Valvular Heart Disease

Number 90 June/July 2004

This *Heartbeat* will cover adult valvular heart disease which primarily involves the aortic and mitral valves. Hemodynamically severe stenosis or regurgitation of these valves is a predictable cause of heart failure (HF) and sudden cardiac death (SCD). During the past four decades, surgery has become the primary intervention for patients with these diseases. Improved non-invasive methods of evaluating cardiac chamber size and function, improved surgical techniques, new knowledge of natural history and predictors, and an increasing array of non-surgical treatments that show potential to alter the natural course of disease—all continuously change the benefit-to-risk ratio underlying management decisions. This makes the timing of surgery a *moving target*.

The net result of these factors has been progressively earlier application of varying types of valve surgery and continuing discussion about the correct mix of drugs, surgery and watchful waiting. In patients with valve disease the goal is to wait and maximize the usage of their native valve (decreasing exposure to unnecessary risk) but not wait too long so as to lead to cardiac damage and poor outcome. This review, based on the American College of Cardiology and American Heart Association Guidelines[1] developed 6 years ago, which are generally applicable with some additional information, will provide a general framework within which to make decisions. They depend on which valve is involved, type of defect (stenosis or regurgitation) and the degree of symptoms or functional impairment. Each case requires a tailored approach.

MITRAL STENOSIS

Etiology and Pathology

The predominant cause of mitral stenosis (MS)—occurring in less than 1% of the population—is rheumatic fever. Rheumatic involvement is present in 99% of stenotic mitral valves excised at the time of mitral valve replacement. Approximately 25% of all patients with rheumatic heart disease (RHD) have pure MS, and an additional 40 % have combined MS and mitral regurgitation (MR). Two thirds of all patients with rheumatic MS are female. Recent MS incidence in the US has markedly diminished because of the preventative treatments for rheumatic fever.

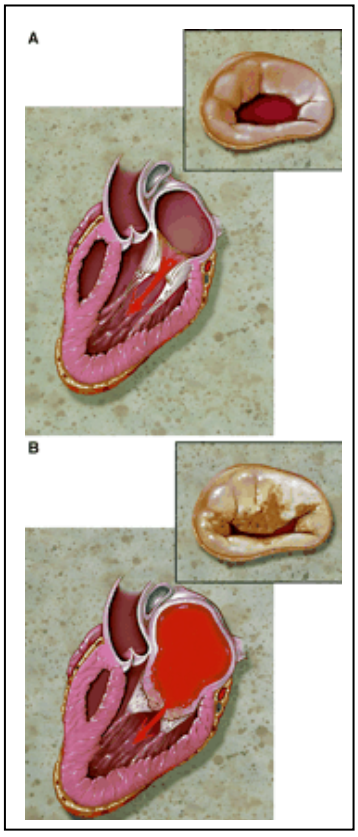

Figure 1. The heart in diastole. A. Normally the heart valve opens to allow blood to flow into the left ventricle; notice the supporting structure of tendon and muscle. B. In patients with mitral valve stenosis, the valve is thickened and has a characteristic domed appearance and restricted opening. The left atrium is typically enlarged.

Asymptomatic MS

There is typically a long period of asymptomatic narrowing. Symptoms (usually after age 45—fatigue dyspnea, orthopnea and paroxysmal nocturnal dyspnea) at rest are rare until the mitral valve area is <1.5cm². Patients with asymptomatic mild MS (valve area >1.5cm²) have an excellent long term prognosis and should be followed yearly for any change in clinical status (exertional dyspnea, orthopnea, or paroxysmal nocturnal dyspnea [PND]) and be educated regarding antibiotic prophylaxis. Annual echocardiography should be performed to monitor progression.

In patients with asymptomatic moderate to severe MS (valve area <1.5cm²) and decreased physical activity, a simple exercise stress test could unmask symptoms, and a stress echo might indicate exercise-induced pulmonary hypertension. These studies should be performed annually for moderate to severe MS.

Medical Treatment. Anything that increases heart rate (HR)—decreasing ventricular filling time, or increases flow by this tight MV—causing volume backup behind, can precipitate symptomatology (eg, stress, exercise, infection, pregnancy or atrial fibrillation). Effective medical treatment is designed to slow HR, allowing a longer period for blood to move from the left atrium into the left ventricle and to reduce pulmonary vascular congestion directly by diuretic administration. This helps some patients feel better, but it does not slow progression of the disease.

