PLENARY LECTURE

Afterload Mismatch in Aortic and Mitral Valve Disease: Implications for Surgical Therapy

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In the management of patients with valvular heart disease, an understanding of the effects of altered loading conditions on the left ventricle is important in reaching a proper decision concerning the timing of corrective operation. In acquired valvular aortic stenosis, concentric hypertrophy generally maintains left ventricular chamber size and ejection fraction within normal limits, but in late stage disease function can deteriorate as preload reserve is lost and aortic stenosis progresses. In this setting, even when the ejection fraction is markedly reduced (< 25%), it can improve to normal after aortic valve replacement, suggesting that afterload mismatch rather than irreversibly depressed myocardial contractility was responsible for left ventricular failure. Therefore, patients with severe aortic stenosis and symptoms should not be denied operation because of impaired cardiac function.

In chronic severe aortic and mitral regurgitation, operation is generally recommended when symptoms are present, but whether to recommend operation to prevent irreversible myocardial damage in patients with few or no symptoms has remained controversial. In aortic regurgitation, left ventricular function generally improves postoperatively, even if it is moderately impaired preoperatively, indicating correction of afterload mismatch. Most such patients can be carefully followed by echocardiography. However, in some patients, severe left ventricular dysfunction fails to improve postoperatively.

Therefore, when echocardiographic studies in the patient with severe aortic regurgitation show an ejection fraction of less than 40% (fractional shortening < 25%) plus enlarging left ventricular end-diastolic diameter (approaching 38 mm/m² body surface area) and end-systolic diameter (approaching 50 mm or 26 mm/m²), confirmation of these findings by cardiac catheterization and consideration of operation are advisable even in patients with minimal symptoms.

In chronic mitral regurgitation, maintenance of a normal ejection fraction can mask depressed myocardial contractility. Pre- and postoperative studies in such patients have shown a poor clinical result after mitral valve replacement, associated with a sharp decrease in the ejection fraction after operation. This response appears to reflect unmasking of decreased myocardial contractility by mitral valve replacement, with ejection of the total stroke volume into the high impedance of the aorta (afterload mismatch produced by operation). Therefore, when echocardiographic studies in patients with severe mitral regurgitation show an ejection fraction of less than 55% (fractional shortening < 30%), an end-diastolic diameter approaching 75 mm and an end-systolic diameter approaching 2.6 mm/m² body surface area, it seems advisable to undertake operation to prevent the development of irreversible myocardial damage, even if symptoms are few or absent.

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Concepts concerning the influence of cardiac loading conditions on the performance of the heart carry significant implications for the management of patients with acquired valvular heart disease and have particular relevance to those valve lesions which mechanically overload the left ventricle (aortic stenosis, aortic regurgitation and mitral regurgitation). Despite continued improvement in surgical results of valve replacement, a significant number of patients continue to exhibit congestive heart failure or die postoperatively despite successful surgical repair of the valve defect. In the latter group, if patients who have complications from intraoperative myocardial damage, prosthetic valve dysfunction, or progressive coronary heart disease are excluded, the primary cause of morbidity and mortality after operation is severe left ventricular myocardial disease (1–18), which undoubtedly was present before operation. Therefore, it is of the utmost importance that an appropriate decision be reached as to the proper timing of operation. Care must be
taken not to wait so long that, despite a technically satisfactory operation, the patient is left with severe, irreversible left ventricular myocardial disease. Yet, it is undesirable to implant a valve prosthesis earlier than necessary, because these devices can cause emboli or become infected and most have a finite life span (19).

Phases of Natural History

Four general phases can be identified in the natural history of patients with long-standing acquired valvular heart disease (Table 1). In current clinical practice, corrective operation is usually recommended when significant symptoms develop during phases 2 or 3. However, whenever operation is recommended in the late stages of disease, it is important that it be carried out before irreversible damage is present (phase 4). Remarkable differences in the response of left ventricular performance to operation have been reported during the past few years, depending on the phase and type of valvular heart disease. For example, as will be discussed subsequently, an increase in ejection fraction can occur postoperatively despite marked preoperative left ventricular dysfunction in severe aortic stenosis (20), whereas a decrease in ejection fraction can occur postoperatively despite adequate preoperative left ventricular function in severe mitral regurgitation (17). To understand such responses, it is desirable to first consider how the normal and failing heart respond to altered systolic and diastolic loading conditions.

Limited Preload Reserve and Afterload Mismatch

A useful general framework for considering left ventricular responses to acute loading conditions as well as to chronic overload is provided by the pressure-volume loop of single contractions and the linear end-systolic pressure-volume relation derived from multiple contractions, described in the isolated heart preparation by Suga and Sagawa (21). Others (22,23) have described similar phenomena in the conscious dog using implanted ultrasonic dimension gauges to measure linear end-systolic pressure-dimension and dimension-wall stress relations in the left ventricle. The position of the linear end-systolic relation can provide a measure of myocardial contractility, since at any level of inotropic state ventricular contractions will fall close to this line regardless of the preload or afterload (22). Pressure-volume data may be usefully employed to describe acute adaptations (Fig. 1), but as will be discussed, the wall stress-volume framework appears more appropriate for conditions in which the geometry of the ventricle is chronically altered (24–26). Force-velocity-length diagrams have also been used to describe acute and chronic adaptations to altered loading (27).

