All valvular heart disease imparts a hemodynamic burden on the left and/or right ventricle. This burden can only be removed effectively by correcting the responsible valvular lesion. Although a percutaneous approach is usually used to correct mitral stenosis, other valve lesions require surgical intervention. Over the past 40 years there has been a persistent improvement in our understanding of the pathophysiology of valvular heart disease and in the surgical techniques for correcting it. These factors have acted in concert to alter our view of the proper timing and applicability of surgery. On one hand it is no longer necessary or even advisable to delay surgery until advanced symptoms are present, and thus surgery is timed earlier today than it was even a decade ago. On the other hand, many but not all patients with far advanced disease, once considered inoperable, are now often helped substantially by valve surgery. However, selection of which of these very ill patients will or will not benefit from valve surgery remains a challenge for all of us. It is this group of patients that is addressed in the review. (J Am Coll Cardiol 2004;44:376–83) © 2004 by the American College of Cardiology Foundation

LOW-GRADIENT AORTIC STENOSIS

Background. Aortic stenosis (AS) is the most common valvular lesion affecting U.S. adults and its incidence is increasing, in part because AS is a disease of aging and the U.S. population is getting older. Once viewed as a “degenerative” disease, AS now is seen as the result of an active inflammatory process that has much in common with atherosclerosis (1–3). For the majority of patients, management is straightforward. Patients have an excellent prognosis as long as they remain asymptomatic, even in the face of severe valvular obstruction (4–6). However, once the classic symptoms of angina, syncope, or dyspnea develop, prognosis drastically worsens if aortic valve replacement (AVR) is not performed (Fig. 1). In fact, about 75% of symptomatic patients will succumb in three years after the onset of symptoms without valve replacement. In general symptoms can be attributed to AS if valve area is <1.0 cm² or if mean transvalvular gradient exceeds 50 mm Hg.

Following AVR for patients whose preoperative left ventricular (LV) function was normal, prognosis is excellent and can return to that of a population unaffected by AS (7). Unfortunately, this excellent outcome does not extend to those patients with preoperative LV systolic dysfunction when the transaortic valve gradient is low (less than a mean gradient of 30 mm Hg) (8–10) (Fig. 2).

Pathophysiology of left ventricular outflow obstruction. In normal subjects there is a small gradient between the LV at the beginning of ejection that rapidly dissipates so that both ventricular and aortic pressures are nearly identical throughout most of systole. In humans, the normal aortic valve area (AVA) is 3.0 to 4.0 cm². As AS develops, little gradient is present until the orifice area becomes less than half of normal. The relationship of gradient to orifice area is best described by the Gorlin formula: gradient = CO²/AVA² where CO = cardiac output and AVA = aortic valve area. Thus, at a CO of 5 l/min and an AVA of 1.3 cm², the gradient across the aortic valve would be only 15 mm Hg. However, as the orifice area shrinks by half again to 0.65 cm², the gradient would exceed 60 mm Hg if output remained constant. At this valve area the LV would have to generate a systolic pressure of at least 180 mm Hg to maintain a normal aortic systolic pressure of 120 mm Hg. Thus, a pressure overload is placed upon the LV. It is generally held that this overload is compensated by concentric LV hypertrophy (11). The law of LaPlace states that the load or stress on any part of the myocardium is equal to ventricular pressure × radius/2 × thickness. Thus, as the pressure term in the numerator increases, it can be compensated by an increase in thickness in the denominator, and ventricular wall stress (afterload) remains normal despite the pressure overload. Ejection fraction (EF), a key measure of ventricular performance, is inversely related to afterload (Fig. 3) (11). Thus as a mechanism for maintaining normal wall stress, hypertrophy is compensatory because it also helps maintain ejection performance. However, the individual hypertrophic response to any given pressure overload is remarkably variable. In some patients, just enough increase in wall thickness develops to normalize wall stress and EF is in the normal range (11). In other patients the amount of concentric hypertrophy is marked, wall stress is actually subnormal, and EF is supernormal (12). In still other
patients, the amount of hypertrophy that develops is inadequate to normalize stress, and excess wall stress leads to a reduced EF. In most cardiac diseases, prognosis is related to LV performance because in most cardiac diseases LV performance is an expression of the integrity of the myocardium and its innate ability to generate force (contractility). However, in patients with AS in whom hypertrophy failed to normalize wall stress (afterload), the resultant reduction in EF does not indicate contractile dysfunction, and prognosis following AVR is excellent (13). This good prognosis stems from the fact that following surgery in such patients, aortic obstruction is removed, afterload is therefore abruptly reduced, and ejection performance improves dramatically.

