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Editorial

Predicting Outcome in Patients With Asymptomatic Aortic Stenosis

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Although the annual risk of cardiovascular mortality has been well described for individuals with symptomatic aortic stenosis, the morbidity and mortality for those with asymptomatic severe aortic stenosis is not as well known. Currently the American Heart Association/American College of Cardiology recommends a "watchful waiting" strategy for those with asymptomatic aortic stenosis.[1] This involves clinical examinations every 6 to 12 months and annual echocardiograms; however, it is unclear what to do with these data in the patient who remains asymptomatic. The asymptomatic patient is generally not referred for aortic valve replacement surgery until the development of symptoms (unless concurrent coronary artery bypass grafting is required or if systolic dysfunction develops).

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Approximately 30% of asymptomatic patients will develop symptoms (angina, heart failure, syncope) within 2 years of diagnosis.[2,3] For those patients who do not develop symptoms, the risk of sudden cardiac death is less than 1% per year, assuming that patients are well monitored for the development of symptoms.[2,3] Although angina and syncope are relatively easy symptoms to elicit, manifestations of heart failure may be subtle. This is particularly true because many of these patients are elderly and attribute reduced exercise capacity to be part of the normal aging process or "slowing down." Vigilance and careful attention to a patient's history are important components of the regular evaluation of patients with aortic stenosis. However, even careful attention to the history may not predict sudden death in patients with severe aortic stenosis. The reluctance to perform surgery earlier than necessary is driven by the morbidity of cardiac surgery and a mortality rate for aortic valve surgery of approximately 3% to 5%, even in patients younger than 70 years.[4] Thus for truly asymptomatic patients, the risk of potential complications like sudden cardiac death and irreversible myocardial dysfunction must be weighed against the risk of surgery. Given the possibility of these outcomes before the development of overt symptoms, investigators have sought to find a reliable way in which to risk stratify patients with asymptomatic aortic stenosis into those who will derive benefit from surgery before symptom development and those who will not. A comprehensive objective approach that could facilitate decision making in such patients has long been sought but has been elusive.

In this issue of *Circulation*, Monin et al[5] describe a scoring system for patients with asymptomatic severe aortic stenosis based on the premise that both the state of the valve and the ventricle must be considered when assessing risk in asymptomatic patients. The risk of valve-specific factors such as aortic valve area, aortic valve calcification, transvalvular gradients, and peak aortic velocity have been well described, but the prognostic value of each or a combination of anatomic and functional valve information has not been consistently predictive of outcome.[6–8] The combination of valve pathology with brain natriuretic peptide (BNP) as a measure of ventricular function and wall stress has not been fully assessed and validated. Monin et al[5] create a scoring system that was first tested in an initial cohort and then validated prospectively in a second cohort. The development group was followed prospectively for 24 months or until the outcome end point was achieved (death from any cause or aortic valve replacement because of development of symptoms or positive exercise testing). The hazard ratio of the score (by quartile) and the performance of the score (by receiver operating characteristic curves) were assessed.

The risk score includes gender, serum BNP, and peak aortic jet velocity at baseline. These variables were chosen because each was shown to be independently associated with adverse outcome. Receiver operating characteristic curves show excellent performance of their risk score calculation as compared with the individual variables in the equation. Direct evidence of the power of the risk score can be seen in the calculated risk score for the 5 subjects who died in the validation cohort during follow-up. There is very little variation in the elevated scores for these subjects (range 15.2 to 19.1), despite the fact that individual variables like BNP or peak velocity varied greatly (range BNP 71 to 521 pg/mL, peak velocity 3.4 m/s to 5.6 m/s). The risk score for all of these subjects predicted event rates exceeding 70%.

Parts of these observations have been previously demonstrated by others. Pelikka et al[7] found that patients with very high peak velocity (≥4.5 m/s) had a higher risk of cardiac death and need for aortic valve replacement than those with peak velocities <4.5 m/s (relative risk 1.48; 95% confidence interval 1.20 to 1.81). A rapid increase in aortic jet velocity over time has been positively correlated with cardiovascular events in patients with asymptomatic severe aortic stenosis.[8] Monin et al[5] did not confirm certain previously recognized predictors of outcome. Aortic valve calcification has been

considered a strong predictor of development of symptoms and outcome in prior work. Rosenhek et al[8] followed a group of 128 patients with severe aortic stenosis and found that, using multivariable analyses including age, gender, coronary artery disease, hypertension, diabetes, hypercholesterolemia, and aortic jet velocity, only aortic valve calcification was significantly associated with death or the development of symptoms leading to aortic valve replacement. The role of aortic valve calcification has also been examined using a variety of imaging modalities, including echocardiography and multislice computed tomography. In a small study of aortic valve calcification, echocardiographic parameters, BNP, and C-reactive protein were compared with aortic valve calcium score by multislice computed tomography.[9] The calcium score was found to be most strongly associated with the development of symptoms. Given these data, it is important to consider why Monin et al find calcification to be of less importance. Valve calcification is difficult to quantify in a reproducible way and reflects an anatomic abnormality that may be discordant from the hemodynamic impact of the aortic valve obstruction, as measured by transaortic velocity and gradients. With the use of BNP and aortic valve velocity, the equation used in the scoring system emphasizes the hemodynamic effects of aortic stenosis at a valve level as well as the hemodynamic impact on the ventricle. It seems intuitive that this should better represent risk for adverse outcome, and this is corroborated in the study.

