

Review Article

Medical Progress

VALVULAR HEART DISEASE

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THE past 15 years have brought a remarkable improvement in the clinical outcome of patients with valvular heart disease. It is impossible to attribute the change to any single advance in the field. However, it is likely that more effective noninvasive monitoring of ventricular function, improvement in prosthetic valves, advances in valve-reconstruction techniques, and the development of useful guidelines for choosing the proper timing of surgical intervention have all worked in concert to improve prognosis. Moreover, advances in minimally invasive surgical techniques may make valve procedures more easily tolerated by the patient.¹

All valvular heart diseases place a hemodynamic burden on the left or right ventricle, or on both ventricles, which is initially tolerated as the cardiovascular system compensates for the overload. However, hemodynamic overload eventually leads to muscle dysfunction and congestive heart failure, and sometimes sudden death. Two major questions must be answered in the management of every case of valvular heart disease: Is the valvular disease severe enough to cause morbidity or mortality for which mechanical intervention would be beneficial? And if the answer to this question is yes, what are the best medical therapy and the best time for surgical intervention to minimize or eliminate morbidity and mortality? We will discuss these questions for the four major acquired left-sided valvular lesions: aortic stenosis, mitral stenosis, nonischemic mitral regurgitation, and aortic regurgitation.

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AORTIC STENOSIS

Recognition

Acquired aortic stenosis is usually an idiopathic disease resulting from degeneration and calcification of the aortic leaflets.^{2,3} Stenosis is more likely to occur in persons born with bicuspid aortic valves than in those with normal tricuspid valves, and it develops earlier, in the fourth and fifth decades of life, in such persons. When the disease is acquired in previously normal tricuspid aortic valves, stenosis develops in the sixth, seventh, and eighth decades. Why some persons are afflicted by this disease whereas others are spared is unknown, but it shares some of the pathologic features of coronary atherosclerosis and is associated with some of the same risk factors, such as hypertension and hypercholesterolemia.⁴

The classic symptoms of aortic stenosis are angina, syncope, and the symptoms of congestive heart failure. Angina develops in aortic stenosis in part because of reduced coronary flow reserve and in part because of increased myocardial oxygen demand caused by high afterload.⁵⁻⁷

The origin of exertional syncope in aortic stenosis remains controversial. According to one theory, an exercise-induced decrease in total peripheral resistance is uncompensated because cardiac output is restricted by the stenotic valve.⁸ Another possible mechanism is the precipitation of a vasodepressor response.⁹

Heart failure in aortic stenosis can be caused by diastolic dysfunction, systolic dysfunction, or both. Diastolic dysfunction results from increased left-ventricular-wall thickness and increased collagen content.¹⁰ Systolic dysfunction results from excess afterload, decreased contractility, or a combination of these factors.⁷

The most common sign of aortic stenosis is a systolic ejection murmur radiating to the neck. The murmur is usually heard best in the aortic area. It often disappears over the sternum and then reappears in the apical area, mimicking mitral regurgitation (Gallivardin's phenomenon). In mild aortic stenosis, the murmur usually peaks early in systole, it is often associated with a thrill, and the carotid upstrokes are well preserved. As the severity of stenosis increases, the murmur peaks progressively later in systole and may become softer as cardiac output diminishes. The carotid upstrokes classically become diminished in amplitude and delayed in time (*parvus et tardus*). The second heart sound may become single as the aortic closing component is lost, or S₂ may become paradoxically split because of delay in left ventricular emptying.

Assessment of Severity

Echocardiography

Although a reasonable estimate of the severity of aortic stenosis can be made during physical examination, echocardiography with Doppler examination of the aortic valve now provides a more accurate assessment of the transvalvular gradient and the area of the aortic valve. Since flow is the product of cross-sectional area and bloodstream velocity, as the bloodstream reaches a narrowing (Fig. 1), velocity must increase for flow to remain constant.¹¹ This increase in velocity, detected by the Doppler technique, can be translated into a gradient (four times the velocity squared) that accurately mirrors the gradient assessed by direct pressure measurement,¹² or the velocity can be used in the continuity equation to estimate aortic-valve area (Fig. 1). Echocardiography is also useful in assessing the extent of left ventricular hypertrophy and in estimating left ventricular ejection performance.

