EDITORIAL COMMENT

Ischemic Mitral Regurgitation, the Dynamic Lesion: Clues to the Cure*

Robert A. Levine, MD, FACC, Judy Hung, MD, FACC

Boston, Massachusetts

Functional ischemic mitral regurgitation (MR) is now receiving increased attention as one of the last frontiers in mitral valve repair as well as a therapeutic opportunity in heart failure (1–5). Valve repair has proved more challenging for ischemic MR than for degenerative mitral valve prolapse, in which surgery is tailored to the detailed anatomy displayed by echocardiography and inspection. Successful valve repair must target the mechanism of dysfunction in the individual patient; to date, however, both understanding of mechanism and targeting of therapy have been elusive for ischemic MR (6–9).

Changes with exercise. Until now, ischemic MR has been evaluated almost exclusively at rest. In this issue of the Journal, Lancellotti et al. (10) for the first time quantitatively measured changes in ischemic MR with semi-supine exercise. The dynamic changes they observed provide mechanistic insights that can sharpen the therapeutic approach in general and clarify the course of action in the individual patient.

Balance of forces. These dynamic changes in MR can best be understood by considering the basic forces acting on the mitral leaflets. Ischemic MR occurs in the setting of normal mitral leaflets but abnormal left ventricular (LV) function and geometry. Ischemic LV distortion leads to papillary muscle displacement and annular dilatation, tethering the mitral leaflets and restricting their ability to close effectively (Fig. 1) (11–21). Annuloplasty addresses only one end of this “tug of war” (22–25). Tethering is compounded by LV dysfunction, which decreases the force needed to close the leaflets in opposition to the tethering (26). This interplay of competing forces creates a dynamic lesion that varies during the cardiac cycle. Noninvasively emulating the approach of Yoran et al. (27,28) and Keren et al. (29), Schwammenthal (30) showed that effective regurgitant orifice area in ischemic MR typically peaks in early and late systole and decreases in midsystole as LV pressure rises and the mitral closing force increases. This behavior was reproduced in vitro by He et al. (14) and shown by Hung et al. (31) to be determined in patients primarily by the midsystolic rise in LV pressure, closing the mitral leaflets more completely, with a lesser contribution from midsystolic annular contraction. Thus, MR variation within the cardiac cycle (32) provides clues to the basic forces influencing leaflet closure (33).

Changes with loading. Ischemic MR also varies dynamically with loading conditions that modulate LV volume. This variation is expressed most dramatically in the operating room, where anesthetic induction and inotropic agents can reduce moderate MR to trace amounts, confounding decisions regarding need for repair (34–36). Dynamic changes with unloading have also been described by Kizilbash et al. (37). In patients with heart failure, effective orifice area is similarly reduced by medical decompression of the LV (38). The dominant factor in these dynamic changes is variation in ventricular geometry as the proximate cause of tethering.

Exercise-induced variation. The current article provides further insight into the pathophysiology of postinfarction MR as a characteristically dynamic lesion. The authors prospectively examined 70 patients with at least mild MR and LV ejection fraction <45%, excluding patients with evidence of exercise-induced ischemia. During semi-supine exercise, the effective regurgitant orifice area was quantified by two complementary Doppler methods. The observed changes were important and largely adverse, with orifice area increasing by >20 mm² (enough to change grade of severity) in nearly 30% of patients. The exception was patients with inferior myocardial infarctions and recruitable systolic function, in whom regurgitant orifice area tended to decrease. Exercise-induced changes in MR did not correlate with degree of MR or LV dysfunction at rest. Instead, they correlated best with changes in mitral valve configuration and mitral apparatus geometry at both ends of the tethered leaflets, including annular dilatation and posterior displacement of the papillary muscles (10).

