Evaluation of Mitral Valve Regurgitation: Implications for Percutaneous Mitral Valve Repair

By ELYSE FOSTER, MD

Isolated mitral valve repair surgery (MVRS) accounts for approximately 8,000 open-heart procedures that are performed each year in centers included in the Society for Thoracic Surgery (STS) database. In 2004, the number of valve repairs almost equaled the number of replacements.1 Currently, the majority of MVRS in the United States is performed for degenerative mitral valve (MV) disease, which now predominates over post-inflammatory rheumatic valve disease in developed countries. For example, at the Cleveland Clinic, 60% of MVRS was for degenerative MV disease, compared to 10% for rheumatic valve disease and 20% for ischemic valve disease.2 Appropriate timing of MVRS remains a challenge for cardiologists, as does accurate quantitation of mitral regurgitation (MR). This issue of Cardiology Rounds discusses the salient etiologies of MR, the natural history of organic MR, the state of the art in echocardiographic quantitation of MR, and the results of surgery after MV repair.

Classification and etiology of mitral valve regurgitation

MR is broadly classified as either organic or functional (Table 1). This classification is more than academic because the mechanism and underlying etiology of MR have important implications for its treatment, whether medical or surgical, valve repair or replacement. In organic MR, there is a primary structural abnormality of the MV that prevents competent valve closure and leads to regurgitation. The most common causes of organic MR include degenerative disease, rheumatic valve disease, endocarditis with leaflet destruction, congenital MV disease, and other rare causes (eg, systemic lupus erythematosus and left-sided carcinoid disease).

Degenerative mitral disease is due to an underlying connective tissue abnormality with so-called “myxomatous changes” in the matrix of valve tissue. In a recent study, immunohistochemical staining for collagen I and III and fibrillin was performed in valves excised from patients with MV prolapse (MVP) who had undergone MV replacement. The staining results from the prolapsed valves were compared with those from normal and rheumatic MVs.3 In the normal valves, there was a characteristic zonal architecture with laminar staining for the proteins confined to the atrialis and spongiosa. In MVP, the staining pattern was disorganized with more intense staining for fibrillin in some regions and absent staining for fibrillin in myxomatous regions. In contrast, the normal architecture was preserved in rheumatic valves, except in areas that were fibrosed. The findings in the MVP valves were consistent with the theory that a defect in fibrillin, similar to that in Marfan’s syndrome, is operative in this disease. On gross pathology, the disease may be localized as fibroelastic dysplasia, or diffuse as Barlow’s syndrome.

Rheumatic or post-inflammatory MV disease is the most common cause of MR worldwide. It usually results in a mixed lesion. Leaflet motion is restricted in diastole, causing stenosis, as well as in systole, causing regurgitation. Hemodynamically significant regurgitation is more common when there is extensive subvalvular disease with fibrosis and scarring of the papillary muscles, and thickening and foreshortening of the chordae tendineae.

Endocarditis can occur in structurally abnormal or normal valves. Typically, less virulent organisms (eg, Streptococcus viridans) infect diseased valves such as those with myxomatous degeneration, while Staphylococcus aureus can affect normal valves. In the latter case, there is usually a high burden of bacteremia (eg, in patients with indwelling lines or using intravenous drugs). Valve destruction can lead
to severe regurgitation, a common cause of heart failure in endocarditis.

In the adult population, congenital causes of MR are rare. The most common is a cleft MV associated with an ostium primum atrial septal defect.

In functional MR, the valvular apparatus is normal or nearly normal and regurgitation is due to an underlying myocardial process. The most common causes are dilated cardiomyopathy and ischemic heart disease. The annulus may be dilated, the papillary muscles splayed, and the leaflets tethered. With global dysfunction, the tethering is symmetrical and the leaflets are tented causing a central regurgitant jet. With segmental dysfunction, the tethering is asymmetrical with restriction of the leaflet ipsilateral to the wall motion abnormality. Most commonly, the posterior leaflet is involved due to an infero-posterior myocardial infarction (MI). The anterior leaflet closes behind the restricted posterior leaflet and the jet is posteriorly directed. An additional cause of MR is systolic anterior leaflet motion that occurs in hypertrophic obstructive cardiomyopathy. The anterior drag on the leaflets as flow accelerates through the narrowed outflow tract leads to malcoaptation, with a posteriorly-directed jet of MR.

