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EDITORIAL COMMENT

Redefining Severe Functional Mitral Regurgitation

Can We Reconcile Guideline Differences?*

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Grading the severity of functional mitral regurgitation (FMR) can be challenging because the mitral leaflets are typically normal, and many adjunctive findings (ie, left atrial dilation, blunted pulmonary vein systolic flow) could be attributed to the underlying left ventricular (LV) dysfunction rather than the MR itself. Hence, it is not surprising that there has been a disparity between US and European guidelines regarding specific cutoff values for defining severe FMR. A key to this difference is that MR could be considered severe based on the amount of MR or its effects on prognosis. The amount of MR can be assessed quantitatively by absolute (regurgitant volume [RVol]) or relative (regurgitant fraction [RF]) MR volume or the effective regurgitant orifice area (EROA), which is most commonly measured by the proximal isovelocity surface area method by echocardiography. Unfortunately, the validation of any imaging methodology for MR severity is hindered by the absence of a true gold standard. In 1997, the assessment of RVol and EROA by proximal isovelocity surface area (and volumetric echocardiography) were validated against biplane LV cineangiography (1). The optimal cutoff values to separate angiographic grades 1-4 were 0.2, 0.3, and 0.4 cm^2 for EROA and 30, 45, and 60 mL for RVol. Despite significant overlap between angiographic grades, these values became engrained in the guidelines as the defining parameters to distinguish grade 1 to 4 MR severity. However, ample data have shown that in FMR, lower quantitative values are associated with an adverse prognosis. A meta-analysis of 53 studies and almost 46,000 patients showed that any degree of FMR was associated with a worse outcome (2). Therefore, although US guidelines considered severe FMR to be an EROA of 0.4 cm^2, RVol of 60 mL, or RF of 50% (based on the amount of MR), European Union guidelines considered severe FMR to be an EROA of 0.2 cm^2 or RVol of 30 mL (based on prognosis). In FMR, lower values for EROA and RVol can be associated with an RF of 50% at smaller LV volumes or lower LVEF according to the Gorlin hydraulic orifice equation (3). Consider a patient with an LV end-diastolic volume of 200 mL and LVEF of 30%; the LV total stroke volume is 60 mL. It would be impossible to have regurgitant volume of 60 mL. Does that mean it is impossible to have severe MR in such a patient? Of course not. An EROA of 0.2 cm^2 and RVol of 30 mL would represent an RF of 50% and also be prognostically significant FMR. This example highlights the disparity between guidelines and illustrates how volumetric and prognostic parameters do not always align.

In this issue of *iJACC*, Benfari et al (4) present a retrospective analysis of a large cohort of patients from the Mayo Clinic that sheds light on this difficult issue and offers a potential solution that could reconcile the differences between guidelines. The authors reported clinical and echocardiographic data from 6,381 patients with FMR and class B or C heart failure (HF) with LVEF of <50% from 2003 to 2011.

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These patients were compared to 2,416 patients with degenerative MR (DMR). There are several key findings. First, the values for EROA and RVol were skewed to the left in FMR, with only 8% of patients having an EROA of ≥0.4 cm^2, compared to 38% of patients with DMR. Second, for every 0.10-cm^2 increment in EROA, there was a stepwise increase in mortality, confirming multiple prior studies. Third, the slope of the EROA-mortality relationship was much steeper in FMR than in DMR, confirming the current thinking that these are 2 very different diseases. Fourth, when adjusted for clinical covariates including LVEF, an EROA of ≥0.3 cm^2 showed a much higher HR for mortality (1.61 [95% CI: 1.41-1.86]) than lower values and was statistically significantly better than either the US or European guideline definitions for predicting mortality in this cohort. The authors suggest that based on these prognostic findings, the guidelines could be reconciled such that an EROA of ≥0.3 cm^2 (corresponding to grade 3 MR) should be considered severe FMR. The higher values in the US guidelines are likely specific but not sensitive for severe FMR; the lower values in the European guidelines are likely sensitive but not specific for severe FMR. Although this is hard to prove in the absence of a true gold standard, it fits hydrodynamic theory regarding the relationship of EROA to RVol and RF in FMR. Perhaps more importantly, basing FMR severity on prognosis avoids the difficulties inherent in volumetric or hemodynamic classification.

