



## Asymptomatic Aortic and Mitral Regurgitation: How Should I Follow the Patient in Practice?

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During the past quarter century, major advances in cardiac valve surgery have resulted in reduced operative mortality and improved long-term postoperative survival of patients undergoing surgery for aortic regurgitation (AR) and mitral regurgitation (MR). However, the management of the asymptomatic patient and the indications for surgery continue to be the subject of considerable controversy and disagreement. Valve replacement or repair continues to entail both immediate and long-term risks, and these risks clearly are not justified in all asymptomatic patients with AR or MR. In general, surgery is indicated when the patient first develops significant cardiac symptoms. Numerous studies have also identified subgroups of asymptomatic patients with evidence of left ventricular (LV) dysfunction who may benefit from early operation before the onset of symptoms. This realization has prompted a movement toward early operation in patients with minimal or no cardiac symptoms who manifest declining LV function. Noninvasive imaging techniques are critical in making this evaluation and have a major impact in management decision making.

### Aortic Regurgitation

#### Indications for Aortic Valve Replacement

Numerous studies have consistently demonstrated that LV systolic function is an important determinant of postoperative prognosis in patients with AR. The presence and severity of preoperative symptoms have an important impact on postoperative survival and postoperative LV function, and symptoms remain the most important indication for aortic valve replacement (AVR). However, symptoms are not the only indication for AVR, as some patients will have already developed irreversible LV dysfunction by the time symptoms develop and will be at risk of postoperative congestive heart failure and death. Several lines of reasoning support the position for early operation in patients with evidence of LV systolic dysfunction, with or without symptoms.

- In symptomatic patients undergoing AVR, preoperative measures of LV pump function at rest (i.e., ejection fraction) are the most sensitive in identifying

patients at risk of postoperative LV dysfunction and congestive heart failure.

- In asymptomatic patients, the time course between the development of LV dysfunction at rest and the onset of symptoms is relatively short: two thirds or more of patients with LV dysfunction develop symptoms requiring operation within 2–3 years.
- Among patients with LV systolic dysfunction, postoperative outcome is related to the severity of preoperative symptoms. The long-term postoperative survival and improvement in LV function are significantly better in asymptomatic patients or mildly symptomatic patients compared to more severely symptomatic patients.
- Survival and reversibility of LV dysfunction after AVR is also dependent on the severity and duration of preoperative LV dysfunction.

These data support the concept that postoperative survival and postoperative LV function will be enhanced favorably if asymptomatic or mildly symptomatic patients with LV dysfunction undergo AVR without waiting for the development of more significant symptoms or more severe LV dysfunction.

#### Natural History of Asymptomatic Patients

Although the concern that some asymptomatic patients with AR may develop irreversible LV dysfunction is a valid one, and although some asymptomatic patients benefit from early AVR, this concern pertains only to a small minority of asymptomatic patients with chronic AR. The vast majority of asymptomatic patients that are encountered in clinical practice maintain normal LV contractile function at rest for many years and usually develop symptoms before or coincident with the onset of depressed contractile function at rest. Asymptomatic patients with normal LV ejection fractions have an excellent prognosis with only a gradual rate of deterioration during conservative, non-operative management. The long-term follow-up experience of such patients indicates that:

- The mortality rate is less than 0.5% per year.
- Less than 4% per year require AVR because symptoms or LV dysfunction at rest develop.
- Patients likely to require AVR over a 10-year period because of symptoms or LV dysfunction can be identified on the basis of severity of LV dilatation by echocardiography and progressive increases in LV cavity dimensions or decreases in resting ejection fraction during the course of serial follow-up studies.
- Patients at risk of sudden death during the natural history of AR appear to be those with extreme LV dilatation on echocardiography (LVDD  $\geq$ 80mm, LVSD  $>$ 55mm).
- Severity of aortic root enlargement also needs to be evaluated by echocardiography.

Thus, the indications for AVR in patients with AR include:

- Onset of important symptoms (angina, dyspnea, presyncope or syncope).
- Onset of LV systolic dysfunction (ejection fraction below normal at rest).
- Development of extreme LV dilatation.
- Development of severe aortic root dilatation (>50 mm).

