Low-Flow Low-Gradient Aortic Stenosis
In Search of Optimal Risk Stratification

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Aortic stenosis (AS) remains a common and important clinical entity and, when severe, is associated with significant morbidity and mortality. Fortunately, definitive surgical therapies have been developed that have significantly altered the natural history of this disease. The clinical challenge is to accurately assess AS severity and identify patients who are most likely to benefit from aortic valve replacement. Both the American and European cardiac societies define severe AS as that associated with an aortic valve area (AVA) of <1.0 cm², a mean transvalvular pressure gradient of >40 mm Hg, and a peak transvalvular flow velocity of >4.0 m/s.1,2 Moderate AS is defined as an AVA of 1.0 to 1.5 cm², a mean gradient of 25 to 40 mm Hg, and a peak velocity of 3.0 to 4.0 m/s, whereas mild AS is associated with less significant abnormalities in these parameters. The classification of stenotic severity, however, is not always so straightforward, and patients are frequently encountered for whom the clinical data are conflicting, including those with AVA in the severe range but with low transvalvular gradient and low transvalvular flow (<40 mm Hg) and low transvalvular flow (<35 mL/m²). These patients with low-flow low-gradient AS (LFLG AS) account for a significant proportion of patients who present for evaluation of severe aortic stenosis.

The majority of patients with LFLG AS have reduced left ventricular ejection fraction (LVEF <50%) and have either severe AS and resultant LV failure ("true AS") or lesser degrees of AS and an unrelated cardiomyopathy ("pseudo-AS"). These 2 entities can often be distinguished through the use of an inotropic challenge1; however, a significant minority of patients with LFLG AS have low transvalvular flow (<35 mL/m²) despite preserved LVEF and have been referred to as having "paradoxical low-flow low-gradient AS." The first series of these patients was published by Hachicha and colleagues, who reported that when compared with patients with normal transvalvular flow, patients with paradoxical LFLG AS had lower transvalvular gradient, lower LVEF, higher afterload as measured by valvulo-arterial impedance, and a higher mortality.4 The authors concluded that patients with LFLG AS with preserved LVEF represent a distinct population of patients with more advanced disease than their counterparts who have severe AS, preserved LVEF, and high transvalvular gradients. Nonetheless, others have suggested that the paradoxical findings in these patients relate at least in part to errors in measurement and inconsistencies in the severity criteria proposed in established guidelines.5,6

In the current edition of Circulation: Cardiovascular Imaging, Adda and colleagues report their findings in 340 patients with severe AS and normal LVEF, focusing their analysis on the characteristics of the subset of patients with LFLG AS.7 In this prospective, multicenter study of consecutive patients, the authors provide several important observations. First, the majority of patients (76% in this series) with severe AS and normal LVEF have high transvalvular gradients, and the severity of AS is not in question. Second, among the 24% of patients with severe AS by valve area calculation, normal LVEF, and low transvalvular gradient, a minority truly have low transvalvular flow rates (=9% of patients in this series), with the remainder having normal transvalvular flow despite the low gradient (normal-flow/low-gradient AS). Third, there are physiological differences between subgroups of patients with severe AS and preserved LVEF, including subtle evidence of LV dysfunction, and these differences may shed light on the pathophysiological mechanisms underlying LFLG AS.

Traditionally, the decision to proceed to aortic valve replacement in patients with severe AS has been heavily biased by the presence of symptoms, the classification of AS severity based on AVA, and the presence of LV dysfunction. Patients with symptomatic severe AS, or with severe AS and depressed LVEF, clearly benefit from aortic valve replacement. For asymptomatic patients who have an AVA <1 cm² and have normal LVEF, a period of watchful waiting has seemed to be an appropriate approach; however, the present data from Adda and colleagues adds to a growing body of literature that suggests that quantification of LVEF is an incomplete assessment of LV systolic function and is likely an inadequate method on which to base clinical decision-making in patients with AS.