Cardiac Catheterization and Coronary Angiography

The severity of aortic stenosis can usually be gauged accurately by noninvasive techniques. However, because patients with aortic stenosis are often elderly and therefore at risk for coronary disease, coronary angiography is usually performed before valve replacement, especially in patients with angina.^{13,14} Although initial attempts to detect coronary artery disease in patients with aortic stenosis by noninvasive techniques appear fruitful, further study will be required before this practice is adopted as routine.^{15,16} In cases where the severity of aortic stenosis cannot be determined by noninvasive testing, invasive measurement of the pressure gradient and determination of cardiac output are performed to derive data from which to calculate the area of the aortic-valve orifice.¹⁷

Timing of Surgery

Except for prophylaxis against endocarditis, there is no proved medical therapy for aortic stenosis. The only effective relief of this mechanical obstruction to blood flow is aortic-valve replacement.¹⁸ Although the noninvasive assessment of the severity of aortic stenosis is quite accurate and thus useful in determining the timing of surgery, it is not severity alone that determines the timing of aortic-valve replacement. Rather, the decision to replace the aortic valve is based on the presence of the classic symptoms of aortic stenosis (noted above) along with a severely stenotic valve.

As shown in Figure 2, the survival of patients with aortic stenosis is nearly normal until the onset of symptoms, when a precipitous decrease in survival occurs.¹⁹ The prognostic importance of symptoms in an early study has been corroborated by more recent

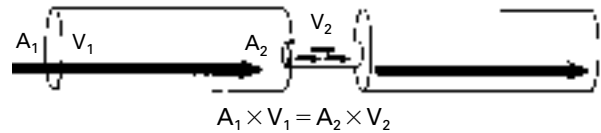


Figure 1. Principles of the Use of Doppler Ultrasonography and the Continuity Equation in Estimating Aortic-Valve Area.

For blood flow ($A_1 \times V_1$) to remain constant when it reaches a stenosis (A_2), velocity must increase to V_2 . Doppler examination of the stenosis detects the increase in velocity, which can be used to calculate the aortic-valve gradient or to solve the continuity equation for A_2 . A denotes area, and V velocity.

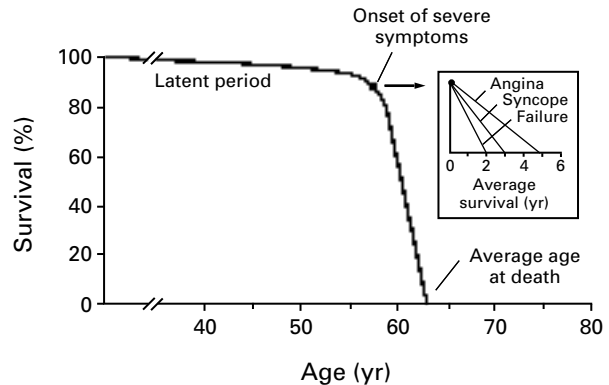


Figure 2. Natural History of Aortic Stenosis.

There is a long latent period of increasing obstruction and myocardial overload, during which the asymptomatic patient has a normal life span. However, once angina, syncope, or heart failure develops, survival is greatly reduced. If the aortic valve is not replaced, approximately 50 percent of patients will be dead within five years after angina develops, 50 percent will be dead within three years after syncope develops, and 50 percent will be dead within only two years after heart failure develops. Adapted from Ross and Braunwald,¹⁹ with the permission of the publisher.

studies in which Doppler echocardiography established the severity of stenosis in initially asymptomatic patients.^{20,21} About 75 percent of patients with symptomatic aortic stenosis will be dead three years after the onset of symptoms unless the aortic valve is replaced.²² Typically, a gradient of more than 50 mm Hg or a valve area of less than 0.8 cm² indicates critical stenosis that is capable of causing symptoms and death. However, there are exceptions to these rules. Some patients with larger valve areas or smaller gradients have symptoms that are clearly due to aortic stenosis. Such patients will benefit from aortic-valve replacement.