The most relevant new information in the current study[5] relates to the additional component of BNP. Severe aortic stenosis causes an increase in left ventricular wall stress that, with time, leads to hypertrophy and fibrosis.[10] B-type natriuretic peptide levels tend to increase in the serum in association with the increased ventricular wall stress. Although patients with elevated left ventricular end diastolic pressure may manifest overt heart failure, a portion of patients may be asymptomatic, despite a similar hemodynamic profile. BNP elevation, reflecting increased LV wall stress, may be useful in indicating subtle left ventricular pathology in asymptomatic patients.[11–14] An association between aortic stenosis and BNP was demonstrated by Lim et al,[11] who studied 70 patients with asymptomatic and symptomatic severe aortic stenosis. Elevated BNP levels were correlated strongly with poor clinical outcomes in all patients. Elevated BNP has been correlated with decreased aortic valve area, increased aortic jet velocity, increased left ventricular mass, and decreased exercise capacity.[12] Valve replacement has been shown to be associated with a decline in BNP, which is consistent with the expected hemodynamic effects of valve replacement.[13] Serial measurements of BNP have demonstrated larger increases in BNP in patients who go on to develop symptoms as compared with those who remain asymptomatic.[14] An increase in BNP over time may signal a progressive increase in left ventricular wall stress, which may lead to or reflect overt worsening of left ventricular function in patients with severe aortic stenosis.

The potential pathophysiological relationship between wall stress and sudden cardiac death is intriguing. The exact mechanism for syncope and sudden death in patients with aortic stenosis has not been fully elucidated.

Tachyarrhythmias or bradyarrhythmias could be associated with low output. Older work has also suggested the possibility of a stretch-induced baroreceptor response that results in inappropriate peripheral vasodilation during states of extreme fiber stimulation and an increase in left ventricular wall stress.[15,16] With a decrease in cardiac output, coronary hypoperfusion may also be a component of this life-threatening complex.[15,16] Whether BNP has potential to predict this unusual event is uncertain.

The prognostic value of BNP has also been demonstrated in a particularly challenging population of patients with low-flow, low-gradient aortic stenosis.[17] BNP levels are higher in those subjects with true aortic stenosis as compared with pseudostenosis, consistent with the concept that BNP is elevated in aortic stenosis because of the effect on wall tension and ventricular stretch associated with the increased afterload. Patients with lower BNP levels (<550 pg/mL) have better outcomes than those with elevated BNP, irrespective of factors such as contractile reserve thought to be important in overall outcome.

There are some limitations to the applicability of this scoring system. The study by Monin at al[5] excludes subjects with more than mild disease in any other valve and excludes patients with significant renal dysfunction. Renal dysfunction likely will limit the application of the score in its current form. The large role that exercise testing plays in this study also raises questions and potentially limits the applicability of this study. The end point of a positive exercise test may have biased the results somewhat, and not all patients in the development cohort had the exercise test at inclusion. This may be important because of the multitude of reasons for not having a patient perform an exercise test, such as physician concern about the risk and physical deconditioning, to name but 2 such reasons. The very reason for which a patient might be excluded from exercise testing may provide important information about overall risk. Additionally, in clinical practice, the use of exercise testing in patients with severe asymptomatic aortic stenosis is limited. The 2006 American Heart Association/American College of Cardiology guidelines for the management of aortic stenosis do not recommend routine exercise testing in patients with severe aortic stenosis, and it is considered a Class IIb recommendation.[1] However, the 2007 European Society of Cardiology guidelines include exercise testing in the algorithm proposed for the evaluation of patients with asymptomatic aortic stenosis[18] and offer that it may be used to guide valve surgery if the patient develops symptoms or manifests hemodynamic instability. Finally, although only 19% of the development cohort subjects who had aortic valve replacement were referred based on the results of an exercise test, the expected relationship between elevated BNP levels (indicative of increased wall stress) and exercise intolerance may make the predictive power of BNP appear greater than it would be in a population that is not having exercise testing results used as an indication for aortic valve replacement.

In conclusion, Monin et al[5] have developed and validated the prognostic value of a scoring system in patients with asymptomatic severe aortic stenosis. The score combines the patient's gender and functional severity of aortic stenosis

with an indirect assessment of left ventricular wall stress. These intuitively sound variables are incorporated into an easy-to-use scoring system that performs very well in predicting adverse outcome. Future studies will be needed to validate this strategy, but the data provide an important advance in consideration of which patients are appropriate for a "watchful waiting" strategy and which patients might benefit from earlier surgery.

Disclosures

None.

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