Prior studies have demonstrated that midwall fractional shortening (a measure of LV systolic function that is less influenced by LV geometry may be a superior measure of LV systolic function in patients with hypertension,8 correlates with the presence of symptoms in symptomatic AS,9 and is reduced in patients with LFLG AS compared with patients with normal transvalvular flow.10 Using 2-dimensional strain imaging, Delgado and coworkers demonstrated that radial, circumferential, and longitudinal strain are reduced in patients with severe AS and preserved LVEF and that aortic...
valve replacement in this population resulted in improvement in strain whereas LVEF remained unchanged. In the present study, Adda and colleagues further this finding by comparing strain in 4 subsets of patients with severe AS and preserved LVEF, specifically those with normal-flow/high-gradient, normal-flow low-gradient, low-flow high-gradient, and LF/LG. While they report abnormalities in strain in all 4 groups, the dysfunction was more marked in the patients with low transvalvular flow and was more significant in longitudinal strain than in radial or circumferential displacement. Furthermore, as demonstrated in prior studies, patients with low transvalvular flow had higher global LV afterload, as indicated by greater valvulo-arterial impedance, higher systemic vascular resistance, and lower systemic arterial compliance, suggesting a more advanced stage of disease.

While it may be intuitive that strain would be decreased in patients with low flow, the presence of increased afterload and decreased strain likely reflect the underlying pathophysiology of LF/LG AS. The chronic exposure of the LV to increased global afterload stimulates compensatory hypertrophy. While initially beneficial, progressive hypertrophy correlates with reduced global longitudinal strain, which appears to be preferentially impaired at an earlier stage than either radial or circumferential strain. This likely relates to the subendocardial distribution of longitudinal fibers in the myocardium, making them more vulnerable to the effects of increased wall stress and subendocardial ischemia that are present in chronic pressure overload states. Despite identifiable abnormalities in longitudinal strain, global ventricular systolic function (ie, LVEF) initially remains normal, owing to preservation of radial strain. Eventually, with longstanding pressure overload states, radial and circumferential strain become impaired, and LVEF subsequently falls. Thus, global LV systolic function as assessed by LVEF provides a relatively late marker of LV systolic dysfunction.

Left ventricular function will, nonetheless, remain an important prognostic indicator in patients with AS and will continue to influence clinical decision-making; however, it is becoming clearer that the assessment of LV function should be based on more sensitive markers than LVEF alone. The results presented by Adda and colleagues provide further evidence that the measurement of strain may be ideally suited as an early marker of LV dysfunction in this setting. Current technology allows for relative ease in obtaining strain data from conventional echocardiographic images, and speckle tracking has several advantages over other measures of myocardial deformation, including the lack of angle-dependence in image acquisition and the ability to assess global, longitudinal, radial, and circumferential strain. The reproducibility of strain measurement has been a challenge in the past, but speckle tracking appears to reduce the variability compared with other modalities. In the present study, the intraobserver, interobserver, and interinstitutional reproducibility for both global and longitudinal strain all ranged from 0.94 to 0.97. Importantly, the reproducibility for radial and circumferential strain were substantially lower, making them less ideal modalities for routine assessment of strain.

How best to apply this technique still needs to be clarified. In patients with severe AS and with resultant symptoms or depressed LVEF, there is probably little impact that strain measurement will have in regard to treatment decisions, although data relating to this are lacking. Similarly, while strain provides important functional/physiological data in patients with severe AS and low transvalvular flow, it is not clear that it provides further clinically important data when the decreased transvalvular flow has already been considered. Nonetheless, strain likely provides a more accurate and quantitative assessment of systolic function in this setting than does flow rate alone. It may turn out that the assessment of strain in the setting of AS has its greatest clinical impact among patients in whom other measures of systolic function are normal (ie, in patients with severe AS, normal transvalvular flow, and high transvalvular gradient). There remain instances in which patients with asymptomatic severe AS experience acute decompensation or sudden cardiac death without apparent preceding symptoms, and, in elderly patients, it is sometimes difficult to differentiate “slowing down” as a result of aging from functional limitation because of hemodynamically significant AS. Where feasible, one might be able to perform stress testing to unmask AS that would benefit from mechanical intervention; however, it is possible that serial assessment of strain might provide early detection of systolic dysfunction and thereby identify a point at which definitive therapy may yield benefit. Nonetheless, with the knowledge we have to date, one should not presume that isolated changes in strain necessitate proceeding to aortic valve surgery or percutaneous intervention.

While the role of strain in the evaluation of AS may not yet be fully defined, the assessment of strain can provide a greater understanding of the temporal changes of LV function in this setting and should be part of a more comprehensive echocardiographic evaluation of patients with severe AS. Incorporation of valvulo-arterial impedance into this comprehensive assessment is likely to help associate symptoms, or lack thereof, with the degree of apparent valvular obstruction. Further investigation will clearly be required to determine the threshold at which these measures should trigger changes in therapeutic plans.

Disclosures
None.

References


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