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STATE-OF-THE-ART PAPER

## The Current Therapy for Mitral Regurgitation

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In addressing the current therapy for mitral regurgitation (MR), it is useful to distinguish primary MR from secondary (functional) MR. In primary MR, abnormalities of one or more of the components of the mitral valve cause it to leak, imparting a volume overload on the left ventricle (LV). Severe prolonged primary MR leads to LV remodeling, myocardial dysfunction, heart failure, and death. Correction of MR, preferably by valve repair rather than replacement, is curative. Severe MR by itself is considered an indication for repair in many centers, and mitral surgery (repair or replacement) should take place when even mild symptoms appear or when ejection fraction approaches 0.60 or end systolic dimension approaches 40 mm. In secondary MR, myocardial damage from infarction or cardiomyopathy produces papillary muscle displacement and annular dilatation, causing a normal valve to leak. Because the MR in this case is not the primary problem, the indications for mitral valve intervention are less certain and considerably more data are needed to aid us in selecting the most appropriate patients for surgical therapy. Percutaneous therapies for both primary and secondary MR have generated much interest, and many different percutaneous technologies are being developed. Future data from randomized trials will help clarify when and in whom these therapies are applicable. (J Am Coll Cardiol 2008;52:319–26) © 2008 by the American College of Cardiology Foundation

In addressing the modern therapy for mitral regurgitation (MR), it is important to distinguish between primary and secondary (functional) MR. In primary MR there is derangement of one or more components of the mitral valve itself, permitting backflow, causing left ventricular (LV) volume overload. If this overload is severe enough and prolonged enough, it results in LV remodeling, dysfunction, pulmonary hypertension, heart failure, and eventually death. Correction of primary MR in a timely fashion reverses these consequences; thus, there is an unchallenged cause-and-effect relationship between the primary MR and its effects on the LV. It is the abnormal valve that makes the heart sick. Conversely, in secondary MR the mitral valve itself is usually normal. However an LV, previously damaged by coronary artery disease and myocardial infarction or by dilated cardiomyopathy, develops papillary muscle displacement and annular dilatation, causing the mitral valve to leak. It is a damaged LV that causes the valve's malfunction. Because this is primarily a ventricular problem, it is less obvious that correcting the MR by itself will be curative or even beneficial. Thus, although the treatment for primary MR is relatively straightforward, the therapy for secondary MR is considerably more controversial.

### Primary MR

#### *Pathophysiology*

Mitral regurgitation imposes a pure volume overload on the LV. In almost all other volume overloads, the excess volume pumped by the LV is ejected into the aorta, where it widens pulse pressure, in turn increasing systolic pressure. Thus most volume overloads, such as anemia, aortic regurgitation, and so on, are actually combined pressure and volume overloads. On the other hand, the extra volume ejected from the LV in MR enters the left atrium and systolic blood pressure is not usually elevated. In fact average systolic pressure in severe MR is about 110 mm Hg, compared with about 150 mm Hg for aortic regurgitation (1). Indeed when load was compared between mitral and aortic regurgitation preload was increased, as would be expected for volume overload pathophysiology (1). However, afterload was normal in MR but greatly increased in aortic regurgitation. It is generally agreed that LV loading represents the mechanical signals that orchestrate LV remodeling. The unique loading conditions of MR generate a unique pattern of remodeling, with the largest radius-to-thickness ratio and the smallest mass-to-volume ratio of the 4 left-sided valve lesions (2). This pattern of remodeling is both adaptive and maladaptive. Increased LV volume allows total stroke volume to increase, in turn increasing forward stroke volume, compensating for the volume lost to regurgitation. In addition the relatively thin LV wall enhances diastolic filling. Indeed MR is one of the very few cardiac diseases in which diastolic

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**Abbreviations and Acronyms**

