Mitral regurgitation (MR) burdens the left ventricle with a volume load that leads to a series of left ventricular (LV) compensatory adaptations and adjustments that vary considerably during the prolonged clinical course of MR.1–4 The early compensatory changes observed in acute MR (ie, utilization of the Frank-Starling mechanism) are gradually replaced by a chronic remodeling process with enlargement of the LV chamber. Eventually, these compensatory adaptations fail, LV dysfunction develops, and transition to a decompensated phase of chronic MR occurs (Table). In the present report, the LV response to MR will be described, the evolution from a compensated to a decompensated state will be discussed, and the therapeutic implications of these events will be considered. Published guidelines provide detailed recommendations for the evaluation and treatment of patients with MR, including those with a variety of comorbidities.5,6 The present review is limited to a discussion of the changes in LV size and function that develop as a result of degenerative disease of the mitral valve (recognized clinically as severe mitral valve prolapse with or without partial flail leaflet) or, less commonly, rheumatic mitral valve disease. Our primary goal is to review the rationale for the use of measurements of LV size and function as guides to the management of patients with MR.

Mitral Regurgitant Volume

The clinical impact of MR is determined by the magnitude of the regurgitant leak (ie, the regurgitant volume) and the time course of development of the regurgitation. Patients with the abrupt onset of severe MR generally present with markedly elevated pulmonary venous pressure, whereas those with chronic MR exhibit prominent ventricular enlargement with increased chamber compliance and lower pulmonary venous pressure.2,7 In this section, the determinants of regurgitant flow will be defined and the assessment of its severity discussed.

Determinants of Regurgitant Volume

The determinants of the mitral regurgitant volume are best explained in the context of the orifice equation.8 This equation, based on the Torricelli principle, states that flow through an orifice varies by the square root of the pressure gradient across the orifice, the duration of flow, and a discharge coefficient. Thus, the principal determinants of the regurgitant volume (and the primary therapeutic targets) are the regurgitant orifice area and the systolic pressure gradient between the ventricle and left atrium. It should be recognized that systemic vascular resistance, LV afterload, and myocardial contractile state are not direct determinants of regurgitant volume.

In many, if not most, patients with MR, the regurgitant orifice area is not fixed and can exhibit dynamic variations that are closely related to changes in LV pressure, volume, and geometry.9 Variations in the systolic pressure gradient across the valve can also affect the severity of the regurgitant volume, but the impact of the pressure gradient is blunted by the presence of a square root sign in the orifice equation. Thus, a 10% to 15% decrease in the pressure gradient results in only a 7% decrease in the regurgitant volume.10 Such a modest impact of the pressure gradient on regurgitant volume is likely responsible, at least in part, for the lack of a clinical benefit of vasodilating drugs or angiotensin-converting enzyme inhibitors in asymptomatic patients with chronic compensated MR.5

Assessment of Severity

The diagnosis of severe MR is made when >50% of the total stroke volume is diverted to regurgitant flow. Moderate MR is said to be present when this fraction is 30% to 50%, and if the regurgitant fraction is <30% the diagnosis of mild MR is made. The regurgitant volume and fraction, and even the regurgitant orifice area, can be determined with quantitative echocardiography-Doppler techniques, but these methods are largely restricted to clinical investigation, and unfortunately, they are not widely applied. The severity of MR is best determined from a combination of 2D echocardiography with Doppler measurements and clinical observations.11,12 With the possible exception of coexisting conditions that might limit ventricular enlargements, the diagnosis of chronic severe MR should be questioned if the ventricle is not enlarged.
Afterload-Shortening Relations
An understanding of the LV response to MR and the stages outlined in the Table requires some discussion and clarification of systolic load and myocardial shortening. The systolic load that opposes myocardial shortening has been described by calculating LV systolic wall stresses (afterload) or by determining the arterial and left atrial input impedance (hydraulic load). The latter has an impact on LV performance, but alterations in impedance are always manifest by variations in LV systolic wall stress that more adequately predict changes in the ejection fraction (EF). According to the Law of Laplace, LV systolic wall stress is directly proportional to systolic pressure and chamber size and inversely proportional to wall thickness. An enlarged chamber will generally manifest a high afterload, unless a proportional increase in wall thickness occurs. Thus, systolic wall stress, calculated according to the Laplace relation, incorporates the effects of a variable ejection impedance, and the EF can be interpreted accurately relative to the prevailing afterload.

