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Aortic Valve Disease

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Key Points

- Calcific disease is the major cause of aortic stenosis.
- Bicuspid aortic valves lead to aortic stenosis in approximately one half of patients who are born with them.
- The classic symptoms of valvular aortic stenosis, angina, syncope, and dyspnea represent a major inflection in the natural history of the disease and indicate the need for surgical correction, and in the absence of surgical therapy an increased risk of sudden death.
- The mainstay of diagnosis of valvular aortic stenosis is the echocardiogram, which, together with Doppler, provide an excellent estimate of the severity of valvular aortic stenosis.
- Patients with low cardiac outputs and some valvular aortic stenosis and those with severe valvular stenosis and reduced left ventricle (LV) function can often be distinguished by a dobutamine infusion test with echocardiography.
- Aortic regurgitation is caused by pathology of the aortic valve leaflets or of the aortic root.
- An Austin Flint murmur (apical diastolic rumble) indicates severe aortic insufficiency.
- Vasodilators may reduce LV volume or delay the development of symptoms in patients with aortic regurgitation (AR).
- Surgical correction of AR is needed when the amount of regurgitation is severe and either symptoms of congestive heart failure (CHF) or angina develop or with evidence of decline in LV function, for example, a fall in the LV ejection fraction (LVEF) below 0.55 or the LV is unable to contract down to 50 to 55 mm Hg at the end of systole.
- Acute AR, such as occurs following perforation of an aortic leaflet by infective endocarditis, is a potentially life-threatening emergency that often requires very early surgical correction.
- Appetite-suppressant drugs may cause pulmonary hypertension and left ventricular valvular lesions, including aortic and mitral valve insufficiency.

Aortic Stenosis

Etiology

The causes of aortic stenosis (AS) and our understanding of them have evolved substantially over the past four decades. Although rheumatic heart disease was once a major cause of aortic stenosis in the developed world, today rheumatic disease is exceedingly rare in those countries. Instead calcific disease is now the major cause of AS. Previously considered to be a degenerative disease, it is now clear that the process is much akin to atherosclerosis.[1–3] The initial plaque of AS resembles that of coronary artery disease (Fig. 15.1).[1] Risk factors such as hyperlipidemia, hypertension, and evidence of systemic inflammation are held in common by both AS and coronary disease.[2] The presence of aortic sclerosis, the earliest phase of AS in which no hemodynamic disturbance is yet present, is associated with increased cardiac mortality.[4] Since the valve abnormality is too slight to cause untoward events, it is presumed that the aortic sclerosis presages subsequent coronary events. Finally a body of data is amassing that shows that hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), commonly used agents in treating coronary disease, are also beneficial in retarding the progression of AS.[5,6] Results of randomized clinical trials are pending.

Another common cause of AS is bicuspid aortic valve. This common congenital abnormality, which occurs in about 1% of the United States population, leads to AS in about half the patients born with it. When AS occurs in such patients it usually develops in the fifth and sixth decades of life, 20 to 30 years earlier than occurs in previously normal tricuspid aortic valves. It is thought that in both bicuspid and tricuspid valves, the etiology of AS, when it occurs, is similar to that of atherosclerosis.

Occasionally, congenital aortic stenosis is detected for the first time in adulthood. This disease differs somewhat from the acquired disease discussed above. In congenital AS, there is usually extensive concentric hypertrophy and

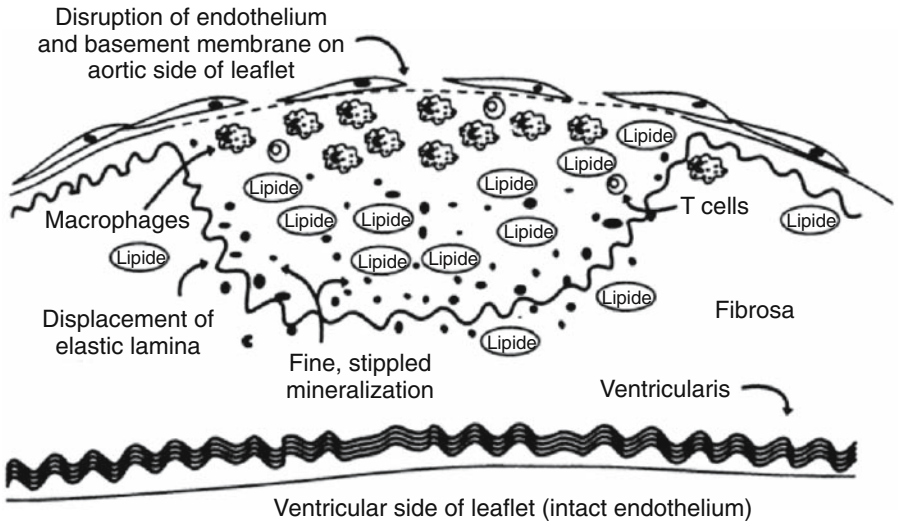

FIGURE 15.1. A schematic representation of the early lesion of aortic stenosis emphasizes the presence of macrophages and lipids similar in nature to the plaque of coronary disease.

supernormal ejection performance.[7] Sudden death is possibly more frequent in the absence of symptoms in congenital versus acquired AS, although data to support this are sketchy. Finally, because the leaflets are joined at the commissures instead of being heavily calcified, balloon valvotomy may produce excellent relief of congenital AS,[8] a result rarely seen in acquired AS.

Pathophysiology and Its Relation to Symptoms

As discussed below, the development of the classic symptoms of AS—angina, syncope, or dyspnea (and other symptoms of heart failure)—represent a dramatic inflection in the natural history of the disease with little risk of sudden death in the asymptomatic state and extreme risk once symptoms have developed. Thus an understanding of the intertwining of symptoms with the disease's pathophysiology is key in understanding the disease.

Pressure Overload

Normally the aortic valve offers little resistance to forward flow. Once open, pressures on both sides of the valve are virtually identical (Fig. 15.2A).[9] Near equalization of systolic pressures in the left ventricle (LV) and aorta remains until the aortic valve area becomes less than half of its normal 3 to 4 cm^2. However, as valve stenosis worsens, a pressure gradient between LV and aorta develops (Fig. 15.2B). This gradient represents the additional pressure work (pressure overload) that the LV must develop in order to propel blood across the narrowed valve.

