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## Timing of Surgical Intervention in Chronic Mitral Regurgitation Is Vigilance Enough?

Brian P. Griffin, MD

**T**iming of surgical intervention in chronic mitral regurgitation (MR) is a complex problem that has been studied extensively. Surgical technique in the treatment of MR has improved considerably over the last decades. Our knowledge of the pathophysiological mechanisms whereby MR exerts its deleterious effects on survival has also increased. Early reports in the literature and newer prospective studies suggest that severe MR is not a benign condition and that, left untreated, it has a high morbidity and eventually mortality. It therefore makes sense to periodically reexamine the rationale and safety of existing practice guidelines. The article by Rosenhek and colleagues<sup>1</sup> in this issue of *Circulation* provides an interesting and important insight into the long-term outcomes when asymptomatic degenerative MR is managed in accordance with the current American College of Cardiology/American Heart Association guidelines.<sup>2</sup> However, it is important in employing these guidelines to first understand the pathophysiological construct and studies that have led to their generation.

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### Pathophysiological Effects of MR

MR produces volume overload of the left ventricle and left atrium. The left ventricle develops eccentric hypertrophy whereby the sarcomeres elongate. Preload increases and the left ventricle dilates in order to maintain a normal forward flow. The increase in afterload resulting from left ventricular dilatation is offset by the fact that the ventricle is pumping much of its volume (regurgitant volume) into a low-impedance circuit (the left atrium). Therefore, afterload may be variably reduced initially in MR and typically only becomes elevated in later stages of the disease as left ventricular size increases further. Thus, ejection indices such as ejection fraction are not considered reliable measures of left ventricular contractile function and remain in the normal range when contractility is already impaired. Load-independent measures of contractile function, such as elastance, are more reliable. However, these measurements are

both time consuming and invasive to perform and are therefore of limited clinical relevance in patient follow-up. Ejection fraction, although somewhat flawed for the aforementioned reasons, is still a useful parameter in chronic MR. An ejection fraction of <60% has been shown to be associated with poorer survival after corrective surgery and likely indicates covert contractile dysfunction in MR patients.<sup>3</sup>

The precise mechanism whereby contractile dysfunction in chronic MR occurs is still unclear. What is clear is that prolonged contractile dysfunction is eventually irreversible even after the MR is relieved and is predictive of both death and congestive heart failure.<sup>4</sup> Symptoms often occur late in chronic MR, most likely as a result of the compliance properties of the left atrium that allow it to accommodate large volumes of blood without a significant rise in pressure. In some instances, pulmonary pressures increase, and although this is associated with poorer survival, it may also protect against the development of symptoms. Covert cardiac dysfunction in chronic MR has been evidenced by elevations in biomarkers also elevated in congestive heart failure such as cytokines and B-type natriuretic peptide.<sup>5,6</sup> Contractile dysfunction may precede symptoms, and therefore evaluation of symptoms alone is inadequate in determining the timing of surgery in chronic MR.

Compensatory mechanisms for chronic MR include the development of catecholamine excess. This has been elegantly demonstrated in an animal model in which  $\beta$ -blockade helped to prevent the contractile dysfunction normally produced by chronic MR.<sup>7</sup> Catecholamine excess may also play a role in humans, and sudden death has been reported in patients with longstanding severe MR who are managed without surgery.<sup>8</sup> Patients with MR are more prone to ventricular arrhythmia than normal, and presumably some of this effect is mediated through catecholamines.<sup>9</sup> Atrial fibrillation is also common in chronic MR and is likely a result of atrial dilatation, and the prevalence increases significantly with time. Atrial fibrillation is also associated with adverse cardiovascular and survival endpoints.<sup>10</sup>

The relationship of contractile dysfunction to the severity of volume overload in MR is not completely clear. A number of studies suggest that left ventricular size, particularly in end-systole, is predictive of outcome, presumably mediated through a reduction in left ventricular contractility. A recent study from the Mayo Clinic showed a close link between the quantitative severity of MR and adverse outcome in conservatively managed patients, suggesting that this effect may be mediated through volume loading.<sup>11</sup> It has also been shown that patients with the most dilated ventricles preoperatively

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are least likely to regain contractile function even after successful corrective mitral valve surgery. In an elegant series of experiments in which high-fidelity measures of left ventricular contractility such as elastance were used, it was shown that left ventricular contractile dysfunction is present in many patients with severe MR despite a normal ejection fraction and that this returned to normal after corrective mitral valve surgery in some but not all patients.<sup>12,13</sup> Therefore, when contractile dysfunction occurs, it may be temporary or reversible if detected and treated in time. The duration and determinants of this window of opportunity are not known.