Clearly established symptoms, with or without stress testing, pulmonary hypertension at rest (>50mm Hg) or with stress (>60mm Hg), and perhaps new onset atrial fibrillation are indications for intervention. Balloon valvotomy or surgery (MV commissurotomy or, if this is not technically feasible, MV replacement) should be considered depending on valve morphology. Balloon valvotomy would be contraindicated in those with intra-cardiac thrombi or significant associated MR and is unlikely to be successful if the valve is severely fibrotic or heavily calcified.

Symptomatic MS

The first symptomatic manifestation of MS is usually exertional dyspnea. However in certain settings, peripheral embolization or frank pulmonary edema can develop without apparent prior symptoms. SCD is rare.

MITRAL REGURGITATION

Etiology and Pathology

MR occurs when disease of the valve leaflets, annulus or subvalvular apparatus causes poor alignment of the leaflets, resulting in a *regurgitant leak.* If regurgitation is severe, the result is volume overload of the LV and ultimately, elevated left atrial pressure.

The most common cause is mitral valve prolapse (MVP)—the most common cause of all valvular heart disease—occurring in 5% of the population.[2] MVP is usually a benign condition. Other causes include rheumatic heart disease (RHD), infective endocarditis, collagen vascular disease, mitral annular calcification (degenerative) and functional MR secondary to ischemia or cardiomyopathy. Left and/or right ventricular dysfunction frequently occurs before symptoms develop. While most deaths are related to HF, the incidence of SCD suggests that ventricular arrhythmias are an important potential consequence of the disease process.

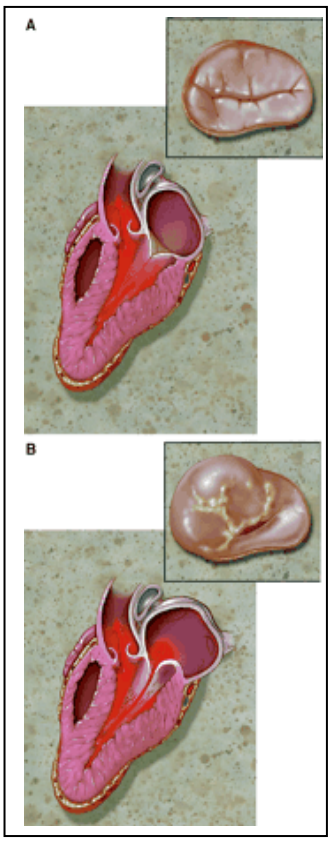

Figure 2. The heart in systole. During contraction of the left ventricle, the heart muscle thickens. A. In normal individuals, the valve has closed, and no blood will leak backward into the left atrium. B. In the patient with both prolapse and mitral regurgitation, the valve does not close completely and part of a leaflet bulges back into the left atrium. There may be enlargement of the left ventricle, an effect of chronic severe regurgitation.

Asymptomatic MR

The prognosis of chronic MR is dependent on both the etiology and severity of the lesion. Preoperative left ventricular ejection fraction (LVEF), a measure of LV function, is the single most important predictor of postoperative outcome. *Patients with asymptomatic severe MR who have LV dysfunction (LVEF <60%) should be referred for surgery.* There is some evidence that patients with asymptomatic chronic severe MR, preserved LV function and atrial fibrillation, or pulmonary artery pressures > 60 mmHg with exercise or > 50 mmHg at rest, and patients with subnormal right ventricular ejection fraction at rest, benefit from surgery.

With improved mortality and morbidity rates being achieved with surgical management, and a small but measurable risk of SCD, cardiologists and surgeons are becoming more aggressive in treating asymptomatic patients with severe MR surgically. Though many cardiologists would wait until LV or RV dysfunction occur before offering surgery to an asymptomatic patient, recent data on late post-operative survival suggest that even in the absence of symptoms or LV dysfunction surgery may be appropriate, provided the MR is severe and the valve seems repairable guided by transesophageal echocardiography[3]—and the operative risk is low. Attentive more frequent clinical follow-up is recommended for patients at relatively high operative risk (e.g. patients 75 years or older) or with doubt

about the feasibility of repair. This aggressive strategy has yet to be endorsed by the ACC/AHA guidelines (limited data). Some centers recommend MV surgery when both left and right ventricular function are well preserved at rest but right ventricular function falls during exercise.[4]

There is little reliable information on the natural history of chronic moderate MR. There is no evidence that such patients benefit from surgery. Symptoms in patients with chronic mild to moderate MR are unlikely to result from the valve disease; such symptoms may require treatments aimed at other underlying conditions. AHA guidelines recommend follow up on a 6-12 month basis. Transthoracic echocardiography should be performed periodically (no more than annually) to assess progression of MR.