A medical history, physical examination, and a carefully performed echocardiogram can elucidate the etiology and mechanism of MR and determine its severity. When a trans-thoracic echocardiogram provides incomplete information, transesophageal echocardiography (TEE) may be an important adjunctive test.

**Natural history of organic MR**

Organic MR may progress due to worsening of the underlying pathology, with subsequent clinical deterioration. For example, chordal rupture in a patient with MVP can cause a sudden increase in MR severity. Endocarditis may also hasten the progression of MR due to its associated leaflet destruction. Even in the absence of these catastrophic complications, MR due to prolapse can progress.

For example, 1 study examined patients with organic MR who had at least 2 echocardiographic examinations averaging 1.5 years apart. On average, MR severity increased according to the following criteria:

- **Regurgitant volume 7.4 mL/yr**
- **Regurgitant fraction 2.9%/year**
- **Regurgitant orifice area 5.9 mm²/yr.**

In rheumatic MV disease, there is ongoing fibrosis and leaflet thickening that can lead to progressive regurgitation, as well as stenosis. Recurrent streptococcal infections may hasten the progression of disease and rheumatic fever prophylaxis is recommended, although its duration is controversial.

The most common reason for clinical deterioration in patients with severe MR is progressive left ventricular (LV) dilatation resulting from chronic volume overload and leading to heart failure, atrial fibrillation, and death. Several hemodynamic stages of MR have been described (Figure 1).³

**In the acute phase**, the left ventricle is not yet dilated; therefore, there is a sudden fall in forward stroke volume. An increased ejection fraction (EF) and low end-systolic volume provide some degree of compensation so the decrement in
Table 2: Clinical and echocardiographic indications for surgery in chronic non-ischemic MR based on ACC/AHA recommendations

<table>
<thead>
<tr>
<th>Class I recommendations</th>
<th>1</th>
<th>Acute symptomatic MR in which repair is likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NYHA Class II-IV symptoms with normal LV function (EF &gt;60%) and LVED &lt;45 mm</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic or asymptomatic patients with mild LV dysfunction (LVEF 50–60%), and/or LVED 50-55 mm</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Symptomatic or asymptomatic patients with moderate LV dysfunction (LVEF 30–50%), and/or LVED 50-55 mm</td>
<td></td>
</tr>
</tbody>
</table>

Class IIa recommendations

<table>
<thead>
<tr>
<th>Class IIa recommendations</th>
<th>1</th>
<th>Asymptomatic patients with preserved LV function and atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Asymptomatic patients with preserved LV function and pulmonary hypertension (PASP &gt;50 mmHg at rest or 60 mmHg with exercise)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Asymptomatic patients with LVEF 50%-60% and LVED &lt;45 mm or LVEF &gt;60% and LVED 45-55 mm</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Patients with severe LV dysfunction (EF&lt;30% and/or LVED &gt;55 mm) in whom chordal preservation is highly likely</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Asymptomatic patients with chronic MR with preserved LV function in whom mitral valve repair is highly likely</td>
<td></td>
</tr>
</tbody>
</table>

Class IIb recommendations

| Class IIb recommendations | 1 | Patients with mitral valve prolapse and preserved LV function who have recurrent ventricular arrhythmias despite medical therapy |

Class III recommendations

| Class III recommendations | 1 | Asymptomatic patients with preserved LV function in whom significant doubt about the feasibility of repair exists |

stroke volume is less than the total regurgitant volume. However, the left atrial pressure rises in response to the sudden increase in left atrial volume and the patient may experience the sudden onset of dyspnea due to pulmonary edema.

