of chronic MR are predominantly due to low cardiac output, especially during exertion, and include fatigue and weakness. Patients with severe MR or those who develop LV contractile dysfunction often complain of dyspnea, orthopnea, and/or paroxysmal nocturnal dyspnea. In chronic severe MR, symptoms of right heart failure (e.g., increased abdominal girth, peripheral edema) may develop as well.

Examination

The physical examination of a patient with chronic MR typically reveals an apical holosystolic (also termed pansystolic) murmur that often radiates to the axilla. The holosystolic nature of the murmur reflects the continued pressure gradient between LV and LA throughout systole (see Fig. 8-5). This description, accurate for rheumatic MR, has several exceptions. For example, in patients with isolated posterior mitral leaflet prolapse, the regurgitant jet is directed anteriorly. In this setting, the murmur may instead radiate to the base of the heart and could be confused with the murmur of aortic stenosis (AS) in that location. Fortunately, the distinction between the systolic murmur of MR and that of AS can be made by simple bedside maneuvers. If the patient is instructed to clench his/her fists and forearms, systemic vascular resistance will increase and the murmur of MR will intensify, whereas the murmur of AS will not. Even more helpful in this distinction is the effect of varying cardiac cycle length (the time between consecutive heart beats) on the intensity of the systolic murmur. In a patient with atrial fibrillation or with frequent premature beats, the LV fills to a degree that

directly depends on the preceding cycle length (i.e., a longer cycle length permits greater left ventricular filling). The systolic murmur of AS becomes louder in the beat after a long cycle length because even small pressure gradients are amplified as more blood is ejected across the reduced aortic orifice. In MR, however, the intensity of the murmur does not vary significantly because the change in the LV-LA pressure gradient is minimally affected by alterations in the cycle length. In addition to the systolic murmur, a common finding in chronic MR is the presence of an S_3, which reflects increased volume returning to the LV in early diastole (see Chapter 2). Additionally, in chronic MR, the cardiac apical impulse is often laterally displaced toward the axilla because of LV enlargement.

In patients with severe acute MR, the character of the systolic murmur is often different, occurring in early to mid systole with a decrescendo quality. The length and quality of the murmur are dictated by the systolic pressure gradient between the left ventricle and the relatively noncompliant left atrium. That is, as the LA pressure rises in systole in acute MR, the LV and LA pressures quickly equalize, thus truncating the murmur. Patients with acute MR often display signs of pulmonary congestion.

The chest radiograph may display pulmonary edema in acute MR but in chronic asymptomatic MR more likely demonstrates left ventricular and atrial enlargement, without pulmonary congestion. Calcification of the mitral annulus may be seen if that is the cause of the MR. In chronic MR, the electrocardiogram typically demonstrates left atrial enlargement and signs of left ventricular hypertrophy. Echocardiography can often identify the structural cause of MR and assess its severity. Cardiac catheterization is used to identify accompanying coronary artery disease and left ventriculography can confirm MR severity. The characteristic hemodynamic finding is a large v wave in the pulmonary capillary wedge pressure tracing (reflective of LA pressure—see Chapter 3). The v wave becomes less conspicuous, however, with progressive LA dilatation and greater compliance over time.

Natural History and Treatment

Acute severe MR is a surgical emergency with a poor prognosis, even with appropriate treatment, with a 30-day mortality rate of 20% to 25%. The natural history of chronic MR is related to its underlying cause. For example, in RHD, the course is one of very slow progression with a 15-year survival rate of 70%. On the other hand, abrupt worsening of chronic MR of any cause can occur with superimposed complications, such as rupture of chordae tendineae or endocarditis, and can result in an immediate life-threatening situation.

The treatment of acute MR almost always requires surgical intervention. Pharmacologic therapy is useful only to stabilize patients until surgery. For example, intravenous nitroprusside is a potent vasodilator that decreases arterial resistance, thereby augmenting forward flow and diminishing the regurgitant volume. In this way, cardiac output and pulmonary congestion may improve at least transiently. Surgical intervention consists of either mitral valve repair (reconstruction of the native valve as described below) or replacement, depending on the underlying cause and valve anatomy.

Management of chronic MR depends on the etiology. In chronic primary MR, the continuous left ventricular volume overload can slowly impair left ventricular contractile function, ultimately, resulting in heart failure. Medical treatment with vasodilators is less useful than in acute MR and has not been shown to delay the need for valve surgery in chronic MR. Surgical intervention should be undertaken in symptomatic patients, or at the earliest sign of LV contractile dysfunction on imaging studies (e.g., a fall in EF to $< 60\%$ by echocardiography) even before symptoms develop. Surgical intervention is also sometimes recommended for patients

with chronic asymptomatic severe primary MR with recent onset atrial fibrillation or findings of pulmonary hypertension.

Surgical options for chronic MR include mitral valve repair or replacement. Mitral valve repair is the preferred operative technique when feasible, and involves the reconstruction of parts of the valve responsible for the regurgitation. For example, a perforated leaf et may be patched with transplanted autologous pericardium, or ruptured chordae may be reattached to a papillary muscle. Mitral repair preserves native valve tissue, and eliminates many of the problems associated with artificial valves described later in the chapter. In patients who undergo repair, the postoperative survival rate appears to be better than the natural history of MR and has provided impetus toward earlier surgical intervention. Operative mortality rates for unselected patients with MR in the Society for Thoracic Surgeons database are less than 2% for mitral valve repair and 5% to 7% for mitral valve replacement. These rates are higher if concurrent coronary artery bypass grafting is performed. In general, mitral valve repair is more often appropriate for younger patients with myxomatous involvement of the mitral valve, and mitral replacement is more often undertaken in older patients with more extensive valve pathology.

In patients with chronic, severe, symptomatic primary MR who are at prohibitive operative risk, a recently developed technique of transcatheter mitral valve repair can be considered. In this procedure, a catheter is advanced percutaneously from the femoral vein into the right side of the heart, then into the left atrium via a puncture through the interatrial septum (similar to mitral balloon valvuloplasty), and advanced into the left ventricle. A mechanical clip is then deployed, which grasps and tethers the anterior and posterior mitral leaf ets together at one location and is left in place, reducing the size of the regurgitant orifice. The procedure has been shown to be safe and effective in prospective observational studies of high surgical risk patients, with improvement in the severity of MR and functional status. However, in a randomized trial of percutaneous repair versus valve surgery for patients with severe primary MR, surgery proved more effective and remains the intervention of choice is patients who are acceptable candidates for an operation.

Because chronic, secondary MR is often a result of left ventricular dysfunction, pharmacologic rather than mechanical intervention is the mainstay of treatment, using a standard combination of heart failure medications, including diuretics, ACE inhibitors or angiotensin receptor blockers, beta-blockers, and aldosterone antagonists (see Chapter 9). Surgical intervention is considered only when a patient with chronic, severe secondary MR has persistent symptoms despite optimal medical therapy.

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is characterized by abnormal billowing of a portion of one or both mitral leaf ets into the LA during ventricular systole, and is frequently accompanied by MR (Fig. 8-6). Other names for this condition include f oppy mitral valve, myxomatous mitral valve, and Barlow syndrome. MVP may be inherited as a primary autosomal dominant disorder with variable penetrance, or it may accompany certain connective tissue diseases, such as Marfan syndrome or Ehlers–Danlos syndrome. Pathologically, the valve leaf ets, particularly the posterior leaf et, are enlarged, and the normal dense collagen and elastin matrix of the valvular fibrosa is fragmented and replaced with loose myxomatous connective tissue. Additionally, in more severe lesions, elongated or ruptured chordae, annular enlargement, or thickened leaf ets may be present. A recent rigorous echocardiographic study indicated that MVP occurs in about 2% of the population and is more common among women, especially those who are thin and lean.