Although occasionally debated, there is general consensus that a major compensatory mechanism for accommodating the pressure overload is the development of left ventricular hypertrophy (LVH). Left ventricular ejection performance is determined by preload, afterload, and contractility. One expression for afterload is wall stress (σ) = $p \times r/2th$, where p is the LV pressure, r is the LV radius, and th is the LV thickness. As the pressure term of this Laplace equation increases in the numerator, it can be offset by concentric LVH that increases the thickness term in the denominator.[10,11] By normalizing afterload, concentric LVH helps to maintain normal ejection performance. Paradoxically, LVH may be pathologic instead of compensatory. In general, in heart disease, LVH is associated with adverse events.[12–14] In addition, LVH may also

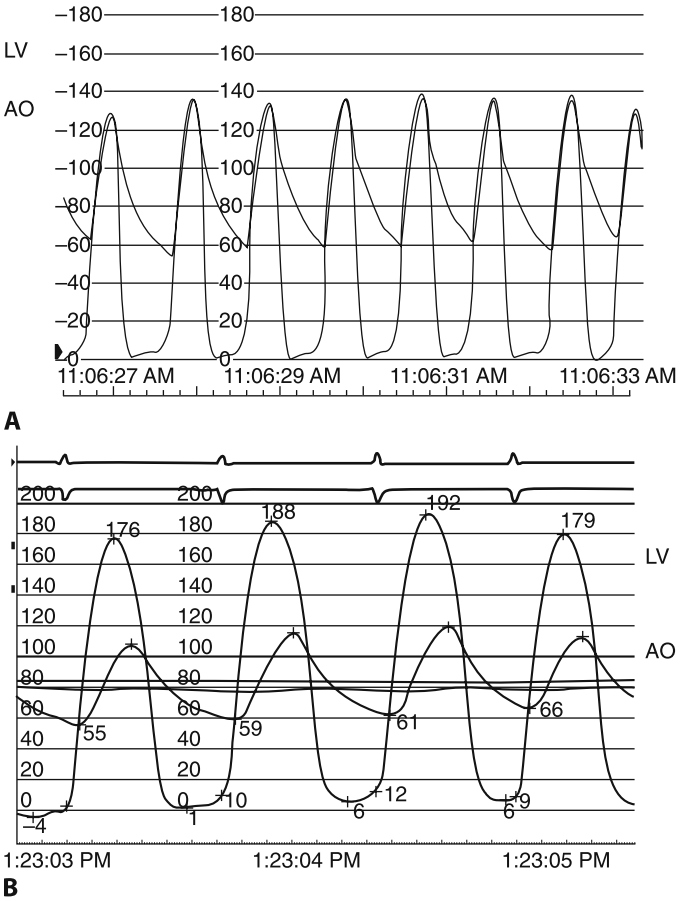

FIGURE 15.2. (A) Simultaneous left ventricular and aortic pressure tracings from a normal subject are shown. (B) The pressure gradient across a stenotic aortic valve.

be responsible in part for some of the symptoms of AS, symptoms that presage morbidity and mortality.

Angina

When angina occurs, it indicates myocardial ischemia that develops when myocardial oxygen demand outstrips oxygen supply. As noted above it would be expected that many AS patients would also have coronary artery disease, and this is so in about half of AS patients.[15,16] However, many patients with AS who experience angina have normal epicardial arteries invoking another cause for angina. In part, angina in such patients is due to diminished coronary blood flow reserve.[17] Normal subjects can increase coronary blood flow six- to eightfold during stress, an increase necessary to meet the oxygen demands of increased workload. However, patients with AS have reduced coronary blood flow reserve of only two- to threefold, a deficit related to LVH. The exact mechanism of this deficit is unknown but is thought to be secondary to the reduced capillary density per gram of myocardium. A second mechanism of reduced flow reserve in LVH is that elevated filling pressure that often accompanies it compresses the endocardium during diastole (when coronary blood flow occurs), in turn impeding blood flow.[18] While reduction in coronary blood flow reserve must in some way play a role in the angina of AS patients, it is not the complete explanation because many patients with severe LVH do not have angina. In fact, wall thickness, valve area, pressure gradient, and other hemodynamic factors have failed to predict when patients with AS will develop angina. The measurable hemodynamic parameter best associated with angina occurrence is diastolic filling time.[19] During every cardiac cycle the heart expends energy during systole when coronary blood flow ceases incurring an oxygen debt. This debt is repaid by coronary blood flow during diastole. The ratio of systolic ejection period (debt period) to diastolic filling time (repayment period) appears to be the best predictor of when angina might develop.

Syncope

Syncope is the temporary loss of consciousness. Cardiac syncope occurs when blood flow to the brain is inadequate to maintain satisfactory perfusion. The mechanism of syncope in AS is not well established, although many theories abound. When syncope does occur in AS it almost always does so during exercise. In normal subjects and in those with AS, exercise causes vasodilatation and reduced total peripheral resistance. Blood pressure is the product of total peripheral resistance and cardiac output. In normals, cardiac output increases more than total peripheral resistance falls during exercise so that blood pressure increases. However, it is thought that in patients with AS who develop syncope, cardiac output is restricted by the narrowed aortic valve. Thus peripheral resistance decreases during exercise while cardiac output is fixed so that blood pressure must fall, in turn leading to syncope in some cases. In other cases, because pressure gradient is proportional to the square of the cardiac output, high LV pressure during exercise is postulated to cause a vasodepressor response, in turn leading to syncope. In still other cases, exercise-induced atrial or ventricular arrhythmias may cause reduced cardiac output and syncope.

Congestive Heart Failure

Heart failure is often classified as deriving from systolic dysfunction, diastolic dysfunction, or both. In AS both portions of the cardiac cycle are usually abnormal. Diastole is usually divided into the isovolumic relaxation phase, the rapid filling phase, and atrial contraction. All may be abnormal in AS. In AS and in conditions causing concentric LVH in general, the isovolumic relaxation phase is delayed.[20] During this active phase of myocardial relaxation, calcium is pumped back into the sarcoplasmic reticulum reducing actin-myosin interaction. Calcium removal is slowed in LVH, presumably due in part to reduced SERCA 2 activity.[21] In turn this delays the onset of the early rapid filling phase, shortening the filling time.