The patient with low gradient, low output, and low EF. In patients whose EF is reduced because of afterload excess, prognosis remains good because contractility is maintained so that EF improves once the afterload excess is removed. However as shown in Figure 4, in the group of patients with low gradient and low CO, EF is depressed in excess of what would have occurred through afterload excess alone (8). In such cases there is severe depression in contractile function. Myocardial dysfunction in AS, as in other heart disease, leads to a poor prognosis. Looking at the same problem from another point of view, when there is a large transvalvular pressure gradient, relief of that gradient following AVR causes a large drop in the pressure term in the LaPlace equation, a large reduction in afterload, and thus a substantial increase in EF. On the other hand, when the transvalvular gradient is small, there is a correspondingly smaller reduction in afterload and thus a smaller improvement in EF following surgery.

Since my colleagues and I first directed attention toward this group of patients, understanding about the condition’s pathophysiology and its therapy has evolved substantially. In that first report, we noted 14 patients with AS who had reduced EF and congestive heart failure (8). Four of the 14 had mean transvalvular gradients of <30 mm Hg and all either died or failed to improve after AVR, whereas the 10 patients with higher gradients all improved following AVR. Subsequently, several other reports confirmed and extended these findings. Lund noted that prognosis following AVR varied indirectly with gradient in a group of more than 600 patients with AS (14). Patients with mean gradients of >125 mm Hg had the longest survival post AVR, whereas patients with gradients of <35 mm Hg had the shortest survival and patients with gradients intermediate to those extremes had intermediate survival. Brogan et al. (9) examined 18 patients with AS and a mean gradient of <30 mm Hg. Eight patients (44%) did poorly following AVR, confirming the poor prognosis of this group of patients. However, 10 patients improved following surgery, demonstrating that not all such patients were doomed to a poor outcome. This premise was confirmed in a much larger group of patients reported by Connolly et al. (10). Operative mortality was 21%, and 50% had succumbed by four years following AVR. However, many patients improved symptomatically, and several had dramatic increases in EF following relief of the outflow obstruction. A recent observational study from the Cleveland Clinic indicates that as a group this low-gradient, low-EF group does better with surgery than with medical therapy (15). Although this study was not a randomized clinical trial, careful matching of

![Figure 1](image-url). The natural history of aortic stenosis. Survival is nearly normal until the symptoms of angina, syncope, or heart failure develop, after which survival abruptly declines. Reprinted from Ross and Braunwald (4) with permission.

Abbreviations and Acronyms
- AS = aortic stenosis
- AVA = aortic valve area
- AVR = aortic valve replacement
- CO = cardiac output
- EF = ejection fraction
- LV = left ventricle
patients who did versus those who did not receive an AVR suggested that patients with similar hemodynamics and comorbidities preoperatively had much better results with AVR. Almost all medically treated patients were dead within three years after identification, compared with a 75% survival in patients with AVR. Although not all preoperative biases were likely accounted for, the extraordinary benefit from AVR in this very ill (and highly selected) group is convincing about the potential benefits of AVR in this group. Still, when all the data are taken together it seems unwise to recommend surgery to all low-gradient, low-EF patients. Rather, it seems advisable to try to risk-stratify patients before surgery in order to decide whether medical or surgical therapy is best for a given patient. This stratification is based on 1) stenosis severity, 2) inotropic reserve, 3) the presence or absence of coronary disease or other valve disease, and 4) other comorbidities.