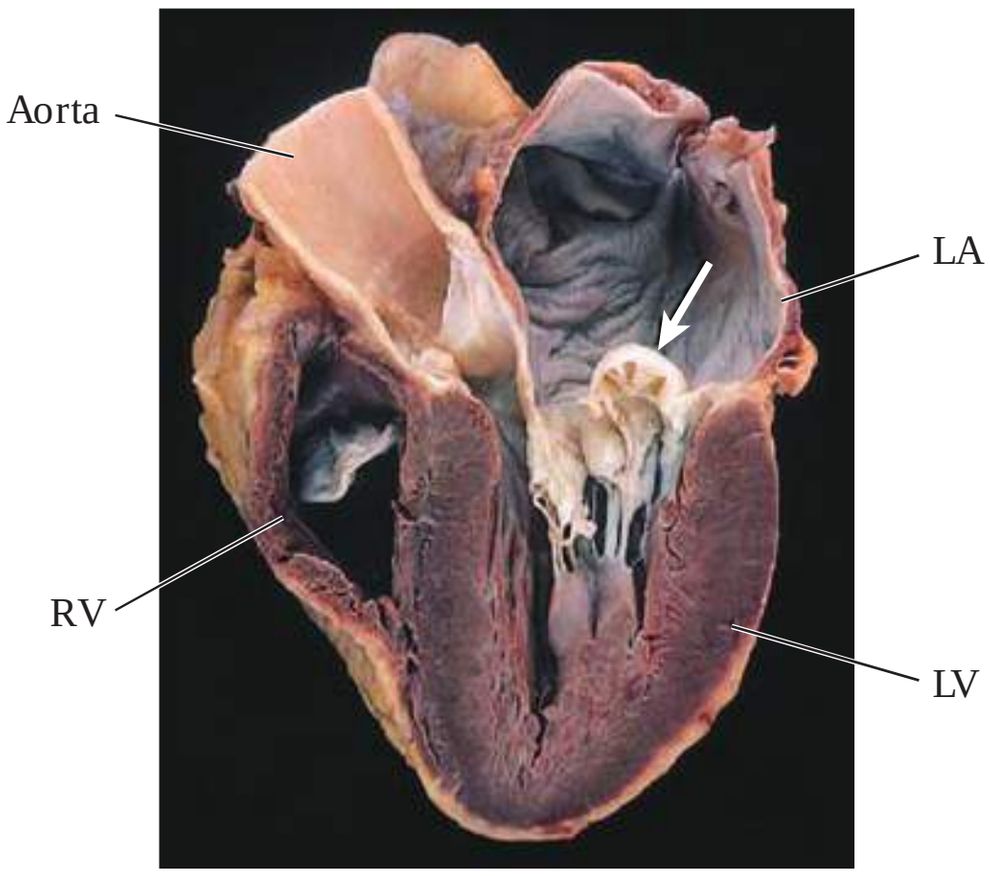


FIGURE 8-6. Mitral valve prolapse. Long-axis view of the left ventricle (LV) demonstrates a myxomatous, elongated appearance of the mitral valve with prolapse of the posterior leaflet (arrow) into the left atrium (LA). RV, right ventricle. (From Schoen FJ, Mitchell RN. The heart. In: Kumar V, Abbas A, Aster JC, eds. Robbins and Cotran Pathologic Basis of Disease. 9th ed. Philadelphia, PA: Elsevier Saunders; 2015.)

MVP is often asymptomatic but affected individuals may describe chest pain or palpitations because of associated arrhythmias. Most often it is identified on routine physical examination by the presence of a midsystolic click and late systolic murmur heard best at the cardiac apex. The midsystolic click is thought to correspond to the sudden tensing of the involved mitral leaflet or chordae tendineae as the leaflet is forced back toward the LA; the murmur corresponds to regurgitant flow through the incompetent valve. The click and murmur are characteristically altered during dynamic auscultation at the bedside: maneuvers that increase the volume of the LV (e.g., sudden squatting, which increases venous return) place traction of the chordae tendineae, limiting and delaying the occurrence of prolapse in systole and cause the click and murmur to occur later (i.e., further from S_1). Conversely, if the volume of blood in the LV is decreased (e.g., on sudden standing), prolapse occurs earlier and the click and murmur move closer to S_1.

Confirmation of the diagnosis is obtained by echocardiography, which demonstrates posterior displacement of a portion of one or both mitral leaflets into the LA during systole. The electrocardiogram and chest radiograph are usually normal unless chronic MR has resulted in left atrial and left ventricular enlargement.

The clinical course of MVP is most often benign. Treatment consists of reassurance about the usually good prognosis and monitoring for the development of progressive MR. Occasionally, rupture of myxomatous chordae in this condition can cause sudden, severe regurgitation and pulmonary edema. Other potential complications include infective endocarditis, peripheral emboli owing to microthrombus formation on the redundant valve tissue, and atrial or ventricular arrhythmias.

AORTIC VALVE DISEASE

Aortic Stenosis

Etiology

Among adult patients, there are three major causes of aortic stenosis (AS): (1) degenerative calcification of a previously normal trileaflet aortic valve, (2) calcification of a congenitally bicuspid aortic valve, and (3) rheumatic aortic valve disease. Degenerative disease of a trileaflet valve shares many pathologic features in common with atherosclerosis, as described below. Bicuspid aortic valves are present in 1% to 2% of the population (with men affected more commonly than women) and such patients typically develop signs of severe valve disease about a decade earlier than patients with the trileaflet, degenerative type of AS. Rheumatic aortic valve disease is now uncommon in developed countries. It is nearly always accompanied by rheumatic involvement of the mitral valve.

Pathology

The pathologic appearance in AS is dependent on its etiology. Degenerative, calcific AS results from a dynamic process of endothelial dysfunction, lipid accumulation, inflammation,

and alteration of signaling pathways that appears similar to atherogenesis. Over time, valvular myofibroblasts differentiate into osteoblasts and deposit calcium hydroxyapatite crystals, resulting in leaflet thickening and stiffening. This process is likely exacerbated by abnormal shear forces, as occur with congenitally deformed (bicuspid) valves, and could explain the earlier presentation of such patients. As with atherosclerosis, risk factors for calcific, degenerative AS include dyslipidemia, smoking, and hypertension (see Chapter 5).

In rheumatic AS, endocardial inflammation leads to organization and fibrosis of the valve and ultimately to fusion of the commissures and formation of calcified masses within the aortic cusps.

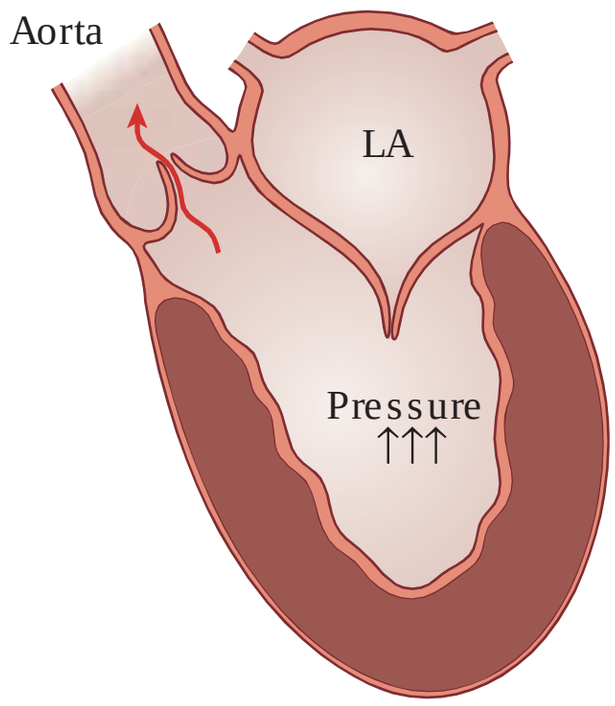


FIGURE 8-7. Pathophysiology of aortic stenosis (AS). The impediment to left ventricular (LV) outflow in AS results in elevated LV pressures and secondary concentric ventricular hypertrophy.

Pathophysiology

In AS, blood flow across the aortic valve is impeded during systole (Fig. 8-7). Progressive reduction of the aortic valve area requires elevation of left ventricular systolic pressure to overcome the impedance to flow to drive blood into the aorta (Fig. 8-8).

Since the obstruction in AS develops gradually, the LV is able to compensate by undergoing concentric hypertrophy in response to the increased pressure load. Initially, such hypertrophy serves an important role in reducing LV wall stress (remember from Chapter 6 that wall stress = (P × r) ÷ 2 h, in which h represents wall thickness). Over time, however, it also reduces the compliance of the ventricle. The resulting elevation of diastolic LV pressure causes the LA to hypertrophy, which facilitates filling of the "stiffened" LV. Whereas left atrial contraction contributes only a small portion of the left ventricular stroke volume in normal individuals, it may provide more than 25% of the stroke volume to the stiffened LV in AS patients. Thus, left atrial hypertrophy is beneficial, and the loss of effective atrial contraction (e.g., development of atrial fibrillation) can cause marked clinical deterioration.