It is clear that EROA is a strong and independent predictor of mortality in FMR. However, there are limitations that must be acknowledged. FMR is dynamic, and the timing of the baseline echocardiogram may be important. Patients with acute decompensated HF may have severe FMR on hospital admission that improves dramatically with correction of volume overload, hypertension, rate control in atrial fibrillation, and so on. Presumably, baseline echocardiography is performed once the patient is in a stable hemodynamic condition, but this is difficult to ascertain in retrospective studies. Longitudinal studies demonstrating the persistence/resolution of MR severity are generally lacking in the medical literature. Although the group mean data for EROA are powerful, their application to individual patients depends on accuracy, reproducibility, and attention to technical details. For this reason, corroboration of EROA by other findings is recommended in all guidelines and was implemented systematically in COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial by using a tiered algorithm (5). The findings of the study by Benfari et al (4) apply to patients with Stage B and C HF; patients with Stage D advanced HF were excluded.

We agree with the concept of classifying significant FMR based on prognosis. However, baseline parameters that predict prognosis may differ from parameters that predict response to therapy. Many studies over the years have shown that treating conditions associated with an adverse prognosis do not necessarily improve outcomes. Examples include treatment of ventricular extrasystoles after acute myocardial infarction, oral inotropes in HF, raising high-density lipoprotein cholesterol, and many others. With regard to treatment of FMR, significant improvement in HF symptoms, LV function, and FMR severity have been documented with neurohormonal antagonists, coronary revascularization, cardiac resynchronization therapy, and transcatheter edge-to-edge leaflet repair (TEER). With regard to TEER, conflicting evidence from 2 randomized trials has generated controversy. In COAPT, which showed striking improvement in multiple endpoints, a tiered algorithm was used to define severe FMR (5). In tier 1, 86% of patients had an EROA of ≥0.3 cm^2 or pulmonary vein systolic flow reversal (common in severe DMR but not FMR). However, in MITRA-FR (Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial, which showed no difference between TEER and medical therapy, 52% of patients had an EROA of ≤0.3 cm^2. Although this provides indirect support for the idea that an EROA of ≥0.3 cm^2 should be used to define severe FMR, there are other hypotheses for the differences between these 2 trials. Optimization of neurohormonal antagonists was verified before randomization in COAPT but was not required in MITRA-FR. COAPT had considerably smaller LV volumes than MITRA-FR and excluded severe right ventricular dysfunction, severe tricuspid regurgitation, and severe pulmonary hypertension. In the study by Benfari et al (4), EROA alone was a predictor of mortality independently of LV size or function or of right heart disease. However, there was a trend ($P = 0.07$) for interaction with LVEF (assessed by quartiles) and a cubic spline analysis (Supplemental Figure 2 in the paper by Benfari et al [4]) showed a marked increase in mortality, with declining LVEF reaching a plateau below an LVEF of 20%. Thus, it is remains likely that LV size and function are important in deciding therapy. In another paper (6) in this same issue of *iJACC*, an artificial intelligence algorithm classified FMR into different phenotypes. The phenotype with smaller LV sizes and dilated left atria, consistent with

disproportionately severe FMR, had the worst prognosis with medical therapy (6). Patients with smaller LV sizes have less potential for significant reverse remodeling with medical therapy and therefore may benefit from earlier consideration of TEER (7). Thus, although EROA is a strong and independent predictor of FMR severity at baseline, there are likely different phenotypes of FMR that respond differently to the many treatment options available. This remains an important area for further investigation.

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