Afterload mismatch in the normal heart. Afterload mismatch (27) can readily be demonstrated when the preload is artificially held constant by means of a pump. Under these conditions, a progressive increase in the aortic and left ventricular systolic pressures (when the ventricle is unable to adapt by the Frank-Starling mechanism) results in a progressive decrease in stroke volume and ejection fraction (afterload mismatch) until finally, at a very high systolic pressure, the left ventricle cannot open the aortic valve and an isovolumetric beat ensues (28–31) (Fig. 1, left). Of course, under conditions when the preload is not artificially fixed and the increase in systolic pressure is modest, the left ventricle can compensate for the increase in pressure and stroke volume will be maintained by an increase in ventricular end-diastolic volume (Fig. 1, right).

Afterload mismatch can also be demonstrated when the normal left ventricle is continuously transfused to markedly increase end-diastolic volume while maintaining left ventricular systolic pressure at a relatively high level (29); with overtransfusion, the limit of preload reserve is eventually reached (in the open chest dog, this occurs at left ventricular end-diastolic pressures > 25 mm Hg) at a point at which all the sarcomeres across the wall are maximally distended (32). At this point, the ventricle behaves as if the preload were fixed and any further increase in the afterload results in a decrease in stroke volume (Fig. 1, right). Thus, under both of these conditions, when the preload reserve is made unavailable by controlling the venous return, or when the limit of preload reserve is reached, the stroke volume of the ventricle is directly related to the level of systolic pressure during ejection (or the afterload, more adequately represented as systolic wall stress) (24,26).

"Afterload mismatch" may then be simply described as inability of the left ventricle, operating in any stable level of inotropic state, to maintain a normal stroke volume against the prevailing systolic load on the ventricle, and it generally occurs in the setting of limited preload reserve. Of course, lowering the afterload alone can result in improvement in stroke volume without a change in myocardial contractility (inotropic state). As described by Suga and Sagawa (21),
if contractility changes, the linear end-systolic pressure-volume relation is shifted upward and steepened (positive inotropic influences) or downward with a less positive slope (negative inotropic influences). Thus, changes in contractility can also markedly alter stroke volume and end-systolic pressure-volume points thereby independent of loading conditions, altering the afterload sensitivity of the ventricle, and afterload mismatch will then occur at different levels of systolic pressure and stroke volume.

Thus, it is apparent that when the preload reserve is fully utilized, altered systolic loading conditions at any level of myocardial contractility can produce dissociations between cardiac performance or function and myocardial contractility. Depending on the loading conditions, left ventricular performance can be markedly impaired while myocardial contractility is relatively normal, or left ventricular performance can be normal in the presence of severely depressed myocardial contractility.

**Acute afterload mismatch in the clinical setting.** From these considerations, it is reasonable to expect that when a sudden severe overload on the ventricle forces it to the limit of its preload reserve, and simultaneously places an excessive afterload on the myocardial fibers, marked depression in ejection fraction may occur despite relatively well maintained myocardial contractility. Examples of such acute severe overload include uncontrolled (malignant) hypertension, which often leads to acute left ventricular failure, severe aortic regurgitation due to infective endocarditis, or severe mitral regurgitation after rupture of chordae tendineae or infective endocarditis. Under these conditions, the pulmonary artery wedge pressure and left ventricular end-diastolic pressure are markedly elevated, and frequently the forward stroke volume is depressed (even though the total stroke volume may be elevated in aortic and mitral regurgitation). Of course, marked elevation of left ventricular end-diastolic pressure might lead to subendocardial ischemia in some patients (33), causing a certain degree of myocardial depression as well. In such settings, the systolic pressure during ejection does not accurately reflect the afterload, since the wall stress is directly proportional to the product of systolic ventricular pressure and ventricular radius and inversely proportional to the wall thickness. Therefore, since acute left ventricular dilation in all three of these
conditions must be accompanied by thinning of the ventricular wall, the peak wall stress will be elevated more than the systolic pressure alone may suggest, further contributing to afterload mismatch.

It is proposed that the responses to therapy either with vasodilators for the treatment of hypertension or in the early management of valvular regurgitation, or with surgical correction of valvular regurgitation, may argue for correction of afterload mismatch as a major mechanism involved in the effect of these therapies. Thus, whenever there is a return to entirely normal left ventricular function after therapy for acute overload, it is proposed that correction of a dissociation between impaired ventricular performance and a relatively normal level of myocardial contractility has occurred. However, further studies will be needed to clearly establish the role of this mechanism in the clinical setting.

Afterload Mismatch in Chronic Valvular Heart Disease

Postoperative studies of the left ventricle in patients having one of the three major valvular lesions that overload the left ventricle have helped to clarify the nature of abnormal left ventricular function observed preoperatively. They have also provided insight into appropriate steps that may be taken to prospectively assess patients with chronic valvular disease to make a proper decision about surgical intervention and the prevention of irreversible left ventricular myocardial dysfunction.

Aortic Stenosis

Natural history. In acquired valvular aortic stenosis in the adult patient, postmortem studies (34) indicate that the onset of significant symptoms of angina pectoris, syncope or heart failure portend a relatively brief life expectancy (3 to 5 years), with an average age at death in men of approximately 63 years. Clinical follow-up studies have tended to confirm these postmortem observations; at cardiac catheterization, patients with demonstrated hemodynamically moderate to severe aortic stenosis have shown a mortality rate of approximately 50% by 3 to 4 years in one study (35) and 57% at 3 years in another (36). Follow-up of young asymptomatic patients with similar hemodynamic findings showed no mortality over a follow-up period averaging 5 years (36). Therefore, in the patient who has symptoms together with physical findings and echocardiographic studies suggesting significant aortic stenosis, cardiac catheterization should be carried out to assess the severity of stenosis (critical stenosis can be defined as a valve orifice area \( \leq 0.75 \text{ cm}^2 \) (\( \leq 0.4 \text{ cm}^2 \) body surface area), to determine whether or not coronary artery disease may be contributing to anginal symptoms, to evaluate the degree of associated aortic regurgitation and to assess left ventricular function.