- CRT** = cardiac resynchronization therapy
- LV** = left ventricle/ventricular
- MR** = mitral regurgitation
- MVR** = mitral valve replacement
- MVR<sub>e</sub>** = mitral valve repair
- RF** = regurgitant fraction

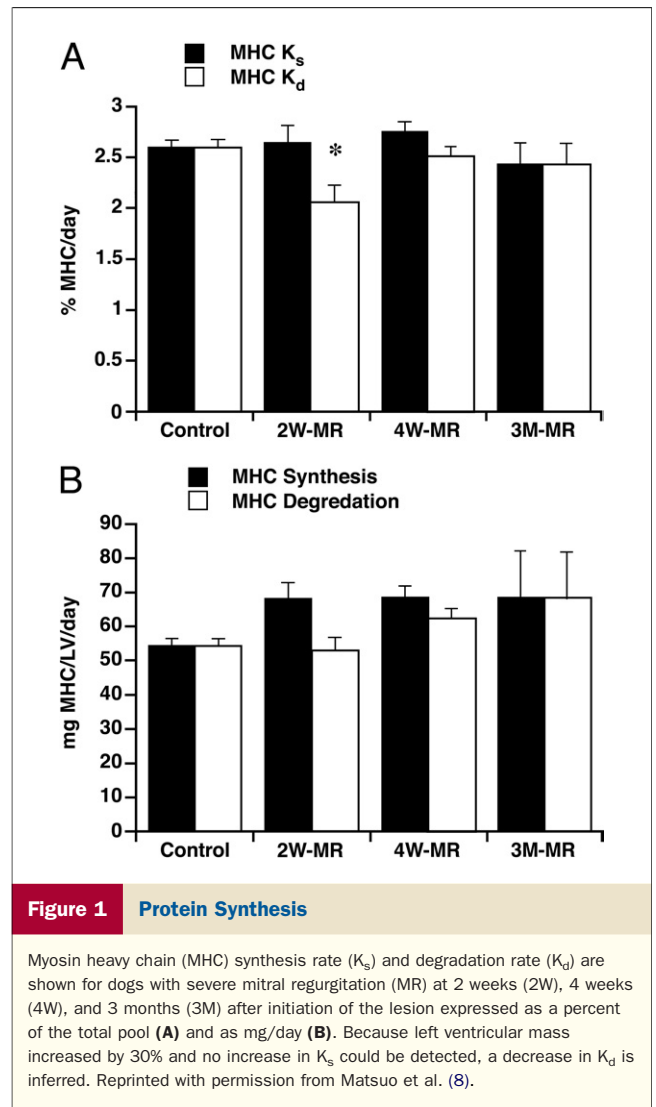
function is supernormal (3,4). However, the increased radius-to-thickness ratio also has its downside. Recall that wall stress ( $\sigma$ ) =  $p \times r/2h$  where  $p$  = LV pressure,  $r$  = LV radius, and  $h$  = LV thickness. Although MR is often viewed as a lesion that unloads the LV by creating a second pathway for ejection, in fact the remodeling pattern, by increasing  $r/h$ , may actually increase afterload. Only in acute

MR is afterload actually decreased; in chronic compensated MR afterload is normal, and in chronic decompensated MR afterload may actually be greater than normal (5).

The mechanism by which hypertrophy develops in MR also seems to be unique. It is well known that myocardial proteins are constantly turning over. For cardiac mass to remain constant, the rates of protein synthesis ( $K_s$ ) and that of protein degradation ( $K_d$ ) must also remain constant. For hypertrophy (increased mass) to occur,  $K_s$  must exceed  $K_d$  either because  $K_s$  increases or because  $K_d$  decreases. In pressure overload, hypertrophy develops from increased  $K_s$  as one might expect (6,7). However, in MR, hypertrophy seems to occur from a decrease in  $K_d$  because no increase in synthesis rate has been detected (6,8) (Fig. 1).

