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EDITORIAL COMMENT

Global Longitudinal Strain in Asymptomatic Chronic Aortic Regurgitation

The Missing Piece for the Watchful Waiting Puzzle?*

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Chronic aortic regurgitation (AR) is an insidious entity and associated with progressive volume and pressure overload on the left ventricle (LV). Patients with chronic severe AR typically have a prolonged and indolent asymptomatic course where progressive LV remodeling takes place before the onset of symptoms and/or LV dysfunction. Importantly, disease progression and the subsequent remodeling response are heterogeneous and not entirely explained by the hemodynamics. This phenomenon provides the opportunity to individualize risk stratification among asymptomatic patients with chronic AR.

For asymptomatic patients with chronic severe AR (stage C), the current valvular management guidelines recommend pre-emptive aortic valve replacement (AVR), when signs of LV decompensation are present, manifest by either a decrease in systolic function (left ventricular ejection fraction [LVEF] <50%) and/or dilation (LV end-systolic diameter index >2.5 cm^2/m^2) (1). However, one could argue that those findings, mostly derived from small and older studies, might already represent an advanced stage of the disease process. Indeed, in a recent publication, investigators from the Cleveland Clinic group challenged the current guideline thresholds. In a contemporary appraisal, the authors identified an increased mortality risk in mostly asymptomatic patients with chronic severe AR, and preserved LVEF >55%, starting at a lower threshold of LV end-systolic diameter index (>2.0 cm^2/m^2) than recommended in current guidelines (2).

Exercise testing has an important role for such asymptomatic patients and is recommended to determine symptom response and objectively assess functional capacity. Lower peak oxygen consumption and exercise capacity seem to be linked with elevated resting pulmonary capillary wedge pressure (3) and elevated N-terminal pro B-type natriuretic peptide (4). The potential role of biomarkers in asymptomatic patients is not currently addressed in the guidelines (1). Although elevated levels of natriuretic peptides may presage the onset of LV decompensation in chronic AR (4) and may be able to provide incremental risk stratification (5–7), larger, multicenter studies are needed to establish their prognostic role in the decision-making process.

Global longitudinal strain (GLS) evaluation using 2-dimensional echocardiography is a promising technique that has gained a lot of interest (8). It seems that GLS is a more sensitive marker of incipient LV dysfunction in many valvular diseases, including patients with chronic AR (9–14). However, these studies have had a short follow-up duration and have used a variety of endpoints including 1-year survival, need for AVR, changes in LV dimensions, and improvement of symptoms. As such, whether GLS might provide superior risk discrimination in patients with chronic AR and preserved LVEF regarding the timing for aortic valve intervention remains unclear. Even when only patients with preserved LVEF are considered, GLS values show marked heterogeneity, perhaps reflecting the preload and afterload dependence of GLS.

In this issue of *iJACC*, Alashi et al. (15) sought to evaluate the incremental role of GLS in asymptomatic patients with chronic severe AR but preserved LVEF and nondilated LV (LV end-systolic diameter

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index <2.5 cm^2/m^2). Such patients, according to current guidelines, should not have prophylactic AVR. This study sought to determine whether: 1) the assessment of baseline GLS offered the opportunity to risk stratify such patients; 2) this would this be equally relevant for those that received early AVR versus those who were followed conservatively; and 3) the association of GLS with outcome with all-cause mortality would be independent of potential competing risks.

This study builds on prior literature that suggested that GLS would have incremental prognostic value for all-cause mortality. Patients with GLS below the median (−19.5%) were more likely to have a shorter survival and this was seen mostly in patients who did not undergo AVR. However, early AVR was associated with significant survival improvement regardless of the baseline GLS and/or LV dimensions. When the authors compared patients with GLS better than median who received AVR with those with preserved GLS but who did no undergo AVR, there was a 2-fold increased mortality (8% vs. 15%; $p = 0.08$), which did not attain statistical significance given the smaller subgroup size, reflective of a type II error. Importantly, GLS remained independently associated with all-cause mortality (hazard ratio: 1.11 per 1% decrease; $p = 0.003$) after multivariate Cox proportional hazards model adjustment and provided incremental prognostic value to the clinical model.

In this large cohort, GLS was feasible in >90% of patients. Adequate training and proficiency is required to improve GLS evaluation (16,17). The same can be said about measuring 2-dimensional LVEF and linear dimensions, which may have even greater measurement variability (18,19). Intervendor and intersoftware variability has improved for GLS, but differences remain and sequential follow-up still warrants the use of the same equipment (20).

