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EDITORIAL COMMENT

Varying Hemodynamics and Differences in Prognosis in Patients With Asymptomatic Severe Aortic Stenosis and Preserved Ejection Fraction

A Call to Review Cutoffs and Concepts*

Frank A. Flachskampf, MD,
Mohammad Kavianipour, MD

Uppsala, Sweden

Management of patients with asymptomatic severe aortic stenosis (AS) and preserved ejection fraction (EF) continues to puzzle cardiologists. The open questions begin with the very definition of the lesion. American guidelines require a valve area <1 cm^2 and a mean gradient >40 mm Hg (1,2), but on the basis of the landmark report of Otto et al. (3), a peak velocity >4 m/s is also regarded as a marker of severe stenosis. However, mean gradients are usually approximately one-half of peak gradients in aortic stenosis, and thus a 4-m/s peak gradient predicts a peak gradient of 64 mm Hg, which typically will correspond to a mean gradient lower than 40 mm Hg, the cutoff for severe AS cited in the

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preceding text. The European guidelines, in turn, use an even higher >50-mm Hg cutoff for mean gradient in severe AS (4). Thus the cutoff sets of valve area, mean gradient, and peak velocity proposed by current guidelines are not entirely consistent, and a call for lowering the area threshold to 0.8 cm^2 has recently been made (5). Another qualifier that at closer scrutiny becomes less clear than desirable is normal left ventricular (LV) (systolic) function. American and European guidelines use a cutoff for EF of 50%, which is well-under 2 SDs of EF in presumably healthy populations (6). Thus, one might infer that in many patients incipient LV dysfunction is misclassified as "normal." This is confirmed by published data showing early impairment of longitudinal LV function in spite of normal EF, presumably signaling LV fibrosis (7). Finally, there is the problem of ascertaining asymptomatic status, which is notoriously difficult in the old population of—often comorbid—AS patients.

The study by Lancellotti et al. (8) in this issue of the *Journal* offers important new insights. The authors followed 150 patients (mean age: 70 years) with aortic valve area <1 cm^2, EF ≥55%, and a normal exercise test over an average of 27 months and examined the occurrence of cardiovascular mortality and aortic valve replacement, which was planned according to current guidelines on the basis of 6 or 12 monthly follow-up visits. Remarkably, no patient was lost to follow-up.

Following a proposition from the Québec group (9), patients were substratified by their mean gradients (<40 or ≥40 mm Hg) and their stroke volume index (<35 or ≥35 ml/m^2), calculated from echo data. Thus, 4 groups were defined: "normal" stroke volume index with high or low gradient, and low stroke volume index with high or low gradient, the latter representing the much discussed "paradoxical low flow, low gradient severe AS"; the term paradoxical refers to the intuitive contradiction between normal EF and low stroke volume index. Furthermore, brain natriuretic peptide (BNP) levels were measured at baseline.

The 4 groups did not differ significantly in age, sex, body surface area, LV volumes, or EF. Although significant differences were present in aortic valve areas, prognosis was not independently associated with this parameter. By multivariable analysis, the following baseline parameters emerged as independently predictive for prognosis: peak aortic velocities, LV end-diastolic volumes, left atrial volume (here measured as left atrial area index), the presence of low stroke volume index, in particular if combined with low gradients ("paradoxical" AS), and BNP. Some desirable data are not reported, such as whether low stroke volume index patients had more concentric remodeling. In the presence of concentric remodeling a ventricle will, at the same EF, generate less stroke volume than one with no concentric remodeling. Furthermore, the presence or absence of pulmonary hypertension was not reported, which might have impacted prognosis.

The follow-up data reveal several important points.