Age

It should be emphasized that even though most patients with aortic stenosis are elderly, the prognosis with surgery, even in an octogenarian, is excellent

in the absence of coexisting illnesses.²³⁻²⁵ Thus, age is not a contraindication to surgery in such patients. Furthermore, the age-corrected survival after aortic-valve replacement in patients older than 65 is not different from that in the general population.²⁶

Balloon Aortic Valvotomy

Balloon aortic valvotomy for adult acquired aortic stenosis is useful only for palliation of the disease. Although the procedure was initially greeted with enthusiasm, interest in balloon aortic valvotomy has waned in recent years. The rate of serious complications, including death, stroke, aortic rupture, aortic regurgitation, and vascular injury, exceeds 10 percent.²⁷ Furthermore, the mortality after this procedure is 60 percent at 18 months, a rate similar to that in an untreated population.²⁸ The event-free survival at two years is only 20 percent, and many patients thought to be candidates only for balloon valvotomy eventually have a good outcome with aortic-valve replacement.^{28,29}

Although the procedure is not lifesaving, it may be useful in alleviating symptoms in patients who are clearly not candidates for aortic-valve replacement because of other medical problems. Some practitioners have successfully used balloon valvotomy as a bridge to aortic-valve replacement in very sick patients. However, no controlled data are available to prove this approach superior to direct aortic-valve replacement.

Stress Testing

Although the presence or absence of symptoms is the key factor in the management of aortic stenosis, in some patients who have vague symptoms or for whom a reliable history is difficult to obtain, exercise testing may be useful to establish the symptomatic state more objectively. However, this procedure is attended by increased risk in patients with aortic stenosis, and it is ill-advised to perform exercise testing in patients who are symptomatic.³⁰ The test can be performed safely in asymptomatic patients or those with vague symptoms if great caution is used and a physician is present.³¹⁻³³ In such patients, exercise testing may provide additional information on which to base clinical decision making.

Patients with Congestive Heart Failure and Reduced Systolic Performance

For most patients with advanced congestive heart failure, even those with a marked reduction in the ejection fraction, aortic-valve replacement provides remarkable relief of symptoms and improved ejection performance, because relieving the obstruction to outflow reduces left ventricular afterload and might also eventually lead to the restoration of contractile function.³⁴⁻³⁶ However, a persistently problematic group of patients with aortic stenosis is the group

with a low ejection fraction and a low transvalvular gradient. Studies of this subgroup of patients have found high operative mortality and persistence of symptoms after surgery in many cases.^{34,37,38} However, it is clear that other patients in this group improve after surgery.³⁸

The criteria for deciding which patients in this group should have aortic-valve replacement continue to evolve. Initial studies indicate that patients in this group may have a favorable surgical outcome if both the cardiac output and the transvalvular gradient are increased by either inotropic stimulation or the administration of nitroprusside.^{39,40} Patients in whom inotropic stimulation augments cardiac output but not the transvalvular gradient form a group with milder stenosis that was not the primary cause of left ventricular dysfunction. Such patients are unlikely to benefit from valve replacement.

Women with Aortic Stenosis

Recently, differences in left ventricular geometry between men and women with aortic stenosis have been recognized.⁴¹⁻⁴³ Women with aortic stenosis are likely to have thicker ventricular walls, which reduces wall stress (which, according to the Laplace equation, is calculated as the product of the left ventricular pressure and the radius, divided by two times the wall thickness), and higher ejection fractions. Preoperative recognition of these differences is important, because postoperative management of low cardiac output requires volume expansion rather than the use of pressor agents.⁴⁴

In summary, aortic stenosis is a disease of aging that is likely to become more prevalent as the proportion of older people in our population increases. Once stenosis has been identified during physical examination, its severity can be accurately quantified by Doppler echocardiography. Asymptomatic patients with aortic stenosis are followed medically until the onset of one of the classic symptoms of aortic stenosis, at which time the aortic valve is replaced. Aortic-valve replacement is successful in most elderly patients and even in many patients with advanced heart failure.