Serial exercise stress testing may be helpful to detect symptoms in sedentary persons. Failure of LVEF to increase or LV end-systolic volume to decrease at peak exercise is an indication of early LV systolic dysfunction. Some authorities suggest that these findings are an indication for surgery, but this is not a universally accepted surgical indication.

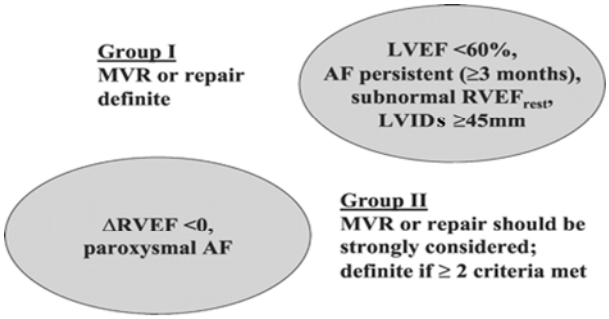

Figure 3. Schema for selecting asymptomatic patients with MR for valve replacement (MVR) or repair.

Other indications for surgery are significant LV dilatation in systole [LV end-systolic dimension (LVIDs) >45mm] and atrial fibrillation. Right ventricular (RV) dysfunction, a reflection of pulmonary hypertension, has important prognostic implications. A decreased RV ejection fraction at rest (RVEF $_{rest}$) with or without LV dysfunction is associated with >50% mortality risk within 2 years (Endnote 4). Like LVEF, RVEF normally rises during exercise. Failure of RVEF to rise despite absence of symptoms and well-preserved LVEF indicates a ≈50% likelihood of HF during the succeeding 3 years, which is 4-fold greater than for patients with preserved RVEF $_{exercise}$.

Symptomatic MR

Almost all patients with acute MR are symptomatic and will need surgical intervention. In patients with symptomatic chronic severe MR of any etiology the prognosis is compromised compared to the asymptomatic patient and surgical intervention is indicated. However, among patients with ischemic MR, it is necessary for the surgeon to determine whether MR is diminished by revascularization before undertaking additional valve surgery. These types of decisions are very difficult and controversial especially with only moderate MR at the time of bypass and are beyond the scope of this article.

When feasible, repair is preferable to valve replacement, as LV function is better preserved and anticoagulation is not necessary. Surgical techniques and mortality continue to improve.

Medical Treatment. Several studies have shown benefit of vasodilator therapy in functional MR associated with LV dilatation and depressed LV function. There is no data to support their use to prevent LV deterioration and improve outcomes for organic MR and they are presently not recommended.

AORTIC STENOSIS

Etiology and Pathology

Aortic stenosis (AS), which affects 2-7% of individuals older than 65 years, is a common valvular abnormality. Most are due to calcific degeneration of either a normal trileaflet or a congenitally bicuspid aortic valve (1% to 2 % incidence which has a 4:1 male predilection). Typically, there is a long asymptomatic period of progressive valvular narrowing and calcification. The *hallmark symptoms of syncope, angina and dyspnea (SAD) appear late* in its course. Generally symptoms don't appear until the valve orifice has become markedly narrowed (<1.0cm²) and calcified. Once symptoms occur, mortality risk is 50% at 2 years. Therefore the onset of symptoms is critical in deciding to proceed to surgery. In this situation, surgical intervention (valve replacement with a mechanical valve, a homograft, an autograft, or a bioprosthesis) is necessary.

Asymptomatic AS

Asymptomatic AS is usually diagnosed on routine physical exam and has a low (~1.5%/yr) risk of SCD. Patients should be educated about typical symptoms and appropriate antibiotic prophylaxis.