Afterload in MR
In acute MR, late systolic volume is reduced and afterload is low, but as the ventricle enlarges and adapts to the chronic volume overload, afterload gradually increases. Eventually, particularly in decompensated MR, afterload exceeds normal. Such afterload excess contributes to a decline in EF. Despite evidence to the contrary (vide infra), the notion persists that afterload is low in chronic MR. Several published studies refute this misconception.

Using echocardiographic measures of LV volume, mass, and geometry, Zile et al found that meridional end-systolic stress was normal in compensated MR and increased in decompensated MR. A tendency was found for peak systolic stress to be increased in both compensated and decompensated MR. Corin et al later confirmed these observations with cardiac catheterization techniques. They calculated circumferential wall stress and found a modest increase in peak systolic stress in compensated and decompensated ventricles. End-systolic stress was increased dramatically in decompensated MR. Other published data support the conclusion that LV afterload ranges from normal to increased in chronic MR. An understanding of these concepts of afterload in chronic MR is important when the clinician evaluates and assesses LV systolic performance and function. For example, a low or borderline EF (ie, 50% to 55%) would obviously indicate depressed LV function if afterload were low; however, it would not be appropriate to conclude that LV function was depressed if the EF were 55% to 60% in the presence of increased or even normal afterload.

Hoslotic MR seen in patients with partial flail leaflets can produce substantial regurgitation prior to the time of aortic valve opening. With most of the regurgitation (and a major reduction in LV volume) occurring in early systole, the time course of systolic wall stress would be substantially different from that seen in patients with late systolic prolapse and late systolic MR. It is not known whether these differences produce different effects on LV size, function, or clinical outcomes, but it is unlikely that the regurgitant volume in late systolic MR would be as large as that seen in hoslotic MR.

Ejection Fraction
The EF, which represents volume strain, is calculated as change in volume divided by initial volume or stroke volume divided by end-diastolic volume. Thus, the EF is appropriately normalized and does not require a consideration of anthropometric issues such as body size. The EF is, however, sensitive to changes in LV hemodynamic loading conditions, but this is not always a disadvantage. For example, even if the LV contractile state remains normal, there will be a tendency for the EF to decline if afterload increases. Thus, a decrease in myocardial contractile state or an increase in LV afterload (ie, during the transition from compensated to decompensated MR) may cause a decrease in the EF. Regardless of the mechanism, a depressed EF can be an indication for surgical correction of MR.

In MR, other indices of systolic function appear to be less useful than the EF. For example, the end-diastolic dimension may not be as accurate in predicting postoperative heart failure and survival as the EF. This could be due at least in part to the requirement for anthropometric normalization of the linear end-systolic dimension; the optimal method for such normalization has not been established. In addition, a given end-systolic dimension could suggest depressed or normal LV function depending on the diastolic dimension. Indeed, if end-diastolic diameter ranged from 55 to 65 mm, an end-systolic diameter of 40 mm would indicate an EF ranging from the lows 50s to the high 60s. The former could be taken as an indication for surgery, whereas the latter would not. Certainly, end-systolic size is not a pure index of systolic function. It is an amalgam of end-diastolic size and contractile function, neither of which is independent of hemodynamic loading conditions. The end-systolic stress-volume ratio might be more useful than the end-systolic volume alone, but in chronically remodeled hearts, this ratio, like systolic elastance, requires consideration of body size and LV geometry. These and other indices of function certainly can be useful in many circumstances, but the EF appears to be the most clinically relevant index of LV systolic function in MR, and it provides a scientifically valid and clinically reliable index on which to base management decisions.