**AS severity.** Logically, the more severe the stenosis, the greater the benefit from relief of the obstruction. From another viewpoint, for the disease to have resulted in severe systolic failure the obstruction must have been so severe that, in turn, stenosis relief should lead to improved function. Indeed, it is hard imagine that replacement of mild-to-moderate disease that preoperatively had produced a 5 to 10 mm Hg gradient would even be entertained. At first blush, this principle should be dealt with easily. Patients with severe AS (i.e., a valve area of <1.0 cm²) should undergo AVR. Unfortunately, valve area, especially valve area calculated at low flow either by the Gorlin or continuity equations, is often inaccurate because of the flow dependence of the calculation (16–18). Calculated valve area is smaller, often dramatically so, at lower CO. Debate continues as to whether this flow dependence represents a real change in orifice area or is due to inherent problems with the formulas. Different studies support both points of view. In the first instance it is presumed that greater output through a stenotic valve opens the valve to a larger orifice area that is reflected more or less accurately by the increased calculated valve area. In the second instance the fact that the discharge coefficients for the Gorlin formula as it pertains to the aortic valve were never developed may play a role. If gradient increases in concert with output, valve area will increase only slightly, and it is presumed that severe fixed valvular obstruction is present. In other cases increased output may result in a significant increase in valve area of >0.3 cm² or calculated valve area exceeds 1.0 cm², a condition sometimes referred to as aortic pseudostenosis (19). For this calculated result to occur, there must be a substantial increase in output without a large increase in gradient, which logically means severe obstruction is absent. However, rational this approach is, it has only been vetted in
Mitral regurgitation imposes a pathophysiology.

Nonischemic Mitral Regurgitation

Small studies, and thus its exact role in decision-making is still unclear. Pharmacologic manipulation was not used in the study (15) where patients with low gradient and low output benefited from AVR. Thus, it is possible that some of the patients who benefited from AVR could have had pseudostenosis. Valve resistance, which is simply mean gradient divided by CO per beat, has been used as an adjunct to valve area in making the distinction between truly severe and milder AS (16). Resistance has the potential advantage over area because it involves no discharge coefficients and because removing the square root sign over the gradient raises the importance of gradient and diminishes the importance of output, making the calculation less output dependent. However, because resistance has never been established as superior to valve area, and because no critical value has been established, resistance must be considered experimental at present.

Inotropic reserve. Irrespective of whether gradient increases appropriately with output during dobutamine infusion, the failure of output itself to increase during inotropic challenge has been convincingly shown to impart a poor prognosis in several studies (20–22) (Fig. 5). Presumably the absence of inotropic reserve defines both severe and irreversible LV dysfunction, in turn imparting a bad outcome following AVR. Thus, AVR seems inadvisable for AS patients whose CO does not increase by at least 25% during dobutamine challenge, although even some patients who have failed inotropic challenge have improved following AVR (22).

Coronary artery disease. In most studies of patients with AS, the copresence of coronary artery disease negatively affects prognosis, and this is true for low-gradient low-EF AS patients as well (10). Reduced prognosis stems from that fact that a second dangerous cardiac disease is now present in conjunction with AS. Additionally, those portions of the ventricle that are dead cannot benefit from the afterload reduction of AVR. On the other hand, if it were clear that some of the LV dysfunction that was present was in fact due to hibernating myocardium, substantial recovery in function could occur post-operatively, not just from the benefits of AVR but also from those of revascularization.

In summary, most patients with AS, even those with low gradient and low output, benefit from AVR. Patients without inotropic reserve and those with a large increase in AVA with increased output are least likely to benefit, although even some in this group may improve following surgery. As yet, a method for defining this last group has yet to be elucidated.

Nonischemic Mitral Regurgitation

Pathophysiology. Mitral regurgitation imposes a “pure” volume overload on the LV. The volume regurgitated into the left atrium decreases forward stroke volume. This loss is compensated by eccentric hypertrophy whereby additional sarcomeres are laid down in series, increasing the length of each myocyte. In turn, cell lengthening increases the volume of the ventricle, enabling it to increase total and forward stroke volume. This overload is tolerated for a variable period, but eventually volume overload causes LV dysfunction. Dysfunction is characterized by a loss of myofibrils (23) and by a blunting of the myocardial force-frequency relationship (24), suggesting compromised calcium handling. As dysfunction develops, activation of the sympathetic nervous system supports inotropic state but leads also to further myocardial damage (25,26). Both experimental and human data indicate that this damage can be reversed by mitral valve repair/replacement (27,28) or by institution of beta-blockade (29).

