EDITORIAL COMMENT

Inhibition of the Renin-Angiotensin System and the Left Ventricular Adaptation to Mitral Regurgitation*

William H. Gaasch, MD, FACC,†
Gerard P. Aurigemma, MD, FACC‡

Burlington and Worcester, Massachusetts

Chronic mitral regurgitation (MR) is most often caused by degenerative disease that results in prolapse, ruptured chordae or partial flail leaflet. With few exceptions, patients with chronic severe MR and symptoms of heart failure and/or left ventricular (LV) dysfunction are candidates for mitral valve repair or replacement (1). However, the indications for such surgery in asymptomatic patients, especially those with normal LV function, remain controversial and depend on a variety of factors such as valve repairability and atrial fibrillation. Many clinicians argue that since there are no symptoms to improve, early surgery not only exposes the patient to perioperative morbidity and mortality, but if repair of the native diseased valve cannot be achieved, the patient will also be exposed to the long-term complications of a prosthetic valve. Thus, many clinicians are reluctant to consider surgical correction of chronic MR in an asymptomatic patient. Medical therapy with a vasoactive drug, were it able to obviate or delay the need for surgery, would obviously be desirable. Unfortunately, there is a persistent uncertainty about the utility of vasodilator therapy in asymptomatic patients with chronic MR. In this issue of the Journal, Perry et al. (2) report their experience with an angiotensin II type-1 (AT1) receptor blocking agent in an experimental model of MR. This work, coupled with previous research by these investigators (3), sounds a cautionary note that should influence clinicians and investigators in their efforts to assess and evaluate the LV response, the hemodynamics and the management of MR.

The LV response. Mitral regurgitation burdens the left ventricle with a volume load that leads to a series of compensatory myocardial and circulatory adjustments (4–6). These adjustments vary over a prolonged course; changes that are operative in acute MR are eventually replaced by normal (4). Moreover, the systolic unloading that is characteristic of acute MR is gradually replaced by normal systolic wall stresses (5). Thus, the enhanced total stroke volume, seen in chronic compensated MR, is “mediated through a normal performance of each unit of an enlarged circumference” (6). At this time, LV contractility and ejection fraction are normal and total stroke volume is high as a result of the large end-diastolic volume and normal systolic function. During this compensated phase of the disease, most patients remain asymptomatic. This would seem to be an ideal time for the use of vasodilator therapy—if such treatment could reliably reduce the volume overload and thereby protect the ventricle from progressive enlargement and decompensation.

The most elusive and poorly understood aspect of the pathophysiology of MR is the nature of the transition from the compensated to a decompensated state. This may occur as a consequence of progressive increments in the regurgitant volume, or a gradual depression of myocardial contractility or both. The decompensated state is characterized by substantial and progressive ventricular enlargement, high LV diastolic pressure and wall stress, increased systolic wall stress and a decline in the ejection fraction. The fall in ejection fraction is a consequence of both depressed LV contractile state and afterload excess. Progressive atrial enlargement and atrial arrhythmias are seen, pulmonary hypertension develops and the patient becomes symptomatic. At this late (i.e., decompensated) stage, there may be irreversible depression of ventricular and atrial function and although some patients may benefit from surgery, an optimal surgical result is unlikely.

Ventricular afterload. As mentioned previously, LV systolic wall stresses are reduced in acute MR, but subsequently the total stroke volume increases via the Frank-Starling mechanism. In addition, the low resistance runoff into the left atrium contributes to an increased ejection fraction and a decrease in systolic volume; according to the law of Laplace, systolic load (i.e., afterload) declines. Thus, in acute MR, an increased ejection fraction and increased total stroke volume occur as a result of an increase in LV preload and a decrease in afterload.

The major change that occurs during the evolution from acute to chronic MR is an enlargement of the ventricle. As this new state develops, the small hyperkinetic chamber of acute MR is converted to a large compliant chamber that is well suited to deliver a large stroke volume. This comes about through a dissolution of collagen weave and remodeling of the extracellular matrix with a rearrangement of myocardial fibers, in association with the addition of new sarcomeres and the development of eccentric LV hypertrophy. As a result, cardiomyocytes are longer (2,3) but preload at the sarcomere level (i.e., sarcomere length) returns toward normal (4). Moreover, the systolic unloading that is characteristic of acute MR is gradually replaced by normal systolic wall stresses (5). Thus, the enhanced total stroke volume, seen in chronic compensated MR, is “mediated through a normal performance of each unit of an enlarged circumference” (6). At this time, LV contractility and ejection fraction are normal and total stroke volume is high as a result of the large end-diastolic volume. The experimental model used by Perry et al. (2) closely resembles this chronic compensated state (i.e., severe MR with LV enlargement and normal systolic function). During this compensated phase of the disease, most patients remain asymptomatic. This would seem to be an ideal time for the use of vasodilator therapy—if such treatment could reliably reduce the volume overload and thereby protect the ventricle from progressive enlargement and decompensation.

From the Departments of Cardiovascular Disease, †Lahey Clinic, Burlington, and the ‡University of Massachusetts Medical School, Worcester, Massachusetts.