Clinical implications. Patients with milder degrees of MR at rest who undergo coronary revascularization are not generally considered to require additional efforts to address the mitral valve. Yet, as this study demonstrates, patients with milder MR may actually have more severe regurgitation when provoked by exercise. These same authors have shown that such exercise–induced increases in MR are accompanied by increases in pulmonary artery pressure (39). These adverse exercise hemodynamics could potentially explain the clinical puzzle of patients who have exertional dyspnea out of proportion to their degree of dysfunction or MR at rest if exercise increases their MR and pulmonary pressures (assuming this scenario is not due to intermittent ischemia with “flash pulmonary edema”). Thus, assessing the true impact of ischemic MR often becomes a “moving

*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.

From the Cardiac Ultrasound Laboratory, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Supported in part by grants R01 HL38176, K24 HL67434, and K23 HL04504 of the National Institutes of Health, Bethesda, Maryland.

See page 1921
target,” engendering discussions among echocardiographers, surgeons, and anesthesiologists. The dynamic nature of ischemic MR can support the contention of some surgeons that decisions should not be based on MR assessment alone, given its dependence on load and volume, but rather on the appearance of restricted leaflet closure, which sets the stage for important MR. This study naturally leads to the question of whether exercise testing should be performed on all patients with ischemic MR. That will require further investigation, but we can anticipate that provocative testing could be most useful when the quantitative and clinical importance of MR are unclear, particularly when MR is mild to moderate at rest.

Is bypass alone sufficient to reduce ischemic MR? Although several studies demonstrate frequent persistence of ischemic MR after revascularization alone (34), others maintain that coronary bypass is sufficient therapy in most patients (40). Moreover, no approach currently predicts in which patients MR will resolve with revascularization alone. Exercise testing may be informative in this controversial decision. This study suggests that exercise-induced reduction in MR caused by improved motion of the inferior LV base would predict that revascularization alone is likely to reduce the MR. If MR persists or increases with exercise, however, the implications are not obvious. Evidence of myocardial viability with low-dose dobutamine could provide comparable information, but the decrease in LV volume with higher dobutamine doses may decrease tethering and MR without predicting lasting benefit off inotropic support (41).

Caveats. Patient position during exercise testing may also influence the degree of MR. This study evaluated MR during semi-supine exercise. As Kelbaek et al. (42) have shown, exercise ventricular volumes are smaller in the sitting than in the supine position, causing functional MR to decrease in the more upright position. However, Oshakken et al. (43) showed that LV end-systolic volume increased with supine exercise in patients with coronary artery disease; the decrease in volume seen in the patients of Lancellotti et al. (10) suggests that they resemble patients exercising in the sitting position (44,45). The increases in MR, therefore, cannot be simply ascribed to positional variation. The authors acknowledge the technical challenges of quantifying MR during exercise, with substantial limits of variation and standard deviations between observers and methods (39), and they recognize the limitations of applying the proximal flow convergence method at only one time point and velocity (30,46).

Clues to the cure. Returning to the principle that successful valve repair must address mechanism, this study provides further evidence for the decisive role of adverse mitral and ventricular geometry in the mechanism of ischemic MR. Increased MR with exercise is associated with greater tethering at both the annular and papillary muscle ends of the leaflets. Unbalanced tethering can therefore be addressed by papillary muscle repositioning, achieved by infarct plication (18,47,48), by external constraint applied to reverse LV remodeling locally (49,50), or by direct traction (51,52). Biventricular pacing can potentially reduce tethering (related to LV end-systolic volume) (53–55) as well as increase mitral valve closing force (56). Additionally, specific chordal modification can minimize mitral leaflet deformity and MR, either alone or combined with annular ring reduction (57). In summary, therefore, the dynamic changes in ischemic MR with exercise provide clues to increasing the effectiveness of therapy by addressing the geometric culprits.

Acknowledgment
The authors thank Shirley Sims for her excellent editorial assistance.

Reprint requests and correspondence: Dr. Robert A. Levine, Massachusetts General Hospital, Cardiac Ultrasound Laboratory, 55 Fruit Street, VBK 508, Boston, Massachusetts 02114. E-mail: rlevine@partners.org.
REFERENCES


45. Manyari DE, Kostuk WJ, Purves PP. Left and right ventricular function at rest and during bicycle exercise in the supine and sitting positions in normal subjects and patients with coronary artery disease. Am J Cardiol 1983;51:36–42.