The onset of muscle dysfunction is often hidden by the favorable loading conditions created by the second pathway for ejection of blood (into the left atrium) present in mitral regurgitation. This second pathway tends to reduce afterload while the volume overload itself increases preload, both effects acting in concert to increase EF to a higher than normal value (30).

Timing of surgery. Obviously surgery should be performed before the advent of the deleterious processes noted earlier. Clinically the current best markers that function is declining are the development of symptoms (31) and the presence of echocardiographic markers of systolic failure. Because postoperative results worsen when either EF falls to <0.60 or when end-systolic dimension approaches 45 mm, it is presumed that these markers herald the onset of muscle dysfunction (32–34).

Is EF ever so low that it precludes valve surgery? To answer this question, some misconceptions about the physiologic effects of restoring mitral valve competence must be resolved. Until about two decades ago, the nearly universal observation was that EF fell following mitral valve replacement for mitral regurgitation. It was assumed that this was the inevitable consequence of removing the favorable loading conditions created by mitral regurgitation noted above. That is, restoration of mitral competence would reduce
preload and increase afterload, forcing EF to fall. Thus, if EF were already reduced, surgery would lower it yet further, making operation untenable in advanced LV dysfunction. Although logical, this scenario turns out to be false. Mitral valve surgery two decades ago usually involved mitral valve replacement during which the mitral apparatus was removed, which at the time was thought to be inconsequential. It was not recognized that the mitral valve and its apparatus were an important functional component of the LV, helping to maintain its shape and contractility (35). We now know it is primarily destruction of the valve apparatus and not the loading changes that result in reduced EF following mitral surgery. We know this because mitral repair, which restores competence without destroying the apparatus, causes little or no reduction in EF (36,37) (Fig. 6). In fact, afterload actually falls rather than rises following repair because the radius term in the LaPlace equation is reduced (37). Recently, Bach and Bolling (38) have reported successful mitral annuloplasty in patients with EFs of <0.20. Thus, almost no one with mitral regurgitation without other comorbidities is inoperable in experienced hands, no matter how low the EF, provided that the valve apparatus is conserved during surgery. On the other hand, if the valve and its attachments cannot be preserved, valve replacement for patients with EFs of <0.35 is probably inadvisable.

These comments pertain to nonischemic mitral regurgitation. Ischemic mitral regurgitation has less favorable results at any level of LV dysfunction, in part because by definition there is a second potentially fatal cardiac disease present. On the other hand, revascularization of viable myocardium during valve surgery may improve function. The complexity of ischemic mitral regurgitation makes recommendation about inoperability in this disease quite problematic. Unlike in nonischemic mitral regurgitation, where valve repair is clearly the treatment of choice, in ischemic disease repair seems to benefit patients with the best preoperative function and fewest comorbidities (39). Presumably, in the highest risk patients prognosis is so compromised that the type of surgery performed has little effect on this poor outcome.

MITRAL STENOSIS

Pathophysiology. As with AS, little hemodynamic disturbance develops until orifice size is compromised to less than half of the normal mitral valve area (4.0 to 5.0 cm²). At that point the small early diastolic gradient normally present at the beginning of systole increases in duration and magnitude, raising left atrial pressure and pulmonary artery pressure modestly. As valve area narrows further, left atrial hypertension leads to pulmonary congestion; at the same time the reduced orifice area limits CO, mimicking LV failure. In fact, in most cases of mitral stenosis LV contractility is normal. However, in about one-third of mitral stenosis patients, reduced preload caused by limited mitral inflow and increased afterload precipitated by reflex vasoconstriction secondary to decreased CO act in concert to reduce ejection performance (40). With still further mitral valve narrowing, secondary pulmonary vasoconstriction worsens pulmonary hypertension, resulting eventually in right ventricular failure.

