Contemporary Approach to Aortic and Mitral Regurgitation

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**H**emodynamically severe aortic regurgitation (AR) and mitral regurgitation (MR) are among the most predictable causes of heart failure (HF) and sudden death (SD). During the past 4 decades, surgery has become the primary intervention for patients with these diseases. However, timing of operation is a “moving target”: surgical techniques have improved dramatically; noninvasive methods have developed for objective interrogation of cardiac size and function, continually enhancing knowledge of natural history and its predictors, and an increasing array of nonsurgical treatments show potential to beneficially alter the natural course of disease. Consequently, the benefit-to-risk relation underlying management decisions changes continually. Simultaneously, the myocardial cellular and molecular pathophysiology of valvular regurgitation is being progressively elucidated, promising new clinical evaluation strategies and novel treatments.

The net result of these factors has been progressively earlier application of valve surgery and continuing discussion about the correct mix of drugs, surgery, and watchful waiting. Guidelines for management of patients with valvular heart diseases were developed by the American College of Cardiology and American Heart Association 5 years ago and generally remain applicable, but new information mandates periodic review.

**Scope of the Problem**

Disease prevalence is not known precisely. However, extrapolation from natural history data suggests that >5 million persons have moderate to severe valvular regurgitation in the United States alone. Prevalence has grown steadily for many years. New York’s State-Wide Planning and Research Cooperative System (SPARCS) database, a compulsory hospital reporting system, indicates that AR and MR discharge diagnoses increased almost 4-fold during the past 20 years, whereas total hospitalizations declined by 20% (Figure 1). Agreement is greatest where data are fewest. It is generally accepted that asymptomatic patients with subnormal LVEF (or echocardiographic fractional shortening [FS]) at rest should undergo operation. This consensus is based on 25% per year progression to HF or death reported from follow-up of 27 patients studied 25 years ago. Because survival is poorer after aortic valve replacement (AVR) among (predominantly symptomatic) patients with subnormal LVEF than among those with normal LVEF, waiting for symptom onset in the asymptomatic patient probably further compro-

**Indications for Valve Surgery**

**The Symptomatic Patient**

Once congestive symptoms are associated with AR or MR, the mortality rate is substantially higher (>20% per year, with some variation depending on symptom severity) than in the nondiseased population, even with relatively preserved left ventricular (LV) function. Valve surgery mitigates symptoms and probably improves, but does not normalize, life expectancy. Outcomes should improve progressively with recent gains in surgical methodology and prostheses. Hemodynamic profiles and event-free survival with current artificial mechanical prostheses have been impressive; increasing survival of newer bioprostheses (15 to 20 event-free years now is common) enables use in progressively younger patients to minimize hemorrhagic and thromboembolic sequelae. Thus, operation in patients with congestive symptoms or exercise intolerance is well justified.

**The Asymptomatic Patient: AR**

Only improved survival can justify surgery in the asymptomatic patient. This is rigorously demonstrable solely by controlled clinical trial; no such study has been or is likely to be performed. Therefore, survival benefits have been inferred from observational comparisons. These are complicated by the paucity of data defining natural history and its predictors in the asymptomatic patient; relevant publications have involved fewer than 700 patients (average follow-up 4 to 14 years) manifesting normal or subnormal LV ejection fractions (LVEFs) in prospective or retrospective studies. Fortunately, results generally are consistent across studies.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000096400.00562.A3

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mises long-term survival, an assumption that until recently had not been assessed formally. However, postoperative survival now has been shown to deteriorate as preoperative LVEF falls progressively below normal and to be affected independently by both LVEF and symptoms18; because LVEFrest gradually falls in patients with AR15,19 (particularly if contractility already is compromised), these findings support AVR for asymptomatic patients with subnormal LVEFrest (Figure 2). Nonetheless, additional descriptors may be useful to refine prognosis even in this group; a recent retrospective analysis reported only 5.8% per year progression to symptoms or death among asymptomatic patients with LVEFrest <55% (versus 2.0% with LVEFrest ≥55%).3