Follow-up is key. The ACC/AHA guidelines recommend annual office visits for patients with asymptomatic aortic stenosis that is mild (valve area

>1.5 cm²), and office visits every 6 months for those with stenosis that is moderate (valve area 1.0–1.5 cm2). Although AS progresses at different rates in different people, the average decrease in area is 0.12cm²/yr. A rapid (>0.3m/sec/yr) rise in echocardiographic trans-aortic jet velocity or severe calcification on echo indicates a poorer prognosis. Annual echocardiography in older patients, with at least moderate AS, particularly those with risk factors for more rapid progression, such as diabetes, coronary artery disease, smoking, hyperlipidemia, or hypertension is reasonable.

Frequent follow-up (at least every 6 months) is extremely important for patients with aortic stenosis that is severe (valve area <1.0cm² or high aortic jet velocity >4.0m/s) but asymptomatic. Intensive questioning about symptoms, and obviously, referral for prompt aortic valve replacement (AVR) when symptoms develop, is very important. In certain situations, for example, among severe AS patients who wish to be more physically active, operation may be appropriate when jet velocity exceeds 4.0m/sec because such patients have an 80% likelihood of developing HF or worse within 3 years.

Although stress testing (any exercise) poses a risk in AS patients, there are considerable data to suggest that the risk is low in patients without symptoms. The development of hypotension, pre-syncope/ syncope, failure of BP to rise normally (≥20 mmHg) with exercise, marked ST segment depression or angina (despite the patient's "asymptomatic history") or complex ventricular arrhythmias (ventricular tachycardia—more than four PVC's in a row) will identify a high risk patient, allowing earlier intervention. An unremarkable response will allow a watchful waiting strategy in a patient with poor functional capacity.

Surgery is controversial. Surgical replacement of the aortic valve is the only effective treatment for severe AS and is performed in patients with a wide age range. Age is not a critical factor for outcome, as older patients generally tolerate valve replacement surgery well. There is some lack of agreement about the optimal timing of surgery in the asymptomatic patient. For those with associated LV dysfunction (LVEF < 50%) attributable to the AS or those with moderate AS or greater who require cardiac surgery for another reason, especially for CABG (CAD is a risk factor for faster progression of AS), surgery is indicated even in asymptomatic patients. Hypotension secondary to stress can be considered equivalent to unmasking symptoms, and is an indication for surgery.

After these indications, the decision to intervene in asymptomatic patients remains a source of hot debate. In patients who truly have no symptoms in spite of critical AS (<0.75cm²), the guidelines recommend watchful waiting as the strategy of choice. Some recommend AVR based only on the calculation of a critically stenotic valve (eg, valve area ≤0.6cm²). Others recommend surgery with severe AS if they have a mean aortic jet velocity of ≥4m/sec or have moderate to severe valvular calcification with a rapid increase in aortic jet velocity (≥0.3m/sec) within one year. Everyone is trying to identify asymptomatic patients who might be at high risk without surgery, but there are no published data to support such an approach. Arguments in favor of surgery in asymptomatic patients with high-risk descriptors are that: (1) Surgery would enable activity that, if desired, would be dangerous if severe AS were present, and (2) Denial or lack of recognition of symptoms, when they develop, could leave a patient with severe AS at risk that could otherwise be reversed with AVR.

Symptomatic AS

AS, once symptomatic, causes substantial morbidity and mortality. Untreated, symptomatic AS is associated with a 2-year survival rate of 50%. ACC/ AHA guidelines recommend prompt referral for AVR at the onset of symptoms. Corrective surgery in this setting almost always produces symptomatic improvement and, from matched controls, appears to be associated with a substantial increase in survival.

New Help. Plasma brain naturetic peptide (BNP) levels are elevated in patients with symptomatic AS. BNP levels may complement clinical and echocardiographic evaluation of asymptomatic AS in determining timing of surgery.[5]

Slowing Progression of AS. AS, like mitral annular calcification, has been linked to the same risk factors associated with CAD.[6] If this speculation is at least partially true, treatment of traditional CAD risk factors such as hyperlipidemia might be expected to slow or reverse the progression of AS.[7 8]

AORTIC REGURGITATION

Etiology and Pathology

Aortic regurgitation (AR) arises from diseases of the aortic root, the aortic valve, or both, which result in poor coaptation or incompetence of the aortic valve

leaflets, resulting in volume overload of the left ventricle. Acute AR is usually caused by infective endocarditis—the most common cause—aortic dissection or acute chest trauma. Patients typically present in acute HF because the LV can't compensate for the increased volume. Acute severe AR must be treated surgically without delay.