**LV dysfunction in MR.** Although MR may be tolerated for a long time in some patients, in others, progression to heart failure with muscle dysfunction may be more rapid (9). This transition to heart failure is paralleled by myocyte dysfunction and sympathetic activation (10–12). In general, regurgitant fractions (RFs) of <0.40 seem to be tolerated indefinitely in both the experimental animal and in humans, whereas RFs exceeding 0.50 usually leads to heart failure. Myocytes and/or myocardial strips taken from subjects in heart failure show loss of contractile elements and abnormalities in calcium handling (13,14). Both correction of the volume overload and beta blockade (at least in animals) can improve contractility at the chamber and sarcomere levels, suggesting that sympathetic overactivity as well as the volume overload itself are implicated in the pathophysiology of the LV dysfunction (12,15,16). Indeed in humans, the sympathetic nervous system is activated in this disease and activity correlates with the amount of LV dysfunction present (11). Thus reduction in the amount of MR present and/or beta blockade might serve as therapeutic targets.

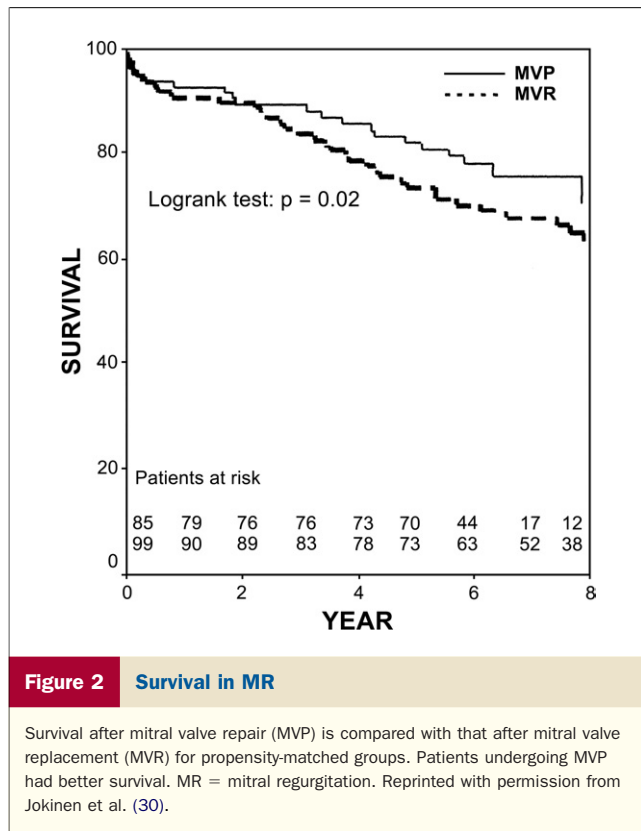
**Medical therapy.** As noted in the previous text, regurgitant fractions of <0.4 seem to be tolerated indefinitely. Thus reducing RF medically seems an attractive goal. It is known that vasodilators are effective in acute MR in reducing RF (17). This occurs as vasodilators preferentially increase forward flow while simultaneously reducing regurgitant flow, partially by reducing aortic impedance and partially by reducing regurgitant orifice area. However, medical therapies for chronic MR have produced disappointing and



conflicting results. Studies of angiotensin-converting enzyme inhibitors have been inconclusive in the therapy of MR in humans (18–21), in naturally occurring MR in the dog (22,23), and in experimental canine MR (24). Likewise, angiotensin receptor blockers also have produced uneven results (25,26), although no large randomized trials have been performed with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Thus, these therapies are not recommended for the prevention of LV dysfunction in MR. However, they are of course recommended for the therapy of heart failure whether or not MR is present.

Beta-blockers have been shown effective in reversing the LV dysfunction caused by experimental MR where the mechanism is one of restoration of sarcomere structure and function (12). Whether these results apply to humans awaits randomized trials for a definitive answer.

