Predicting outcome in asymptomatic aortic stenosis: should we measure the severity of obstruction or its physiological consequences?

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This editorial refers to ‘Left ventricular systolic and diastolic function assessed by tissue Doppler imaging and outcome in asymptomatic aortic stenosis’†, by R.A.H. Stewart et al., on page 2216

‘Information is not knowledge’. Albert Einstein

In patients with severe aortic stenosis, it is well recognized that when symptoms develop, death will ensue unless the obstruction is relieved. Development of cardiac symptoms of angina, syncope, or heart failure indicate that a critical severity of obstruction has occurred and mark a change in the natural history of aortic stenosis. However, symptoms may be subtle, especially in the elderly patient who may have co-morbidities, including arthritis, lung disease, neurological disease, and frailty, that limit exercise capacity. Even if symptoms are realized, these may not be reported by the patient. Moreover, even in the truly asymptomatic patient, it is recognized that aortic stenosis is associated with a small risk of sudden death, which has been estimated at 1% per year.¹

Because of difficulties in determining exactly when the symptomatic stage of aortic stenosis has developed, and because of the risk of sudden death, many efforts have been made to predict outcomes in aortic stenosis accurately. Multiple investigators have tried to characterize the clinical, electrocardiographic, haemodynamic, imaging, and biomarker features which identify the patient at risk of adverse outcome. Echocardiography has become the mainstay of diagnostic assessment in patients with aortic stenosis.

Initial efforts to predict events in aortic stenosis have focused on quantifying the severity of obstruction. More recently, the physiological consequences of the obstruction, namely the effects on left ventricular (LV) mass and systolic and diastolic function, have gained attention (Figure 1). The recent, carefully conducted, multicentre study by Stewart et al.² was intended to combine these interests and to explore the role of tissue Doppler measures of LV systolic and diastolic function and echocardiographic determination of LV mass, along with assessments of aortic valve area and peak velocity. Thus, Stewart et al. sought to determine the role of various measurements for risk stratification of asymptomatic patients with moderate or severe aortic stenosis. The study included 183 patients with ejection fraction >50% and peak velocity by Doppler of >3.0 m/s. The mean age was 70 years and all patients had calcification of the aortic valve; the median aortic valve area was 0.81 cm². Patients were prospectively evaluated at 6 month intervals for the development of cardiac symptoms, and echocardiography was performed at baseline, 12 months, 24 months, and the final visit. LV ejection fraction was measured using single plane volumetrics, and systolic function was further assessed by measurement of peak systolic velocity of the mitral annulus ($S'$). Diastolic function was evaluated by Doppler using transmitral early (E) and late (A) diastolic velocities and E wave deceleration time, and tissue Doppler measurements of the mitral annular early (E') and late (A') diastolic velocities. The ratio E/E' was determined.

During a median follow-up of 31 months, 57% of patients developed symptoms attributable to aortic stenosis (most of whom were referred for aortic valve surgery) and 2% had cardiac events, including three patients who died suddenly and one who had a cardiac arrest and was resuscitated.

Patients who developed symptoms had a higher peak aortic velocity, lower aortic valve area, higher LV mass index, and lower S' velocity at baseline. Considering subsequent echocardiograms, the average rate of increase in peak aortic velocity and decrease in aortic valve area were greater in patients who became symptomatic. Peak aortic velocity was modestly correlated with LV mass and tissue Doppler S', as well as with E' and E/E'. However, in multivariate models, the peak aortic velocity was...
the only significant predictor of development of symptoms; the other variables appeared to add no further information.

Limitations include the small number of cardiac events and the investigators’ approach to assessment of diastolic function. The approach utilized has a high feasibility, but a more sophisticated approach that combines measurements may have been optimal for understanding the physiological consequences of aortic stenosis. Moreover, nearly half the patients studied had hypertension, which could contribute to LV hypertrophy and abnormalities in LV relaxation independent of the severity of aortic stenosis.