During active filling, the pressure-volume relationship is shifted upward and to the left (Fig. 15.3).[20,22] Thus for any given filling volume, filling pressure is increased, reflecting the increased stiffness of the hypertrophied chamber. Stiffness is increased because the left ventricular wall is thicker than normal and because the collagen content of the myocardium is increased. Slowed early relaxation together with a stiffer myocardium result in increased LV filling pressure that is referred to the lungs, resulting in pulmonary congestion. Increased myocardial stiffness also results in greater than normal dependence on atrial contraction for adequate ventricular filling. Thus patients with AS are especially dependent on their left atrial "kick" and may decompensate rapidly if atrial fibrillation occurs.

Systole is also often abnormal in patients with AS. The major determinants of systole are preload, afterload, and contractility. The last two of these properties are often disordered in AS. As noted above, LVH is thought to be a compensatory mechanism that helps normalize afterload, enhancing LV systolic performance. If the amount of hypertrophy that developed were just enough to offset the increased

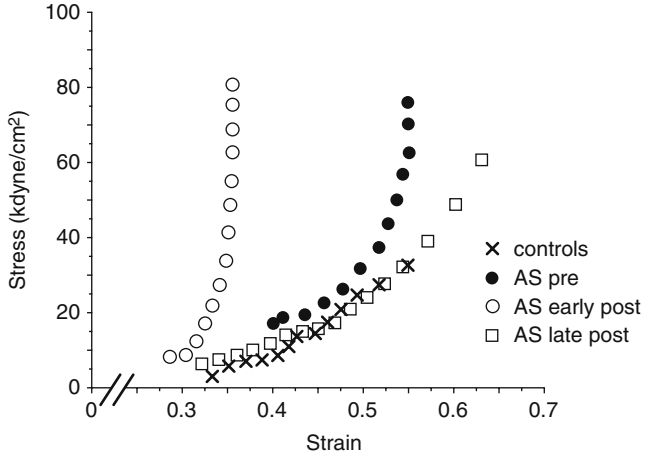

FIGURE 15.3. Myocardial stiffness (stress vs. strain) is shown for control subjects and aortic stenosis patients before, and early and late after aortic valve replacement (AVR). Prior to surgery, myocardial stiffness is greater in aortic stenosis (AS) than in normal subjects. Early after AVR stiffness increases because the muscle elements of the myocardium regress more quickly than the stiffer collagen elements. Eventually, stiffness returns to normal.

pressure term in the Laplace equation, ejection performance should be normal, and frequently it is. However, in some cases the LVH is inadequate to normalize wall stress and thus afterload increases, reducing ejection fraction (Fig. 15.4),[23] in turn leading to congestive heart failure. Interestingly, in some cases (especially in children and older women) the hypertrophy that develops seems in excess of that needed to normalize wall stress, stress is reduced, and ejection fraction is actually increased.[7,24] Although this phenomenon is beneficial for systolic performance, the increased wall thickness impairs diastolic filling.

Although in some cases, reduced systolic performance is due to increased afterload, noted above, in other cases contractility is reduced.[23] Currently, the exact mechanisms responsible for reduced contractility in the face of concentric LVH are uncertain. Myocardial ischemia due to reduced coronary blood flow,[16] abnormal calcium handling,[25] and abnormalities of the myocardial cytoskeleton[26] have been implicated.

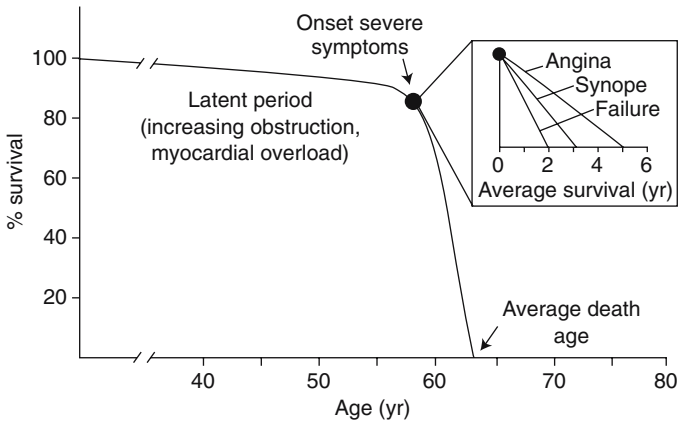

FIGURE 15.5. The natural history of AS is shown, demonstrating a dramatic reduction in survival once symptoms develop.

Natural History

As shown in Figure 15.5, the onset of symptoms in AS is a critical turning point in the natural history of the disease.[27–29] The asymptomatic patient has a nearly normal prognosis, yet once the classic symptoms of angina, syncope, or dyspnea develop, survival is abruptly reduced. In fact, taken as a whole, once these symptoms develop, mortality is about 2% per month. Following the development of angina, about 50% of such patients succumb in 5 years. If syncope occurs, 50% survival is 3 years, whereas the patient with dyspnea or other symptoms of heart failure has a 50% survival of only 2 years without aortic valve replacement. Thus a careful probing history is crucial in managing the patient with AS.

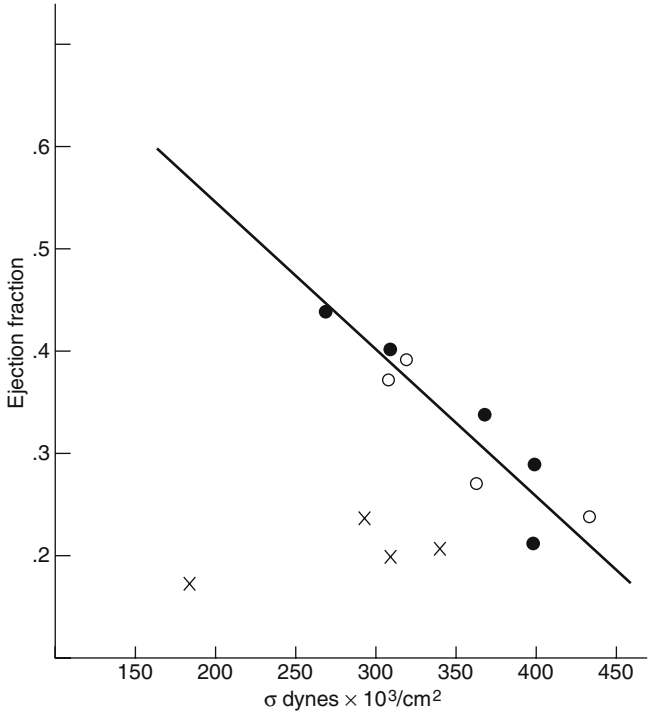

FIGURE 15.4. Afterload (wall stress,σ) is plotted against ejection fraction for aortic stenosis patients in heart failure. In some cases (circles) the reduction in ejection fraction is accounted for by increased stress. In other cases (×'s) ejection fraction is reduced more than can be accounted for by elevated afterload, implying reduced contractility.