MITRAL STENOSIS

Recognition and Assessment of Severity

Mitral stenosis is a sequela of rheumatic heart disease that primarily affects women. Unfortunately, a reliable history of rheumatic fever is often difficult to obtain and thus cannot usually be used as a guide to the likely presence or absence of this disease. In developed countries, the steady decline in the incidence of rheumatic fever has reduced the incidence of mitral stenosis. Both rheumatic fever and mitral stenosis remain common in developing nations.

Patients with mitral stenosis usually have symptoms typical of left-sided heart failure: dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. Less frequently, they have hemoptysis, hoarseness, and symptoms of right-sided heart failure; these symptoms are somewhat more specific for mitral stenosis. Often the patient remains asymptomatic until she becomes pregnant or has atrial fibrillation, when dyspnea and orthopnea are noted.

The symptoms of mitral stenosis stem from increased left atrial pressure and reduced cardiac output, primarily caused by mechanical obstruction of filling of the left ventricle. Although the symptoms are those of left ventricular failure, contractility of the left ventricle is usually normal in mitral stenosis.⁴⁵ However, in some cases, the left ventricular ejection fraction is reduced because of excessive afterload secondary to a reflexive increase in systemic vascular resistance. Since it is the right ventricle that ultimately bears the burden of propelling blood through the mitral valve, right ventricular function is compromised first by the afterload imposed on it by high left atrial pressure and then by the development of secondary pulmonary vasoconstriction.

During physical examination, mitral stenosis is suspected because of the presence of the classic diastolic rumble that follows an opening snap. S_1 is characteristically loud, because the mitral valve is held open by the transmitral gradient until the force of ventricular systole closes the valve. The presence of a loud P_2 , right ventricular lift, elevated neck veins, ascites, and edema indicates that pulmonary hypertension producing right ventricular overload has developed. This is an ominous sign in the progression of the disease, because pulmonary hypertension increases the risk associated with surgery.⁴⁶

Echocardiography is the premier noninvasive diagnostic tool for assessing the severity of mitral stenosis and for judging the applicability of balloon mitral valvotomy. Echocardiography can usually permit an accurate planimetric calculation of valve area⁴⁷ and can also be used to assess the severity of stenosis by measuring the decay of the transvalvular gradient or the "pressure half-time," an empirical measurement.^{48,49} The latter determination is based on the principle that as the severity of stenosis worsens, it takes progressively longer for the transmitral flow velocity to decay. By empirically dividing the constant of 220 by the pressure half-time, one can make an approximation of valve area.⁴⁸

Therapy and Timing of Intervention

For the asymptomatic patient in sinus rhythm, prophylaxis against endocarditis is the only medical therapy indicated. When mild symptoms develop, diuretics are usually effective in lowering left atrial pressure and reducing symptoms. If atrial fibrillation develops, rate control with digoxin, a beta-blocker,

or a calcium-channel blocker is crucial, since a rapid heart rate further impairs left ventricular filling, simultaneously reducing cardiac output and increasing left atrial pressure. Anticoagulant therapy is required, since there is a high risk of embolism in patients with chronic atrial fibrillation and mitral stenosis.

If the symptoms are more than mild, or if there is evidence that pulmonary hypertension is beginning to develop, mechanical relief of the mitral stenosis is indicated, since further delay worsens the prognosis.⁵⁰ In many cases, balloon valvotomy provides excellent mechanical relief that usually results in prolonged benefit, unlike valvotomy in aortic stenosis.⁵¹ The presence of heavy valvular calcification, severe subvalvular distortion, or more than mild mitral regurgitation militates against the use of balloon valvotomy.⁵² In such cases, open commissurotomy, valve reconstruction, or mitral-valve replacement improves survival and reduces symptoms.