Should this study change the guidelines for the evaluation of asymptomatic patients with chronic severe AR? The establishment of risk association is probably insufficient for this purpose, so we should consider the main findings to be hypothesis generating. We need a large, multicenter, prospective, randomized, controlled trial testing the hypothesis of whether using GLS and lower LV dimensions (or LV volumes) cutoffs can provide incremental value in the risk stratification of asymptomatic patients with severe chronic AR. Thus, the important observations in this retrospective study warrant further work. Despite multivariable adjustment, there is a potential for unmeasured selection biases in the decision to undertake AVR. Nonetheless, the main driver of early AVR in this cohort was the associated aortopathy, surgery for which was more aggressive than currently supported by the guidelines (1). In addition, the characteristics and outcomes of those patients in whom GLS was not feasible for measurement is unknown, and this could be equally informative. Whether interval changes of GLS before and after AVR would have a prognostic value also remains unknown.

In conclusion, this important and well-conducted study provides evidence of the prognostic role of GLS as a practical bedside tool in the risk stratification of patients with chronic severe AR. There are several take-home messages. First, GLS assessment joins a number of parameters, including exercise capacity, biomarkers, and comorbidities (in particular pulmonary hypertension) that should be performed in echocardiographic evaluation of AR (17), and it may help the decision-making process regarding surgical timing. Second, one cannot conclude that in asymptomatic patients with chronic severe AR and normal LVEF and LV dimensions, having preserved GLS in isolation is yet an adequate risk stratification method in providing reassurance of a continued watchful waiting strategy. Early AVR seems to be more protective than having a preserved GLS. Perhaps removal of the continued hemodynamic insult of AR might halt unfavorable changes of incipient LV decompensation, which translates into improved outcomes.

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REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

2. Mentias A, Feng K, Alashi A, et al. Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction. J Am Coll Cardiol 2016;68:2144–53.

3. Boucher CA, Wilson RA, Kanarek DJ, et al. Exercise testing in asymptomatic or minimally symptomatic aortic regurgitation: relationship of left ventricular ejection fraction to left ventricular filling pressure during exercise. Circulation 1983; 67:1091–100.

4. Broch K, Urheim S, Massey R, et al. Exercise capacity and peak oxygen consumption in asymptomatic patients with chronic aortic regurgitation. Int J Cardiol 2016;223:688–92.

5. Pizarro R, Bazzino OO, Oberti PF, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe

aortic regurgitation. J Am Coll Cardiol 2011;58:1705–14.

6. Weber M, Hausen M, Arnold R, et al. Diagnostic and prognostic value of N-terminal pro B-type natriuretic peptide (NT-proBNP) in patients with chronic aortic regurgitation. Int J Cardiol 2008;127:321–7.

7. Gabriel RS, Kerr AJ, Sharma V, Zeng IS, Stewart RA. B-type natriuretic peptide and left ventricular dysfunction on exercise echocardiography in patients with chronic aortic regurgitation. Heart 2008;94:897–902.

8. Collier P, Phelan D, Klein A. A test in context: myocardial strain measured by speckle-tracking echocardiography. J Am Coll Cardiol 2017;69:1043–56.

9. Mizariene V, Bucyte S, Zaliaduonyte-Peksiene D, Jonkaitiene R, Vaskelyte J, Jurkevicius R. Left ventricular mechanics in asymptomatic normotensive and hypertensive patients with aortic regurgitation. J Am Soc Echocardiogr 2011;24:385–91.

10. Kaneko A, Tanaka H, Onishi T, et al. Subendocardial dysfunction in patients with chronic severe aortic regurgitation and preserved ejection fraction detected with speckle-tracking strain imaging and transmural myocardial strain profile. Eur Heart J Cardiovasc Img 2013;14:339–46.

11. Lavine SJ, Al Balbissi KA. Reduced longitudinal function in chronic aortic regurgitation. J Cardiovasc Ultrasound 2015;23:219–27.

12. Smedsrud MK, Pettersen E, Gjesdal O, et al. Detection of left ventricular dysfunction by global longitudinal systolic strain in patients with chronic aortic regurgitation. J Am Soc Echocardiogr 2011;24:1253–9.

13. Park SH, Yang YA, Kim KY, et al. Left ventricular strain as predictor of chronic aortic regurgitation. J Cardiovasc Ultrasound 2015;23:78–85.

14. Di Salvo G, Pacileo G, Verrengia M, et al. Early myocardial abnormalities in asymptomatic patients with severe isolated congenital aortic regurgitation: an ultrasound tissue characterization and strain rate study. J Am Soc Echocardiogr 2005;18:122–7.

15. Alashi A, Mentis A, Abdallah A, et al. incremental prognostic utility of left ventricular global longitudinal strain in asymptomatic patients with significant chronic aortic regurgitation and preserved left ventricular ejection fraction. J Am Coll Cardiol Img 2017;10:XXX–XXX.

16. Negishi T, Negishi K, Thavendiranathan P, et al. Effect of experience and training on the concordance and precision of strain measurements. J Am Coll Cardiol Img 2017;10:518–22.

17. Negishi K, Negishi T, Kurosawa K, et al. Practical guidance in echocardiographic assessment of global longitudinal strain. J Am Coll Cardiol Img 2015;8:489–92.

18. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol 2013;61:77–84.

19. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

20. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: the EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr 2015;28:1171–81.e2.

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