Low-Flow, Low-Gradient Aortic Stenosis With Preserved Ejection Fraction
Still a Challenging Condition*

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Current practice of aortic stenosis assessment. Aortic stenosis (AS) has become the most frequent valve disease and has a very poor outcome when left untreated in symptomatic patients. Because aortic valve replacement can—in the best case—normalize survival, timely diagnosis and correct quantification of AS are crucial (1). Current practice guidelines recommend echocardiography as the method of choice, whereas catheterization is only indicated when echocardiography is non-diagnostic or discrepant with clinical data (1,2). Nevertheless, echocardiography remains markedly investigator-dependent in general daily practice. Avoidance of basic sources of error such as velocity underestimation by mal-alignment of Doppler beam and jet or flow miscalculations requires special training and skills that are frequently not present, considering the widespread use of ultrasound. The primary hemodynamic parameters recommended for assessment of AS severity are peak jet velocity, mean gradient, and aortic valve area (AVA) calculated by the continuity equation (2). Although AVA being less flow-dependent would theoretically be the best parameter, transvalvular velocity and gradient remain the more-robust and better reproducible measurements in daily practice. Because very small changes in AVA in the range between 1.2 and 0.8 cm² cause highly significant changes in hemodynamic consequences from unremarkable to severe flow obstruction, very accurate measurement techniques would be required when characterizing stenosis severity solely by AVA. However, such techniques are currently not available. Therefore, an integrated approach including AVA, velocity/gradient, left ventricular (LV) function, flow status, and clinical presentation is strongly recommended (1,2).

Although current guidelines define severe AS by a peak velocity >4 m/s, mean gradient >40 mm Hg, and AVA <1.0 cm², many patients present with discrepant findings with regard to these criteria (2). Most frequently patients might have a small AVA (<1.0 cm²) but nevertheless lower velocity (<4.0 m/s) and gradient (<30 to 40 mm Hg). When measurement errors such as underestimation of left ventricular outflow tract (LVOT) cross-section area, or LVOT velocity that result in underestimation of flow and eventually AVA are excluded and the patient is not of small stature, “low flow conditions” due to poor LV function or less commonly severe mitral regurgitation or mitral stenosis must be considered (2). However, in this situation a small AVA does not necessarily indicate severe AS. Left ventricular dysfunction of other cause might result in a severely reduced AVA of a moderately diseased aortic valve, because of insufficient energy to open the cusps resulting in “pseudo-severe AS.” Although still controversial, dobutamine response with either marked AVA increase or little AVA change but gradient increase might help to separate pseudo-severe from truly severe AS (3). Absence of contractile reserve makes it impossible to distinguish between these entities and predicts particularly poor long-term outcome (4). Nevertheless, valve replacement might improve LV function and outcome even in this subgroup and therefore might be considered following current guidelines (IIb recommendation) (1,5).

The controversial new entity of “paradoxical low-flow, low-gradient severe AS.” Since the group of Pibarot and Dusmenil (6) published for the first time the new entity of paradoxical low-flow, low-gradient (PLFLG) severe AS despite preserved ejection fraction in 2007, assessment of AS has become even more complicated. In this article, Hachicha et al. (6) reported that patients with small AVA and low gradient in the presence of preserved left ventricular ejection fraction (LVEF) who were nevertheless found to have low transvalvular flow (35% of 512 patients) might indeed have severe AS and have a poor outcome if managed medically. Although confirmed by others (7), this entity remains controversial. Minners et al. (8) also reported, in a series of 2,427 patients with AVA <2.0 cm² and preserved LV function, that 30% of the patients had AVA <1.0 cm² but mean gradient <40 mm Hg but suggested that this was mainly caused by inconsistency of currently recommended cutoffs for velocity/gradient and AVA. According to the Gorlin equation in the presence of normal cardiac output, an AVA of 1.0 cm² yields indeed a mean gradient of only 26 mm Hg, and an AVA of ≤0.81 cm² is required to reach gradients of 40 mm Hg and greater (9). On the basis of such findings, Jander (10) proposed to lower the AVA cutoff for severe AS to 0.8 cm² to make the criteria velocity/gradient and AVA criteria consistent. Similarly, Zoghbi (11) re-