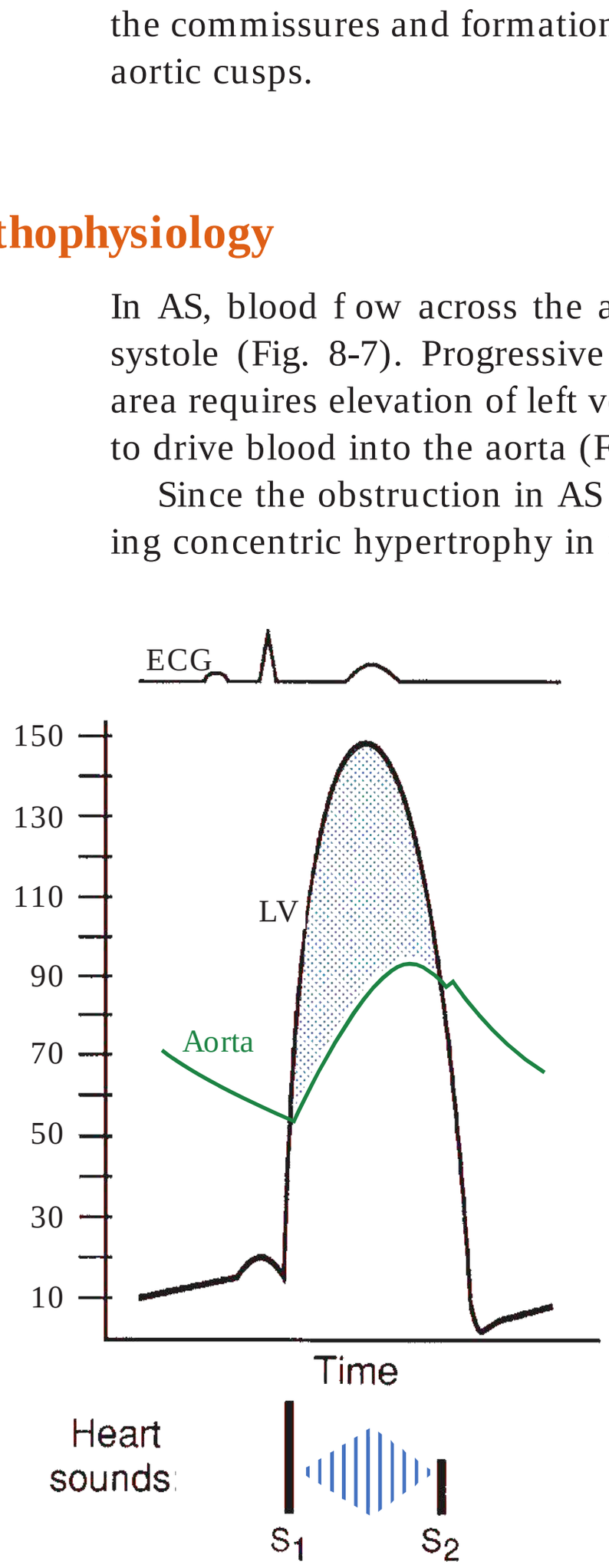


FIGURE 8-8. Hemodynamic profile of aortic stenosis. A systolic pressure gradient (shaded area) is present between the left ventricle (LV) and aorta. The second heart sound (S_2) is diminished in intensity, and there is a crescendo–decrescendo systolic murmur that does not extend beyond S_2. ECG, electrocardiogram.

Three major manifestations occur in patients with advanced AS: (1) angina, (2) exertional syncope, and (3) heart failure, all of which can be explained on the basis of the underlying pathophysiology. Each manifestation, in order, heralds an increasingly ominous prognosis (Table 8-1).

AS may result in angina because it creates a substantial imbalance between myocardial oxygen supply and demand. Myocardial oxygen demand is increased in two ways. First, the muscle mass of the hypertrophied LV is increased, requiring greater-than-normal perfusion. Second, wall stress is increased because of the elevated systolic ventricular pressure. In addition, AS reduces myocardial oxygen supply because the elevated left ventricular diastolic pressure reduces the coronary perfusion pressure gradient between the aorta and the myocardium.

TABLE 8-1 Median Survival Time in Symptomatic Severe Aortic Stenosis

Clinical Symptoms	Median Survival
Angina	5 years
Syncope	3 years
Heart failure	2 years

Derived from Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968;38(suppl.v):61.

AS may cause syncope during exertion. Although left ventricular hypertrophy allows the chamber to generate a high pressure and maintain a normal cardiac output at rest, the ventricle cannot significantly increase its cardiac output during exercise because of the fixed stenotic aortic orifice. In addition, exercise leads to vasodilatation of the peripheral muscle beds. Thus, the combination of peripheral vasodilatation and the inability to augment cardiac output contributes to decreased cerebral perfusion pressure and, potentially, loss of consciousness on exertion.

Finally, AS can result in symptoms of heart failure. Early in the course of AS, an abnormally increased left atrial pressure occurs primarily at the end of diastole, when the LA contracts into the thickened noncompliant LV. As a result, the mean left atrial pressure and the pulmonary venous pressure are not greatly affected early in the disease. However, with progression of the stenosis, the LV may develop contractile dysfunction because of the insurmountably high afterload, leading to increased left ventricular diastolic volume and pressure. The accompanying marked elevation of LA and pulmonary venous pressures incites pulmonary alveolar congestion and symptoms of heart failure.

A normal aortic valve has a cross-sectional area of 3 to 4 cm^2 and a mean systolic pressure gradient between the LV and aorta of less than 5 mm Hg. As the valve area decreases in AS, the pressure gradient rises. When the valve area declines to less than 1.0 cm^2, or the mean pressure gradient increases to greater than 40 mm Hg, a patient is considered to have severe aortic stenosis and symptoms typically appear.

Clinical Manifestations and Evaluation

Presentation

Angina, syncope, and heart failure may appear after many asymptomatic years of slowly progressive valve stenosis. Once these symptoms develop, they confer a significantly decreased survival if invasive correction of AS is not undertaken (see Table 8-1).

Examination

Physical examination often permits accurate detection and estimation of the severity of AS. The key features of advanced AS include (1) a coarse late-peaking systolic ejection murmur and (2) a weakened (parvus) and delayed (tardus) upstroke of the carotid artery owing to the obstructed LV outflow. Other common findings on cardiac examination include the presence of an S_4 (because of atrial contraction into the "stiff" LV—see Chapter 2) and reduced intensity, or complete absence, of the aortic component of the second heart sound (see Fig. 8-8).

On the electrocardiogram, left ventricular hypertrophy is common in advanced AS. Echocardiography is a more sensitive technique to assess LV wall thickness and displays the abnormal anatomy and reduced excursion of the stenotic valve. The transvalvular pressure gradient and aortic valve area can be readily calculated by Doppler echocardiography (see Chapter 3). Cardiac catheterization is sometimes used to confirm the severity of AS and to define the coronary anatomy, because concurrent coronary artery bypass surgery is often appropriate at the time of aortic valve replacement in patients with coexisting coronary disease.

Natural History and Treatment

Mild, asymptomatic AS has a slow rate of progression such that over a 20-year period, only 20% of patients will progress to severe or symptomatic disease. There is no current effective medical therapy for slowing the rate of progression of aortic stenosis. Since the natural history of severe, symptomatic, uncorrected AS is very poor (see Table 8-1), effective treatment requires replacement of the valve.

Aortic valve replacement (AVR) is indicated when a patient with severe AS develops symptoms, or when there is evidence of progressive LV dysfunction in the absence of symptoms. The left ventricular ejection fraction almost always increases after valve replacement, even in patients with impaired preoperative left ventricular function. The effect of AVR on the natural history of AS is dramatic, as the 10-year survival rate rises to approximately 60%.

Unlike its successful role in mitral stenosis, percutaneous balloon valvuloplasty has been disappointing as a sole treatment of adults with calcific AS. Although balloon dilatation of the aortic valve orifice can fracture calcified masses leading to a slight reduction in valve obstruction, up to 50% of patients develop restenosis within 6 months. Valvuloplasty is occasionally used as a temporizing measure in patients too ill to proceed directly to valve replacement, and can also be an effective treatment in young patients with noncalcified bicuspid AS.

In distinction, for patients with severe AS who are at prohibitive or high risk for cardiac surgery, transcatheter aortic valve replacement (TAVR) has emerged as a successful treatment option. This technique involves percutaneous insertion of a specially designed bioprosthetic valve into the narrowed orifice of the stenotic native valve that is first prepared with balloon valvuloplasty. TAVR has been validated in randomized prospective trials, and for inoperable patients, TAVR outcomes are superior to standard medical therapy. In high surgical risk patients, TAVR is noninferior to surgical AVR, with similar 1- and 2-year survival rates, though its use is associated with higher risks of periprocedural stroke and paravalvular regurgitation. Longer-term data indicate that the difference in stroke rates equalizes over time, and it is likely that the use of TAVR will gradually be extended to greater numbers of high and intermediate surgical risk patients.