Physical Examination

The physical examination of the patient with AS is quite instructive as to the severity of the disease. The apical impulse is usually not displaced but is sustained and forceful. The carotid upstrokes are classically delayed and reduced in volume (parvus et tardus; Fig. 15.6).[30] By placing one hand on the patient's forceful apical beat with the other hand on the patient's reduced carotid upstroke, the examiner can deduce the severity of the obstruction between left ventricle and the vasculature. The murmur of aortic stenosis is a systolic ejection murmur radiating to the neck. Thus S_1 is heard followed by a short quiet period as the LV develops enough pressure to initiate ejection at which time the murmur commences. As the severity of AS worsens, the murmur peaks progressively later in systole until it becomes maximal just before S_2. In some cases the murmur is loudest in the aortic area, decreases over the sternum, and increases again over the LV apex (Gallavardin's phenomenon), misleading the auscultator into thinking that two murmurs, one of AS and a second of mitral regurgitation, are present. The murmur of AS may be quite loud and accompanied by a thrill. Paradoxically, as the disease severity worsens, the murmur becomes softer as less stroke volume is delivered to the valve by a progressively impaired LV.[31] Thus a soft murmur by itself should not be taken to indicate that the disease is mild. In most cases the second heart sound becomes single as the aortic component from a dysfunctional valve is lost. Today,

FIGURE 15.6. A normal carotid upstroke (left) is compared to the carotid upstroke of a patient with aortic stenosis (right).

detection of AS usually occurs before severe LV dysfunction develops. Thus paradoxic splitting of S_2 due to delayed emptying of a severely weakened LV, which was noted in older texts, is now rare.

Diagnostic Testing

The electrocardiogram (ECG) and chest x-ray may give clues to the presence of AS, but these modalities are rarely diagnostic. The ECG typically demonstrates the pattern of LVH, although severe AS may exist without such evidence. The chest x-ray may show a boot-shaped heart consistent with concentric LVH. Occasionally the calcified aortic valve is seen in the lateral view. However, the mainstay of diagnosis is the echocardiogram with Doppler interrogation of the aortic valve. While in severe disease two-dimensional (2D) echo demonstrates a thickened, immobile, heavily calcified valve, it is the Doppler examination that can fairly precisely quantify stenosis severity. Because flow equals the area times the velocity, bloodstream velocity must increase when it reaches the narrowed aortic valve. Sound waves transmitted from an ultrasound transducer collide with the accelerating red blood cells that compress the sound waves, increasing their frequency. This increase is detected by the transducer that now acts as a receiver, converting the difference between the frequency sent and the frequency received into a velocity that in turn can be converted into a pressure gradient or valve area.

Because almost all patients with AS are old enough to be at risk for coronary disease and because AS and coronary artery disease hold risk factors in common, most patients with AS should undergo cardiac catheterization to perform coronary angiography prior to aortic valve replacement (AVR), although this test may be replaced by multislice computed tomography (CT) scanning in the future. While several studies have examined the use of nuclear imaging as a noninvasive test to detect the presence of coronary disease, nuclear studies in the presence of AS have not been accurate enough to supplant angiography prior to AVR.[32,33] In most cases the severity of the AS has been assessed accurately noninvasively prior to catheterization, obviating the need to obtain a pressure gradient using simultaneous recording of LV and aortic pressure (Fig. 15.2). However, in a minority of cases, AS severity is still unclear at the time of catheterization, necessitating evaluation of the valve invasively. In that case, valve area is calculated using the Gorlin formula,[34] employing measured cardiac output and direct pressure measurement. In recording the gradient it is crucial that the catheters be placed in the proper position with one catheter well inside the body of the LV and the second catheter placed in the ascending aortic to avoid errors in pressure measurement.[35] However, the need to use two catheters can be avoided by using instead a double-lumen or double-transducer catheter or by a carefully recorded catheter pullback in patients in sinus rhythm.

Medical Therapy

For asymptomatic patients with AS, no medical therapy is indicated other than antibiotic prophylaxis for bacteremia-causing procedures. Once patients develop symptoms, surgery is necessary to prevent death (see below). Thus the only indication for medical therapy in this disease is in the case of symptomatic patients in whom surgery cannot be performed because of existing comorbidities. In such cases diuretics can be used with caution to treat congestive heart failure, and nitrates may be used to relieve angina. Vasodilators may be helpful in severe heart failure but must be used with extreme caution to avoid hypotension.[36] In a recent study, nitroprusside improved hemodynamics in patients with pulmonary edema. This agent is believed to be useful not because it reduces afterload (which is fixed by the stenotic valve) but by reducing LV end diastolic pressure. This action of the agent may improve coronary blood flow, enhancing LV function.

Timing of Surgery

Asymptomatic patients with severe AS have a good prognosis with a minimal risk of sudden death or other complications until symptoms develop.[27–29] Thus as noted above, the onset of symptoms represents a crucial demarcation point in the natural history of the disease and indicates the need for prompt AVR because AVR dramatically improves outcome.[37] In some patients symptomatic status may be hard to ascertain even after obtaining a careful history. In such patients a carefully performed exercise test may be quite helpful[38,39] in confirming symptom status. While exercise testing is clearly contraindicated in symptomatic patients, the procedure is becoming more widely accepted in patients in whom symptomatic status is uncertain. Such patients are likely to exercise anyway, and the development of symptoms during formal testing or evidence of less than expected exercise tolerance indicates a high risk for requiring AVR in the near future.