Experimental studies on effects of chronic pressure overload on the left ventricle. Is the status of left ventricular function preoperatively a critical factor in deciding whether or not to recommend operation in the patient with significant aortic stenosis? To answer this question, it will be desirable to briefly consider experimental and clinical studies concerned with the effects of chronic pressure overload on the left ventricle. Experimental studies during the past few years in conscious dogs have helped to clarify the cardiac adaptations to chronic pressure overload. In chronically instrumented dogs subjected to supravalvular aortic stenosis, measurements of left ventricular chamber diameter, wall thickness and pressure over the course of several weeks after creation of the stenosis showed that when left ventricular systolic pressure was suddenly elevated (> 230 mm Hg), a phase of reduced ventricular performance was followed by recovery. Thus, over several weeks, the extent of chamber shortening, the fractional shortening of the chamber diameter and the end-diastolic minor equator diameter gradually returned to normal (23). Accompanying this recovery of chamber function was thickening of the wall of the ventricle, so that calculated mean systolic wall stress returned to near normal (Fig. 2). Thus, despite persistence of a markedly elevated left ventricular systolic pressure, the fractional shortening (and the ejection fraction) as well as the chamber size were returned to normal by compensatory concentric left ventricular hypertrophy (23). It was also found that the end-systolic pressure-dimension relation (analogous to the end-systolic pressure-volume relation) was substantially shifted upward and to the left in compensated hypertrophy, indicating hemodynamic hyperfunction of the left ventricle (Fig. 3A) (24). However, when wall stress was substituted for left ventricular pressure in calculating the end-systolic relations, the linear end-systolic relations before and after the development of hypertrophy were found to be essentially identical, strongly suggesting that myocardial contractility was normal in compensated pressure overload hypertrophy in this dog model (Fig. 3B) (24).

Clinical studies on left ventricular function in aortic stenosis. In human subjects, recent studies on left ventricular function before and after aortic valve replacement for severe aortic stenosis (37) indicate that in most patients the chamber size and fractional wall shortening, as measured by echocardiography, are normal preoperatively, with a marked increase in left ventricular wall thickness indicating compensated concentric hypertrophy. Such patients were also studied by Henry et al. (37) 6 months after operation, and left ventricular end-diastolic dimension and fractional shortening of the ventricles remained within the normal range. There was also considerable reduction in wall thickness at the follow-up study, indicating regression of hypertrophy after aortic valve replacement. This response indicates a partial reversal of the process of compensated concentric hypertrophy.
Figure 2. Tracing of left ventricular pressure (LVP) and left ventricular internal diameter and wall thickness measured with implanted ultrasonic crystals in a conscious dog before and after the development of chronic concentric hypertrophy due to supravalvular aortic stenosis. The initial response to acute aortic constriction is a marked increase in left ventricular systolic pressure, and end-diastolic diameter increases while the extent of systolic shortening decreases; there is also associated wall thinning. Several weeks after the production of chronic aortic stenosis (right panel), the left ventricular systolic pressure is still elevated, but the left ventricular internal diameter has returned to normal, the extent of shortening has become normal and there is a marked compensatory increase in the wall thickness. (Reproduced from Sasayama et al. [23] with permission of the authors and the American Heart Association, Inc.)

In some patients with aortic stenosis, the ejection fraction is found to be depressed preoperatively. However, Croke et al. (1) reported a remarkable improvement in the ejection fraction at 2 to 12 months postoperatively in six patients with severe aortic stenosis and no associated coronary disease; ejection fraction averaged 13% preoperatively and increased to an average of 45% (range 34 to 75) postoperatively. Studies by Smith et al. (20) in such patients also indicated that, provided perioperative myocardial infarction or prosthetic valve dysfunction did not occur, the ejection fraction studied some months postoperatively markedly increased, often to within the normal range, even if it was below 20% before operation. Likewise, the New York Heart Association functional class in these patients often improved postoperatively to class I or class II. Of interest in this connection are data from a patient with valvular aortic stenosis studied in this institution before operation by left ventriculography, at which time an ejection fraction of 25% was found. He was studied by radionuclide angiography early postoperatively at 1 week, and the calculated ejection fraction was normal (ejection fraction 65%), indicating remarkably rapid recovery of left ventricular function (38). Simultaneous coronary artery bypass grafting was carried out in the patient and may have contributed to this response.

Figure 3. Diagrammatic representation of the adaptation of the left ventricle to chronic pressure overload. A, Left ventricular (LV) pressure-volume relations with the curvilinear diastolic pressure-volume curve and the linear end-systolic pressure-volume relation. Loop A of left ventricular contraction occurs before the development of concentric hypertrophy. Loop B shows the response under conditions of chronic concentric hypertrophy when the left ventricular end-diastolic and end-systolic volumes are normal but the left ventricular systolic pressure is markedly elevated. As shown experimentally, there is a shift of the end-systolic pressure-volume relation upward and to the left, indicating hemodynamic hyperfunction of the ventricle under these conditions. B, Same contractions shown in A plotted as wall-stress volume loops. Loop A before concentric hypertrophy and loop B after concentric hypertrophy are essentially superimposable (wall thickening results in normal wall stress), and they reach the same linear end-systolic left ventricular wall stress-volume relation. Thus, concentric hypertrophy, considered within the wall stress-volume framework, appears to occur without a change in myocardial contractility.
but nevertheless these findings and the late recovery of function suggest that in patients with a depressed ejection fraction preoperatively, an important factor in the improvement of the ejection fraction is mechanical unloading of the ventricle (correction of afterload mismatch), rather than a primary improvement in myocardial contractility caused by the operation. Proof of this hypothesis must await further studies.