Acute MR
With the abrupt onset of MR, the major circulatory impact is on the pulmonary venous pressure. The central circulation is overloaded, but a normal LV compliance limits the increase in end-diastolic volume to a modest rise. This increment in volume produces a preload-dependent increase in LV stiff-
ness, which adds to the pulmonary venous hypertension. LV preload reserve is exploited, and the Frank-Starling mechanism contributes to an increase in the total stroke volume. At the same time, the low-pressure runoff into the left atrium affects a systolic unloading, which also contributes to an increase in stroke volume (Figure 1). Despite these major alterations in the central circulation and the LV, the hemodynamic burden of acute MR is well tolerated by the myocardium. Almost a century ago, Evans and Matsuoka\textsuperscript{23} found that increased flow work added little to the energy requirements of the heart. Later, Urschel and associates\textsuperscript{24} demonstrated that myocardial oxygen consumption increased only minimally during experimental MR, despite a doubling of the total stroke volume.

Thus, the LV response to acute MR includes an increase in preload, a decrease in afterload, an increased EF, and an increased total stroke volume. Although many, if not most, patients with acute MR require urgent surgery, some evolve to a chronic state that has a gradual progression and prolonged natural history.\textsuperscript{25}

### Chronic MR

The natural history of chronic MR is characterized in its early phases by a compensated hemodynamic state, during which most patients remain free of symptoms. Gradually, a progressive and malefic LV remodeling leads to a decompensated stage of chronic MR (Figure 2). This late stage is usually heralded by the development of symptoms, but the progression may be insidious and clinically silent. Thus, it is extremely important to identify deleterious structural and functional remodeling of the LV before the development of irreversible LV dysfunction and to recommend surgical correction of the regurgitant lesion before the decompensated stage is established. To this end, it is necessary to describe and clarify the definitions of the compensated, transitional, and decompensated stages of MR.

Early descriptions of compensated and decompensated stages of MR were based largely on reversibility of the LV dilatation and eccentric hypertrophy, as well as the maintenance of systolic function after surgical correction.\textsuperscript{14,26} Later, a broad spectrum of clinical data that included functional status and exercise tolerance were added, and the definitions of compensated and decompensated MR were refined and utilized in published guidelines.\textsuperscript{5,6} The following discussion of the pathophysiology and ventricular remodeling in MR emphasizes ventricular size and function in compensated MR (in which the remodeling is reversible) and in decompensated MR (in which the eccentric hypertrophic remodeling is irreversible).

### Compensated Stage of MR

The major adaptive change that occurs during the development of a chronic volume overload is an enlargement of the ventricle. As this chronic compensated state develops, the small hyperkinetic ventricle of acute MR is converted to a large compliant ventricle that is well suited to deliver a large stroke volume. Progressive LV enlargement is also seen during gradual progression of the severity of the regurgitation. Such compensatory enlargement comes about through a remodeling of the extramyocardial matrix with a dissolution of collagen weave that allows rearrangement and slippage of myocardial fibers and chamber enlargement.\textsuperscript{4,27} New sarcomeres are added “in series,” and at the ventricular level, eccentric hypertrophy develops. During this process, cardiomyocytes exhibit an increase in length, but preload at the sarcomere level (ie, sarcomere length) does not increase progressively. Indeed, sarcomere lengths tend to return toward normal despite progressive LV enlargement.\textsuperscript{28} As a result, preload reserve is reestablished. In addition to these changes in the cardiomyocytes and the extramyocardial matrix, the LV systolic unloading that is characteristic of acute MR is gradually replaced by normal systolic wall stress.\textsuperscript{14,15} Thus, the enhanced total stroke volume seen in chronic compensated MR is “mediated through a normal performance of each unit of an enlarged circumference.”

During this compensated stage, preload (at the sarcomere level), afterload (at the ventricular level), and both contractility and EF are normal, and total stroke volume is increased as a result of the large end-diastolic volume.

### Transitional Stage of MR

The nature of the transition from the compensated to a decompensated stage remains an elusive and poorly under-
stood aspect of the pathophysiology of MR. This transition may occur as a consequence of a progressive increase in the regurgitant volume, a decrease in LV contractile function, an increase in afterload, or some combination of these factors. During this stage, the EF declines to 50% to 59%. Such structural and functional remodeling of the ventricle is largely reversible if surgical correction of the MR is accomplished during this transitional stage, before the decompensated stage.

