Degenerative mitral regurgitation (MR) presents the physician with a pure engineering problem: a valve leaks, the regurgitant volume overloads a mechanical pump, and if sufficiently severe, the leak must be eliminated. Intrinsic heart muscle function and overall pump performance initially may be normal in patients with chronic MR, even when severe. However, ultimately, left ventricular and left atrial volume overloads, eventually causing right ventricular pressure overload, impair myocardial contractility. If the defective mechanics are not corrected, this process inevitably progresses and leads to heart failure, arrhythmia, and death.

The obvious (and only generally accepted) remedy is a mechanical solution: surgical valve replacement or repair. Reduction in regurgitant volume by pharmacological peripheral vasodilation is theoretically attractive and often is attempted by clinicians because of its apparent short-term hemodynamic benefit both in acute and in chronic MR, first demonstrated with nitrates 4 decades ago and subsequently reported with other drugs. However, in the few studies that have assessed clinical outcomes, no demonstrably beneficial alteration in natural history has occurred. Indeed, in the largest placebo-controlled clinical trial, 1 year of therapy with enalapril was actually inferior to no therapy in its effects on anaerobic threshold at treadmill exercise testing. The demonstration of negative effects on myocardial contractility in preclinical studies and in isolated hearts and myocardial tissue provides the putative explanation for this failure.

Although results with vasodilators have been disappointing, a series of observations in another direction led to an alternative potential magic bullet: β-blockade. For years, concern about the importance of autonomically mediated β adrenergic support of the myocardium resulted in extreme caution in the use of β blocking drugs in patients with MR. Support for this empirical concern became available 2 decades ago when, in an in vitro assessment of human epicardial muscle strips taken from patients undergoing surgery for chronic MR, Mulieri et al found a diminution from the normally expected force-frequency relation and were able to restore function with forskolin, an agent that directly stimulates the β adrenergic receptor system. Consistent with this in vitro observation, less than a decade later, in a series of cardiac catheterization studies in intact patients with MR, Starling et al and Mehta et al showed that systemic sympathetic nervous activity is abnormal in chronic MR. Using sophisticated modeling algorithms, these investigators inferred abnormal reuptake of norepinephrine into intramyocardial nerve terminals. They concluded abnormal reuptake of norepinephrine harmed cardiomyocytes and causing the defect noted by Starling et al and Mehta et al. However, despite the increase in systemic norepinephrine concentrations, in the presence of β blockade, hemodynamics and myocardial contractility improved. This suggested that β adrenergic receptor responsivity also had improved. The putative benefit of β blockade was supported by additional studies from the same institution, with the demonstration of β-blocker-mediated improvement in intrinsic myocardial function in experimental MR in studies that also showed deterioration of function when an angiotensin-converting enzyme inhibitor was administered. These experiments also raised the possibility that the apparent benefit of β blockade was mediated by heart rate slowing (because it was abolished by pacing) rather than by any other interaction with the adrenergic system, but irrespective of precise mechanism the benefit was clear. With growing support for use of β blockade in MR, Varadarajan et al undertook a retrospective chart review to determine the relation of β blockade to clinical outcome among patients with severe MR and normal left ventricular ejection fraction. Their convenience sample was selected from among patients who had undergone echocardiography at their institution. Of the 895 patients in their cohort, 32% were on β blocking therapy of some sort; this group manifested 38% fewer deaths during follow-up than patients who did not receive β blocking therapy, a finding which was statistically independent of age, sex, left ventricular ejection fraction, concomitant coronary artery disease, diabetes mellitus, hypertension, and cardiac valve surgery. These data were particularly promising, but they have not been followed by a prospective randomized controlled...
trial. Thus, question about the appropriateness of prophylactic pharmacological β blockade for asymptomatic MR remains.

In this void, the study in this issue of Circulation: Heart Failure by Pu et al \(^\text{15}\) is potentially very important. Using a rat model of catheter-induced MR, these investigators report that nonselective β blockade with carvedilol, which also has an α blocking effect, does not result in putatively beneficial reverse remodeling or enhancement of left ventricular ejection fraction; indeed, a 12% decrease in heart rate was associated with substantial and statistically significant increases in left ventricular volumes, as well as a decrease in ejection fraction. However, these results cannot be interpreted unambiguously: the reduction in heart rate might be expected to cause the volume changes and might even impact on ejection fraction.

