

Assessment of Normal-Flow Aortic Stenosis Delving Too Deep?

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The increasing complexity of assessing aortic stenosis (AS) will perhaps haunt cardiologists in years to come. Did we over-complicate it, were we overly ambitious in trying to identify those who might benefit from intervention? These are questions that we will be held accountable for by the vast numbers of patients who now carry some form of this diagnosis, and we have reason to be concerned. The previously accepted interventional indicators in AS, predominantly defined by a mean gradient >40 mm Hg and AVA <1 cm² with accompanying symptoms, have now almost become a distant memory. There are currently 4 different subtypes: classic low-flow low-gradient (LFLG), paradoxical LFLG, normal-flow low-gradient (NFLG), and normal-flow high-gradient (NFHG). With these added layers of complexity in AS grading has come some unease regarding appropriate management, with many patients falling below current thresholds for intervention. Indeed, although NFLG AS is included in current guidelines,¹ much thought is now directed toward deciphering its true hemodynamic cost, with some concern that it does not actually represent severe stenosis. With the obvious exception of NFHG, what is lacking is a defining level of evidence regarding expected interventional outcomes, with inconsistent reports of survival advantage. This is an unfavorable situation and has led to debate concerning optimal management, and variation in clinical practice.

See Article by Carter-Storch et al

In this issue of *Circulation: Cardiovascular Imaging*, Carter-Storch et al² offer thought-provoking insights into NFHG and NFLG AS prior to and at 1 year after aortic valve replacement. A small symptomatic population of 87 patients, 54 of whom were diagnosed with NFHG and 33 with NFLG, were studied for evidence of pathological and symptomatic benefit. The most eye-catching result of the study is that after a full year of follow-up, those with NFLG disease derived equivalent symptomatic improvement from surgery despite lack of any significant reverse remodeling (graded by left ventricular mass index at magnetic resonance imaging [MRI]). This is fascinating, and in order to piece together the apparent

offset between symptomatic improvement and ventricular 'healing', the authors have carefully considered many potential factors that could have influenced remodeling, and indeed whether NFLG even represents the same truly severe AS as its high-gradient counterpart.

Remodeling and Global Left Ventricular Afterload

Firstly, one of the highlighted outcomes in this study involved remodeling and its lack of improvement in NFLG disease after surgery. Remodeling in AS is predominantly related to the pressure load created by the stenotic valve and the systemic arterial resistance, a concept succinctly summarized by valvulo-arterial impedance (Z_{va}). In the Carter-Storch trial, it is important to note that those with lower gradients had a lesser degree of remodeling to start with. Why is this? Lower Z_{va} scores suggest that the pressure load faced by the ventricle in the NFLG group was not as significant as in NFHG disease, yet this is the reverse of what we might logically expect. The rationale for lower gradients in those with a normal ventricular pump and no significant mitral regurgitation is that there is potentially a post-valve high-resistance circuit driving down the mean gradient. Indeed, much of the evidence for calculating Z_{va} in the first instance is that, as a measure of global left ventricular afterload, it can explain these reduced trans-valvular gradients.³ Why then is it comparatively low in the low-gradient cohort in this study? The answer could potentially be flow related; although a robust indicator of global left ventricular afterload, Z_{va} is also flow dependent, and it may be that flow was overestimated in some of the NFLG cases as will be discussed later. Another, and perhaps more likely, explanation is that NFLG is in fact a milder form of AS than its high-gradient counterpart.

Diastology and Global Longitudinal Strain

In determining whether NFLG is indeed not representative of truly severe AS, more evidence can be found in the diastology and global longitudinal strain (GLS) profiles of these patients. Much has been written of the dysfunctional diastology that accompanies other subgroups of low-gradient AS,⁴⁻⁶ much has also been written of the correlation between myocardial fibrosis at MRI and degree of diastology dysfunction at echocardiography.^{7,8} However, the NFLG cohort in the study by Carter-Storch et al had more favorable diastology despite comparable fibrotic changes at MRI. It is probable that the lesser degree of ventricular hypertrophy is responsible for the relative preservation of diastology, while high-gradient patients with comparatively more hypertrophy lost diastolic efficiency more rapidly. This again reflects less pressure-dependent effects in this group.