Although the average systolic blood pressure for MR patients available from the literature is about 110 mm Hg, some patients with this lesion are hypertensive. Because



**Figure 2** Survival in MR

Survival after mitral valve repair (MVP) is compared with that after mitral valve replacement (MVR) for propensity-matched groups. Patients undergoing MVP had better survival. MR = mitral regurgitation. Reprinted with permission from Jokinen et al. (30).

hypertension increases the pressure gradient between the left atrium (LA) and LV, it also increases regurgitant volume. Obviously hypertension imparts huge health risks of its own. For these reasons, patients with MR and hypertension should be treated to lower their blood pressure to standard targets using those antihypertensive agents that work best for the individual.

### Surgical Therapy

The basics of MR pathophysiology are noted above. Mitral regurgitation imparts a volume overload on the LV that together with neurohumoral activation leads to LV remodeling and dysfunction. Mitral regurgitation is a mechanical problem that can only be corrected with a mechanical solution, that is, restoration of valve competence, thus removing the volume overload and its deleterious consequences. There is near unanimity that mitral valve repair (MVR<sub>c</sub>) instead of mitral valve replacement (MVR) is the preferred method of MR correction in nonrheumatic valves (27–31). Sparing even the posterior chordae is superior to total ablation of the mitral apparatus (29), and most reports show a lower operative mortality with MVR<sub>c</sub> compared with MVR and better long-term survival (Fig. 2) (30). Thus it is unfortunate that in developed countries where mitral valve prolapse and myxomatous degeneration are the eminently repairable causes of MR that only one-half of such valves are actually repaired (27).

It is important to recognize that the mitral valve is an important component of the LV, serving a major role in LV

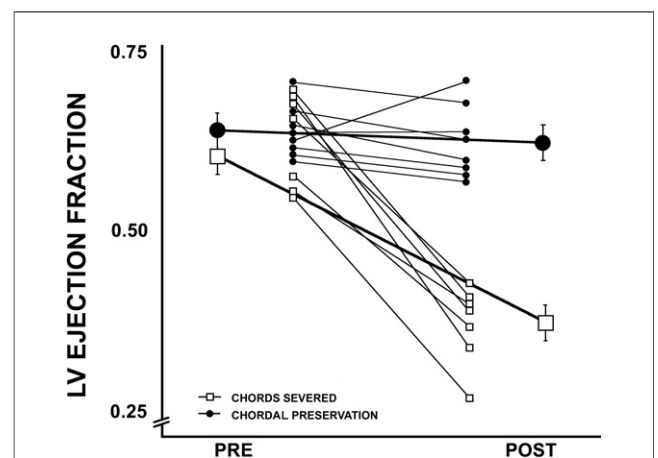
function by helping to maintain LV shape and chamber contractility. Destruction of the mitral valve apparatus at the time of MVR causes an immediate decrease in chamber contractility and an increase in afterload as the radius term in the Laplace equation increases (32,33). It was once believed that ejection fraction decreased after correction of MR because surgery obliterated the low impedance pathway for ejection into the LA, in turn increasing LV afterload. In fact MVR<sub>c</sub> also removes the low-impedance LA ejection pathway but causes only minor changes in ejection fraction, indicating that the large decrease in ejection fraction after MVR is caused by destruction in the mitral valve apparatus instead of its effect on ejection into the LA (33–35) (Fig. 3).

An MVR during which some or all of the chordal attachments between the papillary muscles and valve leaflets are maintained helps to preserve LV function compared with MVR (34,35) and improves exercise capacity (34). Further, one study indicates that replacement with chordal preservation improves mortality and late outcome compared with MVR alone (29).

### Timing of Surgery

**Patients with mild to moderate disease.** Patients with less than severe MR, that is, those with an RF of <0.5, those with a regurgitant volume of <60 ml/beat, and those with a regurgitant orifice area of <0.4 cm<sup>2</sup>, tolerate MR for long periods as long as the disease does not worsen. Currently surgery is not indicated in such patients. Instead they are observed periodically for worsening of disease, the onset of symptoms, and the occurrence of LV dysfunction.