If asymptomatic patients are followed carefully and undergo operation only after the development of one or more of these end points, the operative mortality is very low, long-term postoperative survival is excellent and LV function after operation improves in virtually every patient. Hence, asymptomatic patients with depressed LV contractile function at rest or extreme LV dilatation should undergo aortic valve replacement before the onset of symptoms. In contrast, the great majority of asymptomatic patients with normal LV contractile function at rest can be followed carefully and do not require prophylactic valve replacement to preserve LV function.

### Medical Therapy

Severe AR results in significant increases in LV afterload. It has been known for nearly two decades that afterload reducing agents (nitroprusside, hydralazine and nifedipine) are effective acutely in reducing the regurgitant volume in patients with AR. This translates into reduced LV volumes and increased LV ejection fraction with chronic therapy with hydralazine and nifedipine. Similar effects have been reported with angiotensin-converting enzyme (ACE) inhibitors when there is an associated reduction in blood pressure. Only one long-term study has been performed, however, to determine the impact of afterload reduction on outcome of asymptomatic patients with severe AR. This study showed that long-acting nifedipine slowed the natural progression of the disease toward symptoms and LV dysfunction; patients who did develop LV dysfunction while receiving nifedipine had an excellent postoperative outcome, with normalization of LV function after AVR. Thus, nifedipine does not appear to mask important changes in LV size or function that would put patients at a higher risk of irreversible LV dysfunction. The target dose of long-acting nifedipine is 60–90 mg per day with the goal to achieve a measurable reduction in systolic blood pressure. Such therapy should be reserved for asymptomatic patients with LV dilatation and normal systolic function and not those with either symptoms or impaired LV systolic function. This latter group should be treated surgically and not with chronic vasodilator therapy.

### Management Strategy

Asymptomatic patients with chronic severe AR should be followed carefully with serial evaluations (Figure 1). They should be seen at least at 6-month intervals for careful histories and physical examinations. If there is LV dilata-

tion, as evidence for severe AR, therapy should be initiated with long-acting nifedipine or an ACE inhibitor; with nifedipine preferable as this is the only drug studied long term. Assuming no change in clinical findings, the frequency of echo evaluations can be determined by the previous information regarding severity of LV dilatation, LV ejection fraction and evidence of progressive increases in LV dimensions or declining ejection fraction. Patients with stable LV dimensions with mild-to-moderate LV dilatation (end-diastolic dimension <70 mm, end-systolic dimension <50 mm) may have echocardiograms obtained at yearly intervals, whereas it is reasonable for those with more advanced LV dilatation to undergo echocardiograms every 4–6 months.

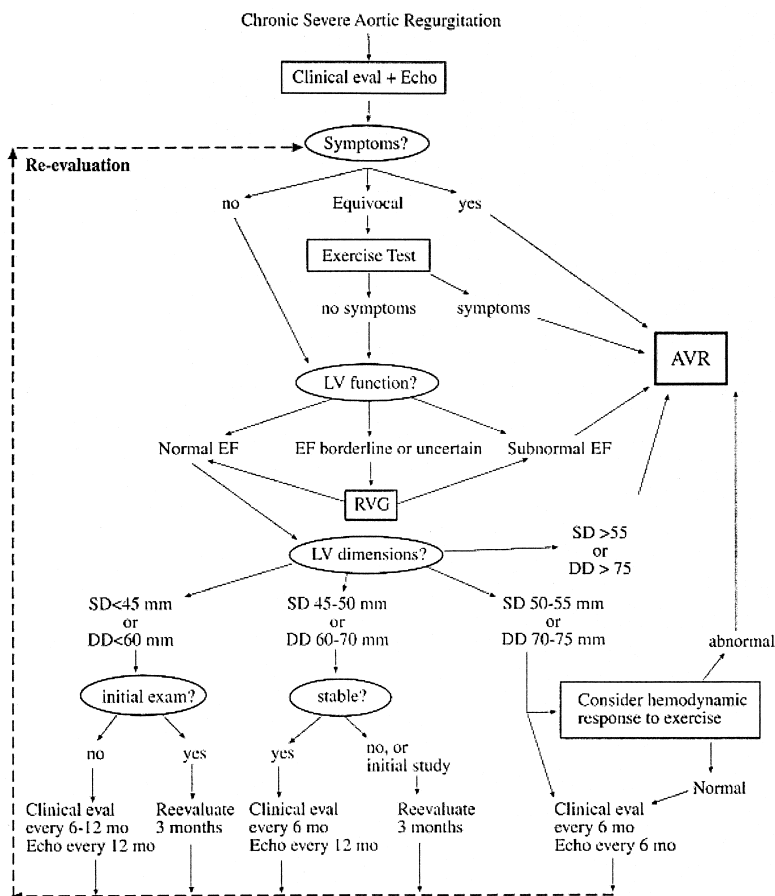
There are three caveats regarding this approach. First, patients with new-onset severe AR may progress rapidly. When a patient is first seen with severe AR and there are no previous echo data to review, it is important to obtain a few echocardiograms at frequent intervals (e.g., an initial echo and then two more over the course of 4 months) to establish the chronicity and stability of the process. This is important even if the patient reports a long-standing heart murmur. Second, patients who do demonstrate progressive LV dilatation or a decline in ejection fraction need to be followed more frequently. Third, severity of aortic root dilatation must also be assessed along with LV size and function.