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.
revert to normal as the ventricle enlarges and adapts to the volume overload. Eventually systolic wall stresses may exceed normal, and in decompensated MR an afterload excess contributes to the decline in ejection fraction. Despite evidence to the contrary, the notion persists that afterload is low in chronic MR. Several published studies refute this misconception (5,7–11). Using echocardiographic measures of LV volume, mass and geometry, Zile et al. (8) found that meridional end-systolic stress was normal in compensated MR and increased in decompensated MR; they also found a tendency for peak systolic stress to be increased in both. Corin et al. (9) later confirmed these observations with cardiac catheterization techniques. They calculated circumferential wall stress and found a modest increase in peak systolic stress in compensated and decompensated ventricles; end-systolic stress was particularly high in decompensated ventricles. Likewise Wisenbaugh et al. (10) and Carabello et al. (11) described normal or increased afterload in patients with chronic MR. Perry et al. (2) also confirm elevated peak systolic stress with values for end-systolic stress that are significantly higher than normal. These and other similarities between their experimental model and MR in humans help validate their work as relevant to human disease.

**Hydraulic determinants of regurgitant flow.** The determinants of mitral regurgitant volume are best understood in the context of the orifice equation. This equation, based on the Torricelli principle, states that flow through an orifice varies by the square root of the pressure gradient across that orifice:

\[ \text{MRV} = \text{MROA} \cdot C \cdot T_s \cdot \sqrt{LVP - LAP} \]

where MRV = mitral regurgitant volume, MROA = mitral regurgitant orifice area, C = constant, T_s = time or duration of systole, LVP = LV mean systolic pressure and LAP = left atrial mean systolic pressure. In many if not most patients with MR, the regurgitant orifice area is dynamic with variations that are dependent on LV geometry. The systolic pressure gradient across the valve also can vary dramatically. These two determinants of regurgitant volume are the primary therapeutic targets in patients with MR and vasodilators have the potential to affect both. It should be emphasized that systemic vascular resistance, LV systolic wall stress (i.e., afterload) and contractile or inotropic state are not direct determinants of the regurgitant volume, and in asymptomatic patients who might be candidates for vasodilator therapy are not primary therapeutic targets.

**The severity of regurgitation.** Left ventricular cineangiography and Doppler echocardiography are widely used to evaluate the severity of MR, but these methods are only semiquantitative (12). Calculations of the regurgitant volume or fraction with catheterization or echocardiographic techniques are more accurate (13), but the methods require careful attention to detail and until recently had not been widely applied. Moderate MR is said to be present when the regurgitant fraction is in the range of 30% to 50%; severe MR is defined as a regurgitant fraction \(>50\%\). It should be noted, however, that the regurgitant fraction varies inversely with the total stroke volume and that an increase in the LV end-diastolic volume and/or ejection fraction might reduce significantly the regurgitant fraction—despite a constant regurgitant volume. The magnitude of the regurgitant volume, and its relation to the end-diastolic volume, can be of signal importance in clinical decision making.

**Clinical vasodilator studies.** The short-term effects of vasodilator therapy in patients with chronic MR have been variable and dependent, among other factors, on the agent employed (14). For example, nitroprusside has produced a consistent decrease in the regurgitant volume and an increase in forward stroke volume, generally accompanied by a reduction in end-diastolic pressure and volume. Nitroglycerin tends to produce a reduction in end-diastolic volume with little effect on regurgitant volume or forward stroke volume. The short-term effects of angiotensin-converting enzyme (ACE) inhibitors appear to be less consistent, but there is a tendency for regurgitant volume to decrease during such treatment.

The long-term use of vasodilator therapy in chronic MR has virtually been limited to ACE inhibitors and AT_1 receptor blockers (14–17). In three recently published studies, the use of these agents produced a decrease in the regurgitant volume, but the average changes were relatively small and there were substantial individual variations in the magnitude of the effect (15–17). A decrease in end-diastolic volume was not uniformly seen (15), and exercise tolerance was not improved (15,16). In one blinded study, therapy was withdrawn from one-third of the patients because of side effects (15); another study that was not blinded did not include information on the patients’ symptoms (17); another did not relate the observed changes to the baseline LV size and function or the severity of regurgitation (16). These and other limitations, including small numbers of patients studied, should limit the enthusiasm for the use of ACE inhibitors or AT_1 receptor blockers in nonhypertensive asymptomatic patients with chronic MR. Nevertheless, these agents are commonly employed in patients with MR (18).

**Experimental studies.** Dell’Italia et al. (3) have previously shown that treatment with an ACE inhibitor (resulting in a reduction in LV angiotensin II levels to normal) failed to attenuate the LV remodeling, enlargement and hypertrophy. The loss of collagen weave, seen in their model of MR, was not affected by the ACE inhibitor, nor was the increase in cardiomyocyte length (3). Based on their observations of “normal” LV angiotensin II levels and the upregulation of AT_1 receptors, they suggested that an AT_1 receptor blockade (alone or in combination with an ACE inhibitor) might be effective in preventing the observed pathophysiologic consequences.