Still unresolved is the proper treatment of patients with mitral stenosis who are asymptomatic except for the presence of atrial fibrillation. This unwanted arrhythmia is associated with extensive morbidity and mortality.⁵³ It is often hoped that correction of mitral stenosis before the atrial fibrillation has become prolonged (and thus more likely to be permanent) will allow the reestablishment of sinus rhythm after valvotomy or surgery. However, there is currently no conclusive evidence that this management strategy is successful. Indeed, some now advocate a combination of the appropriate mitral-valve procedure and the Cox maze procedure in appropriate patients to ensure the maintenance of sinus rhythm postoperatively.⁵⁴⁻⁵⁶

NONISCHEMIC MITRAL REGURGITATION

Recognition and Assessment of Severity

The usual causes of mitral regurgitation are infective endocarditis, myxomatous degeneration of the mitral valve (including the mitral valve prolapse syndrome), collagen vascular disease, spontaneous rupture of the chordae tendineae, and rheumatic fever.

Figure 3 depicts the pathophysiologic stages of mitral regurgitation, progressing from acute mitral regurgitation to chronic compensated mitral regurgitation and to chronic decompensated mitral regurgitation.⁵⁷

Chronic mitral regurgitation is compensated by the development of eccentric cardiac hypertrophy, and cardiac enlargement should therefore be manifest on physical examination. A holosystolic apical murmur heard on physical examination alerts the examiner that mitral regurgitation is present. An S_3 suggests that the disease is severe. However, an S_3 heard in mitral regurgitation does not necessarily indicate the presence of congestive heart failure, since in this situation the sound is caused by rapid filling