Response to operation (Fig. 4). The response to operation of a hypothetical patient with severe aortic stenosis and a depressed ejection fraction preoperatively is shown diagrammatically in Figure 4. With long-standing hypertrophy, moderate depression of left ventricular myocardial contractility may develop, shifting the linear end-systolic wall stress-volume relation somewhat to the right. By use of the Frank-Starling mechanism with increased end-diastolic volume, the ejection fraction may still be maintained within normal limits at a slightly higher wall stress (ejection fraction 60%). However, with further progression of aortic stenosis, the left ventricle reaches the limit of its preload reserve, either because marked hypertrophy with increased diastolic stiffness prevents complete filling or because the limit of sarcomere extension is reached. In this setting, the preload behaves as if it were fixed, and under conditions of limited preload reserve the left ventricle responds to further progression of aortic stenosis with a marked elevation of systolic wall stress. This, in turn, will cause the ejection fraction to decrease (to 33% in this example) due to afterload mismatch, but without further depression of myocardial contractility. After aortic valve replacement, relief of the severe obstruction allows the ventricle to unload effectively at a normal (or low) mean wall stress. With no significant change in myocardial contractility, the end-diastolic volume will decrease and the ejection fraction will markedly improve to 52% postoperatively. Of course, less marked improvement might be expected if the degree of preoperative depression of myocardial function is more severe.

Guidelines for recommending surgery. On the basis of these considerations and the excellent early and late operative results reported in patients with aortic stenosis (39-41), certain important factors in selecting adult patients with acquired valvular aortic stenosis for operation can be identified. These guidelines are summarized in Table 2.

Aortic Regurgitation

Natural history. The annual mortality rate in patients with chronic aortic regurgitation who have symptoms is lower than that in symptomatic patients with aortic stenosis (42). Symptoms typically begin in the fourth or fifth decade, and the average life expectancy in patients with aortic regurgitation is about 9 years after the onset of significant symptoms of left ventricular failure (orthopnea, paroxysmal dyspnea, congestive failure) (8,43,44). Clinical factors existing before operation that portend an unfavorable prognosis after aortic valve replacement (persistent symptoms or late death due to congestive heart failure) have included more than average diuretic therapy, dyspnea on less than one block or when climbing one flight of stairs, the presence of rales, an S3 gallop or a markedly enlarged cardiothoracic ratio and a reduced cardiac index at rest or an elevated pulmonary artery wedge pressure (10). However, hemodynamic severity can correlate poorly with symptoms (44). A high risk group of young patients was identified a number of years ago by Spanuolo et al. (45). Among these young patients with severe aortic regurgitation, those who had
Table 2. Guidelines for Selecting Patients With Acquired Aortic Stenosis for Operation

1. Knowledge of the poor outlook in patients with symptoms of angina pectoris, syncope or left ventricular dysfunction and the relatively favorable course after operation dictate surgical treatment once significant symptoms begin. However:
   A) The presence of critical aortic stenosis should be assured (aortic valve orifice area of 0.75 cm² or less, or 0.4 cm²/m² body surface area or less).
   B) Coronary arteriography should be performed to search for patients in whom coronary artery disease, rather than significant aortic stenosis, is the cause of angina pectoris, and to determine whether or not coronary artery bypass should be performed at the time of aortic valve replacement.

2. Operation should not be denied on the basis of left ventricular dysfunction, even if it is severely reduced (ejection fraction as low as 10 to 20%) since in the great majority of such patients, left ventricular function will improve substantially after operation.

3. At the present time, there is no indication for operation in the absence of symptoms to prevent left ventricular dysfunction since even if dysfunction develops, it is completely or partially reversible.

moderate or marked left ventricular enlargement, electrocardiographic evidence of severe left ventricular hypertrophy with repolarization changes and either a systolic blood pressure greater than 140 mm Hg or diastolic pressure less than 40 mm Hg had an unfavorable outlook, with more than 90% of such patients either dying or developing congestive heart failure or angina pectoris within a 6 year period.

Experimental studies on effects of left ventricular volume overload. Experimental studies in animals (46) have shown that the adaptations to chronic volume overload on the left ventricle consist of hypertrophy of the dilated (eccentric) type, with displacement of the entire diastolic pressure-volume relation to the right. Also, in compensated volume overload (as in pressure overload), studies (47,48) suggest that myocardial contractility can remain relatively normal, the ventricle being able to maintain a normal or high fractional shortening and ejection fraction with normal performance of each unit of an enlarged circumference, so that the markedly enlarged chamber allows delivery of a very large total stroke volume.

Clinical studies on left ventricular function in aortic regurgitation. By such mechanisms, the forward stroke volume and the ejection fraction in compensated aortic regurgitation can be well maintained (49). However, recent studies in patients with compensated chronic aortic regurgitation (50,51) indicate that the end-diastolic wall stress is somewhat elevated and the end-systolic wall stress values are considerably elevated (Fig. 5), providing a potential setting for afterload mismatch.