Asymptomatic Chronic AR

Because of a gradual increase in LV volume (LV compensates with hypertrophy and dilatation) chronic disease has a long asymptomatic period with normal LV function. Patients with chronic mild-to moderate AR and normal LV function are at low-risk and are not candidates for AVR. Yearly evaluation and an echocardiogram every 2-3 years are recommended.

Patients with severe AR are higher risk for events and should be evaluated for symptoms semi-annually and for evidence of LV dilatation or systolic impairment annually via echo. Typical symptoms include exertional dyspnea and/or more severe congestive symptoms (resting dyspnea, orthopnea, and PND); less frequently, angina or pre-syncope/syncope can result from AR.

Lower Risk Severe AR

Patients with severe asymptomatic AR and normal LV function and size are low risk [annual event (HF, subnormal LVEF at rest, SCD) rate < 2%]. ACC/AHA guidelines recommend clinical follow-up every 6 months and echocardiography yearly. Patients who have equivocal symptoms should undergo stress testing to unmask underlying functional impairment.

Higher-risk Severe AR

- Any evidence of LV dysfunction (subnormal LVEF at rest or echocardiographic fractional shortening (FS) [<26%] at rest. This consensus is based on reported 25%/year progression to HF or death (though this progression rate was determined in only 27 patients studied more than 25 years ago).
- Patients with LV end-systolic diameter (LVIDs) ≥55mm or a greater than 5% Δ (change)—decrease—in LVEF at peak exercise have a 10-20 % progression to symptoms or LV dysfunction. Some use a greater than 10% decline and feel that may not be enough to indicate surgery because of the dramatic increase in afterload with exercise. Larger declines in exercise capacity or LVEF especially if the declines occur serially are considered more significant.[9] Normalization of LVEF change for end-systolic stress (afterload) changes from rest to exercise—providing a measure of contractility—has been a particularly accurate prognosticator. (endnote 4)
- Patients with LV end-diastolic diameter (LVIDd) >80mm, a rapid serial decrease in LVEF or increase in LVIDs or LVIDd are associated with subnormal LV function and 7-10 % incidence of HF or death.

Among patients with asymptomatic AR, LV function and size predict clinically important deterioration. Data showing that AVR improves survival are lacking. But the high-risk data and improved surgical techniques suggest that these guidelines will maximize long-term survival (Fig. 4).

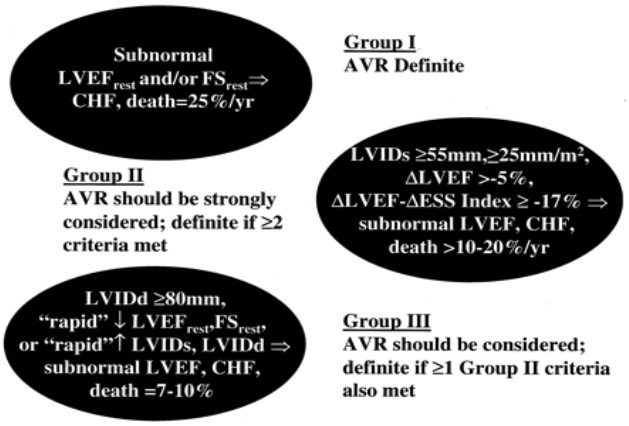

Figure 4. Schema for selecting asymptomatic patients with aortic regurgitation for AVR. Δ indicates change from rest to exercise; ESS, end systolic volume.

LV dilatation increases risk. Patients with LVIDs > 50mm or LVIDd > 70mm should be followed more closely clinically and with echo every 6 months.

Symptomatic chronic AR

All patients with symptomatic severe AR warrant consideration for AVR. If they have clear-cut NYHA III or IV symptoms, symptom relief can be expected with AVR, and there appears to be an associated survival benefit. If symptoms are vague or mild (NYHA Class II) and they don't have objective evidence of decreased exercise tolerance, LV dilatation, or evidence of decreasing LVEF, there is conflicting data as to whether AVR is beneficial, but most experts agree it is justified.