In the chronic compensated state, the left atrium and the left ventricle dilate, accommodating greater volumes at lower pressures and restoring forward stroke volume to nearly normal; EF is increased.

In the chronic decompensated state, the left ventricle starts to fail, with further increases in end-diastolic volume and LV end-systolic volume, and a fall in EF. The forward stroke volume falls and the regurgitant fraction increases. At this stage, the risk of atrial fibrillation increases, as does the risk of heart failure and sudden death; surgical outcome is less satisfactory, with higher early and late mortality.

Functional MR may improve with medical therapy (eg, chronic afterload reduction and beta-blocker therapy) in patients with dilated cardiomyopathy. More recently, cardiac resynchronization therapy in patients with prolonged QRS and poor systolic function was shown to reduce functional MR. However, even in this group of patients, the studies revealing MR reduction with nonsurgical treatments contained small numbers of patients with only short-term follow-up. There are no long-term data on the efficacy of afterload reduction in patients with structural defects. Organic mitral regurgitation must be considered a “surgical” disease, but the optimal timing for surgery is still uncertain.

One retrospective series in 229 patients with hemodynamically significant MR due to a flail leaflet examined morbidity and mortality over a follow-up period of 10 years (5-15 yrs). In 86 patients treated medically, although no specific medical regimen was prescribed, the annual mortality was 6.3%/year. At 10 years, only 10% of the medically-treated patients were free of heart failure, atrial fibrillation, death, or surgery. In contrast, those treated with early surgery had significantly reduced mortality (HR=0.29). Predictors of adverse outcome in the medically-treated group included symptoms (New York Heart Association NYHA class III or IV), older age, and left ventricular ejection fraction (LVEF) <50%. Based on these results, many physicians have advocated early surgery, especially when valve repair is likely.

A final argument proposed for early surgery is to prevent sudden death. In one study, the risk of sudden death was approximately 9% at 5 years and 19% at 10 years. Eighty percent of the sudden deaths occurred in patients with one of the following risk factors: NYHA III or IV symptoms, LVEF <50%, or atrial fibrillation. In the remaining patients, the risk of sudden death was <1%/year and other factors, such as coronary artery disease (CAD), may have been present.

Despite these data (predominantly from a single institution), most clinicians believe that outcome is good if patients are carefully followed, if LVEF does not fall below 60%, or if symptoms do not progress beyond NYHA II. It is generally agreed that the optimal timing for intervention is just before the ventricle enters the compensated state. Clinicians have relied on echocardiography to determine the appropriate timing for intervention, based on studies linking poor outcomes to specific echocardiographic parameters (Table 2).

More sensitive measures of LV systolic function that are less dependent on loading conditions may eventually prove to be more reliable than traditional parameters of LV volumes and EF. Recent studies suggest that measurements of brain natriuretic peptide (BNP) may be useful in predicting who should be referred for surgery. One study suggests that among patients with organic MR, a BNP level >1 pg/mL is predictive of the combined endpoint of heart failure and death and is independently associated with an adverse prognosis when age, sex, MR severity, EF, and NYHA class are included in the model.

Echocardiographic quantitation of MR:

State of the art

The litigation surrounding diet/drug combination therapy – fenfluramine-phentermine (fen-phen) – as well as new surgical therapies for MR, emphasize the critical need for uniform.
Influenced by chamber compliance. With dilation of the left atrium in chronic severe MR, the compliant receiving chamber can accommodate a large volume without an increase in pressure and there may be no flow reversal detected. The author’s experience suggests that systolic flow reversal is infrequently observed in patients with atrial fibrillation. Lesser degrees of MR may be associated with blunting of the systolic flow signal and diastolic dominance. This pattern can be observed with high-filling pressures, even in the absence of MR.

