

EDITORIAL COMMENT

The Case for Measurement of Left Atrial Strain in Patients With Mitral Regurgitation*

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Left atrial (LA) strain is an important measurement that provides insight into LA mechanical properties. It has been associated with left ventricular (LV) diastolic function indexes by Doppler echocardiography as well as outcome events in patients with several cardiovascular diseases.¹ However, there is a paucity of data on LA strain in patients with mitral regurgitation (MR). Some questions to answer include the following: How does MR in and of itself affect LA strain? Is the effect of MR on LA strain modulated by other variables? Is LA strain related to clinical outcomes? What is the effect of MR correction by transcatheter edge-to-edge repair (TEER) on LA strain? and Should we routinely measure and report LA strain?

HOW DOES MR AFFECT LA STRAIN?

First, let us define LA strain. There are 3 components of LA strain that can be measured: reservoir, conduit, and pump or contractile strain.¹ The one that is affected first by MR is left atrial reservoir strain (LARS). LARS is a measure of the change in LA systolic expansion relative to the LA minimum volume that occurs at end diastole.

Significant MR results in an increase in LA systolic expansion, and until the LA minimum volume increases, significant MR would be expected to lead to an increase in LARS. With progressive LA enlargement, LA volumes, including the minimum volume,

increase. When the increase in the LA minimum volume matches the increment in LA systolic filling caused by MR, LARS decreases and falls in the normal range again. The previously described framework holds true if one is looking solely at MR and not other factors that affect LA filling as well as the changes in LA function that affect the LA minimum volume. For example, in patients with obstructive hypertrophic cardiomyopathy and MR secondary to pathologic changes that occur in obstructive hypertrophic cardiomyopathy, after successful treatment of obstruction with mavacamten, MR regurgitant volume decreases at a time when the LA minimum volume has not decreased proportionally, and LARS decreases. However, after comprehensive analysis of LA and LV functions, the decrease in LARS was not caused by the reduction of the MR regurgitant volume but rather the direct adverse effects of the drug on LA function.²

HEMODYNAMIC DETERMINANTS OF LA STRAIN IN PATIENTS WITH MR

Despite the growing interest in LA strain, there are few studies that have examined the hemodynamic determinants of LA strain. The clinical investigations were performed in patients with primary MR or MR in the setting of obstructive hypertrophic cardiomyopathy.^{3,4} The main determinants of LARS in patients with primary MR are the hemodynamic factors that affect LA filling during LV systole, namely LA relaxation, LA operating chamber stiffness, and LV systolic long-axis function, which can be captured by LV global longitudinal strain (GLS).³ With the longstanding duration of significant MR, these 3 variables change in a direction that leads to a decrease in LARS. Thus, LA relaxation (and systolic function) becomes worse, leading to a higher LA pressure in early systole and decreasing the pressure gradient for flow from the pulmonary veins into the left atrium.

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Likewise, LA operating chamber stiffness increases, likely because of the development of interstitial fibrosis.⁵ The increased LA stiffness leads to higher LA systolic pressure for any given LA volume and again lower pressure gradient for flow between the pulmonary veins and the left atrium. Lastly, when LV decompensation occurs, LV systolic function and GLS decrease, leading to a decrease in LA expansion in the LA long-axis direction.

IS LARS ASSOCIATED WITH OUTCOME EVENTS IN PATIENTS WITH MR?

Again, there is a paucity of data to rely on in trying to answer this question. Stassen et al⁶ reported an independent association between significant MR and reduced LARS in 666 patients with more than mild secondary MR. The survival rates at 1, 2, and 5 years were significantly worse in patients with secondary MR and LARS <9.8% vs those with LARS ≥9.8%. Of note, LARS at 9.8% indicates an advanced degree of LA dysfunction. Importantly, the difference in 5-year survival was markedly worse in patients with LARS <9.8% (45% vs 78%). In this series, LARS provided incremental prognostic value over LA volume and LV GLS. In another study that included 338 patients undergoing surgical mitral valve repair, LARS had an independent association with the cardiovascular events of all-cause mortality, new-onset atrial fibrillation, and rehospitalizations. The optimal LARS cutoff value for that study was 23.6%.⁷

TEER AND CHANGES IN LARS

The consensus of the existing literature indicates that as a group TEER results in no significant change in LARS in patients with primary MR.^{3,8,9} However, the individual response is highly variable, with some patients showing no change in LARS and others showing a decrease or an increase. In 1 study, the decrease in LA operating chamber stiffness after TEER was the only variable that was different between patients with and without an improvement in LARS.³ Interestingly, whether at baseline or after TEER, LARS was not related to LA “V”-wave pressure or its magnitude of change after TEER.⁹ How about the effects of TEER on LARS in patients with secondary MR?

THE CURRENT STUDY

In this issue of *JACC: Cardiovascular Imaging*, Pio et al¹⁰ report on the effects of TEER on LARS in 347 patients with significant secondary MR who were

enrolled in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy) clinical trial. The primary objective of COAPT was comparing the effects of TEER + optimized guideline-directed medical therapy (GDMT) with GDMT on outcomes in patients with moderately severe and severe secondary MR. LARS measurements were obtained at baseline and 6 months after TEER. Both groups had markedly reduced LARS values (10.5% ± 3.8% in TEER + GDMT vs 13.8% ± 4.8% in GDMT). The authors looked for LARS improvement in the 2 groups, which was defined by a 15% increase from the baseline. About 60% of the patients randomized to TEER showed an improvement in LARS vs the 40% LARS improvement observed in the GDMT group. Patients without LARS improvement had larger ventricles and higher baseline LARS but similar MR severity and LA volumes to patients with an improvement in LARS. LARS improvement was significantly associated with the combined endpoint of death and heart failure hospitalizations assessed between 6 and 24 months. LA strain improvement conferred similar risk reduction for the endpoints for the patients in the 2 groups. On multivariable analysis, all-cause mortality and heart failure hospitalization risk were reduced by LA strain improvement, TEER treatment, and higher baseline LV ejection fraction, whereas severe MR conferred a higher risk (Table 5).¹⁰

The study presents important novel findings about TEER and LARS changes in patients with secondary MR. The conclusions are well supported by the results. The authors clearly state the limitations, namely post hoc analysis, selection bias, LARS acquisition with different ultrasound systems, and the need for validation in a separate population. This interesting report leaves us with important unanswered questions that could not have been addressed given the study design. Why does LARS improve after TEER or in heart failure patients who are on GDMT? Is the improvement determined by an improvement in LA function? Is the likelihood of improvement already determined before any treatment is initiated based on the burden of LA fibrosis as postulated by the authors? If it is indeed LA interstitial fibrosis that is determining the improvement or lack thereof in LARS, can it be reversed based on the effectiveness and duration of successful treatment as is the case for the left ventricle? What is the impact of change in LV systolic function after the reduction of MR on the change in LARS? Interestingly, LARS improved in the GDMT group where MR was not as effectively treated

as in patients who received TEER + GDMT. This suggests that the proper prescription and dosage of GDMT have favorable effects on LA function.

SHOULD WE MEASURE LA STRAIN IN ROUTINE CLINICAL STUDIES?

This is a rapidly advancing field. There are several diseases other than MR for which LARS has proven useful.¹ One can predict the addition of MR to the existing list. The exact role of LARS in guiding the timing of MR treatment or in outcomes prediction after treatment will only become evident after additional studies become available, preferably as multi-center registries. In parallel, LARS acquisition and

measurement should be embraced in the clinical arena to avoid the gap between the growing scientific evidence and the inability to apply that evidence in day-to-day patient care.

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