Ancillary testing beyond echocardiography is not required in the majority of patients. However, exercise testing is helpful to elicit symptoms or declining effort tolerance in patients with equivocal changes in symptom status. Radio-nuclide angiography is helpful if the echo data are equivocal or of poor quality or when an accurate measurement of ejection fraction is needed. Finally, magnetic resonance imaging or computed tomography may be helpful to supplement the echo measurements in patients with aortic root enlargement. Asymptomatic patients may be followed safely until they exceed the threshold values for AVR noted previously. However, it is reasonable to proceed with AVR in patients who demonstrate significant and progressive increases in LV dimensions close to these threshold values over the course of serial studies.

### Mitral Regurgitation

Patients with MR, like patients with AR, may develop irreversible LV dysfunction while asymptomatic. Survival after mitral valve surgery, with either repair or replacement (MVR), is influenced significantly by age, atrial fibrillation and the preoperative LV ejection fraction. Determining the optimal timing of operation for MR, however, has been elusive since:

- Ejection fraction and other ejection phase indices consistently overestimate true LV function. Deteriorating LV function is often masked by the ability of the left ventricle to eject into the low impedance left atrium. While LV ejection fraction usually increases after op-



**Figure 1.** Management strategy for patients with chronic severe aortic regurgitation. Preoperative coronary arteriography should be performed routinely as determined by age, symptoms and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. Abbreviations: DD = end-diastolic dimension; RVG = radionuclide ventriculography; SD = end-systolic dimension. Reproduced from ACC/AHA Guidelines for Management of Patients with Valvular Heart Disease.

eration for AR, ejection fraction uniformly decreases after operation for MR.

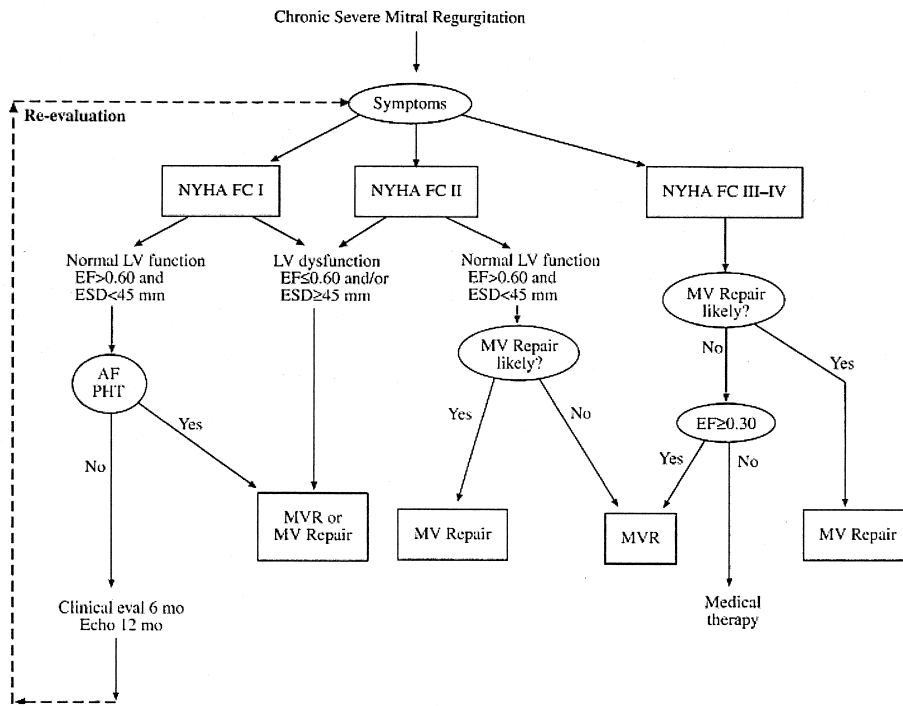
- Data suggest that patients at risk for persistent postoperative LV dysfunction after surgery may possibly be identified by preoperative ejection fraction  $<60\%$  and echo end-systolic dimension  $>45$  mm. The data for survival are stronger with ejection fraction, whereas both ejection fraction and end-systolic dimension are useful in predicting postoperative symptoms and LV functional recovery.
- Despite the early postoperative decrease in ejection fraction, long-term serial postoperative studies demonstrate that LV ejection fraction progressively and consistently increases in the majority of patients over the course of 5 years after MVR.
- Surgical approaches that preserve the mitral apparatus, with either mitral valve repair or chordal-sparing MVR result in substantial improvement in LV function compared to MVR procedures in which the subvalvular apparatus is disrupted. This also translates into improved postoperative survival in patients who undergo mitral valve repair compared to those who receive MVR.

