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EDITORIAL COMMENT

Exercise Testing in Paradoxical Low-Flow Aortic Stenosis

Where Is the Truth?*

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A substantial portion of patients with severe aortic stenosis (AS) (valve area <1.0 cm^2) have mean pressure gradients below the 40 mm Hg traditionally associated with severe AS. If such patients have a normal left ventricular ejection fraction, they have paradoxical low-gradient aortic stenosis (PLGAS), a challenging group to clinically manage (1,2). Although many patients will benefit from aortic valve (AV) replacement (surgical or transcutaneous), other patients have "pseudostenosis," with a valve that would open adequately if only there were sufficient stroke volume, and they need treatment focused on hypertension and drivers of diastolic dysfunction (3,4). The 2014 Valve Guidelines, reflecting the lack of data in these patients, provide scant guidance in making this distinction, stating that valve replacement is reasonable (Class 2a) if "AS [is the] likely cause of symptoms" (5). Although calcium scoring according to computed tomography scans has recently been shown to be useful in assessing PLGAS, a hemodynamic approach is needed to define the true severity of the patient's AS and demonstrate its relation to the functional limitations of the patient (6).

In this issue of *iJACC,* del Villar et al. (7) attempt to define the valvular and vascular response to exercise in symptomatic patients with PLGAS by using invasive and noninvasive data obtained with simultaneous right-heart catheterization and transthoracic echocardiography. All 20 participants had PLGAS and were in sinus rhythm at the time of the study. Important exclusion criteria included known or suspected ischemic heart disease, moderate or greater aortic regurgitation or mitral valve disease (stenosis or regurgitation), concomitant pulmonary hypertension at rest, chronic obstructive pulmonary disease, or uncontrolled systemic hypertension. The study population was predominantly older (mean age 77 years), female (85%), were classified as New York Heart Association functional class II (95%), and were receiving antihypertensive therapy (85%). Interestingly, only one-half of patients had the classic finding of low flow (stroke volume index [SVI] <35 ml/m^2) usually associated with PLGAS. As the patients exercised, continuous cardiac output (and SVI) was measured by using a "true" Fick method (using oxygen consumption from expired gas analysis); valve area was calculated according to continuity by using a Doppler transaortic gradient combined with this hemodynamic SVI as well as with the Doppler SVI (8). From these data, the investigators calculated the valve "compliance," a measure of how readily it opens with increasing flow.

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Utilizing the hemodynamic SVI, del Villar et al. (7) found that AV area increased by an impressive 84 ± 23%, with 70% of subjects having AV area values >1.0 cm^2 at peak exercise, indicating that most of the valves were fairly compliant and indeed were pseudostenotic. The investigators found value in plotting wedge pressure against oxygen uptake (VO_2), illustrating that the steepness of this slope was inversely proportional to exercise capacity; furthermore, the factor most predictive of the pulmonary capillary wedge pressure (PCWP)-VO_2 slope was AV compliance (r = -0.63). Thus, patients with the greatest functional limitation were associated with the most persistently stenotic valves, whereas no resting valve

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or ventricular parameter was predictive of PCWP-VO_2 slope.

On its face, this approach (7), while complex and technically demanding, seems an ideal way to separate the wheat from the chaff among patients with PLGAS. If it could be translated to a fully noninvasive approach with Doppler echocardiographic surrogates for all invasive data, it could be implemented in daily clinical practice. Unfortunately, it is precisely in this noninvasive translation that the method founders a bit. One key finding in the study was that the Doppler and Fick determinations of SVI compared reasonably well at rest (intraclass correlation [a measure that combines traditional Pearson correlation with agreement] $R_{ic} = 0.79$) and at 50% peak VO_2 ($R_{ic} = 0.72$); however, at maximal exercise, the 2 SVI measurements remained correlated ($R = 0.81$) but in poor agreement ($R_{ic} = 0.32$), with Fick-derived SVIs an average of 48% greater than Doppler-derived values. The assumption made is that the Doppler SVI underestimates the "true" SVI, which (naturally) would be the invasive one. Furthermore, it is this dramatic rise in SVI in the last half of exercise that drives much of the increase in AV area that makes most of these patients pseudostenotic.

In general, the increased cardiac output needed for exercise is characterized by an initial phase with a rise in stroke volume to a plateau, followed by a progressive increase in heart rate more prominently in the latter phase. Although traditional normal-flow high-gradient severe aortic stenosis has been associated with a blunted stroke volume response (more heart rate dependent for cardiac output increases) (9), the response was different in the current study population (7). Table 2 in del Villar et al. (7) illustrates the hemodynamic changes with exercise. Paradoxically, the participants seemed to have a continuous rise in stroke volume but a relatively flat heart rate response that plateaued at 50% of peak VO_2. Despite a small left ventricular cavity size (mean end-diastolic volume 62 ml), the average mean Fick stroke volume (multiplying SVI by body surface area) was 100 ml, an inconsistency that may also reflect the challenges of estimating left ventricular volumes by using 2-dimensional echocardiography. The challenges of exercise imaging are more apparent in their Figure 1, which presents the raw data from 1 of the subjects. This subject exercised to 100 W over 10 min but achieved peak VO_2 at 7.5 min and a workload of 75 W, with VO_2 and pulmonary pressures falling even as workload increased. After stopping the effort, there was a further 40% surge in SVI, mediated mainly by a sudden rise in venous oxygen saturation, narrowing the arteriovenous oxygen gradient out of proportion to the more gradual fall in VO_2. These SVI data could lead to a higher calculated AV area than anticipated.

With this in mind, one might rightly question the reflex to assume that the Doppler stroke volume is the "wrong" one. We could hypothesize that with exercise, there is misalignment of the pulsed wave Doppler beam to the flow leading to velocity underestimation by the cosine effect. However, the investigators (7) continued to use the continuous wave Doppler AV gradient, and this measurement should be even more sensitive to positioning than the pulsed wave recording. Indeed, it is actually the Doppler measurements that seem to pass the "reasonableness" test, indicating a greater rise in AV area in early exercise, plateauing by peak VO_2, but generally <1.0 cm^2, indicating true stenosis.

So where does this leave us? First, del Villar et al. (7) deserve praise for undertaking such a complex echocardiography/catheterization study that is so rarely seen these days. The simple idea of exercising PLGAS patients is itself novel; we are comfortable using dobutamine infusion in patients with low-gradient AS with depressed ejection fractions to define the AV response to increasing SVI, but there is far less experience in patients with PLGAS. If we accept the veracity of the Doppler hemodynamic findings, we could assess various echocardiographic surrogates for the PCWP, such as right ventricular systolic pressure (which tended to parallel the rise in PCWP) and the ratio of the transmitral E-wave to the annular e′ wave (E/e′). Neither of these correlations was published in this paper, but perhaps they will appear in subsequent analyses.

This study (7) has ably demonstrated the heterogeneous nature of the PLGAS population, particularly Figure 5 showing the huge spectrum of SVI response to exercise. It is clear we need a range of diagnostic tools to assess these patients, including computed tomography scans for AV calcium score, biomarkers, echocardiographic strain analysis, and cardiac magnetic resonance for biventricular structure and function. A graded hemodynamic exercise protocol added to the mix is a welcome addition to the diagnostic armamentarium.

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