

EDITORIAL COMMENT

Advances in Risk Stratification of Chronic Aortic Regurgitation

Time for a Change in Guidelines?*

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Chronic aortic regurgitation (AR) typically has an insidious clinical course, with a prolonged asymptomatic phase where a progressive left ventricular (LV) remodeling takes place before the onset of symptoms and/or overt LV dysfunction.

In patients with severe AR, the development of heart failure symptoms and the drop of left ventricular ejection fraction (LVEF) are well-known negative prognostic markers and, thus, represent a Class I indication for aortic valve (AV) surgery according to current guidelines.^{1,2} Conversely, defining the appropriate timing for intervention in asymptomatic patients with severe AR and preserved LVEF remains challenging, with an ongoing controversy regarding the optimal triggers for surgical referral and their thresholds. In this subset, AV surgery is recommended in the presence of severe LV dilatation, defined by an LV end-systolic diameter (LVESD) >50 mm or LV end-systolic diameter index (LVESDi) >2.5 cm/m² (with a Class IIa or I indication according to American and European recommendations, respectively).^{1,2} However, this recommendation is supported by old and relatively small studies, and the development of a severe LV remodeling may indicate

an advanced and, at least partially, irreversible stage of the disease. Accordingly, later investigations identified an increased risk of mortality in asymptomatic patients with severe AR and preserved LVEF starting from LVESDi >2.0 cm/m².^{3,4} Based on these data, the latest European guidelines provide a Class IIa recommendation for AV surgery in patients reaching this threshold.¹

Thanks to the significant advances of surgical techniques in the modern era and the consequent decrease in surgical morbidity and mortality, management of asymptomatic patients with severe AR and preserved LVEF is evolving, with a shift toward an earlier surgical referral. In this context, the identification of more sensitive and accurate markers of cardiac damage has gained attention, and several imaging parameters have been proposed as potential triggers for early intervention, including LV global longitudinal strain⁵ and the quantification of extracellular volume fraction by cardiac magnetic resonance (CMR).⁶

Furthermore, recent echocardiographic and CMR studies suggest that LV volumes might provide a better risk stratification in comparison to LV linear dimensions regarding the decision-making for AV intervention.^{7,8} However, these retrospective investigations were performed in mixed cohorts including patients with or without symptoms or LV dysfunction.

Echocardiography is the main imaging technique for the assessment of AR severity and quantification of LV dimensions and LVEF, because it is widely available, safe, suitable for serial examinations, and cost-effective. Notwithstanding the well-known strengths of echocardiography, CMR application is steadily growing because, on the one hand, it has more widespread availability, and on the other hand, data acquisition and analysis are faster and more

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standardized. Notably, in the setting of chronic AR, CMR may offer important advantages compared with echocardiography.^{7,9} In fact, CMR provides a better definition of myocardial borders and blood-tissue interfaces, and thus enables more accurate and reproducible measurements of LV size and function.^{7,9} Additionally, the quantification of forward and reverse flows in the ascending aorta using phase contrast technique enables a better accuracy and reproducibility of the AR grading.⁹ Late gadolinium enhancement and T₁ mapping sequences may also provide information on tissue characterization and myocardial fibrosis quantification. Despite this, current evidence on the prognostic value of CMR data in patients with chronic AR are still limited.

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In this issue of the *Journal of the American College of Cardiology*, Malahfji et al¹⁰ sought to evaluate the prognostic impact of CMR quantitative parameters of LV remodeling and AR severity and to define their optimal thresholds to guide management of patients with chronic AR. This retrospective and multicenter study included 458 *asymptomatic* patients with chronic moderate or severe AR and preserved LVEF (>50%), derived from the Society for Cardiovascular Magnetic Resonance Registry. The primary study endpoint was a composite of the following: development of symptoms, LVEF <50%, guideline-recommended thresholds of LV dilation (left ventricular end-systolic diameter [LVESD] >5 cm, LVESDi ≥ 2.5 cm/m², or LV end-diastolic diameter >6.5 cm) or death under medical management. A secondary study endpoint was also evaluated excluding the referral to AV surgery for LV dilation. During a median follow-up time of 2.4 years, 133 subjects met the primary endpoint. Of importance, indexed LV volumes demonstrated a superior risk discrimination for outcomes than LV linear dimensions. Values of LV end-diastolic volume index higher than 109 mL/m² and of LVESVi higher than 43 mL/m² were identified as optimal cutoffs for prognostic stratification. In line with the current literature,^{3,4} a lower threshold of LVESDi in comparison to the one recommended by the American guidelines (>2.0 cm/m² vs >2.5 cm/m²) was associated with an excess risk of meeting the study endpoint. Moreover, in multivariable models, only indexed LV volumes and not LVESDi were independently associated with the secondary study endpoint (ie, excluding surgical referral for LV dilation). Of interest, one-fourth of the study population fall in discordant categories of

LV end-systolic volume index (LVESVi) and LVESDi (one above and the other below the optimal threshold) and, in this subgroup, only the presence of an increased LVESVi was associated with worse outcomes.

Regarding quantitative parameters of AR severity, regurgitant volume above 47 mL and/or regurgitant fraction (RF) higher than 43% were associated with an increased risk of the primary study endpoint. Interestingly, these thresholds are considerably lower in comparison to conventional cutoffs derived from echocardiography and suggested by current recommendations (regurgitant volume of 60 mL and RF of 50%). This evidence confirms and expands recent CMR data reported by Vejpongsa et al¹¹ comparing LV remodeling in patients with isolated AR or isolated mitral regurgitation and similar regurgitant severity. They found smaller thresholds of AR severity (regurgitant volume >38 mL and RF >35%) associated with the development of symptoms and LV remodeling compared with isolated mitral regurgitation or currently recommended cutoffs.¹¹

Despite the important information provided, some relevant limitations of the present work need to also be acknowledged. Given the retrospective design, these findings should be considered hypothesis-generating and warrant further work. Indeed, selection biases in the referral of patients for CMR as well as in the decision to undertake AV surgery can have influenced the study results. Moreover, in more than one-half of patients who reach the composite study endpoint (66 of 133), the onset of symptoms was the surgical indication, whose evaluation by the clinicians is prone to subjectivity. Data on exercise testing and N-terminal pro-B-type natriuretic peptide may have been informative in this setting; nevertheless, their role in decision-making regarding AV intervention is not clearly defined by current international guidelines. Echocardiographic data were not systematically collected; thus, the correlation between LV remodeling parameters evaluated by the 2 imaging modalities has not been investigated. However, the agreement on AR severity evaluated by echo and CMR was weak. Finally, the investigators did not detect significant differences in the study outcomes between sexes, but this may be related to the large prevalence of men in the study population and the low statistical power of subgroup analysis. Thus, whether sex-specific thresholds of LV remodeling may improve risk stratification in patients with chronic AR and preserved LVEF may deserve further investigations.

In conclusion, this important and well-conducted study is the largest work evaluating CMR quantitative determinants of outcomes in patients with AR and, in line with recent evidence, supports the need to reassess surgical thresholds in asymptomatic patients with severe AR and preserved LVEF. The further validation of these data, ideally in the setting of a randomized controlled trial, would provide much needed evidence to update indications for timing of intervention in AR, with the ultimate goal of delivering adequate and tailored therapies thus improving patients' outcomes.

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