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EDITORIAL COMMENT

Straining for New Prognostic Predictors in Asymptomatic Severe Aortic Regurgitation*

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The optimal timing of surgery for chronic severe aortic regurgitation (AR) in asymptomatic patients with preserved left ventricular ejection fraction (LVEF) remains elusive. To aid in clinical decision-making, sensitive surveillance parameters that mark the critical tipping point when surgical risks are outweighed by long-term benefits of intervention are necessary. Guideline-based recommendations for timing of surgery in cases of asymptomatic severe AR fall within class IIa/IIb categories and continue to rely on LV dimensions (1). However, a review of supporting evidence is a sobering exercise, revealing a few small studies, most of which were conducted more than 2 decades ago (1).

Mounting evidence from a growing body of contemporary data strongly argues for a re-examination of surgical thresholds for severe asymptomatic AR. First, long-term outcomes of conservatively managed asymptomatic severe AR in clinical practice may not be as benign as was previously observed in natural history studies which enrolled a mostly young and healthy cohort of patients (2). Furthermore, there have been advancements in standard and novel surgical techniques and post-operative care that have resulted in lower surgical risks and therefore have minimized the risk of earlier surgical intervention (3,4), Additionally, there are emerging data for more sensitive diagnostic markers of subclinical myocardial dysfunction when patients are still in a "compensated" state which may predict worse outcomes if surgery is further delayed (5,6).

LV global longitudinal strain (LV-GLS) is a promising diagnostic and prognostic tool in patients with severe AR, capable of detecting early impairments in myocardial mechanics which precede decreases in LVEF (7,8). The state of chronic pressure and volume overload of chronic severe AR results in progressive myocardial fibrosis which has been shown to have an inverse correlation with post-surgical LV functional improvement and an association with worse long-term survival (9). Although subendocardial fibrosis is enough to cause changes in LV-GLS, decreases in LVEF occur once fibrosis is more extensive (10). Hence, by the time there is a decrease in LVEF, irreversible myocardial remodeling has likely already occurred. LV-GLS, having been widely accepted as a more sensitive marker of LV dysfunction and a better predictor than LVEF in a multitude of disease processes, is already being used in a variety of clinical settings (11). Although the clinical use of LV-GLS in cases of asymptomatic severe AR has been studied only in a small number of retrospective, observational studies, worsening LV-GLS has been associated with the need for eventual aortic valve replacement and long-term mortality in patients with preserved LVEF (12,13).

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In this issue of *iJACC*, the study by Alashi et al. (14) adds to the evidence supporting the predictive value of LV-GLS in cases of "compensated" chronic severe AR. The investigators retrospectively studied a cohort of 865 patients with asymptomatic or mildly symptomatic significant AR (grade≥3+) and preserved LVEF (≥50%) who underwent aortic valve surgery; the primary outcome was mortality. The authors found that baseline LV-GLS worse than -19%, a threshold value they defined by their prior work (13),

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was associated with reduced survival. Among patients who survived aortic valve surgery, a subgroup of 285 patients had repeat echocardiograms at 3 to 12 months postoperatively. A state of persistently impaired LV-GLS (or a worsening of LV-GLS by 5 percentage points from baseline) on follow-up studies was associated with increased mortality.

Alashi et al. (14) are to be commended for performing this study which is the first to assess the role of baseline and follow-up LV-GLS after aortic valve surgery in this patient population. Their study makes a valuable contribution to the knowledge that LV-GLS may identify patients with early myocardial dysfunction who may benefit from surgery despite having normal LVEF and LV dimensions. The sample size is one of the largest that has been studied on this subject. Despite the study's inherent limitations (single-center and retrospective design), it establishes an association between LV-GLS and long-term survival after aortic valve surgery. More important, the study advances the prospect of using LV-GLS in timing aortic valve surgery in patients with asymptomatic AR. Although the results are convincing, the generalizability of the study findings is limited by several factors. First, the relatively low surgical risk reported in this study cannot be extrapolated to patients being treated at all other centers. The study institution itself, which is a high-volume "Valve Center of Excellence" with low operative and postoperative mortality, may invite the question whether GLS can be widely used to determine timing for surgery in asymptomatic AR patients in less expert institutions. Notably, a significant number of surgeries in this study consisted of aortic valve repairs and used minimally invasive techniques which, although associated with lower surgical risk than standard aortic valve replacement, have not been widely adopted in general practice. Second, indications for surgical intervention were diverse, most of which were performed for aortic rather than aortic valvular pathology, which may confound the results. Third, the LV-GLS cutoff value of -19% was a single-software derived value from data published in an earlier study from the same authors investigating an overlapping cohort of patients as the current study (13). Although the use of GLS may be applicable to other populations with AR, this particular threshold may not apply.

Nonetheless, the present study is an important building block toward establishing the evidence base of LV-GLS as a decision-making tool in timing aortic valve surgery in patients with asymptomatic chronic AR and normal LVEF. Future studies are needed to establish the fact that surgical intervention on the basis of LV-GLS can positively alter the natural history of severe asymptomatic AR and that any long-term survival benefit would outweigh the immediate risk of a surgical intervention in most settings. Unfortunately, a prospective, controlled (randomized or nonrandomized) trial is difficult in this arena because most asymptomatic patients would be reluctant to undergo a major surgical intervention for an indication that has not been well established. However, with robust multicenter validation of the prognostic use of LV-GLS across a broad spectrum of patient populations, vendors, and acquisition methods, following LV-GLS for surveillance in asymptomatic severe AR patients with normal LVEF and dimensions may prove to be a valuable tool for clinical decision-making.

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