

EDITORIAL

Leaning Too Much on the Power of Proximal Isovelocity Surface Area? Don't Forget the Volumetric Method for Quantifying Functional Mitral Regurgitation

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The prognostic value of functional mitral regurgitation (FMR) is well established,¹ and the discordant findings of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation)² and the Mitra-FR (Multicenter Study of Percutaneous Mitral Valve Repair With MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) studies³ have generated significant interest in refining the echocardiographic assessment of FMR to reconcile the 2 studies^{4,5} and optimize selection of patients undergoing FMR who may benefit from transcatheter edge-to-edge mitral valve repair.

See Article by Igata et al.

The American Society of Echocardiography and the European Society of Cardiology guidelines recommend an integrated approach to grading the severity of mitral regurgitation (MR), which incorporates multiple semiquantitative and quantitative parameters, including estimated regurgitant orifice area (EROA), regurgitant volume (RVol), and regurgitant fraction (RF). EROA and RVol are most commonly derived by the

proximal isovelocity surface area (PISA) method, which is prone to inaccuracy because of geometric assumptions of a circular orifice area and spherical PISA shell that are often invalid in FMR.^{6,7} Furthermore, the PISA method does not account for the dynamic nature of FMR, which can have substantial temporal variability. In contrast, the volumetric method uses left ventricular (LV) volume measurements to calculate total stroke volume and the product of the LV outflow tract area and velocity time integral for forward stroke volume. Subsequently, the RVol is calculated as the difference between the total and forward stroke volumes, and the EROA is the quotient of the RVol and mitral inflow velocity time integral. Pitfalls of the volumetric method include underestimation of LV volumes by echocardiography and geometric assumption of the LV outflow tract as a circular area.

In this issue of the *Journal of the American Heart Association (JAHA)*, Igata et al compared the volumetric method with PISA for FMR quantification in a retrospective cohort of 177 patients with moderate to severe FMR of both ischemic and nonischemic cause with a mean follow-up of 3.7 years. The authors found that the PISA method produced larger values of EROA (0.18 versus 0.11 cm²), RVol (24.7 versus 16.9 mL), and

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RF (61% versus 37%) than the volumetric method.⁸ Interestingly, the quantitative measurements of MR were modest despite selecting for patients with overall moderate to severe MR. In terms of prognostic value of the 2 methods, a cutoff of EROA ≥ 0.2 cm² or RVol ≥ 30 mL was associated with increased risk of death or heart transplant only when measured by the volumetric method but not by PISA.⁸

The results of the study by Igata et al add to the body of evidence highlighting the deficiencies of PISA in quantifying FMR.^{6,9,10} Despite the absence of a “gold standard” for comparison, several clues support the possibility of overestimation of FMR with PISA. In the current study, PISA produced nonphysiologic regurgitant volumes in >10% of patients. Interestingly, a similar observation in an analysis of the COAPT study showed the average RF exceeded 100%, although this may also be attributable to underestimation of LV volumes.¹¹ Compared with cardiac magnetic resonance imaging, which may be more reproducible for volumetric quantification of valvular regurgitation,¹² echocardiography seems to systematically overestimate severity by PISA¹⁰ but not necessarily with the volumetric method.¹³ On the other hand, PISA could be expected to underestimate FMR because of the characteristic elliptical or crescentic regurgitant orifice,⁷ although this is not yet well validated.

Thus, the quantitative thresholds for MR severity should be considered in the context of these differences in EROA and RVol depending on method for estimation, particularly for FMR. By American Society of Echocardiography guidelines, severe MR is defined as EROA ≥ 0.4 cm², RVol ≥ 60 mL, or RF $\geq 50\%$,⁷ regardless of method or cause. On the basis of the potential prognostic value of a lower threshold (EROA ≥ 0.2 cm² or RVol ≥ 30 mL) for FMR¹ that has not been replicated in other studies,¹⁴ the European guidelines have adopted this lower threshold for severe FMR. Regardless, using cutoff values based on the EROA or RVol alone to grade MR may fail to capture its complexity given the degree of uncertainty in the derivation of these individual parameters.

To complicate matters further, EROA and RVol are influenced by adverse LV remodeling that serves as the catalyst for FMR, as well as hemodynamic loading conditions. The significance of a given EROA depends on the LV end-diastolic volume, just as the significance of a given RVol depends on the total stroke volume generated. Therefore, regurgitant fraction $\geq 50\%$, which normalizes the RVol to total stroke volume, is generally regarded as perhaps the best quantitative metric of severity in FMR.^{11,15,16} In the study by Igata et al, outcomes were unfortunately not compared according to RF, which could have provided further insight into the differences between the 2 quantification methods (PISA based versus volumetric).

In terms of prognostic value, Igata et al found that the volumetric method correlated with clinical outcomes, whereas the PISA method did not. This result could simply reflect overestimation of FMR by PISA and thus inclusion of lower-risk patients that satisfied the defined EROA and RVol thresholds. However, it is also possible that the volumetric method holds a more direct link to markers of LV remodeling and thus better risk-stratified patients, irrespective of whether it holds superior accuracy for MR quantification. Separating the contribution of MR severity from the degree of cardiac remodeling in determining prognosis in FMR remains a challenge. However, cardiac magnetic resonance imaging may provide further insight into this conundrum, given its capability for more accurate LV volumetric assessment, MR quantification, and myocardial tissue characterization that could hold additional prognostic value.¹⁷

In the modern era of transcatheter interventions, the indication for transcatheter edge-to-edge mitral valve repair has expanded to selected patients with heart failure with FMR, yet uncertainty persists with regard to optimal patient selection and timing of intervention. At the crux of the uncertainty is the fact that the optimal approach to quantify FMR and evaluate its deleterious impact on the cascade of LV remodeling remains elusive. Recent efforts to stratify patients by the “proportionality” of MR relative to the degree of LV remodeling, by indexing EROA or RVol to the LV end-diastolic volume, have not convincingly demonstrated a difference in transcatheter edge-to-edge mitral valve repair outcomes between so-called “MR proportionate” and “MR disproportionate” groups.^{4,5,18–20} The conceptual framework of MR proportionality seems logical, but the ways in which we quantitate both FMR severity and LV remodeling are imperfect. There is also probably more to the equation than MR proportionality, and the importance of other factors, such as LV myocardial fibrosis, pulmonary vascular remodeling, right ventricular function, and anatomic considerations, warrants further study.

In summary, the current study by Igata et al introduces a wrinkle into the fabric of our understanding of FMR quantification by highlighting potential pitfalls of FMR quantification by PISA and reminds us that quantitative echocardiographic parameters are but estimates dependent on method of derivation. Comprehensive echocardiographic assessment of MR leans not only on PISA and requires an integrative, multiparametric approach. Furthermore, quantitative parameters could have variable prognostic significance and capture limited snapshots of the complex interaction between LV remodeling and hemodynamic effects of FMR. Future clinical trials of transcatheter edge-to-edge mitral valve repair and other therapies for FMR should harness the opportunity to incorporate more

quantitative echocardiographic parameters, including volumetric quantification, to refine our understanding of not only FMR assessment but also the role for therapeutic intervention. Advanced imaging techniques with 3-dimensional echocardiography and cardiac magnetic resonance imaging may provide additional valuable insight into the phenotyping of FMR, beyond conventional 2-dimensional echocardiography, and should be explored in future prospective clinical trials.

ARTICLE INFORMATION

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Disclosures

None.

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