What Is Severe Aortic Stenosis and Why Do People Die From It?*

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A 63-year-old man notes that his exercise tolerance has diminished over the past year and that he is limited to climbing 1 flight of stairs, reduced from 2 flights previously. His physical examination reveals a late peaking systolic ejection murmur, and his carotid upstrokes are delayed. Echocardiography finds a transvalvular jet velocity of 3.6 m/s, a mean gradient of 28 mm Hg, a calculated aortic valve area (AVA) of 1.1 cm², a body surface area of 2.1 m², and an indexed valve area of 0.5 cm²/m².

I suspect that most practitioners reading this editorial would find that this clinical picture is consistent with severe symptomatic aortic stenosis (AS) and would recommend aortic valve replacement (AVR), yet only the indexed valve area meets guideline definitions for severe AS. How sure are we, however, that the patient’s AS is truly severe and that AVR is the correct course of action?

Starting with the classic work of Ross and Braunwald (1) and now confirmed by randomized trials, there is no doubt that symptomatic severe AS is a fatal disease treated effectively only by AVR (2,3). There are also truly asymptomatic patients with severe AS who are at increased risk who also may benefit from AVR (i.e., those with very severe AS, those with abnormal stress test results, and probably those with high and increasing levels of biomarkers, especially natriuretic peptides) (3–7). In these asymptomatic patients, certainly regarding severity is even more critical because the benefit is less definite than if symptoms were present. Obviously, the clinical problem posed is in defining the word “severe.” In some cases, the diagnosis is apparent but in others, such as in the aforementioned case, the decision is more difficult because severe is as much a concept as it is a number or group of numbers. Severe AS is that level of left ventricular (LV) outflow obstruction that causes more than mild hypertrophy, abnormal coronary blood flow, and diastolic and systolic LV dysfunction that act in concert to cause symptoms, LV damage, and cardiac death. Could we be so naive as to believe that all patients who, despite their varying genetic backgrounds leading to remarkable variation in response to the same stimulus (8), would all get sick at the same gradient, jet velocity, or AVA? I am sure we are not nor do Berthelot-Richer et al. (9) imply that possibility in their erudite work published in the current issue of iJACC.

Berthelot-Richer et al. (9) asked the question: which of the various ways of judging AS severity was the best screening tool for predicting outcome and which then best predicted who would benefit from AVR? They found that AVA outperformed other measures in this prediction. In comparing surgical options with so-called medical treatment, extensive propensity matching was required. Although propensity matching always leaves one to wonder whether adequate adjustment was really made, perhaps the most daunting is the presence of coronary artery disease. Accordingly, the investigators performed a separate analysis excluding patients with coronary artery disease, and the results were the same. An AVA <1.0 cm² was the best predictor of outcome and therefore arguably the best arbitrator of what constitutes severe AS.

AVA has the advantage of taking gradient (jet velocity) into the context of flow traversing the valve. The following concept has to be true: the more flow through a fixed obstruction the higher the gradient must be (10). It might explain why AVA would outperform other measures, especially in low flow states, but superior performance of AVA was
also found in patients with normal LV function (in whom stroke volume index was also normal). Conversely, because the calculation of AVA requires measurement of flow, outflow tract diameter, and velocity, all which could introduce errors into the results, the simple measurement of velocity (and pari passu gradient) could have the advantage of being directly obtained primary data and of avoiding errors in calculation. But AVA still proved superior. Does that mean that AVA is always superior or the only datum we should rely on? Obviously not! In the example given in the beginning of this editorial, common sense tells us that the information taken as a whole (including the patient’s physical examination) indicates that he had severe symptomatic AS requiring AVR although AVA was not in the severe range. Correction for body surface area indicated severe AS according to the indexed valve area, but it adds yet another variable to the calculation. Logically, larger patients have higher stroke volumes and thus require larger valve orifices. Although indexing is a reasonable approach to this problem, it entails new difficulties. Because it is volume of flow that generates the gradient, normalizing a volume-derived element according to area has its own theoretical problems (11). It would have been of interest had Berthelot-Richer et al. (9) compared AVA directly with indexed AVA (their Figure 3 suggests it may not have performed as well).

In the end, the left ventricle doesn’t know what the valve area is or what the gradient is that is it is ejecting against. Furthermore, our calculations are usually made at rest. Because most people are active during the day and because the gradient increases by the square of the output (10), a doubling of cardiac output quadruples the gradient to which the left ventricle must respond in some way. Thus, it is not surprising that assessment of severity at rest is problematic in many cases (11). It is now the 21st century yet we are evaluating AS severity by using the same (but valuable) tools espoused by Gorlin and Gorlin (10) in 1951, made apt for noninvasive evaluation (AVA, gradient, and its noninvasive correlate jet velocity). Given that different subjects respond to a given pressure overload in individual ways, it is time to use the biology of the left ventricle that has responded to the overload to aid in making management decisions. The addition to the mix of biomarkers and degree of myocardial fibrosis is of intense interest and should augment hemodynamic assessment of what defines severe (12-14). It may be that these variables and other specific biologic changes that occur at one valve area or gradient in 1 patient but not in another will better indicate whether the left ventricle is heading for trouble. They may also indicate correction of the overload irrespective of the exact AVA or gradient, provided we are convinced that the outflow obstruction is severe.

The hemodynamics of AS will always be important in assessing the pathophysiology of the disease because they cause its pathobiology. Coupling hemodynamics with new tools that examine biology should aid clinicians and their patients in making the correct decisions about disease management. In the meantime, except in obviously extreme cases (i.e., a mean gradient of 75 mm Hg), the clinician must use every tool at his or her disposal to assess severity of AS. These tools include a skilled physical examination, AVA, jet velocity, gradient, dimensionless index, and exercise hemodynamics. Add to that armamentarium emerging biological tools and sound clinical judgment, and we should arrive at the correct answer about what is entailed by severe AS.

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