In this issue of the Journal, Perry et al. (2) studied the effects of AT_1 receptor blockade on hemodynamics, LV size
and function and cardiomyocyte length in dogs with MR. Their experimental model is well established (2,3,19), and it resembles severe degenerative mitral valve disease in humans (i.e., chordal rupture and flail leaflet with regurgitant fraction exceeding 50%). By initiating therapy with AT1 receptor blockade at the onset of MR, they were able to assess the effects of a blockade that was present during and after the early adaptation to severe MR. At three months, a substantial vasodilator effect was seen; systemic resistance and LV systolic pressure were significantly lower in the treated than in the untreated group with MR. Despite these favorable vasodilator effects, regurgitant volume remained high and importantly, the eccentric remodeling with ventricular enlargement and cardiomyocyte lengthening was not reversed. Indeed, there was a tendency for end-diastolic and endsystolic volumes and cardiomyocyte length to be greater in the treated group than in the untreated group. Left ventricular angiotensin levels are elevated in this model of MR, and treatment with AT1 receptor blockers reduced the LV angiotensin II levels to normal. This result is similar to that previously observed with ACE inhibition, and the authors conclude that blockade of the renin-angiotensin system promotes dissolution of collagen weave and thereby contributes to increased ventricular size and cardiomyocyte length.

Comment. Severe MR, resulting in LV volume overload and high diastolic wall stress, induces a collagen degradation state with a remodeling of the extracellular matrix that fosters an adaptive LV enlargement. By treating the animals with an AT1 receptor blocking agent during the early adaptive phase (at the onset of MR), Perry et al. (2) further weakened the collagen weave thereby offsetting any beneficial effect on LV size that might be produced by vasodilation. In addition to these actions of ACE inhibitors and AT1 receptor blockers on the LV interstitium, it is possible that a similar deleterious effect is present in prolapsing mitral leaflets (20). It is also plausible that the alterations in the extracellular matrix and ventricular remodeling are influenced by the chymase system and the matrix metalloproteinases, and that their activities as well as those of the cardiac renin-angiotensin system interact and vary over the time course of the disease. Initiation of therapy at a later time (i.e., during the chronic compensated phase) might very well produce a different effect on the LV; such “late” data would appear to be more relevant to humans with chronic MR and should be a high priority for future studies.

Returning to the orifice equation (vide supra), at a constant regurgitant orifice area a modest reduction in the systolic pressure gradient between the ventricle and the atrium would be expected to have minimal impact on regurgitant volume. Indeed, this was the case in the work by Perry et al. (2) in which a 10% to 15% decrease in the pressure gradient would be expected to produce only a 7% reduction (3 to 4 ml) in regurgitant volume. Such a small change is unlikely to be detected with the currently available techniques; Perry et al. (2) did not detect a change. It is possible, therefore, that the persistent LV enlargement was related to the persistence of a large regurgitant volume in a ventricle with a weakened extracellular matrix.

It is also noteworthy that LV end-systolic dimension increased and systolic pressure decreased more in the animals treated with AT1 receptor blockade than in the untreated MR group. These and other data reported by Perry et al. (2) suggest a relative decrease in contractile function with AT1 receptor blockade. Such blockade could blunt the angiotensin II promotion of catecholamine release into the interstitium and thereby produce a depression of contractility (21). The tendency for contractile function to decline requires further research.

Conclusions and future directions. The time for ACE inhibitors and AT1 receptor blocking agents to be regarded as mere vasodilators is long past. Certainly the vasoactive properties are important, but the tissue activity of the renin-angiotensin system is critically related to the structural and functional alterations that occur in the ventricle during its adaptation to volume overload. It cannot be assumed that ACE inhibitors or AT1 receptor blockers invariably protect the heart—particularly during the early phases of MR. The interactive effects of the renin-angiotensin, the chymase and the matrix metalloproteinase systems during the early adaptive and later phases of MR obviously warrant further study.

While no one would argue against the use of ACE inhibitors or perhaps AT1 receptor blockers in myopathic hearts with secondary MR, the available human data do not provide strong support for the use of the agents in asymptomatic patients with valvular MR and normal LV function. When a compelling indication (e.g., hypertension, diabetes) exists for the use of ACE inhibitors or AT1 receptor blockers in a patient with coexisting MR, these drugs can obviously be used. However, a long-term beneficial effect on the regurgitant lesion should not necessarily be expected and most importantly, such therapy should not replace careful clinical follow-up including periodic evaluation of the mitral structure, the severity of regurgitation, as well as LV size and function (1). The provocative study of Perry et al. (2) coupled with a limited published clinical experience, provides strong rationale for a well designed clinical trial that incorporates information on LV size and function, and especially clinical outcome.

Reprint requests and correspondence: Dr. William H. Gaasch, Lahey Clinic, 41 Mall Road, Burlington, Massachusetts 01805. E-mail: William.H.Gaasch@Lahey.ORG.

REFERENCES