Consensus is less complete for patients with normal LVEFrest, although overarching interstudy consistency characterizes the relation between outcome and LV systolic function and size (including change [Δ] in LVEF from rest to exercise, LVEFexercise, FS, LV systolic dimension [LVIDs], and LV diastolic dimension [LVIDd]). The Table compares results of the 2 largest prospective studies of AR natural history4,15,19,20 (each with 104 patients, follow-up ≥15 years [average 7 to 8 years among event-free survivors]). Although the strength of specific predictors differed on univariate analysis, both showed that HF, subnormal LVEFrest, and SD were predicted by several systolic phase descriptors measured at rest or during exercise. LVIDd, a contributor to afterload, was predictive for all events in 1 study,20 although only for development of subnormal LVEFrest in the other4; although significant, the strength of this predictor is less than that of systolic function indices.

Intrinsic myocardial contractility (for which the other measures all are "surrogates") was calculated in only 1 large study4 (as the decrement in ΔLVEF per unit of exercise-induced increment in wall stress [afterload], measured non-invasively by the combination of echocardiographic and radionuclide angiographic data); as predicted by an earlier, smaller series,21 contractility provided superior prognostication compared with surrogates based on LVEF or size alone.4 The population tertile with poorest contractility had a 10-fold greater risk (=40% over 3 years) of HF, development of subnormal LVEFrest, or SD than the tertile with the best-preserved contractility (Figure 3); SD segregated significantly and solely with poor contractility. Recent preliminary data from a second population indicate that contractility best predicts post-AVR survival15; only the tertile with the best-preserved contractility manifests postoperative survival comparable to an age- and sex-matched US census subcohort. When contractility was not measured,19,20 LVIDd emerged as the best predictor on multivariate analysis, consistent with several series1 in which LVIDd ≥55 mm (or LVIDd ≤25 mm/m2 body surface3) predicted high event risk even when LVEFrest and FS were normal.

The prognostic importance of LVIDd is supported by other data12 that indicate that preoperative LVIDd predicts postoperative survival, although not as well as LVEF, and that late

Figure 2. Schema for selecting asymptomatic patients with aortic regurgitation for AVR. Δ indicates change from rest to exercise; ESS, end-systolic stress; and CHF, congestive heart failure.

Figure 3. Relation of contractility (as ΔLVEF–ΔESS index) at study entry to occurrence of subnormal LVEFrest, CHF, or SD during follow-up. Each line represents results of 1 tertile of the study population. Used with permission from Borer et al.4
postoperative survival in patients with LVIDd <80 mm mimics that expected from the age- and sex-matched US census subcohort. Data13 from 1 large series suggested that LVIDd ≥80 mm predicts SD risk, but post hoc analysis of another series has not confirmed this finding.15 identifying contractility as the only predictor. Although SD is relatively uncommon in these patients, clustering of deaths in an objectively defined subgroup impacts on risk/benefit considerations for AVR. Available data are too few to support a stable point estimate of risk. However, if the reported 1% per year incidence in the relevant subgroup4,15 is confirmed on further observation, this alone may warrant AVR as perioperative and further postoperative risks decline.

In summary, among patients with normal LVEFrest/FSrest and no symptoms, LV function/size criteria based on contractility, ΔLVEF, and LVIDs predict clinically important deterioration or death at an annual rate of >10% to 20%. Rigorous demonstration that AVR improves survival in patients with “high-risk” descriptors is lacking. However, observational comparisons with postoperative survival and US census data, the demonstrated deterioration in postoperative outcome as LV function predictably worsens, and recent improvements in surgical techniques and protheses suggest that AVR based on these criteria is appropriate and will maximize long-term survival in the asymptomatic patient (Figure 2).

Prognosis also is inferable from LVIDd and from deterioration rate of LV size and function, even if these descriptors do not pass high-risk segregation points.15,19 However, high-risk deterioration rates are not well defined; preliminarily suggested cutoffs identify patients with a 7% to 10% average annual event risk. Further data are needed before deterioration rates, and LVIDd alone, can provide confident management decisions (Figure 2).

