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EDITORIAL COMMENT

Should Left Atrial Size Influence the Decision to Intervene in Degenerative Mitral Regurgitation?*

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Much has been written about the structural heart remodeling and hemodynamic effects of significant mitral regurgitation (MR) and its prognostic indicators (1-4). Clinically, most patients with significant degenerative mitral regurgitation (DMR)—unless it was caught during an acute presentation with a fail leaflet or ruptured papillary muscle—have had the regurgitant lesion for some time, such that the left ventricle (LV) and left atrium (LA) have already undergone remodeling, with a consequent rise in pulmonary pressure and associated right heart dysfunction. Early animal studies elegantly established how the LA adapts to the volume overload caused by the induction of severe MR, with a gradual decrease in LA pressure and physical enlargement taking place within weeks (5). LA size has thus traditionally been considered an indicator of regurgitation severity.

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In fact, several studies that evaluated LA enlargement with M-mode or, more recently, with 2-dimensional echocardiography have found associations between greater LA size and worse prognosis (4,6,7). The key question, however, is whether severe LA enlargement portends a worse prognosis in DMR independent of other parameters. A new study by Essayagh et al. (8) in this issue of the *Journal* addresses LA size in DMR and its prognostic and management implications.

THE CURRENT STUDY

In brief, the authors evaluated a large cohort of 5,769 consecutive patients with DMR at the Mayo Clinic who were followed for close to 10 years. They documented clinical characteristics and echocardiographic data at baseline; the clinical outcome they evaluated at follow-up was all-cause mortality. LA size was quantitated and analyzed as a continuous variable and categorized at 3 levels of severity ($<$40, 40 to 59, and $\geq$60 ml/m^2), with normal size being 27 $\pm$ 7 ml/m^2. As expected, patients with very severe LA enlargement ($\geq$60 ml/m^2) had the most severe MR (71% severe; 34% flail), along with larger LV and more atrial fibrillation, pulmonary hypertension, and tricuspid regurgitation. It's worth noting that nearly every parameter evaluated (24 of 26; Table 1 in their paper [8]) differed between the 3 groups, and that patients in the very severe category were roughly 1 decade older than patients in the other groups and were more likely to be male. (Curiously, the study did not assess the incidence of coronary artery disease, previous myocardial infarction, hypercholesterolemia, or diabetes.) The authors evaluated prognosis using one model adjusting for clinical variables and another with additional adjustment for LV function, symptoms, and MR grade. Increasing LA size was clearly associated with worse survival; this relationship was attenuated with increasing adjustments, but remained significant. In patients with atrial fibrillation who were analyzed separately, greater LA size still correlated with worse prognosis, although the hazard ratio was lower compared with sinus rhythm for the degree of LA enlargement.

This study builds on the group's previous observations and that of others linking lower survival to LA enlargement drawn from the Mayo Clinic database

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and the MIDA (Mitral Regurgitation International Database) (4,6,7,9). The new data also demonstrate the close inter-relation of LA size and other variables with the severity of MR, which is not surprising given what we know of the pathophysiology of the disease. The significance of this study lies in the large number of observations and extended follow-up that the authors were able to achieve.

LA SIZE AND PROGNOSIS: AN INDEPENDENT RISK?

If LA size is an independent prognostic parameter in DMR, what would be plausible mechanisms for such adverse outcomes? LA size has been shown to be an important prognostic indicator in a wide spectrum of cardiovascular diseases, from acute myocardial infarction to hypertension and cardiomyopathies. In contrast to LV size, the LA enlarges in response to LA pressure and/or volume load (10); thus, LA size is 1 of the criteria for LV diastolic dysfunction (11). Severe LA enlargement in DMR could therefore reflect the combined severity of MR and myocardial remodeling of both LA and LV, possibly providing an early sign of heart failure. In fact, in the current cohort, LV systolic dysfunction in many patients with ≥60 ml/m^2 may be masked, as their LV ejection fraction in the setting of significant MR was similar to those with mild degrees of MR—on average, just above 60%. On the other hand, greater LA size is implicated in the pathophysiology of atrial fibrillation through increased stretch, interstitial fibrosis, and electrical vulnerability (12). Atrial fibrillation may worsen heart failure or predispose to systemic or cerebral emboli and bleeding complications in patients requiring anticoagulation. It is interesting to note that in patients who underwent valve surgery, severe LA enlargement was no longer an independent prognosticator (8), which raises doubt as to whether LA size is truly an independent risk factor. Nevertheless, the prognosis of patients with ≥60 ml/m^2 was worse than those with smaller LA, likely pointing to other effects of longstanding significant MR.

In the current study, having only a baseline assessment, a long-term follow-up without interim evaluation, and an *all-cause* mortality as the sole outcome measure limits our ability to understand the underlying mechanism of increased risk associated with progressively larger LA (8). Additional data more specific to cardiovascular outcomes, including cardiac events and heart failure hospitalizations, would have strengthened the inferred causal relation of LA size to mortality. Last, given the significant differences in baseline characteristics among the different groups of LA size in nearly every parameter, statisticians would acknowledge that one cannot adjust for all factors. The independence of LA size as a risk factor, although plausible, can thus not be completely ascertained.

IMPLICATIONS FOR DMR ASSESSMENT AND MANAGEMENT

None of this takes away from the fact that this is the largest series of DMR patients to be studied with echocardiographic measurements to address the prognostic role of LA volume among other parameters. While questions remain regarding whether LA size is an *independent* risk predictor in DMR, there is no denying that increasing LA size, particularly when very severe (> twice normal), carries a poor prognosis. In DMR, this prognosis could be related to MR severity and its duration, LV dysfunction (overt or masked systolic/diastolic), atrial fibrillation, or pulmonary hypertension/right sided dysfunction, among other possibilities. Furthermore, a severely enlarged LA will predispose the heart to atrial fibrillation, adding cardiovascular risk.

In my view, there are 2 implications for LA size in chronic DMR. First, a very severely enlarged or enlarging LA should be considered a sensitive though less-specific marker of significant MR in the overall assessment of the heart's adaptation to volume overload. Transthoracic echocardiography is the first-line diagnostic modality to evaluate the etiology and severity of MR. Because MR assessment by color Doppler may be difficult in DMR with very eccentric jets and poorly visualized valves, a severely enlarged LA in this situation, particularly in sinus rhythm, should prompt further evaluation with either transesophageal echocardiography or cardiac magnetic resonance imaging (13).

The second implication is the timing of intervention on the mitral valve. Guideline recommendations for valve surgery take into account several factors in patients with severe DMR, including symptoms, ventricular remodeling and function, atrial fibrillation, pulmonary hypertension, and feasibility of repair. Currently, the American College of Cardiology/American Heart Association guidelines do not single out LA size as a trigger for intervention in severe DMR (1), whereas the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines mention an LA size ≥60 ml/m^2 in sinus rhythm as a Level IIA recommendation (based on an earlier, smaller cohort) (2). With the current study, and in line with previous data, addition of such a recommendation to the American College of Cardiology/American Heart Association guidelines would be

appropriate. It would not be as a sole recommendation, but instead similar to and within the same category as the current triggers of new-onset atrial fibrillation and pulmonary hypertension in the asymptomatic patient (1). These triggers are conditional on the presence of both severe MR (to increase specificity) and the high feasibility of MV repair (if earlier intervention is targeted). Although it is unlikely we could evaluate the overall cardiovascular outcome of such an approach in a randomized trial, large registries and databases would help shed light on the effects of such adjustments in practice.

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