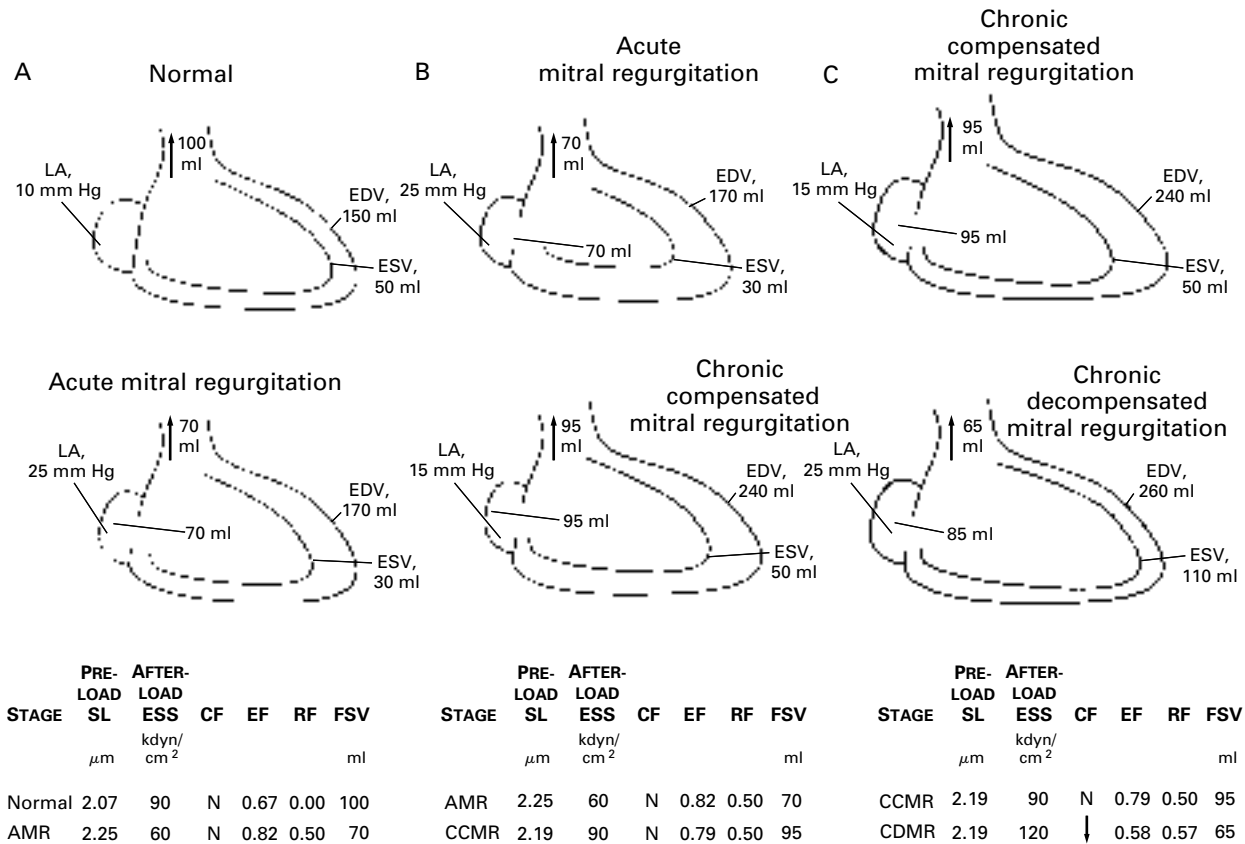


Figure 3. Pathophysiologic Stages of Mitral Regurgitation.

Panel A shows the transition from normal physiology to acute mitral regurgitation (AMR). The volume overload of acute mitral regurgitation increases preload sarcomere length (SL) so that end-diastolic volume (EDV) increases from 150 to 170 ml. The presence of a new pathway for the ejection of blood into the left atrium (LA) reduces afterload, described as end-systolic stress (ESS), and therefore end-systolic volume (ESV) is reduced from 50 to 30 ml. The ejection fraction (EF) increases acutely, but because 50 percent of the total stroke volume is regurgitated into the left atrium, resulting in a regurgitant fraction (RF) of 0.50, forward stroke volume (FSV) is reduced from 100 to 70 ml. The increased volume in the left atrium raises pressure there from normal to 25 mm Hg. Panel B shows the transition from acute mitral regurgitation to chronic compensated mitral regurgitation (CCMR). The development of eccentric hypertrophy has increased end-diastolic volume from 170 to 240 ml. The now larger ventricle has an increase in afterload because the radius applied in the Laplace equation for stress has increased. This in turn increases end-systolic volume to normal. The presence of eccentric hypertrophy, however, allows for an increase in total stroke volume as well as forward stroke volume. Enlargement of the left atrium allows the volume overload there to be accommodated at a lower filling pressure (15 mm Hg). The ejection fraction is supernormal. Panel C shows the transition to chronic decompensated mitral regurgitation (CDMR). The now weakened ventricle can no longer contract well, and end-systolic volume therefore increases from 50 to 110 ml. Forward stroke volume is reduced, and cardiac dilatation leads to an increased regurgitant fraction. However, the still favorable loading conditions permit the ejection fraction to remain normal (0.58). CF denotes contractile function; N, normal; and the downward arrow, depressed. Reproduced from Carabello,⁵⁷ with the permission of the publisher.

of the left ventricle by the large volume of blood stored in the left atrium in diastole. Echocardiography confirms enlargement of the chamber, and color-flow examination of the mitral valve establishes the pattern of disturbed flow caused by regurgitation across the mitral valve.

Although a variety of methods of quantifying the severity of regurgitation have been used, none have met with universal success. Currently, echocardiography provides only a semiquantitative estimate of the severity of mitral regurgitation. Left ventriculography

performed during cardiac catheterization provides an additional but also imperfect estimate of the severity of mitral regurgitation. However, catheterization is used only when surgery is being contemplated, and it is not suitable for longitudinal follow-up.

Timing of Surgery

Unlike the stenotic lesions, regurgitant lesions may progress insidiously, causing left ventricular damage before symptoms have developed.⁵⁸ Thus, although the presence of symptoms in chronic mitral regurgi-