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EDITORIAL COMMENT

The Keys to Personalizing the Decision for Valvular Intervention in Secondary Mitral Regurgitation*

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Secondary or functional mitral regurgitation (sMR) is a disease of the left ventricle (LV) (which is enlarged, more spherical, and has impaired function) that alters the functioning of the mitral valve (which is tethered to the enlarged LV and may also have annular enlargement). On the basis of negative randomized trials (1,2) and many observational studies of addressing the mitral regurgitation (MR) (3), the main focus of therapy was previously the impaired LV. MR quantification was a secondary consideration to understanding the response and behavior of the LV. In the current era of successful percutaneous intervention for MR (4,5), the importance of accurate assessment of both parameters has become extremely important.

A number of techniques have been described for echocardiographic quantitation of MR (6), including effective regurgitant orifice area (EROA), regurgitant volume (RV), regurgitant fraction (RF), and vena contracta width. The last is simple, but most useful at the extremes of mild (<0.3 cm) and severe (>0.7 cm) MR (7), so the other 3 indices of regurgitation are most widely used. Measurement of the EROA using 2-dimensional imaging and color Doppler in sMR is laden with technical limitations and assumptions (8). Perhaps the 2 most important are that the proximal isovelocity surface area (PISA) measurements are supposed to be made on a hemisphere (which is rarely the case in sMR), and the size of the PISA varies during systole, because as the LV volume decreases, the tethered valve leaflets are able to settle into the annular plane, reducing MR (9). The accuracy of RV and RF calculations using the continuity equation is no less challenging, because area calculations are subject to measurement error and assumptions about the shape of inflow and outflow orifices (10). The use of 3-dimensional imaging to calculate the PISA and even directly measure the regurgitant orifice is possible, but presents challenges in temporal and spatial resolution (6). Cardiac magnetic resonance may provide another opportunity for MR measurement (11), but has yet to replace echocardiography. However, although much of the published reports address methodologic strengths and limitations of these techniques, there is a more fundamental issue in sMR, and that is that there is no consensus as to what defines sMR, severity. The European Society of Cardiology guidelines define severe sMR on the basis of an EROA of 20 mm^2 and RV of 30 ml (7). The American College of Cardiology/American Heart Association guidelines use similar cutpoints to primary MR (EROA 40 mm^2) (12), and the American Society of Echocardiography (13) uses an EROA of 30 mm^2 if the regurgitant orifice is elliptical (which it almost always is in sMR).

SEE PAGE 2506

In this issue of the *Journal*, Bartko et al. (14) seek to provide a solution to the controversy about thresholds for sMR. They assessed sMR using conventional quantitative parameters (EROA, RV, RF) in 423 heart failure patients taking guideline-directed medical therapy and followed them over 5 years. sMR severity was consistently associated with 5-year mortality, evidenced by a standardized hazard ratio of 1.42 (95% confidence interval [CI]: 1.25 to 1.63;

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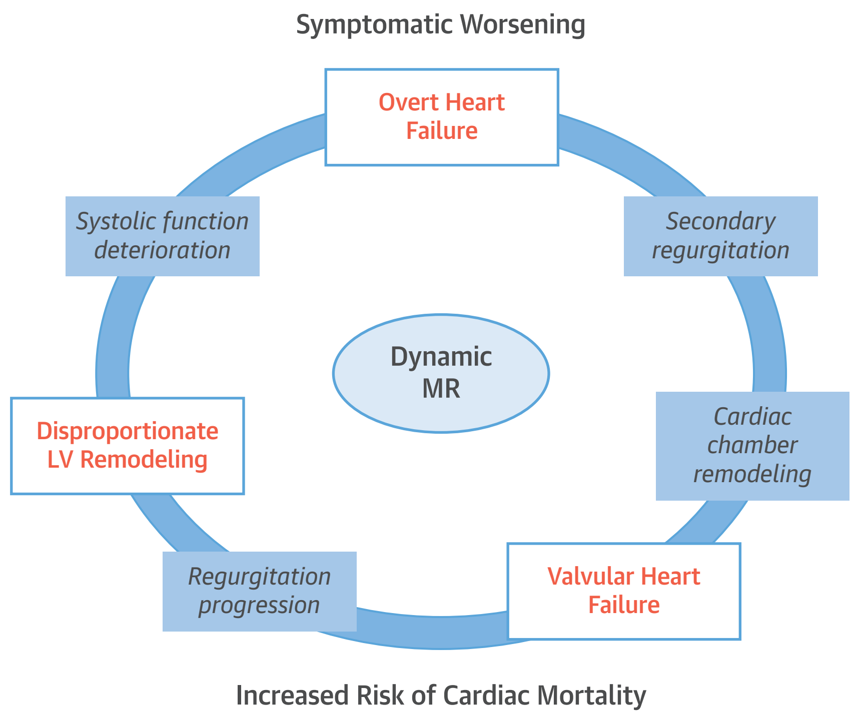
FIGURE 1 Ventricular and Valvular Contributions to sMR



LV = left ventricular; MR = mitral regurgitation; sMR = secondary mitral regurgitation.

$p < 0.001$) for EROA, 1.37 (95% CI: 1.20 to 1.56; $p < 0.001$) for RV, and 1.50 (95% CI: 1.30 to 1.73; $p < 0.001$) for RF, including after adjustment for clinical confounders. The use of spline curves showed a linear increment of risk, which they stratified as low risk (EROA <20 mm^2 and RV <30 ml), intermediate risk (EROA 20 to 29 mm^2 and RV 30 to 44 ml), and high risk (EROA ≥30 mm^2 and RV ≥45 ml). In the intermediate-risk group, a RF ≥50% was associated with poor outcome ($p = 0.017$). A combination of EROA, RV, and RF showed a significantly better discrimination compared with the currently established algorithms.

The attractive aspect of this work is that the investigators provide prognostic evidence to support their proposed cutoffs, albeit with the possibility of different interpretations of the spline curves. Although the patient recruitment for the successful COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) study was based on the American Society of Echocardiography criteria (4), and therefore included more severe MR than the French MITRA-FR study (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) (5), these trials also had differences in baseline medical therapy and LV function. The presence of incomplete guideline-directed therapy at baseline in the MITRA-FR study meant that both intervention and control patients could reverse-remodel. Thus, there is an increasing awareness of the need to distinguish the dominant contributor—valve or ventricle. In "proportionate" FMR (15), the LV end-diastolic volume (LVEDV) is in line with what would be expected to generate severe MR at a certain level of ejection fraction, in which case, steps to reverse remodel or otherwise improve the LV would be most effective. In "disproportionate" sMR or valvular heart failure (16), the severity of MR exceeds what would be expected for the degree of LV enlargement (**Figure 1**), and so the symptoms are driven by MR. This situation corresponds to the COAPT trial, where MR was 30% greater and LV volume 30% less than in the MITRA-FR study. By contrast, the MITRA-FR study failed, not just because the MR was mainly moderate, but in part because the LV was too remodeled to benefit from the procedure. In general, a favorable valve intervention might be expected with an EROA of 40 mm^2 if the EDV were <250 ml, and with an EROA of 30 mm^2 if EDV were <200 ml (15).

Precise noninvasive quantification of sMR and LV function are both difficult. In addition to both signals being influenced by each other, they are dynamic and load-dependent. However, the times of assessing sMR on the basis of the size of the color jet and a qualitative evaluation of LV function are over. We have powerful new tools for addressing this serious problem, but they need to be selected for the right people.

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