Asymptomatic Patients With Severe Aortic Stenosis Are Not All Created Equal

A Role for Stress Performance and Heart Rate Recovery During Stress Echocardiography?

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Aortic stenosis (AS) is a relentless disease that, once symptomatic, carries a grim prognosis with 2-year survival in the absence of aortic valve replacement (AVR) of <50%.[1] Associated left ventricular systolic dysfunction defined as a left ventricular ejection fraction of <50% is also prognostically important, so that symptoms or reduced left ventricular ejection fraction carry class I indications for AVR in both the American College of Cardiology and American Heart Association (ACC/AHA)[2] and the European Society of Cardiology (ESC)[3] guidelines for the management of valvular heart disease. Of the symptoms with which AS is associated—angina, syncope/presyncope and those of heart failure—the most common are those associated with heart failure with dyspnea predominating. Notwithstanding the clinical significance of symptoms, it may be difficult to discern whether the patient with AS is asymptomatic simply because he or she has scaled back physical activity as an underappreciated symptom avoidance strategy (pseudoasymptomatic). It was with the primary goal of determining whether the asymptomatic patient is truly asymptomatic and capable of reasonable activity or pseudoasymptomatic that stress testing, typically exercise stress echocardiography (ESE), has emerged as an important tool in the evaluation and management of patients with AS. Indeed, it carries a class IIA indication in the current ACC/AHA guidelines for patients with classic severe AS (peak velocity ≥4 mps and mean gradient ≥40 mm Hg).[2] The implication of a test that is positive as defined by symptoms is that the patient is considered to be symptomatic and, therefore, a candidate for AVR. Thus, exercise-induced symptoms also carry class I indications for surgery in both the ACC/AHA[2] and the ESC[4] guidelines. Other ESE outcomes including a fall or <20 mm Hg rise in systolic blood pressure,[5,6] mean gradient increase of >18[5] or 20[7] mm Hg, ventricular arrhythmias,[6,7] ≥2-mm ST depression,[5,6] and an exercise-induced fall in left ventricular ejection fraction[8] have also been shown to be predictive of spontaneous symptom onset,[5–8] symptom-driven AVR,[5,7] and sudden cardiac death.[5–7] However, the link between ESE results other than symptoms and outcomes has not been entirely consistent,[9] and death has been a rare event typically occurring only after patients have become symptomatic.[6,7] In particular, ECG changes have been reported to be inadequately discriminating,[9] particularly in women. Thus, these ESE measures of test positivity carry no (EKG changes, fall in EF, and ventricular arrhythmias) or only IIA (fall in blood pressure)[2,3] or IIB (>20 mm rise in gradient)[3] indications for AVR.

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Although exercise-induced chest pain and presyncope/syncope may be confidently identified, the adjudication of exercise-induced dyspnea is more challenging. Even the fittest of test subjects will become short of breath with exercise albeit at high workloads or prolonged exercise. What is required, therefore, is confidence that the onset of dyspnea is at an unexpectedly reduced workload and that it is attributable to AS.[3] Attribution of dyspnea to AS may be difficult if the patient also has, for example, lung disease or is deconditioned due to obesity or musculoskeletal problems. It would be helpful, therefore, to have additional hard ESE outcomes that are prognostically important.

In this issue of *Circulation: Cardiovascular Imaging*, Masri et al[10] provide an important addition to the literature of ESE in AS by reporting the incremental prognostic use of exercise tolerance (as measured by % age- and sex-predicted metabolic equivalents (METs) achieved) and 1-minute post exercise heart rate recovery (HRR) after symptom limited treadmill ESE. With 533 patients with severe AS and left ventricular ejection fraction of ≥50%, the study is much larger than earlier studies of ESE in AS and the follow-up (mean of 6.9 years) is longer. The primary outcome was all-cause mortality.