First, although EF was normal by inclusion criteria in all groups and EF values did not predict adverse prognosis on multivariable analysis, low stroke volume index independently predicted impaired prognosis. This is important, because commonly normal EF and normal stroke volume index are taken to be more-or-less equivalent. However, the present study makes it likely that EF >50% is too crude a measure of LV function and in particular is incapable of reflecting early damage to longitudinal myocardial function. Parameters like longitudinal velocities, mitral annular excursion, or longitudinal strain seem better-suited for this task. In fact, longitudinal strain in this study was significantly reduced in the low stroke volume index groups. Concordantly, BNP levels were higher in the low stroke volume index groups. This supports the suggestion of the authors

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From the Department of Cardiology, Uppsala University, Uppsala, Sweden. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

that these patients represent a group with more advanced disease, perhaps with more fibrotic remodeling. Unfortunately, the groups with low stroke volume index were quite small (n = 15 and n = 11 in the high and low gradient groups, respectively), somewhat tempering the strength of the conclusions. Another explanation for their low stroke volumes could be the significantly increased valvulo-arterial impedance, a measure of LV afterload, in the low-stroke volume index groups.

Second, "paradoxical" low stroke volume index, low-gradient aortic AS was found in 7%. These patients, in spite of their "moderate" mean gradients of 33 ± 5 mm Hg, had the worst prognosis of the whole cohort. They had a 5-fold higher hazard ratio (5.22; 95% confidence interval: 2.02 to 14.1) for death or aortic valve replacement than patients with ≥35 ml/m^2 stroke volume index and high gradients. This is in line with other reports on impaired prognosis in paradoxic AS (9,10). However, it contrasts starkly with a recently published retrospective analysis from the Simvastatin and Ezetimibe in Aortic Stenosis study (11), which reported near-identical survival curves for patients with paradoxical AS (aortic valve area <1 cm^2, mean gradient <40 mm Hg) compared with patients with moderate AS (aortic valve area 1 to 1.5 cm^2, mean gradient <40 mm Hg), both with normal EF. As the authors of the present study appropriately point out, patients with paradoxical severe AS in the Jander et al. (11) study had lower body size than their comparators, and after correction for this, their stroke volume index averaged 35 ml/m^2, so that presumably approximately one-half of them did not truly have low (<35 ml/m^2) stroke volume index. Furthermore, stroke volume index calculated from the reported LV volumes (instead of LV outflow tract stroke volumes) results in even higher values. Moreover, patients were differently selected in the 2 studies.

Third, 3 of 150 patients died suddenly during follow-up. The incidence of sudden cardiac death in asymptomatic severe AS has often been debated. Rosenhek et al. (12) reported 1 sudden death in 123 initially asymptomatic patients followed over an average of 22 months; Otto et al. (3) saw no sudden death in 123 patients followed over a mean of 2.5 years. Thus, the study confirms that incidence of sudden death in such patients, if followed-up regularly and carefully, is lower than 1%/year.

How might the results of this study impact the management of patients with asymptomatic severe AS (area <1 cm^2) with preserved EF ? First, it re-emphasizes the utility of close follow-up (6- to 12-month intervals) and liberal use of exercise to confirm lack of symptoms. Next, it confirms that some of these patients have mean gradients <40 mm Hg (and peak velocities <4 m/s), thus not fulfilling standard guideline criteria. Of these, those with relatively low stroke volumes (stroke volume index <35 ml/m^2) seem to have worse disease, perhaps more fibrosis, and a worse prognosis. These are further characterized by impaired longitudinal function (e.g., lower longitudinal strain but also lower longitudinal tissue velocities and mitral plane excursion) and higher BNP levels. Thus, the study also calls for a more complete evaluation of AS severity than just the peak and mean gradient and EF. We must remember, however, that "composite" parameters like valve area by continuity or stroke volume suffer from the compounded risks of measurement error. Therefore, the first reflex in the presence of a surprising, "paradoxic" set of echo data should be critical review of the raw data, in particular outflow tract diameter and both continuous-wave and pulsed-wave Doppler signal quality. If confirmed, these patients should perhaps be further evaluated with regard to LV longitudinal function and BNP. Clear guidance as to which cutoffs might prompt valve replacement is missing so far, but studies like the present report help making informed individual decisions.

Reprint requests and correspondence: Dr. Frank A. Flachskampf, Akademiska Sjukhuset Ingång 40 våning 5, 751 85 Uppsala, Sweden. E-mail: frank.flachskampf@medsci.uu.se.

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