Response to operation. Studies of left ventricular function in patients with aortic regurgitation carried out preoperatively and again at 6 months to 1½ years postoperatively have generally shown substantial reductions in chamber volume and wall thickness and improvement in the ejection fraction (12,52,53). An example of one such study (12), in which echocardiographic left ventricular dimensions and

![Figure 5. Wall stress values in control subjects (C) with normal left ventricular function and in patients with chronic severe mitral regurgitation (MR) and aortic regurgitation (AR). Mean wall stress values at end-diastole, peak systole and end-systole are shown in all three groups of patients. Values are mean ± standard deviation. The asterisk indicates a significant (p < 0.05) difference from the control group. (Reproduced from Wisenbaugh et al. [50], with permission.)](image-url)
Figure 6. Adaptations in chronic aortic regurgitation. A. The diastolic pressure-volume and linear end-systolic wall stress-volume relations are shifted to the right in compensated aortic regurgitation compared with normal. Diagrammatic left ventricular pressure-volume loops show that in aortic regurgitation, the ventricle is able to deliver a large stroke volume with an ejection fraction (EF) in the normal range despite a somewhat elevated systolic wall stress. B, Wall stress-volume loops of the left ventricle in a hypothetical patient in whom mild left ventricular dysfunction has shifted the end-systolic wall stress-volume relation to the right (solid line) of the compensated relation (dashed line). The limit of preload reserve has been reached and wall stress is elevated, causing a decrease in the ejection fraction in this example (Pre Op 45%). Postoperatively, correction of afterload mismatch by aortic valve replacement allows the end-diastolic and end-systolic volume relations to shift to the left, and the lower wall stress during ejection allows the ejection fraction to return to normal (Post Op 55%).

Persistent left ventricular dysfunction postoperatively. Such favorable responses of the diastolic pressure-volume relation have been documented (Fig. 8, top), but...
in some patients with markedly dilated left ventricles, this improvement may not occur. In a few patients with severe aortic regurgitation studied in our laboratory pre- and postoperatively, there was considerable reduction in left ventricular end-diastolic pressure due to correction of the regurgitant leak, but the diastolic left ventricular radius-pressure relation (analogous to the diastolic pressure-volume curve) was not altered. The left ventricle simply moved down a single curve, suggesting the presence of irreversible myocardial fibrosis (Fig. 8, bottom) (7). Moreover, force-velocity studies suggested associated irreversible depression of systolic function. More recent studies by Henry et al. (37) in patients with severe aortic regurgitation who underwent preoperative echocardiography suggested that if the fractional shortening measured by echocardiography was less than 25% and the end-systolic dimension was greater than 55 mm, a high percent of patients developed late congestive heart failure or died after operation. On the basis of angiographic findings, Borow et al. (11) reported that patients with a left ventricular end-systolic volume index exceeding 60 ml/m² body surface area before operation exhibited a reduced fractional shortening after operation (at an average of 2 years), and a number of such patients remained in functional class III or died postoperatively; the ejection fraction alone was not a good predictor of outcome. Investigations by Gaasch et al. (9,13) suggested that when the ratio of left ventricular chamber volume to wall thickness exceeds 3.8, reflecting inappropriate ventricular dilation, the outlook after operation is unfavorable. More recently, Gaasch et al. (13) identified a subgroup (about 20%) of patients with severe aortic regurgitation who postoperatively had increased late mortality and failed to show a reduction in heart size or muscle mass; the ratio of left ventricular radius (R) to end-diastolic wall thickness (WTh) was increased in all patients in this subgroup, but overlapped that in other patients, whereas the presence of both an end-diastolic diameter greater than 38 mm/m² and an end-systolic diameter greater than 26 mm/m², or the presence of both an elevated end-systolic diameter and a high product of systolic pressure and end-diastolic R/WTh ratio (>600), had good predictive accuracy.

Other studies (55–57) suggest that late outcome after operation for aortic regurgitation is less favorable in patients with preoperative depression of left ventricular function, regardless of symptom level before operation. Turina et al. (56) examined the causes of improved early and late survival in the period from 1975 to 1979 compared with 1970 to 1974, and found that early mortality decreased from 3.5 to 2.0% and 5 year survival increased from 80.1 to 90.6% in the later period. In the 1975 to 1979 postoperative period, patients had less severe symptoms (for example, 15 of 100 patients were in functional class I), less cardiomegaly, lower left ventricular end-diastolic pressure (19 versus 33 mm Hg) and higher ejection fraction (54 versus 50%). In all patients who died in heart failure while awaiting operation or after operation, the left ventricular end-diastolic volume index exceeded 200 ml/m² and ejection fraction averaged 37%, but in a few it was normal. However, in the 1975 to 1979 period when patients were operated on before the onset of severe clinical and hemodynamic deterioration, no patient died postoperatively of heart failure. Other studies (57) indicated that when the preoperative ejection fraction is 45% or greater, late mortality between 2 and 5 years decreases. A few studies (54) showed little correlation between functional class preoperatively and preoperative indexes of left
ventricular function, and even if left ventricular function remained depressed postoperatively, some patients exhibited a stable and active condition. Therefore, operation usually should not be denied on the basis of depressed left ventricular function.