**Effective regurgitant orifice area (EROA)**

In the early 1990s, a method based on color-flow Doppler mapping of the proximal jet convergence was developed to measure the area of the mitral regurgitant orifice. This method takes advantage of the converging hemispheres of color that represent increasing flow velocity as blood approaches the narrow orifice, otherwise known as PISA (proximal isovelocity surface area). The peak flow velocity through the MV is obtained from the continuous wave Doppler jet of MR. Accurate alignment of the Doppler beam with the MR jet is essential to optimize the peak velocity. Based on the continuity equation, the orifice area is calculated (Figure 3). An EROA >0.40 cm² is consistent with severe MR (Table 3).

**Regurgitant volume (RV) and regurgitant fraction (RF)**

Mitril RV can be measured by several methods. The preferred is to calculate the total LV stroke volume from the difference between the end-diastolic and end-systolic volumes computed from the 2-dimensional biplane method of disks. The RV represents the total stroke volume minus the forward stroke volume (FSV). The FSV is the product of the cross-sectional area of the LV outflow tract and the velocity time integral (VTI) of LV outflow. An alternative method uses the difference between the total flow across the MV measured by pulsed Doppler at the level of the mitral annulus and the FSV. Finally, RV can be derived from the product of the EROA by PISA (see above) and the stroke distance across the regurgitant orifice (VTI of the continuous wave MR jet). An RV of 45-59 mL/beat is considered moderately severe (3+), while >60 mL/beat is severe (4+) (Table 3). The RF is the fraction of the total stroke represented by the RV. An RF of 40% to 49% is considered moderately severe and ≥50% severe (Table 3).
Vena contracta width

The vena contracta represents the narrowest point of the MR jet and occurs at the orifice or immediately downstream. The diameter is best measured via a magnified, parasternal, long-axis view optimized to visualize the zone of proximal convergence, the vena contracta, and the expanded jet entering the left atrium. Only the “aliased” mosaic portion of the jet should be measured (Figure 4). The cutpoints for mild and severe are <0.3 cm and >0.7 cm, respectively.

Integrative approach

In grading MR severity, it is optimal to use an integrated approach without reliance on any single measure. Quantitation is most important when discordance exists among several of these variables or between the echocardiogram and the clinical or angiographic findings. Quantitation is also critical for efficacy assessments of emerging therapies (eg, percutaneous valve repair), and comparisons to existing treatments. Entry criteria for trials of these therapies must base MR severity on quantitative rather than qualitative criteria. Finally, hemodynamics at the time of the evaluation must be considered. Blood pressure should be optimally controlled at the target recommended for that patient.

Results of surgery for mitral valvarepair

Outcome measures after surgery for MR include early and late survival, recurrence of MR, and the need for reoperation. Outcome depends on a number of preoperative factors including age, symptoms, LV function, atrial fibrillation, the etiology of the MR, as well as the presence of CAD. The major operative determinants are whether concomitant coronary artery bypass graft (CABG) or a second valve procedure (usually aortic valve replacement or tricuspid valve repair) is required. The other major issue thought to affect survival is whether the valve is repaired or replaced.

Preoperative determinants

Preoperative predictors of adverse surgical outcomes associated with both increased early and late mortality include older age, NYHA class III/IV symptoms, LVEF <60%, pre-existing atrial fibrillation, and associated CAD, as well as extent of coronary disease. In one series of 614 patients undergoing MV surgery, 190 were ≥70-years-old. The operative mortality was similar, approximately 3.5%, in both younger and older patients. However, 7-year survival was worse in the elderly (49%) compared to 72% in the younger patients. Nevertheless, for older patients with minimal symptoms (NYHA III/II) and EF >40%, the 7-year freedom from complications-related death was excellent at 90% and similar to younger patients.16

Other studies confirm the importance of age as a predictor of operative mortality that is independent of other factors.17,18 Symptoms have been shown to be an important predictor of both early and late mortality.17,19 In one study, operative mortality was 5.4% in patients with NYHA III/IV symptoms compared to 0.5% in those with NYHA I/II. Ten-year survival was 48% compared to 76% in less-symptomatic patients.20 In this study, atrial fibrillation and associated CAD were also independent predictors of mortality.

