Exercise Hemodynamics and Risk Assessment in Asymptomatic Aortic Stenosis

Running title: Bonow; Asymptomatic aortic stenosis

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Journal Subject Codes: [19] Valvular heart disease; [31] Echocardiography; [125] Exercise testing; [38] CV surgery: valvular disease

Key words: aortic stenosis; echocardiography; Editorials; exercise physiology; exercise testing; pulmonary hypertension
Over a half century ago in *Circulation*, Dr. Paul Wood aptly described aortic stenosis (AS) as “a simple mechanical fault which, if severe enough, imposes a heavy burden on the left ventricle and sooner or later overcomes it”\(^1\). Our subsequent understanding of the pathophysiology of AS, with more sophisticated tools than those at Dr. Wood’s disposal, has confirmed his concept. Severe chronic pressure overload and outflow obstruction beget left ventricular (LV) hypertrophy and its attendant myocardial fibrosis and impaired coronary vasodilator reserve, leading to LV systolic and diastolic dysfunction, progressing ultimately to the anticipated symptoms of dyspnea, angina, and presyncope or syncope, which are harbingers of death within a few years. Once symptoms develop, the treatment strategy is clear, as aortic valve replacement (AVR) improves symptoms, improves LV function, and improves survival. The indications for AVR in asymptomatic patients, however, remain less clear and the subject of ongoing debate\(^2-4\).

Although the current evidence-based guidelines recommend a watchful waiting approach for most patients, with no class I indications for surgery in asymptomatic patients with normal LV systolic function\(^5,6\), numerous studies have shown that patients with severe AS have a high likelihood of developing symptoms and requiring surgery within 3 to 5 years\(^7-10\), and some series have reported that asymptomatic patients with severe AS are also at risk of death when managed without surgery\(^11,12\). As the operative risk of AVR is low in experienced centers\(^11,13\), there is intense interest in identifying the subsets of asymptomatic patients who have the highest likelihood of dying or developing symptoms over the short term who might benefit from early preemptive AVR rather than a watchful waiting approach.

Determining which patients with AS are truly asymptomatic is not an exact science. Patients often have difficulty describing their exercise limitations and may appear to be asymptomatic because they have downgraded their activities to limit dyspnea. In addition,
interpreting mild exertional dyspnea as a cardiac symptom is complex in the many patients who are elderly, deconditioned and/or overweight. Exercise testing has been proposed as one means of identifying higher risk patients, by unmasking symptoms or abnormal blood pressure responses. Several studies have shown that patients who develop symptoms or fail to increase blood pressure with exercise testing have a high likelihood of developing symptoms within a few years and requiring AVR. However, in such studies a post-test referral bias may be operative, with the possibility that the stress test results themselves might bias physicians to intervene earlier in those with abnormal tests, thereby inflating the predictive value of exercise test responses. In addition, all patients (and normal individuals) sooner or later develop limiting symptoms with exercise testing, and deconditioned or frail patients are likely to have low exercise capacity. Determining a cardiac versus noncardiac symptom response can be highly subjective.

Against this backdrop, noninvasive assessment of exercise hemodynamics with Doppler echocardiography emerges as an attractive alternative to exercise testing without imaging, with the potential to provide much more objective insights into exercise physiology than symptoms and blood pressure measurements alone, that can add to the echocardiographic assessment at rest of severity of AS and its impact on LV function. Previous work has shown that the change in aortic valve gradient with exercise may be useful in stratifying risk in patients with asymptomatic AS, with 2 studies reporting that increases in the mean gradient of 18-20 mmHg or more during exercise identify patients likely to develop symptoms or die during mean follow-up periods of 15 to 19 months. The exercise-induced increase in mean valve gradient yielded independent prognostic information that was additive to resting valve gradients and exercise capacity. As in most studies of exercise testing in asymptomatic patients with AS, the patient...
samples were small and the composite endpoint was driven by patients developing symptoms with only a few deaths (and many of the deaths preceded by symptoms).

In this issue of Circulation, Lancellotti et al.\textsuperscript{19} confirm their previous observations linking increases in aortic valve gradient with exercise to outcomes in patients with severe asymptomatic AS and extend their work with novel data addressing the relationship between exercise induced pulmonary hypertension and outcomes. The data relating pulmonary artery pressure with exercise and subsequent death, heart failure and AVR have important implications for future patient management.