The Asymptomatic Patient: MR

MR differs fundamentally from AR by impacting 3 primary shock organs (the LV, the left atrium, and the right ventricle [RV]) rather than the LV alone. Outcome in asymptomatic patients depends on the status of both ventricles and on atrial rhythm. In MR, the volume-loaded LV faces relatively low impedance to outflow and normal or subnormal afterload, even when myocardial dysfunction is established. Consequently, in MR, LVEF systematically is higher relative to intrinsic LV contractility than in the normal LV or in AR, which suggests a potential prognostic utility of direct measurement of LV contractility.22 However, a universally accepted contractility measure has not been defined, in part because timing of end diastole is ambiguous: LV ejection begins into the left atrium before the aorta. Although invasive22 and noninvasive23 contractility indices are related to outcome, LVEF remains the best-validated predictor. Prognostically important myocardial dysfunction exists when LVEF is <10% greater than the nominal lower normal limit (commonly 50% with echocardiography). When echocardiographic LVEF is <60%, even among asymptomatic/minimally symptomatic patients (New York Heart Association functional class [FC] I-II), long-term survival after mitral valve (MV) replacement (MVR)/MV repair is less good than if LVEF is ≥60% and also fails to achieve that expected in the age- and sex-matched subcohort of the US census.24 Therefore, most asymptomatic patients should undergo surgery if LVEF falls below 60%, especially if, echocardiographically, MV repair is technically appropriate (possibly providing perioperative mortality and late morbidity advantages over MVR25). Although no controlled trial of MV surgery has been performed, operation on the asymptomatic patient with LVEF <60% is defensible because (1) late postoperative survival deteriorates progressively as LVEF falls further below 60% among FC I-II patients; (2) average annual mortality is 4.1% among unoperated FC I-II patients with severe MR due to flail leaflet, exceeding the US census comparator, a tendency enhanced if LVEF is <60%;11 (3) postoperative mortality exceeds census expectations among patients with LVEF ≥60% and FC III-IV symptoms24; and (4) HF predictably will appear during 5 (average) to 10 (maximum) years in asymptomatic patients with well-preserved LVEF.7,11

Despite these compelling arguments, combination of FC I and II patients confounds the supporting data. It is difficult to differentiate mild (FC II) from absent (FC I) cardiac symptoms. Nonetheless, when they exist, congestive symptoms indicate pulmonary hypertension, either during exercise alone (when heart rate increases and diastolic left atrial emptying time decreases) or also at rest, causing abnormal RV pressure loading. RV dysfunction predictably ensues, first during exercise and ultimately at rest, with important prognostic implications. In the unoperated patient, subnormal RV ejection fraction at rest (RVEFrest), with or without LV dysfunction or symptoms, is associated with >50% mortality risk within 2 years6; most deaths are sudden (tending to be associated with nonsustained ventricular tachycardia [VT] on 24-hour ambulatory electrocardiography among those with RV dysfunction26). Like LVEF, RVEF normally rises during exercise. Failure of RVEF to rise despite absence of symptoms and well-preserved LVEF indicates an ~50% likelihood of HF during the succeeding 3 years, which is 4-fold greater than for patients with preserved RVEFrest.7,27 Among patients with subnormal LVEF and/or RVEF before MVR, the best predictor of late postoperative survival is preoperative RVEF.27 Pulmonary hypertension, putatively the primary basis of RV dysfunction,4 probably predicts risk irrespective
of LVEF, but supporting data and empirically useful segregation points are lacking.

Cardiac dimensions and atrial fibrillation (AF) also are prognostically important. Paralleling findings in AR, LVIDs ≥45 mm predicts relatively compromised survival after MV surgery, despite well-preserved LVEF. Persistent AF before operation compromises late postoperative survival; paroxysmal AF may have similar implications. The effect of MV surgery on AF-mediated risk is not known, nor is it known whether surgery prolongs survival for asymptomatic patients with AF with well-preserved RV and LV function; indeed, late after successful surgery and hospital discharge in normal sinus rhythm, as many as 15% of patients develop AF. However, development of the maze procedure, which relieves AF in >80% of affected patients by surgically isolating atrial regions usually responsible for chaotic electrical activity, has increased the acceptance of AF as an indication for MV surgery. Important gaps in supporting data exist, but until they are filled, persistent AF alone and frequently recurring AF paroxysms are reasonable indications for MV (plus Maze) surgery. Natural history effects of catheter-based Maze procedures or of antiarrhythmic drugs for paroxysmal AF without MV surgery remain to be determined, although current drug therapy produces no survival benefit for patients with AF without MR.