**Patients with asymptomatic severe MR with normal LV function.** Patients without symptoms of dyspnea, orthopnea, or paroxysmal nocturnal dyspnea who have normal LV function have an excellent short-term prognosis, and many



**Figure 3** Results of Repair Versus Replacement

Ejection fraction before and after mitral valve surgery with preservation of the mitral valve apparatus (solid circles) is compared with ejection fraction before and after mitral valve surgery with removal of the apparatus (open squares). Reprinted with permission from Rozich et al. (33).

experts would observe such patients until early symptoms or evidence of LV function develops. However, patients with severe MR are likely to develop symptoms, LV dysfunction, or atrial fibrillation within a relatively short period of time (2 to 3 years), especially in the face of a flail leaflet (9). Thus many centers would consider repairing such valves shortly after discovery. Repair offers low mortality in such patients (<1% in experienced centers [31]) and reduces the risk of unwanted sequelae and the need for close longitudinal follow-up for the onset of symptoms or LV dysfunction. Indeed the recent American Heart Association/American College of Cardiology guidelines on valvular heart disease recommend surgery for such patients at a IIa level (most would favor surgery) where there is a >90% likelihood the valve can be repaired (27). However, as the recommendation implies, MVR (instead of repair) would be most unfortunate in such patients because a patient who did not need surgery at that time would receive a prosthetic valve and its attendant risks.

**Symptomatic patients with normal LV function.** Although ventricular function is a key determinant of outcome in all valvular heart disease, symptoms have a major impact on prognosis even when LV function is normal (Fig. 4) (36). Thus surgery, preferably MVR<sub>e</sub>, should be performed once even mild symptoms develop (27).

**Asymptomatic patients with LV dysfunction.** Although LV function may improve after MVR<sub>e</sub> this is by no means certain, and while sophisticated measures of LV function are available, they are impractical for daily use. However, when ejection falls toward 0.60 or when end-systolic dimension approaches 40 mm, post-operative outcome worsens, suggesting that these are fairly reliable markers for clinically important LV dysfunction (27,37,38). Thus, irrespective of symptomatic status, surgery, preferably MVR<sub>e</sub>, should be

performed once these objective benchmarks for LV dysfunction are reached.

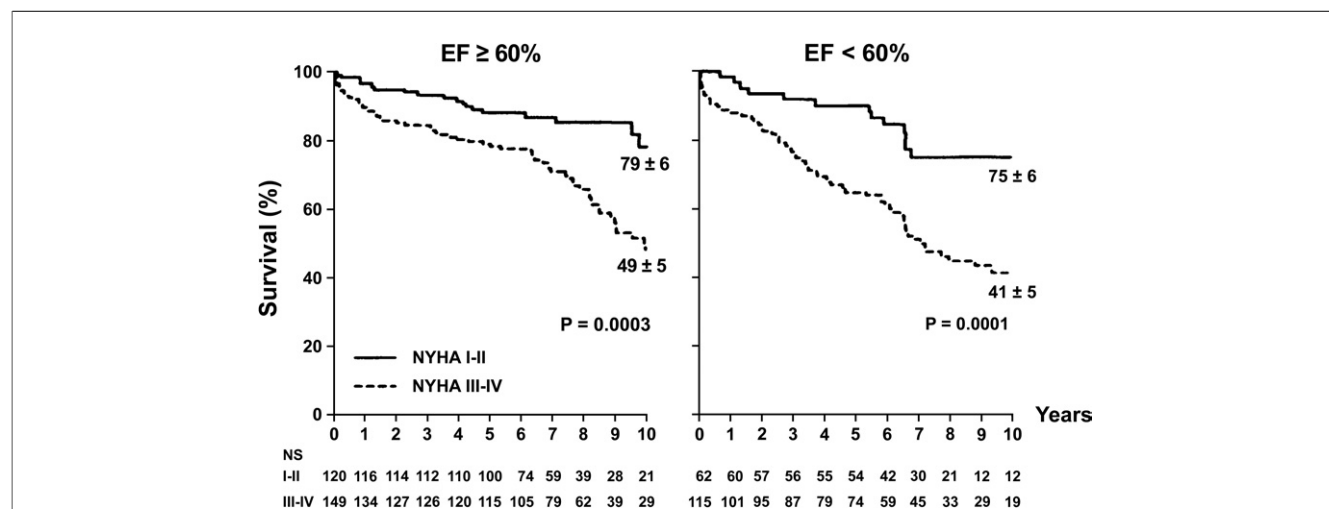
**Elderly patients with MR.** In many earlier reports, advanced age had a major negative impact on the outcome of mitral valve surgery (28,37). Patients age >75 years undergoing MVR had an operative mortality as high as 31%. However, more recent studies in the elderly show a marked improvement in operative mortality and late survival, especially when MVR<sub>e</sub> is used (39,40). Although it seems unwise to recommend surgery to asymptomatic elderly MR patients who have normal LV function, surgery should not be withheld in older symptomatic patients, especially when MVR<sub>e</sub> is likely.