**Surgery for symptomatic patients with severe left ventricular dysfunction.** A continuing issue has been whether patients with severe aortic regurgitation in whom significant depression of left ventricular function is detected should undergo surgical treatment, even if they have no or few symptoms. Although the studies just cited suggest that operation generally should be recommended in such patients, recent studies by Bonow et al. (58) shed additional light on this problem. These investigators studied patients with severe chronic aortic regurgitation who were initially asymptomatic and had normal fractional shortening values. Among 77 such patients followed objectively by echocardiography during an average follow-up period of 49 months, 12 patients underwent aortic valve replacement because of the development of symptoms (11 patients) or the onset of severe left ventricular dysfunction without symptoms (1 patient). Therefore, among these initially asymptomatic patients who had normal left ventricular function, less than 4% per year required valve replacement. In the 12 patients who developed symptoms and required operation, the average initial left ventricular end-diastolic and end-systolic dimensions were higher than in the other patients; by late follow-up before operation, the smallest end-diastolic dimension in this group was 67 mm, and in all but two patients it was greater than 70 mm. In 5 of the 12 patients, the end-systolic dimension increased substantially during follow-up; in 10 patients it was greater than 50 mm, and the fractional shortening decreased by more than 5 percentage points in half of the patients (it was ≤ 28% in all but 2 patients). The response of left ventricular ejection fraction to exercise was abnormal in all 12 subjects, but it was also abnormal in a significant proportion of the other patients, and did not appear to independently predict later outcome better than did the echocardiographic data obtained at rest (58). In all 12 patients, the radionuclide left ventricular ejection fraction improved substantially after operation (average postoperative values between 45 and 58%), and left ventricular end-diastolic dimensions decreased.

**Indications and guidelines for surgery.** It may be concluded that with careful follow-up by echocardiography, deterioration of left ventricular function can often be detected and tends to occur simultaneously with the onset of symptoms. Therefore, in patients who present with or develop mild to moderate depression of left ventricular systolic function and a few or no symptoms, operation can be deferred for a time provided that the patient is closely monitored. However, rather than basing a final decision for operation on echocardiography alone, it is advisable to perform cardiac catheterization to confirm the echocardiographic findings; thus, it has been shown that in aortic regurgitation, because of the eccentricity of the left ventricular chamber, there can be a substantial error in calculating chamber volumes from the echocardiographic dimensions (59,60). In patients older than 40 years of age who have angina pectoris, coronary arteriography may also be indicated to assess whether or not associated coronary atherosclerosis is of significance. In those few patients with marked cardiomegaly, substantial systolic dysfunction and severe hemodynamic abnormalities, operation should be recommended regardless of symptom status (Table 3). An exercise test may be of additional aid in this decision (58).

Information on the natural history of patients with chronic aortic regurgitation who have significant symptoms, and the comparatively favorable outlook after aortic valve replacement (39–41), make a decision concerning the appropriate time for surgical treatment relatively simple. In patients with few or no symptoms, knowledge of the various measures related to left ventricular size and function that have been shown to be associated with a poor operative result or late death, as well as the reversible abnormalities in these measures that are often associated with the onset of symptoms,

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**Table 3. Guidelines for Selecting Patients With Aortic Regurgitation for Operation**

1. The downhill clinical course in chronic aortic regurgitation once significant symptoms occur is more gradual than in aortic stenosis, but if aortic regurgitation is severe and limiting symptoms are present, operation is usually indicated. Left ventricular systolic function is often normal, but even if it is moderately impaired, left ventricular size and function improve after operation.

2. In patients without symptoms who have normal or mildly impaired left ventricular function, careful follow-up with echocardiography is indicated since deterioration of left ventricular function and onset of significant symptoms usually coincide.

3. Operation should be considered to prevent irreversible myocardial changes in patients in whom symptoms are few or absent when left ventricular dysfunction and enlargement become significant (confirmed by angiography): ejection fraction less than 40%, fractional shortening less than 25% plus either A or B:

   A) Left ventricular end-diastolic diameter approaching 70 mm or 38 mm/m² body surface area (end-diastolic volume index approaching 200 ml/m²) and end-systolic diameter approaching 50 mm or 26 mm/m².

   B) Both end-systolic diameter approaching 26 mm/m² and a radius/wall thickness ratio at end-diastole × systolic pressure greater than 600.
usually make it possible to arrive at an appropriate decision. Guidelines for the selection of adult patients with chronic aortic regurgitation for operation are summarized in Table 3.

Mitral Regurgitation

Natural history. In chronic mitral regurgitation, the natural history after the onset of symptoms tends to be the most gradual among the three lesions under discussion (42). Even when symptoms of severe fatigue, dyspnea or orthopnea due to left ventricular dysfunction commence, they generally respond well to digitalis, diuretic drugs or vasodilators, and frequently the patient may respond favorably for many years to enhanced therapy during exacerbations of symptoms. The presence of persistent, severely limiting symptoms (New York Heart Association functional class III) has long been considered an indication for operation. Although overall surgical results have been generally quite good in patients with chronic mitral regurgitation, when the results of valve replacement for mitral stenosis versus mitral regurgitation are compared, the survival curves in some reports (61) indicate a considerably lower late survival rate for patients with mitral regurgitation. This suggests the possibility that in some patients with chronic mitral regurgitation, surgery has been delayed too long. In a clinical analysis of factors predicting increased mortality during a 5 year follow-up after mitral valve replacement for chronic mitral regurgitation, Cunha et al. (62) found that the presence of atrial fibrillation, increased left atrial dimension on echocardiography, increased left ventricular size and fractional shortening less than 30% all predicted increased mortality, supporting the view that earlier operation to preserve left ventricular function may have been indicated in some patients.