### Effects of Corrective Surgery for MR

Surgical intervention improves symptoms, and a survival benefit has been reported on the basis of multivariate analysis in series in which some patients have undergone surgery.<sup>11,14</sup> There has been no randomized trial of surgery versus conservative therapy for this condition. Outcome appears generally better in terms of survival, left ventricular function, and morbidity when repair rather than prosthetic replacement is performed.<sup>15</sup> Valve repair is the preferred approach to surgical treatment of MR and appears to restore a normal life expectancy to most patients with degenerative MR but is still not universally performed in situations in which it is generally feasible. Technical prowess in its performance also varies widely such that more complex repair procedures may not be referred to an appropriately competent surgeon.

### Current Guidelines for Surgical Intervention in MR

Current guidelines (originally published in 1998) suggest surgical intervention in severe MR if there are significant symptoms or at the onset of signs of left ventricular dysfunction that have previously been shown to adversely affect outcome, such as an ejection fraction of <60% or significant left ventricular dilatation with an end-systolic dimension of  $\geq 45$  mm.<sup>2</sup> The guidelines stress the importance of using mitral valve repair for correction of MR when feasible and in general suggest a lower threshold to intervene surgically when mitral valve repair appears both feasible and likely. The guidelines also suggest that surgery may be indicated even in the absence of symptoms or signs of left ventricular dysfunction when atrial fibrillation ensues or when pulmonary pressures are elevated to >50 mm Hg at rest or >60 mm Hg on exercise. The guidelines suggest that surgery is not generally indicated in asymptomatic patients with preserved left ventricular function even if mitral valve repair is feasible.

### Are the Guidelines Good Enough?

The current guidelines recommend that surgical intervention be performed once an end point associated with poorer long-term outcomes is reached. Although there appears to be a window of opportunity for reversibility of the structural changes in the heart, it is conceivable that such an approach might be associated with suboptimal outcomes at least in a subset of patients. A number of authors have called for a different standard of referring patients with chronic MR for surgery.<sup>11,14</sup> They suggest that if the valve is both severely

regurgitant and repairable, postponing surgery exposes the patient to unnecessary risk in an era in which mitral valve repair in specialized centers has a very low morbidity and mortality. Thus, they recommend elective surgery early rather than late in such patients. Two studies in particular, both from the Mayo Clinic, have highlighted the poor outcomes in patients with severe MR who were managed conservatively rather than surgically. One of these studies, published in 1996, involved 229 patients with flail mitral valves where flail was used as a surrogate for severe MR in the pre-Doppler era.<sup>14</sup> The 86 patients treated medically in this study had a much higher than expected mortality of 6% per year. At 10 years, the majority of these patients had experienced heart failure, and all but 10% had died or had undergone surgery. Surgery was an independent predictor of better survival in multivariate analysis in this retrospective study. In another study published in 2005, the authors prospectively evaluated 456 patients with chronic MR with quantitative MR techniques.<sup>11</sup> Mortality was 22% at 5 years. A major independent determinant of survival was the quantitative severity of the MR assessed by regurgitant orifice area. They found that those patients with a regurgitant orifice area  $\geq 0.4$  cm<sup>2</sup> had a 5-year survival of 58%, which was inferior to that of a matched control population (78%). Surgical intervention was again a highly significant independent determinant of better survival. A drawback of both of these studies is that patients were managed by their individual physicians, and it is unclear how frequently they were evaluated or what criteria were used to determine when surgical intervention was appropriate. Although the information in these studies is important and compelling regarding the poor outcome associated with chronic MR when treated conservatively, it does not necessarily provide us with a comprehensive evaluation of the effectiveness of the current guidelines.