**Patients with far advanced disease.** When it was believed that closure of the LA ejection pathway obligated an increase in afterload and a decrease in ejection performance, patients with primary MR and low ejection fraction were considered inoperable. It was reasoned that increased afterload would lead to a prohibitive further decline in LV function. It is now known that although prognosis is reduced in such patients, MVR<sub>e</sub> can improve symptoms and is relatively well tolerated (41). It is assumed that MVR, which by itself worsens LV function, would not be effective in such patients, although data from randomized trials of MVR<sub>e</sub> versus MVR are lacking.

## Secondary MR

### Pathophysiology

As noted in the previous text, the pathophysiology of primary MR is relatively straightforward. The incompetent valve causes an LV volume overload, leading to ventricular remodeling, myocardial dysfunction, and heart failure. Correction of the MR and of the volume overload in a timely



**Figure 4 Outcome and Symptoms**

Survival of patients after surgery for MR with normal ejection fraction (EF) (left) and with reduced EF (right) are shown. Advanced New York Heart Association (NYHA) functional class had a large impact on survival in both groups. MR = mitral regurgitation; NS = nonsignificant. Reprinted with permission from Tribouilloy et al. (36).

fashion leads to reversal of its pathophysiological consequences. However, the pathophysiology of secondary MR is much more complex. Here myocardial damage either through one or more myocardial infarctions or from dilated cardiomyopathy has caused an anatomically normal valve to leak. Even if the MR is corrected, the underlying muscle disease will still exist. This fact must contribute to worsened prognosis of secondary MR (42-44). Thus the advantages of correction of secondary MR are less clear. Is the MR a relatively innocuous bystander like the fever in infection, or is the MR a major contributor to the negative prognosis of secondary MR, a prognosis that is in fact much worse than that of primary MR?

It is clear that the presence of MR in ischemic and dilated cardiomyopathies worsens prognosis (Fig. 5) (42). However, these data have 2 potentially very different interpretations. On one hand, it may be that the volume overload created by the MR adds a greater pathologic burden to an already adverse condition. On the other hand, it may simply be that poorer ventricular function is the cause of the poorer prognosis and that the MR simply is an indicator of the poorer LV function. The issue is central to the therapy for the condition. If secondary MR is a cause for worsened prognosis, it should represent a reasonable target for therapy. However, if secondary MR is simply a byproduct of disturbed LV geometry and function, correction of secondary MR may have little impact on outcome.