The excellent postoperative results after MV repair, the survival deficit once LVEF deterioration or symptoms occur, and the small but measurable SD risk of unoperated MR even in asymptomatic patients with ≥60% LVEF have led some to undertake surgery solely because severe MR exists. In support, the following is clear: (1) despite some etiology-based modulation, MR increases progressively (by 7.5 mL/year in regurgitant volume in 1 study); (2) volume loading ultimately will cause LV dysfunction; (3) MV repair often provides near-normal anatomic relations between valve, subvalvular apparatus, and LV; (4) perioperative mortality risk of MV repair is near zero, and thromboembolic sequelae are minimal without anticoagulation; and (5) postponing surgery results in SD risk that might be avoidable. This argument presumes that reliable prediction of functional deterioration and SD is not possible, that repair can or should be applied to all valves, and that the excellent results reported for MV repair in relatively selected populations during the past decade can be extrapolated if more generally applied and will be maintained during the relevant 30- to 40-year follow-up. These unproven assumptions may be correct. However, alternative arguments must be considered. (1) MR-related SD risk may be predictable; as noted, isolated RV dysfunction (measurable noninvasively), especially with nonsustained VT (and, possibly, abnormal heart rate variability) on ambulatory electrocardiography, identifies patients at risk even without symptoms or LV dysfunction. RVEF has not been measured in most prognosis studies, which precludes the evaluation of this factor in those investigations. (2) Preliminary data indicate that SD risk persists postoperatively, even if LVEF and RVEF are normal, and is predictable from VT on postoperative 24-hour ambulatory electrocardiography. (3) Although virtually any valve can be repaired, MV repair may not be optimal for rheumatic valves or some markedly deformed or severely myxomatous valves. Even in high-volume centers, recurrent valve dysfunction requires reoperation in up to 10% of patients within an average of <2 years. Also, as many as 10% of patients expecting MV repair instead receive MVR when nonoptimal anatomy is not recognizable from presurgical echocardiography. (4) Improved surgical procedures and prostheses frequently and regularly appear, improving outcome. Therefore, unless benefit-to-risk considerations clearly favor early operation, postponement of surgery when objective evidence indicates low risk may benefit the patient and should be considered.

Because of the prominence of postsurgical SD, antiarrhythmic drugs or internal cardioverter defibrillators (ICDs) may be appropriate for selected patients after MV surgery. Relevant studies have not been performed; indeed, the efficacy of programmed electrical stimulation to identify likely responders also is not known. In this void, it may be prudent to consider prophylactic antiarrhythmic treatment for patients who have LV or RV dysfunction and nonsustained VT after MV surgery, but the appropriate modality is unclear; a recent study of nonischemic cardiomyopathy demonstrated no outcome difference between treatment with amiodarone or ICD. Appropriate monitoring frequency to detect nonsustained VT must be determined, although preliminary prognostic studies successfully used 24-hour ambulatory electrocardiography no more than annually.

In summary, MV surgery is appropriate for asymptomatic patients with severe MR who manifest LV dysfunction, LVIDs ≥45 mm, AF, or RV dysfunction. However, for asymptomatic patients without AF and with well-preserved LVEF/RVEF/ΔRVEF and LVIDs, prophylactic surgery is less well supported; a more conservative approach also is defensible (Figure 4).