Data on the predictive value of MR etiology are variable.21 However, one study demonstrates that the etiology of MR, as determined by TEE, influenced repairability and operative and late mortality. Comparing MVs with floppy, organic nonfloppy, and ischemic/functional lesions, floppy valves were associated with the highest rates of repair (90%, 63%, and 75%, respectively), the lowest operative mortality (1.7%, 5.7%, and 15.6%, respectively) and the highest 5-year survival (86%, 69%, and 50%, respectively).22

Operative determinants

The need for associated CABG or a second valve procedure has a significant impact on operative and long-term outcomes. Most studies show that valvarepair is associated with lower mortality than valve replacement.21,22 However, a large case-control study from Emory demonstrates that survival is similar with repair and replacement in patients aged ≥60 years and in those with associated CABG.21

The rate of re-operation after valve repair is similar to that after replacement.23 However, re-operation is required more frequently for anterior leaflet repairs than for posterior leaflet repairs.24 When only posterior leaflet repairs are compared to MV replacement, the re-operation rate is lower.22

Recurrent MR and the need for re-operation

Factors contributing to the rate of recurrent MR include the site of repair, the use of an annuloplasty ring, and the etiology of MR. A recent study from Belgium reported the rate of developing recurrent MR after MV repair in 242 patients who had echocardiograms pre-discharge, at 30 days, and every 6 months thereafter, for a mean follow-up of 8 years; 65% had a posterior leaflet prolapse. While the freedom from re-operation was 94%, 73% of patients had more than trivial MR and 29% had more than moderate MR. The rate of developing more than moderate MR was approximately 4%/year.25 Factors adversely influencing MR recurrence included the lack of an annuloplasty ring, the lack of sliding annuloplasty, and use of chordal shortening.

Summary

Despite the clear advantages of surgical MV repair over valve replacement in patients with MR, in terms of
avoiding anticoagulation and the lower risk of endocarditis, there is still a considerable rate of recurrent MR and no clear advantage in some populations. Moreover, a recent study examining the use of MV annuloplasty repair in patients with severe LV dysfunction did not show a survival benefit. Various percutaneous approaches are being developed that may offer additional options for patients with MR.

References

Elyse Foster, M.D. is Professor of Clinical Medicine and Anesthesiology, holds the Areaxe Vilensky Endowed Chair in Cardiology, is Director of the Echocardiography Laboratory, Moffitt Hospital, and Director of the UCSF Adult Congenital Heart Disease Practice, all at the University of California, San Francisco. After receiving her M.D. at Tufts University School of Medicine, Boston, Dr Foster did post-graduate training at the Boston University Medical Center, Boston. Amongst her awards, she has received the Best Doctors in America award and American Heart Association Service Recognition Award in 2004. She is on the Boards of numerous medical journals and has published widely in her field of interest, echocardiographic detection of cardiovascular abnormalities.

Dr. Foster has received grants from Evolve, Inc. and Guidant Corporation

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Corporation

© 2005 Brigham and Women’s Hospital, Boston, Massachusetts, which is solely responsible for the contents. The opinions expressed in this publication do not necessarily reflect those of the sponsor or sponsor, but rather are those of the author based on the available scientific literature. Publisher: SNELL Medical Communication Inc, in cooperation with Brigham and Women’s Hospital, Boston, Massachusetts. ©Cardiology Rounds is a Trade Mark of SNELL Medical Communication Inc. All rights reserved. The administration of any therapies discussed or referred to in Cardiology Rounds should always be consistent with the recognized prescribing information as required by the FDA. SNELL Medical Communication Inc. is committed to the development of superior Continuing Medical Education.