Several features of the study of Lancellotti et al\textsuperscript{19} are noteworthy. All patients studied had severe AS with valve area indexes less than 0.6 cm\textsuperscript{2}/m\textsuperscript{2}, preserved LV systolic function, and “normal” exercise tests, thus excluding those with diminished exercise capacity (<75 watts), failure to increase blood pressure at least 20 mmHg, or development of ≥2 mm ST-segment depression. Although few patients had pulmonary hypertension at rest, which is a known high risk finding\textsuperscript{20,21}, over one half of patients in their series (55%) developed pulmonary hypertension with exercise, defined as a systolic pulmonary artery pressure greater than 60 mmHg (as estimated from the tricuspid valve regurgitant jet). Exercise-induced pulmonary hypertension was related to the severity of AS as determined by the peak and mean valve gradient at rest and also during exercise. Exercise pulmonary hypertension was also associated with greater increases during exercise in LV volume, LV stiffness (estimated from the e’ wave velocity) and left atrial volume. Thus, these data suggest that increases in pulmonary artery pressure with exercise unmask patients with severe AS in whom the relationship between LV hypertrophy and left atrial compliance is compensated at rest, but marginally so, such that an increase in outflow gradient during tachycardia and augmented stroke volume is poorly tolerated,
triggering LV dilatation and increased LV filling pressures, leading to sudden increases in left atrial and pulmonary pressures. This concept that these patients are on the cusp of clinical deterioration is supported by the significant association between exercise induced pulmonary hypertension and subsequent cardiac events during the mean follow-up period of 19 months. Patients with pulmonary hypertension during exercise had roughly twice the event rate as those without pulmonary hypertension (67% versus 36%), and all 7 deaths occurred in patients with pulmonary hypertension with exercise. Peak aortic ejection velocity at rest was the strongest hemodynamic determinant of the combined endpoint of death and symptomatic deterioration, but exercise pulmonary hypertension was an independent determinant in a multivariate model, thus adding incremental prognostic information to the resting and exercise aortic valve gradient.

One would anticipate that patients with exercise-induced pulmonary hypertension might have more severe or earlier symptoms with exercise, reduced exercise capacity, or higher exercise heart rates but, interestingly, there was no difference in these exercise variables between those with and those without exercise pulmonary hypertension. Exercise capacity and other measures of exercise performance were also not associated with outcome. Although this may be related, in part, to the exclusion of patients who developed symptoms at low workloads, the data do demonstrate the unique value of intracardiac hemodynamic measurements in those with more normal exercise capacity.

There are several issues regarding these data that may limit their general applicability. The investigators studied patients using a semi-supine exercise protocol, with Doppler measurement of hemodynamics during the peak of exercise, in keeping with the previous studies of exercise hemodynamics in patients with asymptomatic AS. Thus, these data cannot be extrapolated readily to results that might be obtained in the many laboratories in which stress
echocardiography is performed using upright treadmill exercise with imaging performed during the immediate post-exercise phase, when hemodynamics may be changing dramatically and unpredictably. Obtaining the noninvasive hemodynamic measurements during peak exercise is technically challenging, and even in the hands of these experienced investigators, exercise data could not be obtained in 35 of 140 patients (25%). In addition, pulmonary artery pressure with exercise was estimated with the assumption that right atrial pressure was constant between rest and exercise, which may not be the case in patients with AS, especially those with dramatic increases in pulmonary artery pressure with exercise. Finally, it is also uncertain whether these unique measures of pulmonary artery pressure with exercise, which provide important physiologic insights but are difficult to obtain, will provide better prognostication than other emerging determinants of risk, such as serum biomarkers (most notably BNP \(^22\)) and measures of interstitial myocardial fibrosis by cardiac magnetic resonance imaging\(^{23,24}\).

Although the exercise hemodynamics provided important prognostic information in this study, with a twofold increase in cardiac events in those with versus those without exercise pulmonary hypertension, it is noteworthy the overall event rate was quite high, with 53% of patients dying or developing symptoms during a mean follow-up period of only 1.5 years, even after the exclusion of the highest risk patients. One might question, with this high event rate, whether it would be reasonable to recommend early operation for all patients with such severe AS as determined with resting echocardiography\(^{2,4}\), considering age and comorbidities, and whether the added cost and complexity of stress echocardiography or other markers of risk will yield improved clinical outcomes. The field of valvular heart disease has been held back compared to other areas of cardiovascular medicine because of the lack of definitive prospective clinical trials. A clinical trial to determine whether AVR or conservative management is the most
appropriate strategy for patients with severe asymptomatic AS, and to determine the most
effective method of risk stratification, is needed to guide the future management of this very
prevalent disease.

**Conflict of Interest Disclosures:** None.

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_Circulation_. published online July 25, 2012;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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