Cardiac adaptations to chronic mitral regurgitation. In several aspects, they resemble those of chronic aortic regurgitation, with a shift of the diastolic pressure-volume and pressure-wall stress relations to the right of normal (Fig. 9A) (49). In the compensated state, myocardial contractility may be preserved in the presence of such volume-overload hypertrophy (63), but in contrast to aortic regurgitation, the peak and end-systolic wall stress values in mitral regurgitation remain normal (Fig. 5) (50). In such patients, the ejection fraction often is in the high normal range (65% in the example in Fig. 9A). Thus, the low

Figure 9. Diagrammatic representation of adaptations to severe chronic mitral regurgitation. A, Wall stress-volume loops of the left ventricle under normal conditions and in the presence of eccentric hypertrophy, in which the diastolic volume-wall stress relation and linear end-systolic wall stress-volume relation are shifted to the right. In chronic mitral regurgitation, the low impedance leak into the left atrium during early and late ventricular ejection with a normal level of mean wall stress allows the ventricle to eject a greatly increased stroke volume, with a high normal (65%) ejection fraction. B, Diagram of a hypothetical patient in whom depressed myocardial contractility has shifted the end-systolic wall stress-volume relation downward and to the right preoperatively (depressed), although the ejection fraction (EFx) is maintained at a level of 50% because of the low wall stress during early and late ejection due to severe mitral regurgitation. Postoperatively, the early and late phases of contraction have become isovolumetric, the ventricle carries a higher wall stress early and late during ejection and ejection fraction has decreased (POST OP 37%) due to development of afterload mismatch with no further depression of myocardial contractility. (Modified from Ross J Jr [25] with permission of the author and the Annals of Internal Medicine.)
impedance leak into the left atrium allows the left ventricle to unload throughout systole (including the pre- and post-ejection phases). In fact, studies from our laboratory (63) in patients with chronic mitral regurgitation who had a regurgitant fraction averaging 41% showed that nearly half of the regurgitation occurred before aortic valve opening (63). Wall stress is lower than normal during early and late systole, and the reduced afterload contributes to the increased total stroke volume delivered by the enlarged ventricle (Fig. 9A) (58). Recent experimental studies (64) suggest that the end-systolic wall stress-volume relation in the left ventricle is shifted somewhat to the right several weeks after severe mitral regurgitation is produced in the normal dog. However, such a displacement must exist if a very large normal heart is compared with a small normal heart over the same systolic pressure range, and a modest shift of this type may occur during volume overload hypertrophy (51). Thus, in this type of hypertrophy, some type of normalization for heart size will be required before end-systolic relations can be interpreted relative to a depression of myocardial contractility (65,66).

Clinical studies using echocardiography. Clinical studies carried out with echocardiography (corroborated by radionuclide angiography) in patients with chronic mitral regurgitation preoperatively and late postoperatively have described a subset of patients who fail to improve and show persistent congestive heart failure or die postoperatively. In studies from our laboratories (17), two groups of patients were identified. In one group, the preoperative left ventricular end-diastolic dimension averaged approximately 60 mm and the ejection fraction averaged 70%; at late follow-up postoperatively (average 15 months) the end-diastolic dimension decreased (Fig. 10) along with a reduction in the cross-sectional area at the minor equator of the ventricle, indicating regression of hypertrophy. In these patients, the end-systolic dimension diminished slightly from an average of 35 mm preoperatively, and consequently there was a decrease in the calculated ejection fraction from an average of 70 to 59% (Fig. 10) and fractional shortening decreased from 40 to 31%. In contrast, in a second, smaller group of patients, the end-diastolic dimension was more markedly elevated preoperatively (average 80 mm) and failed to diminish at late postoperative study, while the cross-sectional area remained fixed (Fig. 10). In addition, the average end-systolic dimension increased from approximately 58 mm preoperatively to approximately 67 mm, with a consequent marked reduction in ejection fraction from a low normal value of 57% preoperatively to 26% at late follow-up (Fig. 10), with fractional shortening values averaging 29 and 14% preoperatively and late postoperatively, respectively (17). None of these patients had evidence of intraoperative myocardial damage.

Recently, Zile et al. (18) reported similar findings and additional observations. One group of their patients responded in a manner similar to that of our larger group, with regression of hypertrophy and a modest decrease in the calculated fractional shortening from 35% preoperatively to 26% postoperatively. However, in a smaller group of patients, hypertrophy failed to regress and the average fractional shortening decreased from 27 to 17% at postoperative studies (18). In addition, in the studies by Zile et al. (18), the patients who showed a deterioration in left ventricular function postoperatively remained symptomatic despite medical therapy, and all could be identified preoperatively if both the left ventricular end-systolic dimension exceeded 26 mm/m² body surface area and fractional shortening was less than 31%, or if both the end-systolic dimension exceeded 26 mm/m² body surface area and the end-systolic left ventricular wall stress index exceeded 195 mm Hg (the product of systolic pressure and radius/wall thickness ratio at end-systole).

Cardiac responses to mitral valve replacement: persistent left ventricular dysfunction. It seems likely that the response to operation in the subgroup of patients who showed postoperative deterioration in left ventricular function and failure of hypertrophy to regress was due to unmasking by the mitral valve replacement of depressed myo-
cardial contractility that was present preoperatively. Thus, in mitral regurgitation, a normal ejection fraction can exist preoperatively with markedly depressed myocardial function (17, 18). As diagrammed in Figure 9B, the linear end-systolic wall stress-volume relation is markedly shifted downward and to the right preoperatively, indicating depressed myocardial contractility, but ejection fraction is relatively well maintained (in this example 50%) because of systolic unloading into the left atrium early and late during ventricular ejection, with a normal or somewhat high peak systolic wall stress (50, 67). After mitral valve replacement the total stroke volume must be ejected into the high impedance of the aorta, producing afterload mismatch postoperatively, with a decrease in ejection fraction to 37% in this example (Fig. 9B). Thus, postoperatively, instantaneous wall stress early and late during ejection must increase, although the peak value may remain normal, since the ventricle now ejects entirely into the aorta and early and late contraction is now isovolumetric. Moreover, as Brutsaert et al. (68) have shown, increased loading during late systole and early diastole markedly accelerates relaxation. Therefore, it is postulated that the sharp decrease in the ejection fraction postoperatively in this condition is related primarily to relative mechanical overload with afterload mismatch on the impaired ventricle, rather than to a further depression in myocardial contractility (Fig. 9B).