The Asymptomatic Patient: Combined AR/MR

Specific strategies are not rigorously supported. However, by the time patients with combined severe AR/MR are symptomatic, LVEF and RVEF are more compromised than in similarly symptomatic patients with isolated AR or MR. For AR/MR, RV dysfunction best predicts postoperative mortality. With perioperative mortality after AVR/MVR now <5% in symptomatic patients, even with associated coronary artery disease (CAD), surgery should be considered in asymptomatic patients meeting any of the criteria for AR or MR alone.
Concomitant CAD
Effects and management of concomitant CAD in patients with AR or MR are complex issues that will not be detailed here. There is general agreement that hemodynamically severe CAD should be addressed at valve surgery in patients with nonischemic valvular disease, precluding the potential need for later, higher-risk reoperation. Observational studies suggest life-prolonging benefits of this approach. However, available data suggest that patients who undergo coronary plus valve surgery manifest higher perioperative mortality than patients with CAD who undergo valve surgery alone. This may relate to selective application of bypass grafting for particularly severe CAD, but surgical technical factors also may contribute. With progressive technical improvements in percutaneous coronary angioplasty, the relative efficacy of pre- or postoperative catheter-based interventions requires investigation.

Management is more controversial when MR is ischemic (which is increasingly common with advancing age) or secondary to cardiomyopathy. MV surgery appears to be indicated when ischemic or cardiomyopathic MR is severe and is not widely used, but is controversial when MR is moderate or less; some data support MR-mitigating effects of coronary surgery alone, whereas other experience suggests deterioration when moderate ischemic MR is left unoperated. More data are needed.

Monitoring Prognostic Indices
Progression from mild to at least moderately severe regurgitation generally requires many years; at this point, myocardial function begins to deteriorate, also relatively slowly. Therefore, if symptoms do not supervene, the precision of repeated objective imaging is needed to identify changes that mandate altered management. Once MR or AR first is confirmed by echocardiography, repetition may be prudent within 3 to 6 months to ensure relative lesion stability. Thereafter, mild regurgitation generally requires reevaluation at 2-year intervals; more severe lesions should be checked annually. Once regurgitation is severe, asymptomatic patients with AR and normal LVEFrest progress to symptoms, subnormal LVEF, or SD at a rate of 5% to 6% per year; the corresponding rate for MR is approximately 10% per year. Objective indices deteriorate slowly, but interpatient variation is sufficient to warrant annual assessment to avoid missing prognostically important changes; symptoms should be sought semianually if not spontaneously reported. When AR or MR is severe, echocardiography alone may not provide optimal prognostic information. As noted, prognostication may be most accurately achieved for AR by combining resting echocardiography and rest-exercise radionuclide cineangiography to measure LV contractility; predictive standards for echocardiographic stress (exercise or pharmacological) have not been developed. Similarly, the utility of RVEF (rest and exercise) for MR and the relative inadequacy of echocardiography for RVEF quantification suggest consideration of radionuclide-based study. Exercise-tolerance testing, with and without electrocardiography but without imaging, provides limited prognostic data in AR and is inversely related to pulmonary artery pressure and RVEF exercise primary prognostic indices, in MR. However, prognostic efficiency is inadequate for decision making in asymptomatic patients, although exercise testing can unmask symptoms that indicate surgery when history is ambiguous.

Afterload-Reducing Drugs for the Asymptomatic Patient
Drugs that reduce LV afterload should minimize myocardial damage from valvular regurgitation and postpone the need for operation. However, most drugs have many pharmacological effects (often incompletely understood) in addition to those putatively underlying the desired clinical benefit. Despite one attractive pharmacological effect, clinical benefit may not be the net result when drug and disease interact; acceptability of chronic prophylactic drug therapy for AR or MR requires empirical demonstration of clinical benefit. At present, with the exception of long-acting nifedipine administered to asymptomatic hypertensive patients with AR, such evidence is not available. Administration of afterload-reducing drugs for at least several months has been reported for fewer than 300 asymptomatic patients with AR and fewer than 25 with MR. Additional factors limit understanding of the role of these drugs. Study designs include both prospective randomized and retrospective studies, populations vary from 6 to 72 per regimen, agents span several “classes,” and in all cases but 1, outcome is measured with surrogates (eg, LV function or size) rather than clinical end points, despite the lack of a predictable relation between modulation of surrogates and clinical events. Most importantly, at study entry, patients with AR often had clearly established systolic hypertension (>140 mm Hg), a condition long associated with risk for clinical deterioration in AR and for which the risk-reducing benefit of antihypertensive therapy is well established in the absence of valve disease. Indeed, in the single AR trial that demonstrated an event-reducing benefit (of nifedipine compared with digoxin), average systolic pressure was 150 mm Hg, with many patients far exceeding this value. More recently, preliminary findings from retrospective analysis of 82 consecutive patients with AR entered prospectively into a Cornell natural history study associated nonrandomized drug treatment with increased mortality. Thus, except perhaps for specific drugs in hypertensive patients, additional data are needed to define the role, if any, of currently available drugs in asymptomatic patients with AR.