When symptoms are present, the question arises as to whether the patient's AS is severe enough to be their cause. While no "critical" valve area is agreed upon, because symptoms appear at a wide variation in the valve area,[40] in general, if the valve area is $<1.0\,cm^2$ or if the mean gradient exceeds 50 mm Hg or if peak jet velocity exceeds 4.0 m/s, severe AS is usually present and the patient's symptoms are logically attributable to it. Because reduced cardiac output reduces gradient, severe AS may be present in patients with heart failure and lower gradients. However, in most such patients, the ratio of outflow tract velocity to velocity at the aortic valve is <0.25, another index of severe aortic stenosis.

Asymptomatic Patients with Severe Aortic Stenosis

Although stenosis severity is important in the progression to symptoms, no valve area or gradient has been shown to cause symptoms by itself. Not surprisingly, then, some patients develop severe asymptomatic AS. While the short-term prognosis in such patients is excellent without surgery, there is still a small but definite risk of sudden death.[29,41] Obviously there is also a small but definite risk of morbidity and mortality related to aortic valve replacement and to complications resulting from the presence of a prosthetic valve.[42–47] Thus the clinician is faced with a dilemma. Whether the strategy is surgery in the absence of symptoms or watchful waiting, there is a small but definite risk. While there is no

definite solution to the problem, one strategy is to use the results of exercise testing as noted above. For the truly asymptomatic patient who performs well on the treadmill, there is no compelling reason to proceed with AVR. If symptoms are manifest during the test, or if there is hypotension or arrhythmia, early AVR should be considered. The difficulty in knowing how best to manage the asymptomatic patient with severe AS has led to an interest in biomarkers. Recent studies have found elevated B-type natriuretic peptide (BNP) in some asymptomatic patients with severe AS. In one study elevated BNP greatly increased the risk of symptom onset in the year following the initial test.[48]

Aortic Valve Replacement in Patients with Reduced Ejection Fraction

As shown in Figure 15.4, in some AS patients with low ejection fractions, reduced ejection performance is due to the afterload excess caused by high systolic LV pressure and limited hypertrophy inadequate to normalize wall stress. In such patients AVR causes a prompt reduction in afterload, ejection fraction returns to or toward normal, and prognosis is excellent.[23] However, in other patients, those with a low transvalvular gradient, ejection fraction is depressed below that which can be attributed to afterload mismatch. In this case there is severe LV muscle dysfunction and outcome following AVR is much less favorable. However, some such patients may improve dramatically following AVR,[49–51] and the obvious clinical challenge is to judge which low gradient, low ejection fraction patients are likely to benefit from AVR.

The first task is to divorce true aortic stenosis from a condition sometimes referred to as aortic pseudostenosis. In the former case severe valve disease has led to severe LV dysfunction, a low output, and a low gradient. In the second condition, a ventricle weakened from another cause such as coronary disease is unable to open a mild to moderately stenotic valve to its full aperture. In both cases the valve area at rest will be quite reduced. However, in true stenosis, when cardiac output is increased by exercise or inotropic infusion, the gradient increases in tandem and the valve area increases only slightly.[52–55] In pseudostenosis when cardiac output is increased, the gradient does not increase proportionately and as a consequence calculated valve area increases substantially, often to >1.0 cm^2. Because such patients do not have severe aortic stenosis as the cause of their heart failure, they are unlikely to benefit from AVR.

For the patients with severe aortic stenosis and low gradient and low ejection fraction, response to dobutamine infusion is an important indicator of prognosis. As shown in Figure 15.7, if dobutamine infusion increases cardiac output by >20% (with inotropic reserve, group I), prognosis following AVR is much better than similar patients treated medically and much better than those patients without inotropic reserve (group II) treated medically or with AVR.[56]

The Patient with Mild to Moderate Aortic Stenosis Undergoing Coronary Revascularization

As noted above, AS and coronary disease are likely to be manifestations of the same pathologic process and thus often coexist. Not infrequently, a patient who requires coronary revascularization also has AS. When the AS is severe, obviously both are corrected during the same surgery. A more problematic situation arises when the patient requiring bypass surgery has milder AS, AS of severity that by itself, would not be a reason to perform AVR. On the one hand, concomitant AVR adds surgical risk and exposes the patient to the risks of harboring a prosthetic valve. On the other hand, leaving significant valve disease behind at the time of coronary revascularization may result in a second operation in the near future if the patient's AS progresses rapidly. It appears that for patients with moderate AS and a gradient of >30 mm Hg or an aortic valve area of <1.3 cm^2, AVR should be performed at the time of coronary (or other heart) surgery.[57] For gradients of <10 mm Hg, AVR should be avoided. In the middle ground, with gradients between 10 and 30 mm Hg, valve morphology at echocardiography may be helpful, providing an impetus toward AVR for heavily calcified immobile appearing valves.

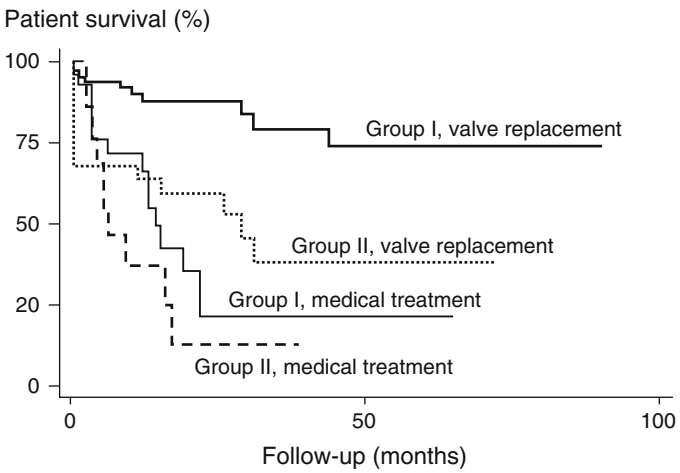

FIGURE 15.7. The outcome of low-gradient, low-ejection fraction patients is shown. Patients with inotropic reserve treated with AVR had the best results by far.

The Elderly Patient with Aortic Stenosis

It is well known that elderly patients, even those in their nineties, may have an excellent result following AVR. Indeed age-corrected survival following AVR for AS is normal for patients over the age of 65.[58] Nonetheless, the elderly patient is subject to a host of comorbidities that affect outcome.[59–61] In recommending AVR for the elderly patient, the co-presence of coronary disease, neurologic deficits, and renal and pulmonary dysfunction all worsen prognosis and must be taken into consideration. Especially in this age group, the patient's expectation of outcome and lifestyle must be considered in choosing AVR therapy.