### Medical Therapy

Whereas there are no conclusive data showing that medical therapy is effective in patients with primary MR, it must be recognized that almost all patients with secondary MR have heart failure. As such, patients with secondary MR should be treated with standard heart failure therapy, which typi-

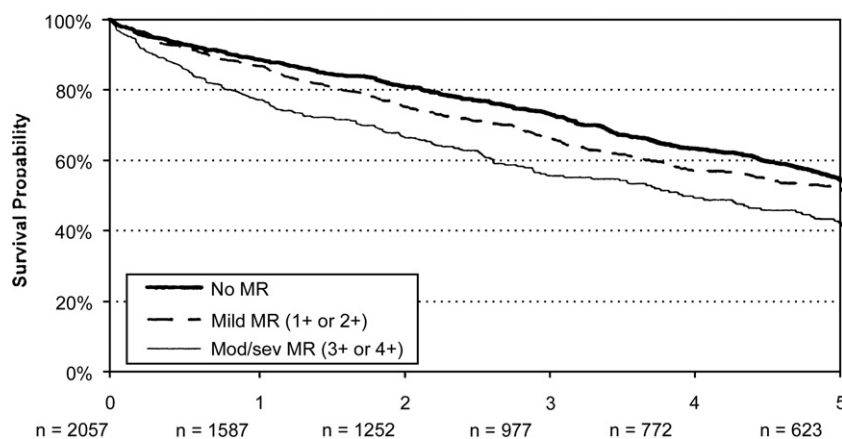
cally includes angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), beta-blockers, diuretics, and aldosterone antagonists. Although these agents may alter regurgitant volume, their major thrust is at the antecedent heart failure.

### Resynchronization Therapy

Because wall motion abnormalities are often part of the cause of secondary MR, it is logical that electrical cardiac resynchronization therapy (CRT) would have a therapeutic role here, and indeed it does. In selected patients, CRT reduces the amount of MR and improves cardiac output and symptomatic status (45).

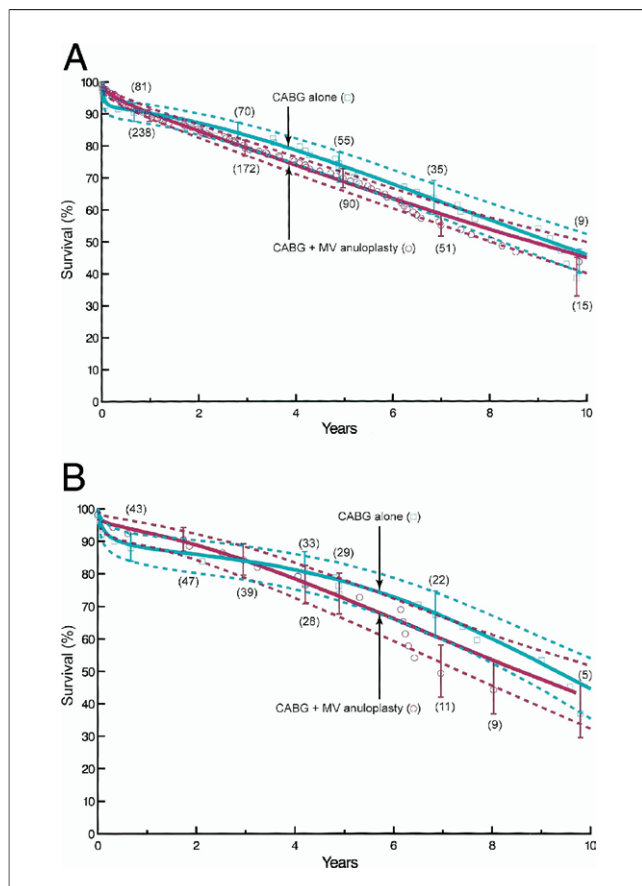
### Outcome of Correction of Secondary MR