Afterload-reducing drugs should be less effective in MR, commonly associated with normal afterload, than in AR. Effects of drugs on surrogates have been variable, and no clinical outcome studies have been reported. Recent experimental reports indicate that despite apparent improvement in LVEF, ACE inhibitors and angiotensin receptor blockers may not improve or may even reduce intrinsic contractility in MR, an effect ascribed to drug-mediated changes in extracellular matrix (ECM) characteristics. No mandate currently exists for prophylactic drug therapy for asymptomatic patients with MR. Finally, the interaction between drugs and the implications of prognostic tests remains undefined.

Experimental (Future) Therapy
In patients with cardiomyopathy, HF, and secondary MR, biventricular pacing has reduced MR severity while improving other measures of cardiac function. Rigorous assess-
ment of efficacy and comparison (or additive benefit) to MV surgery\textsuperscript{59} in this population is needed. Applicability to patients with primary or secondary MR without severe ventricular dysfunction remains speculative. In vitro or in vivo recellularization by autologous (host) fibroblasts of bioprosthetic or decellularized allograft valve scaffolds (the latter treated to render them antigenically inactive) combines desirable transvalvular flow patterns and freedom from thromboemboli while reducing valve calcification compared with other types of bioprostheses.\textsuperscript{47} Robotic valve surgery promises morbidity reduction, possibly justifying valve surgery earlier in the course of disease. Catheter-based insertion of valves mounted on stents offers potential benefit similar to that of robotics, although technical problems for insertion of left heart valves\textsuperscript{48} are not fully resolved. Perhaps more importantly, growing elucidation of the myocardial cellular/molecular pathophysiology of volume loading promises novel treatments to retard HF. Abnormal myocardial norepinephrine release has been implicated in the pathogenesis of very early stages of myocardial dysfunction in MR, which suggests the potential prophylactic role of \(\beta\)-blockers.\textsuperscript{22,44} LV cardiomyocyte hypertrophy in regurgitant valve diseases has been related primarily to inhibition of normal contractile protein degradation rather than to enhanced synthesis\textsuperscript{49} (and in contrast to pressure loading). The functional consequences of this finding are not yet clear. Finally, primary myocardial fibrosis recently has been demonstrated to result directly from abnormal strain on myocardial fibroblasts in AR, characterized by production of ECM relatively rich in noncollagen components.\textsuperscript{50} These proteins appear to be involved in mediating the myocyte-matrix interaction necessary for maintenance of normal LV contractile function. Elucidation of the molecular transduction pathways underlying the fibroblast response to AR may support both novel therapy and cellular descriptors for prognostication. However, until the pathology of fibrosis in AR/MR is more completely understood and, specifically, until the ECM components that contribute to HF in valvular regurgitation are identified, prophylactic therapy with agents believed to reduce HF in part by pharmacological ECM alteration (eg, ACE inhibitors and spironolactone) is premature and may be deleterious.\textsuperscript{45}

Thus, emerging data on natural history and prognostication to guide timing of surgery, along with recurring gains in surgical procedures and prostheses, continually improve outcome for patients with AR and MR. New surgical techniques and growing understanding of the fundamental biology of the myocardial response to valvular regurgitation promises further improvement in the form and timing of therapy.

Acknowledgments

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References


Key Words: regurgitation ▪ surgery ▪ heart failure ▪ death, sudden
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Circulation. 2003;108:2432-2438
doi: 10.1161/01.CIR.000096400.00562.A3

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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