It can also be seen from Figure 9B that the ratio of end-systolic wall stress (which is low) to end-systolic volume (which is high) should be reduced preoperatively in chronic mitral regurgitation, particularly when myocardial contractility is reduced. When this ratio was studied by Carabello et al. (69) in patients with chronic mitral regurgitation, they found that such individuals had a lower than normal ratio (below the lower limit of normal of 4.0 units). However, patients who postoperatively exhibited heart failure and reduced left ventricular function had a preoperative value lower than the other patients (< 2.5 units) despite an ejection fraction that was not different from that of the other patients (69). Thus, such an index may prove more useful in the future than ejection fraction for evaluating patients with chronic mitral regurgitation.

**Role of cardiac catheterization.** In reaching a final decision regarding operation, cardiac catheterization is often advisable to confirm the severity of mitral regurgitation, to carry out coronary arteriography in patients older than 50 years of age and to evaluate left ventricular function. Left ventriculography may also contribute to understanding the cause of regurgitation, (for example, coronary heart disease versus organic valve disease) which may influence the decision to operate or the type of operative procedure.

**Selection of patients for surgery.** On the basis of clinical information concerning the natural history and results of operation in patients with mitral regurgitation and the unfavorable response of the left ventricle to correction of mitral regurgitation in some patients, it is possible to develop some principles for selection of patients with chronic mitral regurgitation for operation. These are summarized in Table 4.

**Comments and Conclusions**

**Aortic stenosis.** The considerations just reviewed imply that in patients with valvular heart disease knowledge of the effects of altered loading conditions on the left ventricle is highly important in reaching a proper decision concerning the timing of corrective operation. In acquired valvular aortic stenosis in the adult patient, M-mode and two-dimensional echocardiography are helpful in diagnosis but often inconclusive for reaching a decision concerning operation (70), although recent studies (71) indicate that Doppler estimates of aortic valve gradient may be more reliable for determining the severity of stenosis. Nevertheless, cardiac catheterization and coronary arteriography are almost always desirable when the clinical examination and echocardiographic findings suggest the possibility of significant stenosis. Surgical treatment should be recommended in the patient with symptoms in whom hemodynamically significant stenosis is established since the outlook without op-

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**Table 4. Guidelines for Selecting Patients With Mitral Regurgitation for Operation**

1. The downhill clinical course is relatively gradual in chronic mitral regurgitation once symptoms begin, and left ventricular dysfunction may develop insidiously.

2. With significant *limiting symptoms* and severe mitral regurgitation, operation is usually indicated provided left ventricular function is good or not severely depressed (ejection fraction < 40%). Even when left ventricular function is sustained preoperatively, the ejection fraction will deteriorate to some degree after operation.

3. In patients with severe regurgitation who have *few or no symptoms*, operation should be considered to preserve left ventricular function provided serial noninvasive studies of the left ventricle show ejection fraction less than 55%, fractional shortening less than 30% plus either A or B:
   - A) End-diastolic diameter approaching 75 mm and end-systolic diameter approaching 50 mm or 26 mm/m² body surface area (end-systolic volume approaching 60 ml/m²).
   - B) Both an end-systolic diameter approaching 26 mm/m² and a radius/wall thickness ratio at end-systole × systolic pressure approaching 195 mm Hg.
eration is extremely poor, whereas with surgical treatment it is quite favorable regardless of the preoperative level of left ventricular function.

Aortic regurgitation. Among patients with chronic valvular regurgitation, we can now begin to identify by non-invasive means those patients who are developing depression of left ventricular function. In chronic aortic regurgitation, postoperative depression of left ventricular function is becoming less of a problem since the current tendency is to operate earlier (54). Recent studies (57) suggest that in many patients with chronic aortic regurgitation, symptoms will occur before or at the time depression of left ventricular function becomes manifest. Moreover, if the patient is asymptomatic and left ventricular size and function are not markedly abnormal, a delay until the onset of symptoms or to verify significant and progressive left ventricular dysfunction can be justified since left ventricular function tends to improve postoperatively even if it is moderately depressed before operation (25,57,72). In those relatively few patients with severe aortic regurgitation and no symptoms who have depressed function and a markedly enlarged ventricle or progressive depression of function, some guidelines have been offered (Table 3) for considering operation whenever left ventricular function and size approach certain limits found to be associated with irreversible myocardial damage.

Mitral regurgitation. Chronic mitral regurgitation poses a more difficult problem. It is important that patients with few or no symptoms who have cardiomegaly due to severe mitral regurgitation be studied regularly by echocardiography to detect early depression of left ventricular function. In those patients who exhibit deterioration toward certain limits (Table 4), present information indicates that operation should be recommended even if symptoms are mild because once the ventricle reaches those limits, left ventricular function may seriously deteriorate postoperatively. If left ventricular function has markedly deteriorated, it is possible that the natural history of the patients may be more favorable without operation. As more experience is gained with valve reconstructive procedures for mitral regurgitation (73), which are being performed with increasing frequency in some centers (74,75), more enthusiasm may develop for earlier operation in patients with chronic mitral regurgitation and few symptoms. In any case, it appears that we are waiting too long to recommend corrective surgery in some patients with chronic mitral regurgitation.

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