Aortic Regurgitation

Etiology

Aortic regurgitation (AR), also termed aortic insufficiency, may result either from abnormalities of the aortic valve leaflets or from dilatation of the aortic root. Primary valvular causes include: (1) bicuspid aortic valve (in some patients AR predominates over aortic stenosis), (2) infective endocarditis (due to perforation or erosion of a leaflet), and (3) rheumatic heart disease (due to thickening and shortening of the aortic valve cusps). Primary aortic root disease results in AR when the aortic annulus dilates sufficiently to cause separation of the leaflets, preventing normal coaptation in diastole. Examples include age-related degenerative dilation of the aortic root, aortic aneurysms, and aortic dissection, which are described in Chapter 15.

Pathophysiology

In AR, abnormal regurgitation of blood occurs from the aorta into the LV during diastole. Therefore, with each contraction, the LV must pump that regurgitant volume plus the normal quantity of blood entering from the LA. Hemodynamic compensation relies on the Frank–Starling mechanism to augment stroke volume. Factors influencing the severity of AR are analogous to those of MR: (1) the size of the regurgitant aortic orifice, (2) the pressure gradient across the aortic valve during diastole, and (3) the duration of diastole.

As in MR, the hemodynamic abnormalities and symptoms differ in acute and chronic AR (Fig. 8-9). In acute AR, the LV is of normal size and relatively noncompliant. Thus, the volume load of regurgitation causes the LV diastolic pressure to rise substantially. The sudden high diastolic LV pressure is transmitted to the LA and pulmonary circulation, often producing dyspnea and pulmonary edema. Thus, acute severe AR is usually a surgical emergency, requiring immediate valve replacement.

In chronic AR, the LV undergoes compensatory adaptation in response to the long-standing regurgitation. AR subjects the LV primarily to volume overload but also to an excessive pressure load; therefore, the ventricle compensates through chronic dilatation (eccentric hypertrophy, with replication of sarcomeres in series—see Chapter 9) and, to a lesser degree, increased thickness. Over time, the dilatation increases the compliance of the LV and allows it to accommodate a larger regurgitant volume with less of an increase in diastolic pressure, reducing the pressure transmitted into the LA and pulmonary circulation. However, by accommodating the large regurgitant volume, the aortic (and therefore systemic arterial) diastolic pressure drops substantially. The combination of a high LV stroke volume (and high systolic arterial pressure) with a reduced aortic diastolic pressure produces a widened pulse pressure (the difference between arterial systolic and diastolic pressures), a hallmark of chronic AR (Fig. 8-10). As a result of the decreased aortic diastolic pressure, the coronary artery perfusion pressure falls, potentially reducing myocardial oxygen supply. This, coupled with the increase in LV size (which causes increased wall stress and myocardial oxygen demand), can produce angina, even in the absence of atherosclerotic coronary disease.

Compensatory left ventricular dilatation and hypertrophy are generally adequate to meet the demands of chronic AR for many years, during which affected patients are asymptomatic. Gradually, however, progressive remodeling of the LV occurs, resulting in systolic

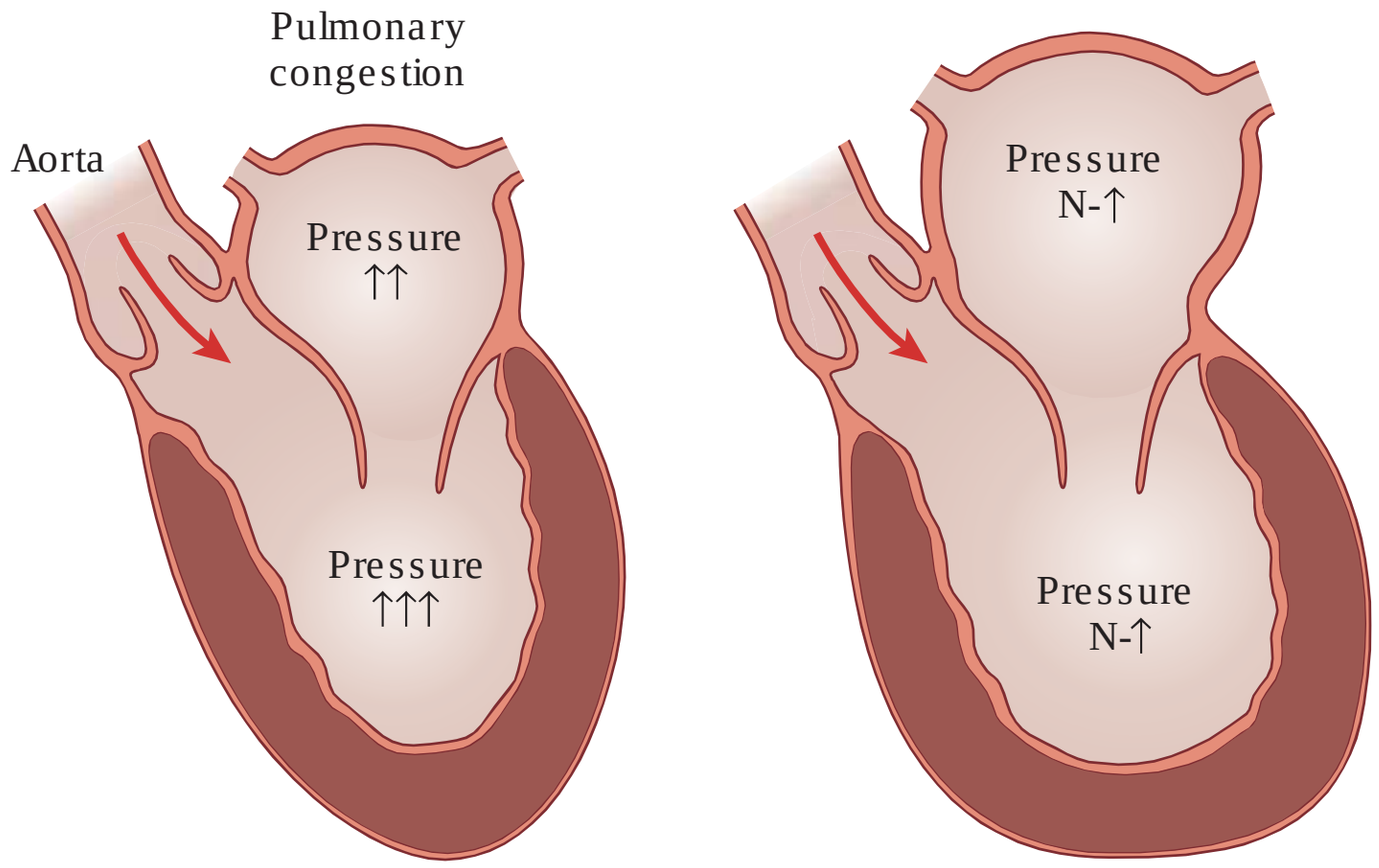


FIGURE 8-9. Pathophysiology of acute and chronic aortic regurgitation (AR). Abnormal regurgitation of blood from the aorta into the left ventricle (LV) is shown in each schematic drawing (red arrows). In acute AR, the LV is of normal size and relatively low compliance, such that its diastolic pressure rises significantly; this pressure increase is reflected back to the left atrium (LA) and pulmonary vasculature, resulting in pulmonary congestion or edema. In chronic AR, adaptive LV and LA enlargement have occurred, such that a greater volume of regurgitation can be accommodated with less of an increase in diastolic LV pressure, so that pulmonary congestion is less likely. N, normal.

dysfunction. This causes decreased forward cardiac output as well as an increase in left atrial and pulmonary vascular pressures. At that point, the patient develops symptoms of heart failure.

Clinical Manifestations and Assessment

Presentation

Common symptoms of chronic AR include dyspnea on exertion, fatigue, decreased exercise tolerance, and the uncomfortable sensation of a forceful heartbeat associated with the high pulse pressure.