The available data indicate the following indications for mitral valve surgery for MR:

- Patients with substantial symptoms.
- Asymptomatic or mildly symptomatic patients who develop atrial fibrillation.
- Asymptomatic patients with ejection fraction  $<60\%$  or with progressive decline in ejection fraction during serial studies into the low normal range.
- Asymptomatic patients with progressive LV dilatation on serial echocardiographic studies (LV end-systolic dimension  $>45$  mm).
- Asymptomatic patients with pulmonary hypertension (PA systolic pressure  $>50$  mm Hg).
- The threshold for operation may be lowered in patients who are ideal candidates for mitral valve reparative procedures.

### Medical Therapy

Unlike AR, afterload is not increased in patients with chronic MR. Hence, therapy with afterload reducing agents does not have a sound physiologic basis, in the absence of hypertension or heart failure, and the available data indicate



**Figure 2.** Management strategy for patients with chronic severe mitral regurgitation. Abbreviations: AF = atrial fibrillation; EF = ejection fraction; ESD = end-systolic dimension; FC = functional class; NYHA = New York Heart Association; PHT = pulmonary hypertension. Reproduced from ACC/AHA Guidelines for Management of Patients with Valvular Heart Disease.

that these agents have little effect on severity of MR or on LV function. The number of patients studied to date with afterload reducing drugs is very small, and there are no long-term data indicating clinical efficacy. In the absence of data indicating a favorable hemodynamic or clinical response, therapy with afterload reducing drugs is not recommended.

### Management Strategy

The management of patients with chronic MR, in general, is similar to that of patients with AR, with several notable exceptions. Patients should be followed carefully with serial clinical and echocardiographic evaluations, and surgery should be performed in those who develop symptoms of evidence of LV contractile dysfunction (Figure 2). The threshold values for proceeding with surgery for MR include an ejection fraction  $<60\%$  and/or an end-systolic dimension  $>45$  mm, values which differ significantly from the surgical end points for AR. Surgery should also be considered if there is evidence for pulmonary hypertension (systolic pressure  $>50$  mm Hg), which can be assessed by Doppler echocardiography. Onset of atrial fibrillation is a further indication for surgery, even if episodic, and it is reasonable to perform ambulatory electrocardiographic monitoring periodically, once every year or two, to detect occult atrial fibrillation. The thresholds for surgery may be lowered in patients who appear to be excellent candidates for mitral valve repair, and there are several centers in the U.S. with excellent results of mitral repair, in whom surgery is now recommended in all patients with severe MR who are candidates for repair. Although such an aggressive ap-

proach may not be warranted in all patients in all centers, it is reasonable to proceed with mitral valve repair in asymptomatic patients who develop new onset of severe MR, for example, those with mitral valve prolapse who develop a new flail leaflet and in those with chronic MR in whom the degree of MR suddenly and severely worsens.

### Suggested Reading

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