Decompensated Stage of MR

Decompensated MR is characterized by substantial and progressive LV dilation, elevated LV diastolic pressure, increased systolic wall stress, and an EF <50%. The decline in EF is a consequence of depressed myocardial contractile state, LV afterload excess, or both. Such malefic structural and functional remodeling of the ventricle generally precludes an optimal result after surgical correction of the regurgitant lesion. This does not necessarily imply that patients with an EF in the range of 30% to 50% cannot benefit from surgery. Indeed, corrective surgery is recommended, but the clinical outcomes are not as favorable (or predictable) as those in patients with higher EF.5

Patients with signs and symptoms of MR with severely depressed systolic function (ie, EF <50%) can present a difficult diagnostic and management dilemma. It can be difficult to establish whether the primary problem is that of MR causing LV dilatation and dysfunction or a cardiomyopathic process leading to secondary (ie, “functional”) MR. Such a quandary should be approached by (1) an assessment of mitral valve morphology and the mechanism of MR to determine whether evidence of primary valve disease exists, such as myxomatous changes, and (2) utilization of quantitative methods that provide regurgitant volume and regurgitant fraction. A regurgitant fraction that is <50% is not expected to lead to severe LV dysfunction and dilatation. In this case, consideration should be given to a diagnosis of cardiomyopathy. It can also be helpful to determine the ratio of regurgitant volume to the end-diastolic volume. A high ratio indicates severe MR that is a potential target for corrective surgery. By contrast, a low ratio suggests severe decompensated MR or a cardiomyopathic process.29

If a patient exhibited moderate LV enlargement (end-diastolic diameter of 65 mm or end-diastolic volume of 130 mL/m²), an EF of 30%, a regurgitant fraction of 50%, and a regurgitant volume of 20 mL/m², the ratio of regurgitant volume to end-diastolic volume would be only 20/130, or 0.15. This should suggest severe, irreversible LV dysfunction. By contrast, a patient with the same end-diastolic volume, an EF of 50%, and a regurgitant fraction of 50% would have a ratio of regurgitant volume to end-diastolic volume of 33/130, or 0.25. The higher ratio of 0.25 indicates a potentially reversible phase of chronic MR. This ratio is mathematically equivalent to the product of EF and regurgitant fraction, which makes it possible to determine noninvasively and can potentially aid in the management of patients with chronic MR.

LV Response to Corrective Surgery

Early echocardiographic studies by Schuler et al26 and Zile et al14 described the temporal response of the left ventricle to mitral valve replacement and suggested a predictive value of preoperative measures of LV size and function. In most of these patients, the LV end-diastolic dimension declined substantially after surgery, but some failed to exhibit this favorable decrease in LV size. In both studies, patients who achieved a normal LV end-diastolic dimension had a better functional result than those with persistent postoperative LV enlargement. These disparate responses to valve replacement provided the basis of our current terminology that emphasizes compensated and decompensated LV function in chronic MR and stimulated a wide search for parameters that might predict the postoperative result and thereby aid in the optimal timing of surgery.

The early studies also revealed a consistent decline in LV EF after mitral valve replacement. This was thought to be a consequence of an increase in LV afterload that was causally related to closure of the low-impedance left atrial leak. Such a mechanism may very well contribute to the decline in EF that is seen in patients with decompensated MR, persistent postoperative LV enlargement, and afterload excess. However, those patients exhibiting a postoperative normalization of LV chamber size tend to exhibit normal or near-normal values for systolic wall stresses before surgery and normal values after surgery. Thus, a postoperative decline in EF (with valve replacement in compensated MR) does not appear to be a consequence of afterload excess.14

An alternative explanation for the postoperative decline in EF can be developed by comparing the different functional results of total valve replacement (with and without preservation of the subvalvular apparatus) with those of valve repair and preservation of the subvalvular apparatus.30,31 When the valve, including the subvalvular apparatus, is replaced with a prosthesis, the ventricle becomes more spherical, long-axis shortening declines, and the EF falls. By contrast, valve repair or replacement with preservation of the subvalvular apparatus is not associated with a significant fall in the EF. By preserving the continuity between the mitral apparatus and the LV wall, systolic function is preserved despite closure of the low-impedance left atrial leak. Thus, the LV response to corrective surgery depends largely on the functional state of the ventricle before surgery and the surgical procedure that is performed.