The study by Rosenhek et al<sup>1</sup> in this issue provides a more precise evaluation of the current practice guidelines in MR in that they studied a cohort of 132 asymptomatic patients with severe degenerative MR in a prospective manner clinically and with echocardiography. Patients were evaluated and followed up over a 5-year period by the same group of physicians, and the current guidelines were used to determine the appropriateness of surgery in individual patients. In this closely monitored study, overall mortality was not increased compared with a control population. Only  $\approx 30\%$  of patients required surgery at 5 years, and fewer than half required surgery by 8 years. Patients with flail valves had outcomes similar to those without flail. Symptomatic deterioration was the most common indication for surgery and was twice as likely to necessitate surgery compared with a change in the size or function of the left ventricle. The judicious use of the current guidelines as exemplified in this article was associated with a low risk of postoperative left ventricular dysfunction. This occurred in 4 patients, 2 of whom underwent mitral valve replacement and 2 of whom had coronary artery disease. Thus, this study provides reassuring data that the current guidelines in the management of chronic MR are safe and effective when implemented appropriately and when

patients are followed up at regular intervals clinically and with echocardiography.

Therefore, should we postpone surgical intervention in all patients with chronic MR until the end points in the guidelines are met? This certainly appears to be a safe approach in a structured environment in which patients are followed up closely and regularly. Many patients with excellent exercise tolerance and minimal symptoms wish to defer surgery for as long as possible, and this appears feasible with the use of the strategy outlined in the guidelines. Our group has used stress echocardiography as an adjunct to clinical and Doppler echocardiographic testing when following up MR patients, especially in those in whom there is a concern that symptoms may be occurring or when the left ventricular size or function is approaching the end points at which surgery is recommended.<sup>16</sup> The addition of the stress component allows evaluation of other parameters of interest such as pulmonary artery systolic pressure at peak exercise, functional capacity, and the response of the left ventricle to exercise, ie, the “contractile reserve.” In a study of preoperative patients before mitral valve repair, we found that a reduction in end-systolic volume at peak exercise over that at rest and an improvement in ejection fraction at peak were better predictors of left ventricular function postoperatively than the preoperative resting ejection fraction. A recent study indicated that when contractile reserve is absent in chronic MR patients, ie, when there is a failure of left ventricular function to improve with exercise or left ventricular end-systolic volume to decrease, those patients tend to demonstrate progressive left ventricular dysfunction when treated medically, which persists after corrective surgery in  $\approx 20\%$  of patients.<sup>17</sup>

Should we offer patients a choice of elective early surgery in asymptomatic chronic MR before the end points in the guidelines are met? The guidelines appear to work well when patients are followed up closely and diligently by an interested expert. This is not possible for every patient, and it may be appropriate to intervene early in selected patients if access to appropriate expert care is difficult for them and if certain conditions are met. The first of these is to determine whether the MR is truly severe by quantifying this when possible. It is important, however, to recall that the effect of severe MR on ventricular size and function is determined not only by the severity of the regurgitation when it occurs but also by its duration. Severe MR that occurs in the latter half of systole is seen frequently and may occur with relatively modest effects on ventricular and atrial size and thus may be of less risk in causing contractile dysfunction. Therefore, one should be careful in referring an asymptomatic patient to surgery with a normal-size left ventricle or atrium. This should suggest an absence of significant loading of the left ventricle by the MR and mandate an analysis of the duration of the MR on a continuous wave Doppler tracing. Patients with severe MR but a small left ventricle and left atrium are at greater risk of systolic anterior motion after mitral valve repair, and although this is usually correctable by appropriate surgical technique, in some instances it may require valve replacement for correction. It is also imperative when one refers a patient with chronic MR for elective surgery to determine that the valve has a high likelihood of successful repair at the

institution where the patient is being referred for surgery. This is possible in most instances in prolapse or flail of the posterior leaflet but is more difficult in other conditions and especially in anterior leaflet prolapse or flail or when both leaflets are prolapsing.

In summary, the price of maintaining normal left ventricular function and therefore survival in chronic asymptomatic MR is vigilance. The current guidelines for managing patients with severe chronic MR provide an adequate margin of safety to the patient when followed rigorously and conscientiously. In instances in which such vigilance is difficult, elective surgery may be appropriate to forestall complications as long as the MR is truly severe, the left ventricle shows signs of volume loading, and the valve has a high likelihood of being repaired.

## Disclosures

None.

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