Although results of Pu et al \(^\text{15}\) are at odds with some of the earlier reports cited above, consistent with Pu et al, Sabri et al \(^\text{16}\) had found failure of β blockade to affect reduction of left ventricular volumes in experimental MR a decade ago. Almost simultaneously with the findings of Sabri et al, \(^\text{16}\) a similarly disquieting result was reported by Stewart et al \(^\text{17}\) in a short-term clinical crossover study in which 25 patients received metoprolol during a 2-week interval alternating with a 2-week placebo interval. As in the animal study, the statistically significant increases in left ventricular systolic and diastolic volumes found by Stewart et al \(^\text{17}\) could not be interpreted unambiguously because of the average 10 beats per minute reduction in heart rate with β blockade. Perhaps importantly, however, the changes observed in the clinical study were markedly and disproportionately less than those seen in the experimental animals, emphasizing the difficulty in direct extrapolation from preclinical to clinical results. Moreover, in the clinical study, left ventricular ejection fraction, stroke volume, and regurgitant volume were unaffected by the treatment, suggesting that ventricular volumes alone might not be adequate surrogates for outcomes of clinical interest in MR.

Most recently, Ahmed et al \(^\text{18}\) studied β blockade in 38 patients with moderate to severe chronic MR, with left ventricular ejection fraction >55% and without evidence of clinically important coronary artery disease or New York Heart Association Functional Class III or IV heart failure. Patients were randomized to β blockade with metoprolol or to placebo; treatment was continued for 2 years. In contrast to preclinical results of Pu et al, \(^\text{15}\) β blockade observed in patients of Ahmed was associated with significant increase in left ventricular ejection fraction and early diastolic filling rate, but with no significant effect on left ventricular end systolic or diastolic volumes, strain rate, or wall thicknesses or mass measures. The study was too small to assess clinical outcomes meaningfully, although during the 2 years of follow-up, mitral valve surgery was deemed necessary in 6 patients in the placebo group but in only 2 patients who underwent β blockade (\(P=0.23\)). Clearly, it will be important to determine the basis for the apparent difference in reverse remodeling observed in rats by Pu et al \(^\text{15}\) and in humans by Ahmed et al. \(^\text{18}\)

These differences notwithstanding, the unique contribution of Pu et al \(^\text{15}\) is mortality data, not previously available in animals or humans from prospective assessments in MR. Thus, survival during a follow-up corresponding to a substantial portion of the rat’s expected life span fell from 96% with placebo to 88% with carvedilol. This is the most worrisome of the findings of Pu et al, \(^\text{15}\) and must be considered seriously amid the growing enthusiasm for a properly sized prospective clinical trial of β blockade for chronic nonischemic MR. However, the results of Pu et al \(^\text{15}\) also must be considered in the context of the report of Plante et al \(^\text{19}\) in which β blockade with metoprolol was undertaken in rats with surgically created aortic regurgitation. In this study, 40 rats were randomized to β blockade or no treatment and followed up to 1 year. Left ventricular volumes were indistinguishable over time in treated and untreated rats but ejection fraction increased modestly in the treated group. In contrast to the MR studies, the dose of metoprolol used had no effect on heart rate. Most importantly, survival improved dramatically and significantly with β blockade: 60% of treated rats survived the full year versus only 35% of the untreated rats. MR and aortic regurgitation are very different diseases mechanically and biologically. It is inappropriate to draw firm inferences from differential effects of treatment in the 2 diseases. However, the success of β blockade observed in rats of Plante, combined with the suggestive clinical results of Ahmed et al, \(^\text{18}\) indicates that the issue cannot be considered resolved as yet.

Many questions remain as to the conclusions that can be drawn from data of Pu et al \(^\text{15}\) for clinical application. First, of course, there are biological differences of potentially great importance between the hearts of rats and of humans. \(^\text{20}\) Second, MR in animal models is created by acute intervention and is severe from the outset, whereas chronic MR in humans can develop gradually over time, potentially impacting the myocardial response. Duration of MR in studies of animal models, even if normalized for species life expectancy, is shorter than that which can be expected in humans. Thus, direct extrapolation from results of animal studies to humans is fraught with hazard. Also, differences in heart rate response in different studies may have importantly affected outcome, as they do in nonvalvular heart failure. In addition, although all drugs that can block β-1 receptors have ≥1 pharmacological action in common, they differ in others, often markedly. It is not clear, therefore, that the results of Pu et al \(^\text{15}\) with carvedilol, a nonselective β blocker with additional α blocking effects, should be mirrored by the results of Ahmed et al \(^\text{18}\) with metoprolol, a β-1 selective β blocker without α effects.

Finally, however, as noted initially, MR is an engineering problem; its best solution is mechanical. The issue before us is whether the myocardial effects of the leaking valve can be diminished and outcomes improved by adjunctive pharmacological therapy. The results of Pu et al \(^\text{15}\) strongly suggest that carvedilol, and perhaps β blockers as a group, do not provide the much sought magic bullet. However, as the foregoing discussion suggests, enough doubt remains so that further assessment is needed before we totally eliminate β blockade as a potential option for MR.

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