The authors report that lower % age- and sex-predicted METs (hazard ratio, 1.15) and slower HRR (hazard ratio, 1.22) along with Society of Thoracic Surgery (STS) score (hazard ratio, 1.2) were associated with higher longer-term mortality, whereas AVR (hazard ratio, 0.26) was associated with improved survival. Furthermore, addition of % age- and sex-predicted METs to STS score resulted in significant reclassification of longer-term mortality risk. The proportion of long-term deaths in the subgroup achieving <85% of age- and sex-predicted METs, seemingly an empirical cutoff, was significantly higher than in those achieving ≥85% (45 [32%] versus 59 [15%]).

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Methodologic Considerations

To understand the clinical implications of these findings, it is important to look for methodologic sources of potential bias.

Study Group

In this study, the authors' diagnosis of severe AS was based on an indexed valve area of <0.6 cm^2/m^2. Scrutiny of table 2[10] highlights that not all subjects had classic high-gradient severe AS with average peak velocities of <4 mps and an average mean gradients of <40 mm Hg. In addition, the body mass index of 28±5 kg/m^2 indicates that some of the patients were obese. In combination, these introduce some degree of uncertainty as to the validity of the diagnosis of severe AS in all subjects. In addition, roughly 40% had reduced stroke volume (<35 cc/m^2). By inference, the study group contained patients with low-gradient, low stroke volume preserved left ventricular ejection fraction AS, a heterogeneous group at least some of whom may have more advanced LV dysfunction than those with preserved stroke volume. It would be interesting to know whether the exercise variables that were evaluated in this study were equally prognostically important in this low stroke volume, low-gradient group versus those with classic high-gradient AS.

Similarly with roughly one quarter of the subjects having bicuspid aortic valves, perhaps accounting for the relatively young mean age of 66 years and contributing to the sex differential (over three fourths of subjects were males), it would be interesting to know whether % age- and sex-predicted METs achieved and HRR were equally important in subgroups defined on the basis of valve morphology, age, and sex. This would be important information to be gained in the additional studies that the authors note would be needed to validate the results of this study. Other important confounders in this study are coronary artery disease, smoking, and hypertension present in ≈30%, 50%, and 70% of the study group, respectively. Although the authors provide reassurance that the key findings of the study hold even with the elimination of patients with coronary disease from the analysis, it may not be possible to exclude patients with smoking, hypertension, and other comorbidities known to affect mortality. The prevalence of many of these comorbidities is, however, captured in the STS risk calculator used here in an off-label way, and it is reassuring that both % age- and sex-predicted METs achieved and HRR are additive to the STS risk calculator in predicting outcomes. One assumes that none of these subjects had concomitant diseases with high short-term mortality (eg, terminal malignancies) if they had been referred for consideration of AVR, although it would be more reassuring if this had been explicitly stated.

Reference Age- and Sex-Predicted METS

Although the authors used age- and sex-predicted exercise tolerance (as gauged by METs achieved) using the approaches of Morris et al[11] for men and Gulati et al[12] for women, it is worth noting that these studies included few patients in the elderly population in whom AS is typically encountered (only 9 men aged >80 years in the Morris study). Indeed, the nomograms provided in these references do not extend beyond age cutoffs of 70 to 75 years. Thus, it may be imprecise to indicate that the cutoffs used truly allow reference to normal age- and sex-adjusted predicted values.

Outcomes

The primary outcome in this study is all-cause mortality with 104 deaths in total, 15 documented noncardiac deaths and 12 deaths occurring post AVR (3 within 30 days and an additional 9 within 1 year). Although it would be preferable to limit the analysis to cardiac mortality, this can be challenging even in prospective studies and impossible in a retrospective study such as this. It is reassuring that a secondary analysis excluding those who clearly had noncardiac death confirmed the results of the primary analysis.

Similarly, it would be difficult in a retrospective study such as this to use symptom onset as an end point as has been used in other studies. Time to AVR, however, for those in whom the test results did not result in immediate AVR, might have served as a surrogate and an informative secondary outcome. The authors note that mortality was reduced in patients who underwent AVR, which is consistent with earlier reports on the favorable impact of surgery[13] and, more recently, transcatheter aortic valve replacement[1] in symptomatic patients with severe AS. Although this may argue indirectly that deaths in this study were related to AS, it may also be that patients with comorbidities expected to shorten life did not undergo surgery even if/when they became symptomatic.