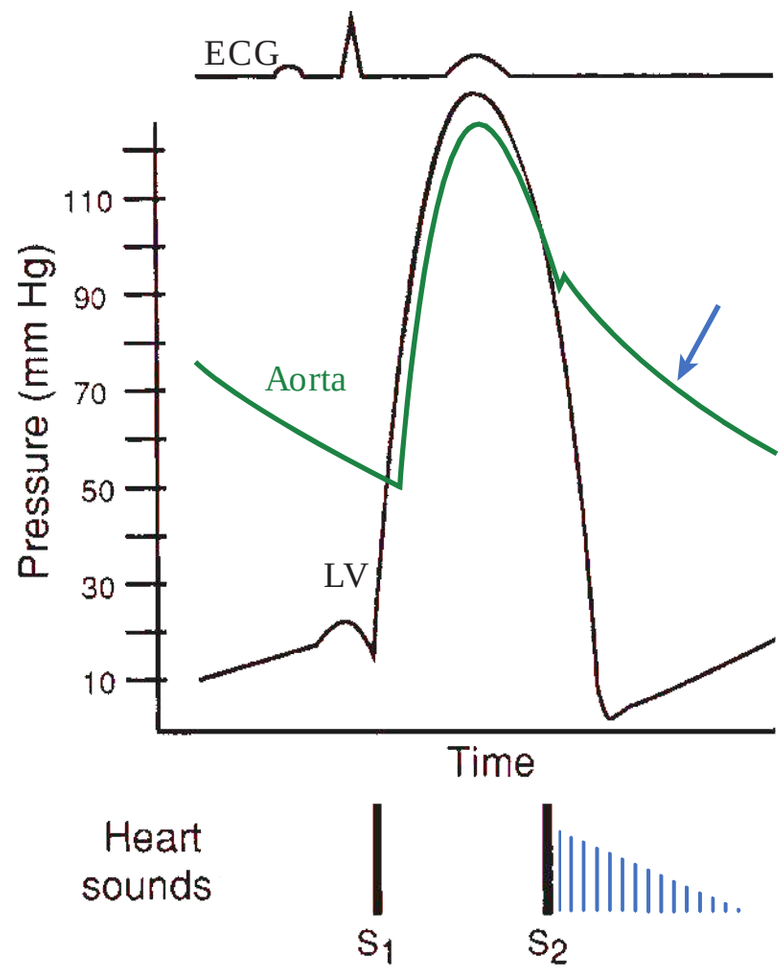


FIGURE 8-10. Hemodynamic profile of aortic regurgitation. During diastole, the aortic pressure falls rapidly (arrow), and left ventricular (LV) pressure rises as blood regurgitates from the aorta into the LV. A diastolic decrescendo murmur, beginning at the second heart sound (S_2), corresponds with the abnormal regurgitant flow. ECG, electrocardiogram.

Examination

Physical examination may show bounding pulses and other stigmata of the widened pulse pressure (Table 8-2), in addition to a hyperdynamic LV impulse and a blowing murmur of AR in early diastole along the left sternal border (see Fig. 8-10). It is best heard with the patient leaning forward, after exhaling. In addition, a low-frequency mid-diastolic rumbling sound may be auscultated at the cardiac apex in some patients with severe AR. Known as the Austin Flint murmur, it is thought to reflect turbulence of blood flow through the mitral valve during diastole owing to downward displacement of the mitral anterior leaflet by the regurgitant stream of AR. It can be distinguished from the murmur of mitral stenosis by the absence of an OS or presystolic accentuation.

In chronic AR, the chest radiograph shows an enlarged left ventricular silhouette. This is usually absent in acute AR, in which pulmonary vascular congestion is the more likely finding. Doppler echocardiography can identify and quantify the degree of AR and often can identify its cause. Cardiac catheterization with contrast angiography can be obtained for further quantification of the degree of AR, and assessment of coexisting coronary artery disease.

Treatment

Data from natural history studies indicate that clinical progression of patients with asymptomatic chronic AR and normal LV contractile function is very slow. Therefore, asymptomatic patients are monitored with periodic examinations and assessment of LV function, usually by

TABLE 8-2 Examples of Physical Findings Associated with Widened Pulse Pressure in Chronic Aortic Regurgitation

Name	Description
Bisferiens pulse	Double systolic impulse in carotid or brachial artery
Corrigan pulse	"Water-hammer" pulses with marked distention and collapse
Hill sign	Popliteal systolic pressure more than 60 mm Hg greater than brachial systolic pressure
Quincke sign	Capillary pulsations visible at the lip or proximal nail beds

serial echocardiography. Patients with asymptomatic severe AR may benefit from afterload reducing vasodilators (e.g., a calcium channel blocker or an angiotensin-converting enzyme inhibitor) for treatment of accompanying hypertension. However, such agents do not prolong the compensated stage of chronic AR.

Symptomatic patients, or asymptomatic patients with severe AR and impaired LV contractile function (i.e., an ejection fraction less than 0.50), should be offered surgical correction to prevent progressive deterioration. Studies of such patients show that without surgery, death usually occurs within 4 years after the development of angina or 2 years after the onset of heart failure symptoms.

TRICUSPID VALVE DISEASE

Tricuspid Stenosis

Tricuspid stenosis (TS) is rare and is usually a long-term consequence of rheumatic fever. The OS and diastolic murmur of TS are similar to those of MS, but the murmur is heard closer to the sternum and it intensifies on inspiration because of increased right heart blood flow. In TS, the neck veins are distended and may show a large a wave as a result of right atrial contraction against the stenotic tricuspid valve orifice when sinus rhythm is present (see Chapter 2). Patients may develop abdominal distention and hepatomegaly owing to passive venous congestion. Percutaneous balloon dilatation or surgical correction (valvuloplasty or valve replacement) is usually required.

Tricuspid Regurgitation

Tricuspid regurgitation (TR) is usually functional rather than structural in nature; that is, it most commonly results from right ventricular enlargement (e.g., owing to pressure or volume overload) rather than from primary valve disease. Among patients with rheumatic mitral stenosis, 20% also have significant TR (of whom 80% have functional TR because of pulmonary hypertension with right ventricular enlargement, and 20% have structural TR resulting from rheumatic involvement of the tricuspid valve). A rare cause of TR is carcinoid syndrome, in which a type of neuroendocrine tumor (usually in the small bowel or appendix, with metastases to the liver) releases serotonin metabolites into the bloodstream. These metabolites are thought to be responsible for the formation of endocardial plaques in the right side of the heart. Involvement of the tricuspid valve immobilizes the leaflets, often resulting in substantial TR and, less often, TS.

The most common physical signs of TR are prominent v waves in the jugular veins (see Chapter 2) and a pulsatile liver because of regurgitation of right ventricular blood into the systemic veins. The systolic murmur of TR is heard at the lower left sternal border. It is often soft but becomes louder on inspiration. Doppler echocardiography readily detects TR and can quantify it. The treatment of functional TR is directed at the conditions responsible for the elevated right ventricular size or pressure, and diuretic therapy; surgical repair of the valve is indicated in severe cases.

PULMONIC VALVE DISEASE

Pulmonic Stenosis

Pulmonic stenosis (PS) is rare, and its cause is almost always congenital deformity of the valve. Carcinoid syndrome, described in the previous section, is another rare etiology, in which encasement and immobilization of the valve leaflets can occur. The systolic

crescendo–decrescendo murmur of PS is usually loudest at the second or third left intercostal space close to the sternum. It may radiate to the neck or left shoulder and is often preceded by an ejection click (see Chapter 2).

PS is considered to be severe if the peak systolic pressure gradient across the valve is greater than 80 mm Hg, moderate if the gradient is 40 to 80 mm Hg, and mild if the gradient is less than 40 mm Hg. Only patients with moderate-to-severe gradients are symptomatic. In such cases, transcatheter balloon valvuloplasty is usually effective therapy.

Pulmonic Regurgitation

Pulmonic regurgitation (PR) most commonly develops in the setting of severe pulmonary hypertension and results from dilatation of the valve ring by the enlarged pulmonary artery. Auscultation reveals a high-pitched decrescendo murmur along the left sternal border that is often indistinguishable from AR (the two conditions are easily differentiated by Doppler echocardiography).

PROSTHETIC VALVES

The patient who undergoes valve replacement surgery often benefits dramatically from hemodynamic and symptomatic improvement, but also acquires a new set of potential complications related to the valve prosthesis itself. Because all available valve substitutes have certain limitations, valve replacement surgery is not a true "cure."

Currently available valve substitutes include mechanical and bioprosthetic (derived from animal or human tissue) devices (Fig. 8-11). One example of a mechanical valve is the St. Jude prosthesis, a hinged bileaflet valve consisting of two pyrolytic carbon discs that open opposite one another. Mechanical valves, while durable, present foreign thrombogenic surfaces to the circulating blood and require lifelong anticoagulation to prevent thromboembolism.