The Percutaneous Approach to Aortic Stenosis

Although balloon aortic valvotomy (BAV) is useful in children with congenital AS, the calcified lesion of acquired AS in the adult does not respond well to BAV. After a modest acute reduction in stenosis severity,[62,63] restenosis recurs usually within 6 months and BAV has not been shown to

alter the high mortality of symptomatic AS.[64] Thus BAV is reserved only as a palliative measure for patients in whom AVR is impossible because of comorbid conditions.

Percutaneous aortic valve replacement is being examined as a therapy for AS. After the native valve is dilated by expansion of a large balloon, a stented bioprosthesis is deployed into the aortic annulus. Although residual calcium deposits existing from the native valve may restrict seating, leading to mild aortic regurgitation, the initial results in patients in whom surgical AVR was contraindicated are promising.[65]

Aortic Regurgitation

Etiology

Aortic regurgitation (AR) is caused by pathology of either the valve leaflets or the aortic root. As noted above, bicuspid aortic valve is a common congenital abnormality often associated with aortic stenosis. However, in other cases this same defect may lead to aortic regurgitation. In such cases there is usually concomitant dilatation of the proximal aortic root leading to valve cusp separation and incompetence. While such expansion was often labeled "poststenotic" dilatation when even mild AS was present, it is now recognized that abnormalities inherent in root composition are responsible for its dilatation.[66] Such dilatation (annuloaortic ectasia) may also be seen in patients with tricuspid aortic valves and is associated with aging and hypertension. Other causes of aortic regurgitation include infective endocarditis aortic dissection, Marfan syndrome, rheumatic fever, and collagen vascular disease, especially ankylosing spondylitis. Appetite-suppressant drugs have also caused both aortic and mitral valvular insufficiency (see later in the chapter).

Pathophysiology and Its Relation to Symptoms

As shown in Figure 15.8,[67] AR imparts a volume load on the left ventricle, as the cardiac output that regurgitates into the LV during diastole must be compensated for by an increase

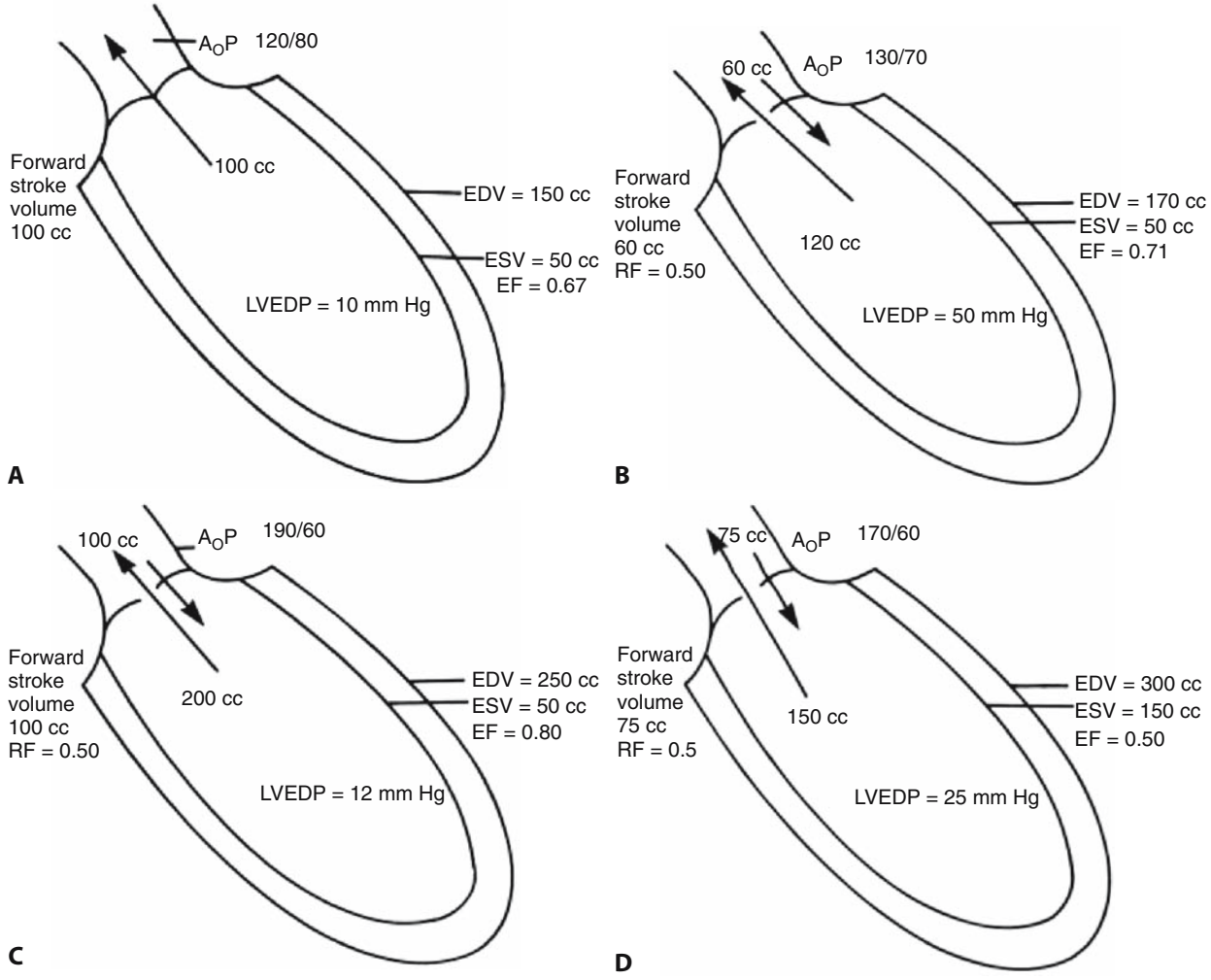

FIGURE 15.8. The pathophysiologic stages of aortic regurgitation (AR). Normal physiology (A) is contrasted with acute AR (B). In acute AR little left ventricle (LV) dilatation has occurred so that total stroke volume and forward stroke volume are reduced. The large filling volume due to the AR is thrust into a small LV resulting in high LV filling pressure. (C) Compensatory left ventricular hypertrophy (LVH) has developed. Cardiac enlargement now allows normal forward stroke volume and LV filling pressure. The large total stroke volume results in a wide pulse pressure that is responsible for many of the signs of AR. (D) Muscle dysfunction has developed, resulting in increased end systolic volume, reduced forward stroke volume, and elevated LV filling pressure. LVEDP, left ventricular end-diastolic pressure.