Comparison With Previous Studies

Although the impact of % age- and sex-predicted METs achieved and HRR are the main thrust of this study, this large series provides important confirmation of earlier studies performed with smaller numbers of patients and with shorter follow-up. First, it confirms the safety of ESE for asymptomatic AS, with no reported ESE-associated deaths or malignant arrhythmias. This is consistent with the favorable safety profile of ESE in earlier reports.[5–7,9,14] Note should be made, however, of the careful supervision of patients during stress testing in this study with vital signs at 1-minute intervals during stress and for 6 minutes into recovery and the general recommendation is that ESE in patients with AS be closely supervised by a cardiologist.

Second, using a new metric of test performance (% age- and sex-predicted METs achieved), this study notes that a large number of patients presenting themselves as asymptomatic did poorly when formally stressed with 26% achieving <85% age- and sex-predicted METs and 24% achieving 85% to 100%. This is consistent with reported rates of test positivity using a more expanded range of end points (symptoms,[5–9] abnormal blood pressure response,[5–7] ventricular arrhythmias,[6,7] and ST-T changes[5,6]) with, in general one third of patients experiencing symptoms and up to 67% considered positive if ECG changes are included.[6] It is interesting that in this study, fewer patients experienced dyspnea (8%), angina (3%), abnormal blood pressure response (6%), dizziness (0.6%), and arrhythmias (1%) than in earlier studies, although patients who achieved <85% age- and sex-predicted METs were more likely to have these findings. Rather, in this

study generalized fatigue was the dominant symptom at peak stress (81%).

It is also interesting that end points evaluated in other studies were not confirmed to predict all-cause mortality here although, as noted, these end points were relatively rare in this study (ventricular arrhythmias in 1% and increase in mean gradient of ≥20 mm Hg in only 17%). The findings of this study do not detract from the important consensus message in other studies that other end points predict symptom onset and, therefore, identify a high-risk group. Similarly, although the measures evaluated here could be determined with exercise only stress, the body of evidence from other ESE studies supports the importance of parameters obtainable only by echocardiography, and, therefore, the position that testing in patients with asymptomatic AS should be done with ESE.

Limitations

Beyond the limitations discussed in previous paragraphs, it should be noted that as ESE was done with treadmill stress in this study, the results may not be generalizable to supine bicycle stress. In addition, as only 1 stress echo was performed and no information about subsequent symptom onset is provided, this study does not determine the ability of these findings to predict symptom onset in subjects whose test does not elicit classic symptoms but who have reduced exercise tolerance. Indeed, if this information about symptom onset were available, it is possible that % age- and sex-predicted METs and HRR would be shown to be predictive of symptom onset because earlier studies have reported that AS-related death is typically seen only in patients who have become symptomatic.[6,7] Monitoring for symptom onset would be an important component of prospective studies that will be needed to confirm the findings of Masri et al[10] because this information would influence the degree to which % age- and sex-predicted METs and HRR in the absence of symptoms would be viewed as drivers for early surgery. In other words, if these measures predict symptom onset and cardiac death is seen only in those who have become symptomatic, it could be argued that close follow-up waiting for spontaneous symptom onset is an acceptable strategy with patients with reduced % age- and sex-predicted METs and slow HRR identified as a high-risk group. Finally, these results may not be entirely generalizable to the current era in which transcatheter aortic valve replacement has emerged as a disruptive technology because AVR in this study was done exclusively surgically with patients undergoing transcatheter aortic valve replacement excluded.

Conclusions

In this large retrospective study, the authors provide data that suggest that % age- and sex-predicted METs achieved and HRR are important considerations in interpreting the results of ESE in patients with asymptomatic AS. In doing so, they provide a compelling argument that these 2 easily obtained parameters should be included in all such clinical stress tests and in related future research studies.

Disclosures

None.

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