In contrast, bioprosthetic valves display a very low rate of thromboembolism and do not require long-term anticoagulation therapy. The most commonly used bioprostheses are made from glutaraldehyde-fixed porcine (pig) valves secured in a support frame. In addition, bovine (cow) pericardium and human homograft (aortic valves harvested and cryopreserved from cadavers)

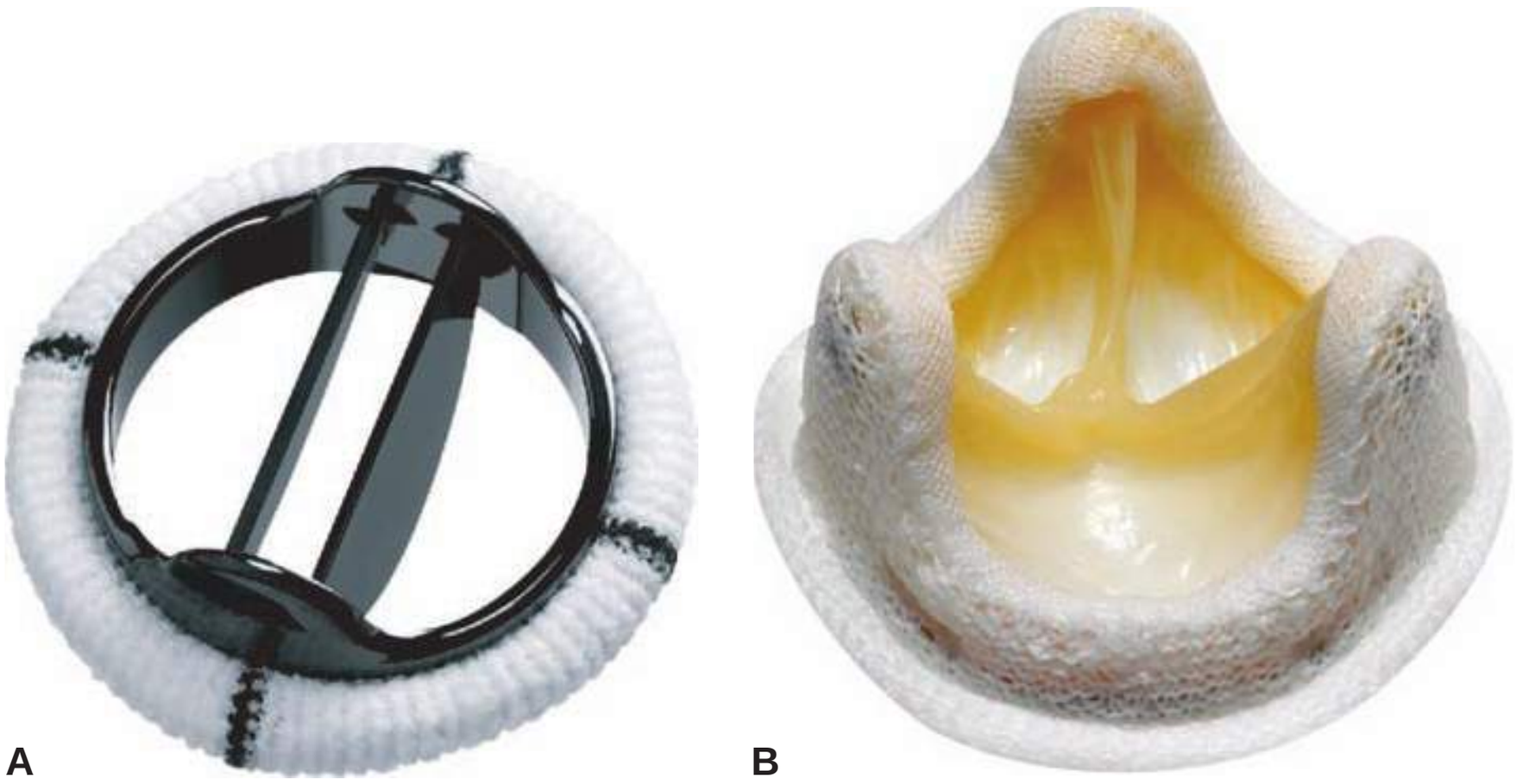


FIGURE 8-11. Examples of prosthetic heart valves. A. St. Jude mechanical bileaflet valve in the open position. (Courtesy of St. Jude Medical, Inc., St. Paul, MN.) **B.** A bioprosthetic aortic valve with leaflets in the closed position. (Courtesy of Medtronic, Inc., Minneapolis, MN.)

prostheses are used. For patients who undergo AVR because of endocarditis, human homograft replacements are especially useful because they have low rates of subsequent reinfection.

Bioprosthetic valves have limited durability compared with mechanical valves, and structural failure occurs in up to 50% by 15 years after implantation. The principal causes of failure are leaflet tears and calcification. Failure rates vary greatly depending on the position of the valve. For example, bioprosthetic valves in the mitral position deteriorate more rapidly than those in the aortic position. This is likely because the mitral valve is exposed to higher closing forces, resulting in greater leaflet stress than that experienced by aortic prostheses.

Common to all types of valve replacement is the risk of infective endocarditis (discussed in the next section), which occurs with an incidence of 1% to 2% per patient per year. If endocarditis occurs in the first 60 days after valve surgery, the mortality rate is exceedingly high (50% to 80%). If endocarditis occurs later, mortality rates range from 20% to 50%. Reoperation is usually required when endocarditis involves a mechanical prosthesis because an adjacent abscess is frequently present. Some cases of bioprosthetic valve endocarditis may respond to antibiotic therapy alone.

Given their respective advantages and disadvantages, the mortality and complication rates of mechanical and bioprosthetic valves are similar for the first 10 years after replacement. In 20-year follow-up studies of randomized, controlled trials, mechanical valves have been shown to be superior to bioprosthetic valves for event-free survival, except for bleeding complications related to anticoagulation therapy. Therefore, the decision about which type of prosthesis to use in a patient often centers on (1) the patient's expected lifespan in comparison to the functional longevity of the valve, (2) risk-versus-benefit considerations of chronic anticoagulation therapy, and (3) patient and surgeon preferences. Mechanical valves are often recommended for younger patients and for those who will be tolerant of, and compliant with, anticoagulant therapy. Bioprosthetic valves are generally suitable choices for patients 65 years of age or older and for patients with contraindications to chronic anticoagulation.

INFECTIVE ENDOCARDITIS

Infection of the endocardial surface of the heart, including the cardiac valves, can lead to extensive tissue damage and is often fatal. Infective endocarditis (IE) carries an overall 6-month mortality rate of 20% to 25%, even with appropriate therapy, and a 100% mortality rate if it is not recognized and treated correctly.

There are three clinically useful ways to classify IE: (1) by clinical course, (2) by host substrate, or (3) by the specific infecting microorganism. In the first classification scheme, IE is termed **acute bacterial endocarditis (ABE)** when the syndrome presents as an acute, fulminant infection, and a highly virulent and invasive organism such as Staphylococcus aureus is causal. Because of the aggressiveness of the responsible microorganism, ABE may occur on previously healthy heart valves. When IE presents with a more insidious clinical course, it is termed **subacute bacterial endocarditis (SBE)** and less virulent organisms such as viridans streptococci are typically involved. SBE most frequently occurs in individuals with prior underlying valvular damage.

The second means of classification of IE is according to the host substrate: (1) native valve endocarditis, (2) prosthetic valve endocarditis, or (3) endocarditis in the setting of intravenous drug abuse. Of these, native valve endocarditis accounts for 60% to 80% of patients. Different microorganisms and clinical courses are associated with each of these categories. For example, the skin contaminant Staphylococcus epidermidis is a common cause of prosthetic valve endocarditis, but that is rarely the case when endocarditis occurs on a native heart valve. Intravenous drug users have a propensity for S. aureus endocarditis of the right-sided heart valves.

The third classification of IE is according to the specific infecting microorganism (e.g. S. aureus endocarditis). As described below, the most common responsible organisms are gram-positive cocci. Certain bacterial strains that cause endocarditis are associated with particular anatomic sources. For example, viridans group streptococci usually originate from oropharyngeal tissue. Endocarditis due to Streptococcus bovis (more recently termed S. gallolyticus) commonly arises from the gastrointestinal tract and should prompt investigation for colonic polyps or adenocarcinoma.

Although the remainder of this discussion focuses on the endocarditis syndromes based on clinical course, it is important to recognize that all three classifications of IE are used.

Pathogenesis

The pathogenesis of endocarditis requires several conditions: (1) endocardial surface injury, (2) platelet–fibrin–thrombus formation at the site of injury, (3) bacterial entry into the circulation, and (4) bacterial adherence to the injured endocardial surface. The first two conditions provide an environment favorable to infection, whereas the latter two permit implantation of the organism on the endocardial surface. The most common cause of endothelial injury is turbulent blood flow resulting from preexisting cardiac or intravascular abnormalities, including acquired valvular heart lesions (e.g., mitral regurgitation or aortic stenosis), congenital heart diseases, and hypertrophic cardiomyopathy (see Chapter 10). Endothelial injury may also be incited by foreign material within the circulation, such as indwelling venous catheters, prosthetic heart valves, and other implanted cardiac devices.