Patients with symptomatic AR and any signs of LV dysfunction or dilatation need prompt referral for AVR. Degree and duration of LV impairment along

with severity of symptoms all negatively effect prognosis in terms of post-op LV function, incidence of HF and survival after AVR, so timing is crucial. ***Close follow-up of patients with severe AR and this "moving target" is imperative.***

Medical Treatment. There is some evidence that afterload reduction with long-acting nifedipine *can slow* the progression of severe AR and the need for AVR in those without indication for AVR but have already developed systolic hypertension (found in approximately 1/3 of patients with severe AR.[10] There is no basis for the use of nifedipine or any other after-load reducing drug in mild to moderate AR, unless the patient is hypertensive. Patients with mild to moderate AR have an excellent prognosis, and no beneficial effects of vasodilators have been demonstrated in this group. It is important to note that no outcome data exist with any vasodilator other than nifedipine; other drugs including ACE inhibitors and angiotensin receptor blockers have multiple pharmacological effects that experimentally may even cause functional deterioration.

The use of beta-blockers has not been studied in chronic AR. However, beta-blockers should be used cautiously in those with severe AR because the lengthening of diastole increases the regurgitant volume.

CONCLUSION

The management of valvular heart disease should be based on individual assessment of risk to benefit ratio. The first step is to define the severity of the valve lesion by quantitative methods largely based on echocardiography. (Some are adjusting these measurements for body size as much as possible as regards valve area in stenosis and LV dimensions.[11]) Next, confirm the presence or absence of symptoms by an accurate history. Exercise testing may be very useful as a method of achieving an objective insight into the true level of incapacity or lack of it. The third step is to perform an individual risk evaluation by objective testing to predict the chances of clinical events or LV dysfunction and the risks and benefits of early intervention. Last discuss your recommendation of intervention or careful medical follow up with the patient and family. If medical follow up is adopted, the changes that would lead to intervention should be decided in advance and explained to the patient and his/her family.

Acknowledgments

Many thanks to our special guest editor for sharing his time and expertise in preparing this update.

Special Guest Editor:
Jeffrey S Borer MD, FACC
Gladys and Roland Harriman Professor of Cardiovascular Medicine
Director, Howard Gilman Institute for Valvular Heart Diseases
Chief, Division of Cardiovascular Pathophysiology
Weil Medical College of Cornell University.

Geoffrey Zarrella, DO
First Year Cardiology Fellow
UMDNJSOM.

Mario L Maiese, DO, FACC, FACOI
Associate Professor of Medicine UMDNJSOM
Mail to: maiese1@comcast.net

[1] Bonow RO et al. American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease. *J Am Coll Cardiol* 1998; 32: 1486-1582.
[2] Turi ZG. Mitral Valve Disease. *Circulation* 2004; 109: e38-e41.
[3] Thompson HL et al. Timing of surgery in patients with chronic, severe mitral regurgitation. *Cardiol Rev* 2001; 9(3): 137-143.
[4] Borer JS, Bonow RO. Contemporary Approach to Aortic and Mitral Regurgitation. *Circulation* Nov 18 2003; 108:2432-2438.
[5] Bergler-Klein J et al. Natriuretic peptides predict symptom-free survival and post-operative outcome in severs aortic stenosis. *Circulation* 2004; 109: 2302-2308.
[6] Faggiano P et al. Progression of valvular AS in adults: Literature review and clinical implications. *Am Heart J* 1996; 132: 408-417.
[7] Palta S et al. New insights into the progression of aortic stenosis: implications for secondary prevention. *Circulation* 2000; 101: 2497-2502.
[8] Novaro GM et al. Effect of hydroxymethylglutaryl coenzyme A reductase inhibitors on the progression of calcific aortic stenosis. *Circulation* 2001; 104: 2205-2209.
[9] Reginelli JP et al. The challenge of valvular heart disease: When is it time to operate? *Clev Clin J Med* June 2004; 71: 463-482.
[10] Scognamiglio R et al. Nifedipine in asymptomatic patients with severe AR and normal LV function. *N Engl J Med* 1994; 331: 689-694.
[11] Lung B et al. Recommendations on the management of the asymptomatic patient with valvular heart disease. *European Heart Journal* 2002; 23: 1253-1266.