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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.

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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_e = 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 (σ) = p × 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

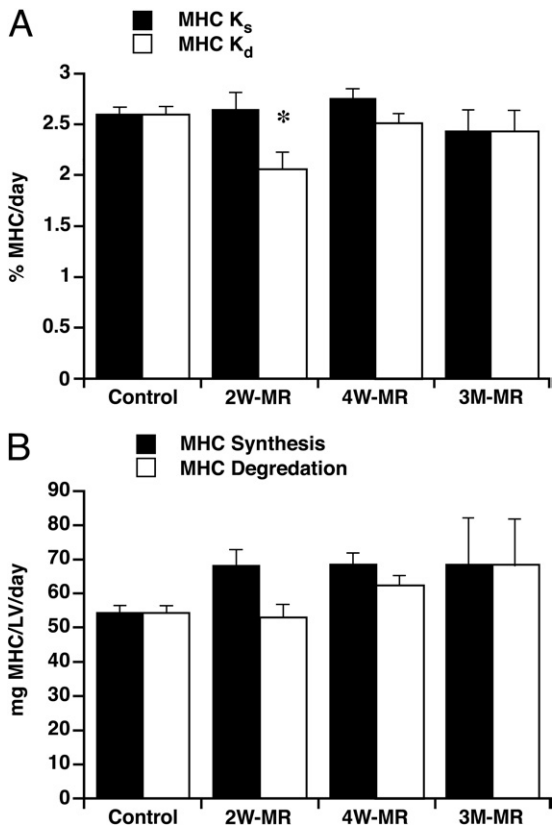

Figure 1 Protein Synthesis

Myosin heavy chain (MHC) synthesis rate (K_s) and degradation rate (K_d) are shown for dogs with severe mitral regurgitation (MR) at 2 weeks (2W), 4 weeks (4W), and 3 months (3M) after initiation of the lesion expressed as a percent of the total pool **(A)** and as mg/day **(B)**. Because left ventricular mass increased by 30% and no increase in K_s could be detected, a decrease in K_d is inferred. Reprinted with permission from Matsuo et al. (8).

conflicting results. Studies of angiotensin-converting enzyme inhibitorshave 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