Comprehensive assessment of diastolic function includes assessment of myocardial relaxation, LV stiffness, and filling pressures. Abnormal relaxation is associated with prolonged isovolumic relaxation time, decreased E/A ratio, and E' velocity <8 cm/s. LV stiffness may be estimated by the deceleration time of the mitral E velocity or the A-wave duration. The E/E' ratio can provide an estimate of LV filling pressure but should be used in combination with other Doppler parameters as well as with consideration of the LV ejection fraction. Left atrial size reflects the chronic, cumulative effects of filling pressures. Strain and strain rate imaging may also be used for detecting early forms of regional myocardial dysfunction.

Echocardiographic markers of the severity of aortic stenosis, namely Doppler-derived aortic valve area as determined by the continuity equation, mean gradient, and peak velocity across the aortic valve, are recognized to be predictors of outcomes. Aortic valve area and peak velocity predict symptom development and mortality. Patients with a peak velocity \( \geq 4.5 \text{ m/s} \) have a 1.3-fold greater likelihood of developing symptoms and a 1.5-fold greater likelihood of having surgery or cardiac death compared with those with peak velocity >4 m/s but <4.5 m/s. However, these markers of severity are imperfect and, even in natural history studies of hundreds of patients, no specific cut-off has been identified which accurately identifies the patient at highest risk. In asymptomatic patients with severe aortic stenosis who have died suddenly, aortic valve velocities ranged from 4.0 to 5.8 m/s and aortic valve areas ranged from 0.53 to 1.28 cm\(^2\). Although patients who had events during follow-up tended to have higher velocities and smaller valve areas, there was broad overlap in these values with those who did not have events. In the uncommon situation when the valve cannot be well visualized with transthoracic echocardiography, excellent visualization of the valve may be accomplished with transoesophageal echocardiography. Computed tomography can assess the amount of calcification; the extent of aortic valve calcification has also been associated with outcome and probably parallels the severity of obstruction. Cardiac catheterization is currently reserved for uncommon situations in which non-invasive tests are inconclusive.

It is not surprising that focusing on the valve area alone is imperfect, as patients vary greatly in size and shape. For example, a valve area of 1.0 cm\(^2\) may be sufficient for a 60 kg woman but inadequate for a 150 kg man. An approach to account for this has been to index valve areas, usually to body surface area. Indexing for body size is appropriate in children and adolescents. However, this approach is controversial in adults, as normal valve area does not increase with excess weight. Nevertheless, indexing, at least
for lean body size, makes sense from a physiological standpoint and should be considered for adults at extremes of body size.

Considering the limitations of the valve area approach to evaluating patients with aortic stenosis, assessment of the physiological consequences of the obstruction, including assessment of LV systolic and diastolic function and mass, is appealing for predicting outcome in severe aortic stenosis. At least in theory, these approaches seem most appropriate for risk assessment in aortic stenosis, and various methods have been explored. LV hypertrophy may be detected by electrocardiography or echocardiography, and is associated with the development of symptoms. In aortic stenosis, LV systolic and diastolic dysfunction are predictive of mortality and may take years to recover after valve replacement. Left atrial size, an indicator of diastolic function, has been shown to be an independent predictor of mortality in asymptomatic patients with severe aortic stenosis. Myocardial fibrosis as detected by cardiac magnetic resonance imaging and pulmonary hypertension by Doppler echocardiography have been associated with increased mortality in patients with aortic stenosis. B-type natriuretic peptide has also been associated with perioperative survival, and may parallel symptom onset. Exercise testing is another way of assessing the physiological significance of obstruction, and may result in symptoms, ST-segment depression, hypotension, or ventricular arrhythmias in the patient in whom the obstruction has resulted in physiological compromise.

For optimal assessment of the patient with aortic stenosis, all information available to the time of echocardiography should be considered. Thus, not only the appearance of the valve and its area and gradient, but also the physiological consequences of the stenosis, namely LV hypertrophy, systolic and diastolic dysfunction, left atrial enlargement, and pulmonary hypertension, should be considered. It is a combination of this information, as well as careful consideration of the patient’s history, that will result in optimal clinical decision-making. We still lack knowledge of exactly when to intervene in the asymptomatic patient with severe aortic stenosis, but our tools for assessment and our understanding of how to use them continue to improve.

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References