Once an endocardial surface is injured, platelets adhere to the exposed subendocardial connective tissue and initiate the formation of a sterile thrombus (termed a vegetation) through fibrin deposition. This process is referred to as nonbacterial thrombotic endocarditis (NBTE). NBTE makes the endocardium more hospitable to microbes in two ways. First, the fibrin–platelet deposits provide a surface for adherence by bacteria. Second, the fibrin covers adherent organisms and protects them from host defenses by inhibiting chemotaxis and migration of phagocytes.

When NBTE is present, the delivery of microorganisms in the bloodstream to the injured surface can lead to IE. Three factors determine the ability of an organism to induce IE: (1) access to the bloodstream, (2) survival of the organism in the circulation, and (3) adherence of the bacteria to the endocardium. Bacteria can be introduced into the bloodstream whenever a mucosal or skin surface harboring an organism is traumatized, such as from the mouth during dental procedures, or from the skin during illicit intravenous drug use. However, while transient bacteremia is a relatively common event, only microorganisms suited for survival in the circulation and able to adhere to the platelet–fibrin mesh overlying the endocardial defect will cause IE. For example, gram-positive organisms account for the majority of cases of endocarditis largely because of their resistance to destruction in the circulation by complement and their particular tendency to adhere to endothelial and platelet surface proteins. The ability of certain streptococcal species to produce dextran, a bacterial cell wall component that adheres to thrombus, correlates with their inciting endocarditis. Table 8-3 lists the infectious agents reported to be the most common causes of endocarditis in modern tertiary centers; staphylococci (especially S. aureus) and streptococci are the most frequent. Of note, the proportion of patients with viridans group streptococci is higher in series of patients with community-acquired endocarditis.

Once organisms adhere to the injured surface, they may be protected from phagocytic activity by the overlying fibrin. The organisms are then free to multiply, which enlarges the infected vegetation. The latter provides a source for continuous bacteremia and can lead to several complications, including (1) mechanical cardiac injury, (2) thrombotic or septic

TABLE 8-3 Microbiology of Infective Endocarditis in Tertiary Centers

Organism	Incidence (%)
Staphylococci	
S. aureus	31.6
Coagulase negative	10.5
Streptococci	
Viridans	18.0
Enterococci	10.6
S. bovis	6.5
Other streptococci	5.1
Other organisms (e.g., gram-negative bacteria, fungi)	8.7
Culture negative or polymicrobial	~9.4

Derived from Fowler VG Jr, Miro JM, Hoen B, et al. Staphylococcus aureus endocarditis: a consequence of medical progress. JAMA. 2005;293:3012–3021.

emboli, and (3) immune injury mediated by antigen–antibody deposition. For example, local extension of the infection within the heart can result in progressive valvular damage, abscess formation, or erosion into the cardiac conduction system. Portions of a vegetation may embolize, often to the central nervous system, kidneys, or spleen, and incite infection or infarction of the target organs. Each of these is a potentially fatal complication. Additionally, immune complex deposition can result in glomerulonephritis, arthritis, or vasculitis.

The epidemiology of IE has evolved in recent decades as bacteria resistant to antibiotics have become ubiquitous in the hospital setting and have spread into the community. Antibiotic resistant strains such as methicillin-resistant S. aureus and vancomycin-resistant enterococci have become more common and are associated with increased mortality rates from IE.

Clinical Manifestations

A patient with acute IE is likely to report an explosive and rapidly progressive illness with high fever and shaking chills. In contrast, subacute IE presents less dramatically with low-grade fever often accompanied by nonspecific constitutional symptoms such as fatigue, anorexia, weakness, myalgia, and night sweats. These symptoms are not specific for IE and could easily be mistaken for influenza or an upper respiratory tract infection. Thus, the diagnosis of subacute IE requires a high index of suspicion. A history of a valve lesion or other condition known to predispose to endocarditis is helpful. A thorough history should also inquire about injection drug use, recent dental procedures, or other potential sources of bacteremia.

Cardiac examination may reveal a murmur representing underlying valvular pathology that predisposed the patient to IE, or a new murmur of valvular insufficiency owing to IE-induced damage. The development of right-sided valve lesions (e.g., tricuspid regurgitation), although rare in normal hosts, is particularly common in endocarditis associated with intravenous drug abuse. Serial examination in ABE may be especially useful because changes in a murmur (i.e., worsening regurgitation) over time may correspond with rapidly progressive valvular

destruction. During the course of endocarditis, severe valvular destruction may result in signs of heart failure, which is the leading cause of death in patients with IE.

Other physical findings that may appear in IE are those associated with septic embolism or immune complex deposition. Central nervous system emboli occur in up to 40% of patients, often resulting in new neurologic findings on physical examination. Injury to the kidneys, of embolic or immunologic origin, may manifest as f ank pain, hematuria, or renal failure. Lung infarction (septic pulmonary embolism) or infection (pneumonia) is particularly common in endocarditis that involves right-sided valves.

Embolic infarction and seeding of the vasa vasorum of arteries can cause localized aneurysm formation (termed a mycotic aneurysm) that weakens the vessel wall and may rupture. Mycotic aneurysms may be found in the aorta, viscera, or peripheral organs, and are particularly dangerous in cerebral vessels, because rupture there can result in fatal intracranial hemorrhage.

Skin findings resulting from septic embolism or immune complex vasculitis are often collectively referred to as peripheral stigmata of endocarditis. For example, petechiae may appear as tiny, circular, red-brown discolorations on mucosal surfaces or skin. Splinter hemorrhages, the result of subungual microemboli, are small, longitudinal hemorrhages found beneath nails. Other peripheral stigmata of IE, which are now rarely encountered, include painless, f at, irregular discolorations found on the palms and soles called Janeway lesions; tender, pea-sized, erythematous nodules found primarily in the pulp space of the fingers and toes termed Osler nodes; and emboli to the retina that produce Roth spots, microinfarctions that appear as white dots surrounded by hemorrhage.

The systemic inf ammatory response produced by the infection is responsible for fever and splenomegaly, as well as for a number of laboratory findings, including an elevated white blood cell count with a leftward shift (increase in proportion of neutrophils and immature granulocytes), an elevated erythrocyte sedimentation rate and C-reactive protein level, and in approximately 50% of cases, an elevated serum rheumatoid factor.

The electrocardiogram may help identify extension of the infection into the cardiac conduction system, manifest by various degrees of heart block or new arrhythmias. Echocardiography is used to visualize vegetations, valvular dysfunction, and associated abscess formation. Echocardiographic assessment can consist of transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), as described in Chapter 3. TTE is useful in detecting large vegetations and has the advantage of being noninvasive and easy to obtain. However, while the specif city of TTE for vegetations is high, the sensitivity for finding vegetations is less than 60%. TEE, on the other hand, is much more sensitive (> 90%) for the detection of vegetations and myocardial abscess formation and can be particularly useful for the evaluation of infection involving prosthetic valves.

Central to the diagnosis and appropriate treatment of endocarditis is the identification of the responsible microorganism by blood culture. Once positive culture results are obtained, treatment can be tailored to the causative organism according to its antibiotic sensitivities. A specific etiologic agent is identified approximately 90% of the time. However, blood cultures may return negative if antibiotics have already been administered or if the organism has unusual growth requirements.

Even after a careful history, examination, and evaluation of laboratory data, the diagnosis of IE can be elusive. Therefore, attempts have been made to standardize the diagnosis, resulting in the now widely used Duke criteria (Table 8-4). By this standard, the diagnosis of endocarditis rests on the presence of either two major criteria, one major and three minor criteria, or five minor criteria. Positive blood cultures and endocardial involvement detected by echocardiography provide the strongest evidence for IE and are considered major criteria. Minor criteria relate to clinical risk factors and findings on physical examination.

TABLE 8-4 Modified Duke Criteria for Diagnosis of Infective Endocarditis (IE)[a]

Major Criteria	Minor Criteria
I. Positive blood culture, defined as either A or B A. Typical microorganism for IE from two separate blood cultures 1. Streptococci viridans, S. bovis, HACEK group; or 2. Staphylococcus aureus or enterococci, in the absence of a primary focus B. Microorganisms consistent with IE from persistently positive blood cultures 1. Blood cultures drawn >12 hr apart, or 2. All of three, or most of four separate cultures drawn at least 1 hr apart 3. Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer >1:800 II. Evidence of endocardial involvement, defined as A or B A. Echocardiogram positive for endocarditis: 1. Oscillating intracardiac mass, or 2. Myocardial abscess, or 3. New partial detachment of prosthetic valve B. New valvular regurgitation	Predisposing cardiac condition or intravenous drug use Fever (≥38.0°C) Vascular phenomena (septic arterial or pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions) Immunologic phenomena (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor) Positive blood cultures not meeting major criteria or serologic evidence of infection with organism consistent with IE

[a]Clinical diagnosis of definite endocarditis requires two major criteria, one major plus three minor criteria, or five minor criteria. Possible endocarditis requires one major plus one minor criteria or three minor criteria.