Once the concept that correction of MR had to increase afterload and decrease ejection fraction was dispelled, patients with MR and very low ejection fraction from cardiomyopathy (ischemic or idiopathic) could be considered for surgery. Bach and Bolling (46) reported on partial correction of secondary MR using a restrictive annuloplasty ring. By reducing annular diameter, this simple procedure significantly reduced the amount of MR present and was well tolerated with an operative mortality of <5%. One year later, 75% of the patients were still alive and LV volumes decreased significantly, likely reducing afterload by decreasing the radius term in the Laplace equation, the mechanism by which there was a modest increase in LV ejection fraction. Others have shown similar results (47). In the Acorn trial, patients with secondary MR were randomized to receive either MVR<sub>c</sub> alone or MVR<sub>c</sub> plus an external restraint device. Importantly, substantial reverse remodeling occurred in the MVR<sub>c</sub> (48) only group, as it has in other reports (49).



**Figure 5** Functional MR and Survival in CHF

Survival for patients with heart failure is shown for varying severities of MR. Patients with moderate to severe MR had a significantly worse outcome. CHF = congestive heart failure; MR = mitral regurgitation. Reprinted with permission from Trichon et al. (42).



**Figure 6 Results of Mitral Surgery in CHF**

Unadjusted (A) and propensity-adjusted (B) survival of patients with secondary MR are shown and separated into groups of coronary artery bypass graft (CABG) surgery alone or CABG surgery plus mitral anuloplasty. No difference in survival was detected. Reprinted with permission from Mihajlevic et al. (50). MV = mitral valve; other abbreviations as in Figure 5.

As yet there is no proof that such surgery prolongs life. In fact in nonrandomized data from the Bolling group, there was no evidence of improved survival (44). Further, some have questioned whether surgery in ischemic MR improves survival and/or long-term quality of life (Fig. 6) (50). It is clear from the disparate results published in the literature that a large randomized trial is needed to identify the proper role of MVR and MVR<sub>c</sub> in the treatment of patients with secondary MR.

In coronary revascularization alone versus combined revascularization and mitral surgery, it is general practice to correct severe MR during coronary artery bypass graft surgery. However, even this mode of therapy has been questioned. Diodato et al. (51) found no increased risk to adding MVR<sub>c</sub>, but neither did they find long-term benefit, and others have raised the same issue (52). Although it seems clear that the presence of even moderate MR worsens prognosis for those undergoing coronary artery bypass graft surgery (53), there is a clear divergence of opinion about whether MR should be corrected during revascularization (54,55).

## Percutaneous Therapies

The potential for mechanical relief of MR without surgery has ignited much interest, spurring the advance of several new technologies. Two basic types of interventions are being developed. One group of interventions apposes the center of the 2 mitral leaflets, producing a double-barrel opening and reducing or eliminating MR while avoiding mitral stenosis (56). A second group of interventions utilizes the close proximity of the mitral annulus to the coronary sinus. By inserting devices into the coronary sinus that mechanically alter its shape, the shape of the annulus is also altered, in turn helping to restore mitral competence (57,58). Early experience shows that these devices can be effective. However, the role in our armamentarium for treating MR awaits development of more data.

## Summary

Primary MR imparts a volume overload on the LV, leading to LV eccentric hypertrophy and remodeling. Although this remodeling is essential to compensating forward stroke volume, it eventually leads to myocardial systolic dysfunction and increased afterload despite the tendency of MR to unload the LV. Current medical therapy is not effective in treating the condition. On the other hand, timely MVR<sub>c</sub> reverses or prevents LV dysfunction and is the preferred method of therapy. Unfortunately this procedure is still underutilized in the U.S.

On the other hand, secondary MR stems from an already-damaged LV. Although surgical mortality has declined for this entity (59), long-term outcome is still poor, presumably because correction of the MR cannot by itself correct the underlying muscle dysfunction. Best management for secondary MR includes standard therapy for heart failure and CRT in selected patients. There must surely be a role for surgery and possibly for percutaneous devices. However, their exact roles have yet to be determined, and until more data are available, equipoise should hold sway in our thinking about these therapies.

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