Predictive Value of Preoperative Data

Having described the LV response to corrective surgery in compensated and decompensated MR, it appeared to be possible to predict the postoperative results from preoperative data. Angiographic and echocardiographic data that appeared to provide prognostic information included (1) a subnormal EF or low fractional shortening and (2) a large end-systolic volume or dimension. These early studies were later expanded to include prediction of postoperative heart failure and even survival.20,21 Such predictive and prognostic clues do not directly identify an optimal time for corrective surgery, but they certainly should influence our decisions about surgery. Indeed, the published guidelines rely heavily on such information.5

A most important prospective outcome study by Rosenhek et al32 confirms the utility of the published guidelines. These
investigators used a “watchful waiting” approach in 132 patients with severe MR and recommended surgery only if the patients met the criteria outlined in the guidelines. Their indications for surgery were (1) the development of cardiac symptoms that were thought to be caused by MR; (2) an EF <60% or fractional shortening of the minor-axis diameter <32%, which is equivalent to an EF that is <60% \(13,33,34\); (3) an end-systolic diameter of 45 mm or 26 mm/m²; or (4) pulmonary hypertension or atrial fibrillation. Thirty-five patients were treated surgically in the first 5 years, and no postoperative deaths occurred. Only 4 patients exhibited postoperative LV dysfunction; 2 of these had undergone mitral valve replacement, and the other 2 had coronary bypass surgery with reduced LV function before surgery. During the follow-up period, only 2 deaths were thought to be related to MR, and overall survival did not differ from the “expected cumulative survival.” This study provides strong support for the use of the published guidelines for the management of chronic MR.5,6

**An Unresolved Issue**

Current guidelines for the management of patients with valvular heart disease are based in part on the information reviewed herein. Unfortunately, most such data, particularly surgical outcomes, were obtained decades ago. In the modern era, a remarkable improvement in surgical techniques, particularly mitral valve repair, has resulted in improved outcomes.25 This may be a rationale for considering earlier surgery, but it may also be a rationale for reconsidering the EF limit of 60% that is recommended in the guidelines. For example, survival data obtained in the 1980s and published in 1994 indicate that patients with an EF of 50% to 60% exhibit a similar postoperative survival as those with MR and an EF exceeding 60%.20 In asymptomatic patients without coronary disease, the 5-year survival rate was 90% and 93% in these 2 groups, respectively. A more recent analysis of surgical outcomes indicates that survival trends have continued to improve by 1992 to 1995.25 Most of the patients in that report were symptomatic, most had significant LV enlargement, and many had an EF <60%. Despite these risk factors and other comorbidities, postoperative survival of the patients was not significantly different from expected survival. Thus, it appears that the continued improvement in surgical techniques and a better understanding of LV function in MR allow safe and effective surgery in patients with evidence of borderline or mild LV systolic dysfunction (ie, transitional stage of MR). As suggested more than 25 years ago, an EF limit of 55% might well be appropriate in the current era.36

**Management**

Having identified a patient with what appears to be hemodynamically significant MR, the physician must consider at least 3 issues. Management decisions should be based on quantitative assessments and should not be based on any single measurement or observation. First, the severity of the regurgitation should be established. Corrective surgery is indicated only if the regurgitation is severe. Given the difficulties in quantifying severity, it is prudent to question the diagnosis of severe chronic MR when little or no LV or left atrial enlargement is found. Second, the patient’s symptoms should be assessed and evaluated. In the absence of cardiac symptoms, many, if not most, physicians hesitate to recommend surgery unless clear and reliable evidence of LV dysfunction exists, or some other factor (eg, the development of atrial fibrillation, patient’s wishes and expectations) must be considered. By contrast, surgery is indicated in symptomatic patients regardless of whether LV function is normal or abnormal (with the exception of those with the most severe LV dysfunction; vide supra). Third, the functional state of the LV must be evaluated. Corrective surgery should be considered in an asymptomatic patient when the EF enters the transitional stage (EF 50% to 60%) and is strongly recommended before the decompensated stage (EF <50%).

**Disclosures**

None.

**References**


Key Words: contractility ■ hemodynamics ■ remodeling ■ ventricular function, left ■ regurgitation ■
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