HACEK, Haemophilus spp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella spp., and Kingella kingae.

Derived from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–638.

Treatment

Treatment of endocarditis entails 4 to 6 weeks of high-dose intravenous antibiotic therapy. Although empiric broad-spectrum antibiotics may be used initially (after blood cultures are obtained) for patients who are severely ill or hemodynamically unstable, specific, directed therapy is appropriate once the causative microorganism has been identified. Surgical intervention, usually with valve replacement, is indicated for patients with persistent bacteremia or fever despite appropriate antibiotic therapy, for those with severe valvular dysfunction leading to heart failure, and for individuals who develop myocardial abscesses or recurrent endocarditis-related thromboemboli.

Prevention

An additional essential concept is prevention of endocarditis by administering antibiotics to certain susceptible individuals before invasive procedures that are likely to result in bacteremia. The American Heart Association recommends such antibiotic prophylaxis for the cardiac conditions that place them at the highest risk for developing an adverse outcome from IE, as delineated in Table 8-5, when such individuals are subjected to procedures listed in the table.

TABLE 8-5 Antibiotic Prophylaxis for Infective Endocarditis

Cardiac conditions for which antibiotic prophylaxis is reasonable[a]

1. Presence of a prosthetic heart valve or prior valve repair with prosthetic material
2. Prior history of endocarditis
3. Certain congenital heart diseases (CHD):
   - Unrepaired cyanotic CHD (described in Chapter 16)
   - Completely repaired congenital heart defects with prosthetic material, during the first 6 months after the procedure (i.e., prior to protective endothelialization)
   - Repaired CHD with residual defects adjacent to the site of prosthetic material (which inhibits endothelialization)
4. Cardiac transplant recipients who develop cardiac valve abnormalities

Procedures that warrant antibiotic therapy for conditions listed above

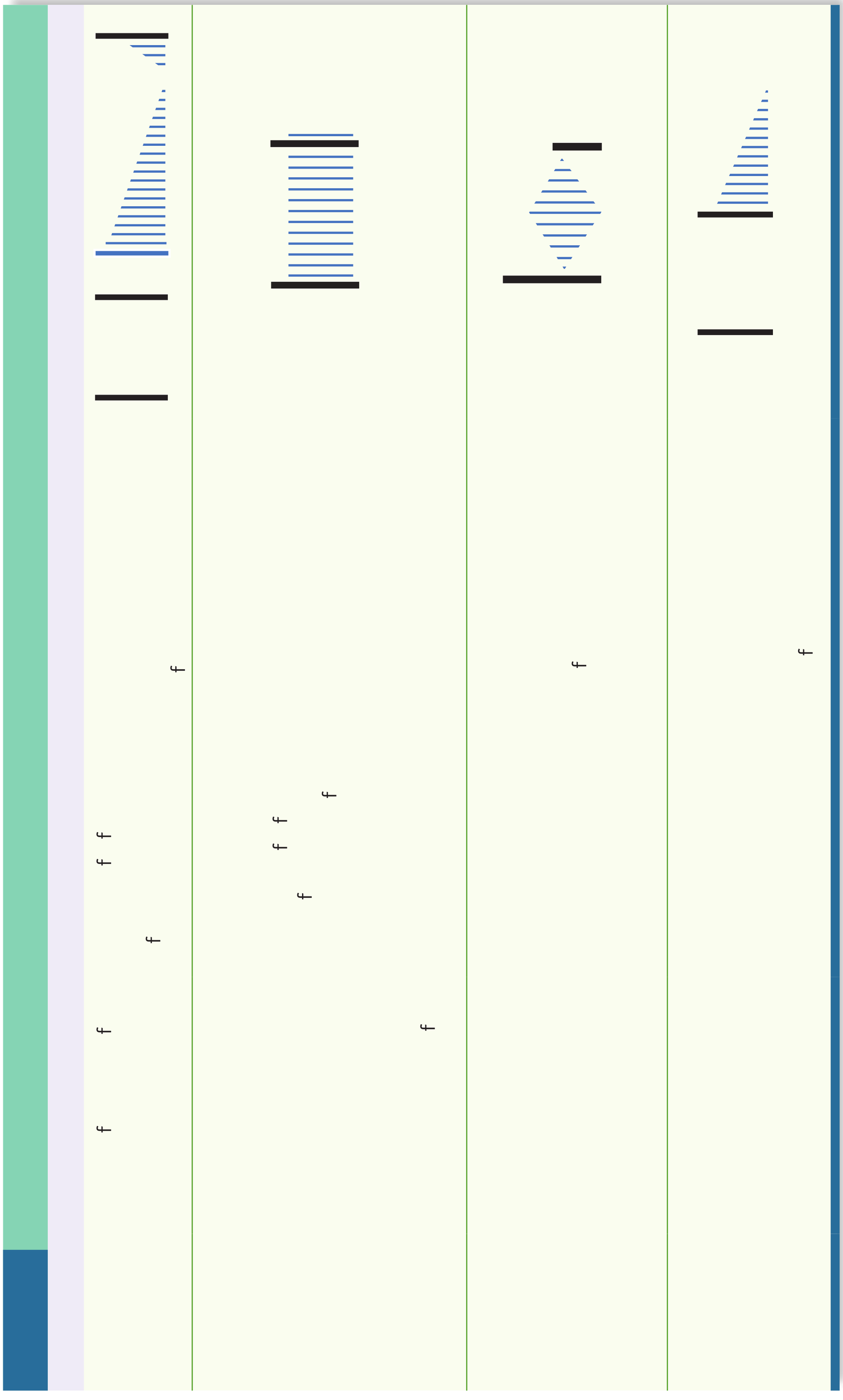
1. Dental procedures that involve manipulation of gingival tissue, manipulation of periapical region of the teeth, or perforation of the oral mucosa
2. Upper respiratory tract procedures, only if involves incision or biopsy of mucosa (e.g., tonsillectomy, bronchoscopy with biopsy)
3. Genitourinary or gastrointestinal procedures, only if infections of those systems are present
4. Procedures on infected skin or musculoskeletal tissue

[a]The conditions on this list have the highest risk of adverse outcomes from endocarditis.

Derived from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736–1754.

SUMMARY

- Unifying principles do not govern the behavior of all valvular heart diseases—effective management requires identification of the valve abnormality, a determination of its severity, and an understanding of the pathophysiologic consequences and natural history of the condition (Table 8-6).
- Diagnosis of valvular disease is assisted by transthoracic echocardiography (TTE), which allows for staging of disease severity; in selected patients, additional investigation with exercise testing or cardiac catheterization may be necessary to define the significance of the condition.
- Management of patients with stenotic or regurgitant valves involves serial clinical and echocardiographic assessments; pharmacologic therapy is sometimes prescribed for symptomatic improvement, but recognition of timely indications for valve repair or replacement is essential.
- Mitral stenosis usually results from prior rheumatic fever; left atrial (LA) enlargement and atrial fibrillation are common.
- Mitral regurgitation (MR) results from disruption of the structural integrity of any of the components of the mitral valve apparatus or their coordinated action; with chronic MR, LA enlargement, and left ventricular (LV) volume overload are typical.
- In mitral valve prolapse, the valve leaflets are elongated, and the normal dense collagen and elastin matrix of the valvular fibrosa is fragmented and replaced with loose myxomatous connective tissue; one or both leaflets bow into the LA during systole resulting in lack of coaptation and mitral regurgitation.
- Aortic stenosis has three primary causes: (1) degenerative calcification of a previously normal trileaflet aortic valve, (2) calcification of a congenitally bicuspid aortic valve, and (3) rheumatic valve disease; the primary hemodynamic consequence is LV pressure overload with compensatory LV hypertrophy; cardinal symptoms are chest discomfort, exertional dyspnea, and exertional light-headedness.



- Aortic regurgitation may result either from abnormalities of the aortic valve leaf ets or from dilatation of the aortic root; the primary hemodynamic perturbation is LV volume overload.
- Tricuspid stenosis is rare and is usually a long-term consequence of rheumatic fever.
- Tricuspid regurgitation is usually functional (due to RV enlargement) rather than structural in nature.
- Pulmonic stenosis is rare, and its cause is almost always congenital deformity of the valve.
- Pulmonic regurgitation most commonly develops in the setting of severe pulmonary hypertension and results from dilatation of the valve ring by an enlarged pulmonary artery.
- The pathogenesis of endocarditis requires endocardial surface injury, platelet–fibrin–thrombus formation at the site of injury, bacterial entry into the circulation, and bacterial adherence to the injured endocardial surface.

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