in total stroke volume. However it must be recognized that this large compensatory total stroke volume increases pulse pressure and systolic pressure. Thus the volume overload of AR is also associated with a significant pressure overload. In fact, systolic wall stress in AR may be as high as occurs in AS and the lesion more typically thought of as a pressure overload.[68,69] Accordingly, LV wall thickness in AR is greater than normal as the ventricle remodels to accommodate the increased pressure demands on the LV.[70] This combined pressure and volume overload causes LV mass in AR to be the greatest of all the valvular heart diseases.

Aortic regurgitation may be tolerated in the compensated state for years. Compensation is provided by ventricular remodeling (Fig. 15.8) whereby the enlarged LV can pump enough extra stroke volume to maintain adequate perfusion even during exercise. At the same time the enlarged LV can accommodate the increased filling volume of the LV at fairly normal filling pressure, preventing pulmonary congestion. Eventually, however, eccentric hypertrophy fails to compensate for the volume overload and concentric hypertrophy fails to normalize systolic wall stress, both acting in concert to reduce cardiac output. In turn, increased residual LV volume and diastolic dysfunction lead to elevated LV filling pressure. At this point in the course of the disease, CHF symptoms may appear.

While much less common in AR than in AS, angina may occur with normal epicardial coronary arteries. Angina is presumed to be caused by the reduced coronary flow of reserve of LVH together with reduced diastolic aortic pressure for driving coronary flow. This same reduction in diastolic pressure may occasionally be associated with syncope.

Rare symptoms of AR include flushing episodes, carotid artery pain, and an annoying awareness of the heartbeat.

Physical Examination

The physical examination of the patient with AR is rich with dynamic findings. Palpation of the precordium finds an active point of maximum impulse, displaced downward and to the left. The diastolic blowing murmur typical of AR is heard best over the left upper sternal border when the patient is sitting upright and leaning forward. A diastolic rumble may also be heard at the apex. This murmur (Austin Flint) arises from the mitral valve. Its origin is thought to be due to either relative mitral stenosis, as LV filling from the aorta tends to close the mitral valve in diastole, or the aortic jet striking and vibrating the mitral valve. In either case the presence of an Austin Flint murmur usually indicates severe AR.

The large total stroke volume and widened pulse pressure of AR generate myriad signs. These include de Musset's sign (bobbing of the head in cadence with the heartbeat), Duroziez's sign (a to-and-fro bruit over the femoral artery when it is compressed by the bell of the stethoscope), Quincke's pulse (plethora and blanching of the nail bed when traction is placed on the nail), and Corrigan's pulse (rapid upstroke and brisk downstroke of the carotid pulse). Perhaps the most reliable indicator or severe AR is Hill's sign, which is augmentation of systolic pressure in the leg by >40 mm Hg more than in the arm.

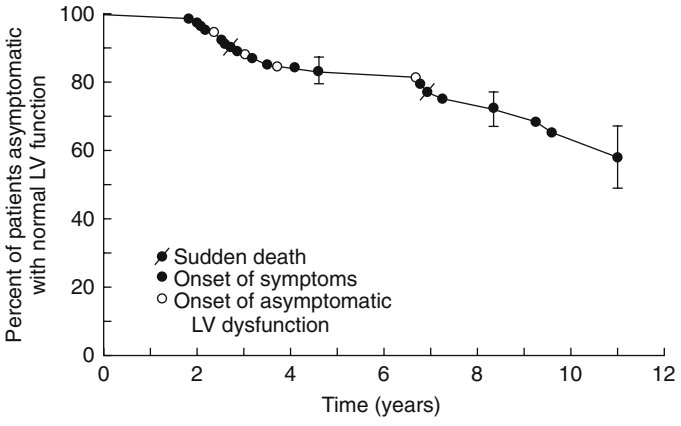

FIGURE 15.9. The natural history of AR is shown. The onset of symptoms or LV dysfunction occurs at a rate of about 4.5%/year.

Therapy

Medical Therapy

As noted above, aortic regurgitation increases left ventricular afterload. Thus it is logical that afterload reduction therapy might be advantageous. In fact several studies have shown either reduction in LV volume or a delay to onset of symptoms when vasodilators were added to the regimen.[71–74] In most cases vasodilators were administered to asymptomatic patients with normal LV function. Recently nifedipine administered to patients already manifesting LV dysfunction provided a long-term mortality benefit following AVR even though the drug had been discontinued following surgery.[75] The mechanism of this benefit is unknown. Which vasodilator is the best agent to use is unknown because no direct comparison of chronically used agents has ever been made. While use of vasodilators in this disease of high afterload is logical, such use should be weighed against preliminary reports of failed long-term benefit.[76]

Surgical Therapy

Aortic regurgitation, like all valvular heart diseases, is a mechanical problem that requires a mechanical solution. Although a minority of regurgitant aortic valves can be repaired, for the most part the mechanical solution for AR is AVR. Thus as with AS, surgery should be timed to avoid unnecessary patient-years of risk from a prosthetic valve complication, but must be timed early enough to avoid the risk of persistent LV dysfunction following AVR. The natural history of several AR is shown in Figure 15.9.[77] The average risk of developing symptoms or asymptomatic LV dysfunction is about 4.5% per year. Thus many patients can tolerate severe AR for a decade or more without negative sequelae. However, once more than mild symptoms occur[78] (Fig. 15.10) or if LV dysfunction develops and is allowed to persist, the prognosis is reduced.[79–83] While the exact definition of LV dysfunction is unclear, the prognosis diminishes when LV ejection fraction falls below 0.55 or when the LV is unable to contract down to 50 to 55 mm Hg at the end of systole. It is