Timing of mechanical intervention. Unlike the other valve lesions, mitral stenosis can be corrected in most cases percutaneously using balloon valvotomy. In cases where extensive calcification and valve deformity preclude balloon valvotomy, surgical commissurotomy or mitral valve replacement is performed. Because sudden death is extraordinarily rare in asymptomatic patients, there is little to compel mechanical intervention before symptom development. The exception to this rule is the development of asymptomatic pulmonary hypertension. Pulmonary hypertension increases surgical mortality by up to fourfold, and thus intervention should be performed once pulmonary hypertension is detected, irrespective of the presence of symptoms (41) (Fig. 7). Otherwise, mechanical intervention should be provided once more than mild symptoms are present because prognosis worsens with symptom severity.
Is it ever too late to intervene mechanically in mitral stenosis? It is important to realize that whereas pulmonary hypertension worsens prognosis in mitral stenosis, pulmonary pressure usually returns to or toward normal following successful intervention. Thus, the presence of even severe pulmonary hypertension and right heart failure are not contraindications for valvotomy or surgery. Further reassurance that pulmonary pressure will fall following surgery can be gleaned from preoperative inhalation of nitric oxide (42). A significant fall in pulmonary pressure preoperatively with this test usually indicates that pulmonary pressure will revert toward normal postoperatively. In general, it is almost never too late to provide mechanical correction for mitral stenosis. Even when severe comorbidities exist, an attempt at balloon valvotomy is usually warranted and is often successful.

AORTIC REGURGITATION

Pathophysiology. Although both mitral and aortic regurgitation impart a volume overload on the LV, the pathophysiology of the two lesions are actually quite different from one another (43). In aortic regurgitation the extra volume that leaked into the LV during diastole is expelled into the aorta during diastole. Thus, total aortic stroke volume is large whereas forward stroke volume is reduced. Because pulse pressure is directly related to stroke volume, pulse pressure is widened in patients with aortic regurgitation, in turn producing almost obligatory systolic hypertension. On the other hand, in mitral regurgitation the extra stroke volume is pumped into the left atrium, and thus aortic stroke volume is reduced and systolic blood pressure tends to be low. Therefore in aortic regurgitation there is volume and pressure overload, whereas in mitral regurgitation, the volume overload is pure. These differences in load cause differences in LV geometry and in the response of the LV to valve replacement. In aortic regurgitation there is not only increased chamber size, but also a modest increase in wall thickness while in mitral regurgitation wall thickness tends to be less than normal (44). Preload is increased in both conditions; in aortic regurgitation there is often substantial afterload excess whereas afterload is normal in mitral regurgitation. These different loading conditions result in different changes in load and in LV performance following valve replacement or repair. As noted before, following mitral valve repair afterload is modestly reduced and preload is also reduced, netting no change in postoperative EF. If the mitral valve apparatus is destroyed at surgery, afterload increases postoperatively, preload decreases, and EF falls significantly. In contrast, following AVR, systolic hypertension disappears, afterload is greatly decreased, and EF increases, often returning to normal even if preoperative depression is severe (45,46) (Fig. 8).

Timing of surgery. As with mitral regurgitation, surgery for correction of aortic regurgitation should be performed when even mild symptoms appear because further delay worsens prognosis (47). As with mitral regurgitation, asymptomatic LV dysfunction can develop in aortic regurgitation. Because excess afterload reduces ejection performance in aortic regurgitation, somewhat worse ejection performance can be present in aortic regurgitation than in mitral regurgitation without indicating depressed contractility and irreversible myocardial damage. Thus surgery should occur before EF falls below 0.55 or before end-systolic dimension exceeds 55 mm (48). Because some cases of sudden death have been reported in patients with very large LVs, surgery should also be contemplated for an end-diastolic dimension of >75 mm.

Is it ever too late for AVR in aortic regurgitation? As noted earlier, the element of afterload excess present in patients with aortic regurgitation improves following valve replacement, in turn increasing ejection performance while reducing filling pressure and increasing forward CO. Thus, AVR should be offered to most patients, even though they have missed the opportunity for the best surgical outcome and even when EF is depressed and end-systolic dimension exceeds 55 mm. Although there are few data to support the concept, patients unable to generate an LV pressure above 120 mm Hg are likely to have less afterload reduction following AVR and are probably very poor surgical candidates.

Summary. Over the past three decades the best timing for valve replacement and guidelines for it have been developed and confirmed. However, some patients still come to medical attention well beyond this optimal timing window. Even in most of these, advances in surgical technique allow most to be operated successfully, although prognosis is still reduced in such patients. Aortic stenosis patients with low gradient and low EF without inotropic reserve and mitral...
regurgitation patients with low EF in whom the valve apparatus cannot be preserved constitute the small group of patients in whom valve replacement should probably not be performed.

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