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GLS indices were similar between groups. GLS is a marker of longitudinal ventricular function, which is predominantly the work of the subendocardium, whose fibers are orientated longitudinally thereby predominantly generating long-axis function. Middle layer fibers are arranged circumferentially, and the subepicardial layer more obliquely rendering it the major contributor to thickening and short-axis function. The authors have not described the sites of fibrosis; therefore, it is possible (but unlikely) that the low-gradient subgroup experienced proportionately more fibrosis in the vulnerable subendocardium. In other words, these less hypertrophied ventricles may have lost longitudinal function in a similar manner to those with higher gradients but been spared a marked deterioration in diastology by the relative lack of hypertrophy. This is purely speculative, and without direct evidence from the study, it is impossible to say exactly what influenced these measures. Regardless, the equivalence in strain indices suggests that pump function was preserved in both groups, and the lower gradients in those with NFLG cannot be attributed to overestimation of LV performance.

Flow and Its Estimation in AS

An important reservation in labeling those with relatively low gradients as having “normal flow” is a concern regarding SVi calculations. Derived from spectral Doppler, the calculation involves dividing the cross-sectional area of the left ventricular outflow tract (LVOT) and associated Doppler velocity envelope by body surface area. This method of SV calculation is prone to the same errors as often seen in the continuity equation; both are highly dependent on LVOT diameter and acquiring a suitably representative velocity envelope that does not exhibit excessive spectral dispersion. Little wonder then that the generated figures often do not correlate well with those obtained by MRI. As the concept of low-gradient AS expands, there will be a need to confidently identify those who truly are of low flow as opposed to those in whom flow has been underestimated. The authors could have used computed tomography-derived LVOT areas as part of the SV calculation, and it would have been interesting to see if that would have resulted in a reclassification of some of the NFLG cohort into having milder AS.⁹

Current with this, flow rate itself is gaining traction as a marker of severity in AS and perhaps a more accurate reflector of transaortic flow than SVi. Recently, in a cohort of the SEAS study (Simvastatin and Ezetimibe in Aortic Stenosis),¹⁰ flow rate was credited as identifying true flow through the valve. The calculation is straightforward, Doppler-derived SV divided by systolic ejection time and should theoretically correlate more closely with true flow than SVi, as it accounts for any prolongation of ejection time, which could reduce the transvalvular flow rate. There may, therefore, be a role for flow rate calculation when discrepant indices of severity are reported, potentially reducing erroneous labeling of low flow. It is possible that in the current article, this might have identified a few cases in which flow was overestimated by stroke volume calculations.

The final comment that should be made regarding flow in NFLG regards the symptomatic benefit of aortic valve replacement in this group. Ostensible lack of reverse

remodeling or improvement in other markers of wall stress, notably BNP, makes pump efficiency an unlikely source of symptom improvement. It seems in this small study that relief of obstruction to flow is the predominant determinant of symptomatology.

Role of Stress Echocardiography

What the authors have not touched on is the role of stress echocardiography in defining which of these patients with low AVAi at rest and incongruously low gradients, despite normal SVi, may have increased gradients during stress that would have reassured the surgeon regarding the severity of stenosis. The relatively poor exercise tolerance in those with NFLG as assessed by 6MWT is a clue to lack of valve compliance with stress but could equally be the result of deconditioning. Regardless, the role of stress echocardiography in evaluating this particular subgroup of patients has not been well explored, and NFLG has yet to be included in current guidelines on the use of stress echocardiography in nonischemic indications.¹¹ Indeed, considering the difficulties outlined in diagnosing this subtype, careful data acquisition by resting echocardiography is of higher priority.

Is NFLG a Less-Severe Form of AS?

There are undoubtedly instances when genuinely severe AS will be accompanied by lower gradients despite good ventricular systolic function and appropriate SVi: most commonly, high Zva, significant mitral regurgitation, and systemic hypertension. However, in the present study, none of these was the case, meaning that by exclusion, this may represent less-severe disease. In support of this is the larger AVAi at baseline in the low-gradient group together with lower aortic calcium burden at computed tomography, a proven surrogate both for degree of stenosis and survival.¹² This would fit with available survival data indicating that NFLG is associated with significantly lower event rates than LFLG,^{13–15} strongly suggesting that the NFLG entity is in fact a halfway house between moderate and severe AS.

Conclusions

Carter-Storch et al have provided a thought-provoking narrative on the nuances of AS, highlighting its increasing complexity. An array of descriptors that is unrivalled in valvular heart disease has been suggested to guide decision making; indeed, if this approach was applied to the mitral valve, it is likely that anarchy would soon follow. Therefore, while being mindful of the subtleties of AS pathology, the worry is that some patients will be incorrectly risk stratified as we delve deeper into the quagmire, becoming fixated by shades of disease rather than using common sense to identify those most at risk.

Disclosures

None.

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