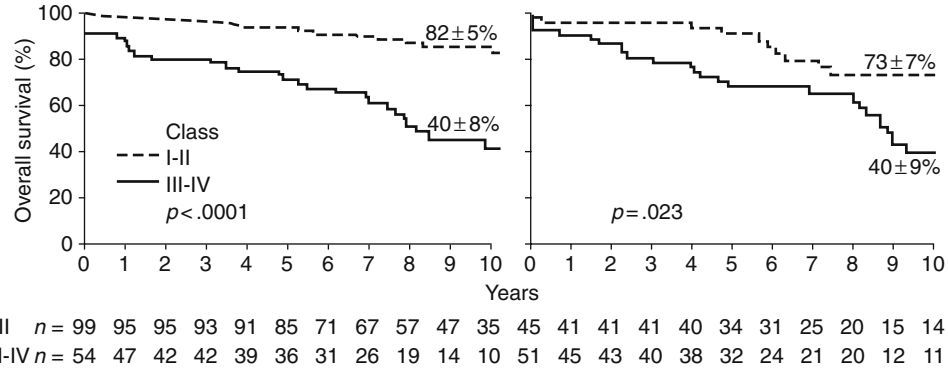

FIGURE 15.10. Outcome of patients with AR and reduced ejection fraction (left panel) and normal ejection fraction (right panel) is shown. In either case, advanced symptoms greatly reduced survival following AVR.

presumed that these benchmarks represent evidence of significant LV dysfunction. Thus AVR should be performed in AR patients if even mild symptoms occur or if there is evidence of LV dysfunction as noted above. Following surgery, reduction in afterload allows LV ejection fraction to improve, especially if LV dysfunction has been present for less than 15 months.[78,84]

Acute Aortic Regurgitation

Acute severe aortic regurgitation (AR), such as might occur following the perforation of an aortic leaflet by infective endocarditis, is a potentially life-threatening emergency that is often underrecognized. Treated medically, this disease has up to 75% mortality while surgical intervention reduces risk to 25% or less. Recent analysis clearly favors early surgery in such patients.[85] In acute severe AR, the unprepared small LV must accept a large regurgitant volume, in turn increasing LV diastolic filling pressure. At the same time, diastolic aortic pressure falls due to increased run-off of blood into the LV. The net result is reduced driving pressure for coronary blood flow, potentially leading to myocardial ischemia, setting up a vicious cycle of reduced coronary flow leading to reduced LV function leading to reduced coronary flow, etc. Of concern is that this pernicious physiologic state is difficult for the clinician to recognize. As noted above, the physical examination of the patient with chronic AR is very dynamic, based on increased total stroke volume and pulse pressure. However, in acute AR, there has been no time for LV dilatation; thus most of the findings of chronic AR are absent. Instead the murmur of AR is short and unimpressive because rapid LV filling at high pressure reduces the gradient for AR. Also rapid LV filling from AR causes early closure of the mitral valve so that s_1 is soft. Yet if preclosure of the mitral valve is confirmed echocardiographically, the prognosis without AVR is dire.[86] While medical therapies to stabilize the patient are often attempted, they usually fail. Vasodilators used to decrease the amount of AR also reduce systemic blood pressure in patients who are often hypotensive to begin with. Pressor agents with vasoconstrictor properties increase the amount of AR and thus are deleterious. On the other hand, delay in performing AVR because of fear that the replacement valve will become infected is unjustified because reinfection even with valve insertion within 48 hours of a positive blood culture is extremely rare, especially when a homograft is inserted.[87] Thus in acute AR, extreme vigilance for the earliest evidence of heart failure must be practiced, and steps toward AVR must be initiated as soon as such evidence is recognized.

Obesity Drugs, Valvular Heart Disease, and Pulmonary Hypertension

Fenfluramine and Phentermine

The appetite-suppressants dexfenfluramine and the combination of fenfluramine and phentermine (Fen/Phen) have been associated with an unanticipated outbreak of valvular heart disease associated with their administration.[88] Pulmonary hypertension occurs in association with another appetite suppressant, aminorex fumarate.[89] Aminorex (Menocil) resembles epinephrine and amphetamine in chemical structure, and its toxic effects have been attributed to the release of norepinephrine and other catecholamines.[90] Aminorex became available in 1965 in Austria, Germany, and Switzerland, and in the next 7 years the incidence of pulmonary hypertension increased by approximately 10-fold.[89] Pulmonary hypertension in humans associated with aminorex use often progresses, but it may regress when the drug is discontinued. Fen/Phen usage has also been associated with the development of pulmonary artery hypertension.[91]

In the mid-1990s, more than 18 million prescriptions were filled for Fen/Phen, mainly for overweight women.[91] There had already been occasional reports of pulmonary hypertension in association with the use of fenfluramine[92] and phentermine alone.[93] Connolly et al.[88] from the Mayo Clinic had already published a series of patients taking Fen/Phen who had developed left ventricular valvular lesions, most frequently aortic insufficiency, but also mitral insufficiency that was sometimes severe enough to require surgical valve repair or replacement. The cardiac valve lesions in patients who have taken Fen/Phen are very similar to those seen in patients with metastatic carcinoid tumors, and both appear to be a consequence of very high serotonin concentrations in the blood.[93,94] It appears that selected appetite suppressant drugs, such as Fen/Phen, diminish the ability of the lungs to extract serotonin from the circulation.[95] It has been speculated that (1) an inherited susceptibility to aminorex and fenfluramine predisposes individuals to vasoconstriction and obliterative pulmonary vascular lesions predominantly in the precapillary muscular arteries and arterioles of

the lungs; and (2) impaired clearance by the lungs of biologically active substances, such as serotonin, enables toxic concentrations of the agent to reach and damage LV heart valves, leading to aortic or mitral valvular regurgitation.[91]

Based on data showing the prevalence of abnormal valve regurgitation of approximately 30% in 291 patients treated with dexfenfluramine, dexfenfluramine phentermine, or fenfluramine-phentermine as compared to 2% in controls, fenfluramine and dexfenfluramine were withdrawn from the market in 1997.[96,97] Efforts to identify the incidence of aortic or mitral valve regurgitation in patients using dexfenfluramine have suggested that 7.6% of patients using dexfenfluramine and 2% of controls develop at least aortic or mitral insufficiency, with mild AR being the most frequent lesion.[96] Other factors also related to the development of valvular heart disease in these patients include older age, higher blood pressure, and shorter time from discontinuation of the drug.[96]

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