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ported in an editorial that a review of 1,115 consecutive patients with AS showed an appropriately corresponding AVA cutoff close to 0.8 cm² in patients with normal flow. The position that low-gradient “severe” AS with preserved LVEF is mostly moderate AS that is just misclassified due to inconsistency of recommended criteria for AVA and gradient seems to be supported by a recent study by Jander et al. (12). In 1,525 patients included in the prospective SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial, the authors identified 184 with moderate AS and 435 with “low-gradient severe” AS (AVA <1.0 cm², mean gradient ≤40 mm Hg). Outcome with regard to valve-related events, major cardiovascular events, or cardiac death did not differ between these 2 groups. However, the series of Hachicha and others (6,7) differed markedly from the patient population of Jander (12). While the SEAS trial followed asymptomatic low-risk patients with mild or moderate AS to study the effect of lipid lowering on the progression of AS, the other studies included symptomatic patients with older age and more comorbidities. In particular, most were hypertensive and had LV hypertrophy, whereas normal wall thickness relative to LV size was present in SEAS. Thus, in the study by Jander, measurement errors, small body size, and inconsistency of guideline criteria are more likely to be a frequent reason for a low gradient in the presence of a small AVA. In any case, this study highlights that an uncritical, too-liberal use of “low-gradient severe AS” might lead to surgical procedures in patients who will not benefit. The study also demonstrates once more the limitations of the continuity equation. The use of the LVOT diameter with assumption of a circular LVOT area frequently leads to an underestimation of this area with consequent underestimation of the transvalvular flow and thus the AVA. We have previously reported that this error might lead to an underestimation of the AVA by, on average, 0.2 cm² (13). Stroke volumes calculated by volumetric approach were indeed approximately 20% higher than those calculated by Doppler in the study by Jander, indicating that the percentage of low-flow conditions was probably overestimated and that AVAs might frequently have been underestimated.

New data to support the entity of PLFLG severe AS. In this issue of the Journal, Clavel et al. (14) sought to further elucidate the discrepancies between previous studies and to confirm the concept of PLFLG severe AS. In this study, 187 patients with PLFLG severe AS were retrospectively matched according to the gradient with 187 patients with moderate AS and according to the AVA with 187 patients with high-gradient severe AS. After adjustment for age, sex, symptoms, coronary artery disease, diabetes, type of treatment, and LVEF, patients with PLFLG severe AS had a 1.88-fold increase in overall mortality and a 2.87-fold increase in cardiovascular mortality compared with moderate AS, and aortic valve replacement was significantly associated with improved survival (hazard ratio [HR]: 0.50). The authors conclude that the finding of a low gradient cannot exclude the presence of severe AS in patients with small AVA and preserved LVEF, that a more comprehensive diagnostic evaluation should be used to corroborate the stenosis severity, and that aortic valve replacement might improve outcome after confirmation of PLFLG severe AS.

This important study definitely adds to our current knowledge of this challenging subgroup of AS patients. Nevertheless, there remains a number of unresolved issues, and the authors are wise by being rather careful with their conclusions.

This retrospective analysis matched groups only by hemodynamic criteria. The PLFLG patients were significantly older and had higher prevalence of female sex, coronary artery disease, hypertension, and small LV cavities. Although adjustment for the aforementioned risk factors was performed, relevant differences in their severity—particularly in the extent of hypertensive disease—cannot be excluded; and important risk factors such as pulmonary, renal, or peripheral arterial disease that have impact not only on outcome but also on the decision for surgery were not included. Thus, there remains some concern with regard to confounding factors. It could still be that PLFLG patients—and, there again, those who did not undergo surgery—were just sicker with regard to comorbidities, compared with the other groups. Although surgery was associated with improved survival in this group, the HR was only 0.50 compared with 0.18 for high-gradient AS, indicating a smaller effect of surgery on survival. One explanation could be that these patients had too-advanced disease or that they had more severe comorbidities unaffected by valve replacement or even increasing operative risk. Finally, it could be that only a subgroup of patients within the PLFLG patients indeed had severe stenosis and thus benefit from surgery. What is even more concerning when interpreting these results is that the HR of 0.50 in PLFLG AS is close to that of 0.44 in moderate AS. Although the latter just did not reach statistical significance (p = 0.09), the former just reached significance (p = 0.04). Although the numbers are close, the authors would probably not conclude (even if both were significant) to operate on moderate AS. For these reasons the results have to be interpreted with caution and must be considered hypothesis-generating rather than providing evidence.

It is also important to recognize that patients with PLFLG AS in this study seem to be typically elderly (predominantly women) with hypertension. Hypertension might indeed be a key player in this context. Left ventricular hypertrophy and increased fibrosis as they were reported in another recent study (15) might be due to or at least be heavily affected by long-lasting hypertension rather than presenting more advanced stage of AS. The extent of hypertensive disease might have influenced the presence of symptoms as well as the observed outcome of these patients. Overall, the study might conclude that the PLFLG severe AS exists but cannot entirely solve the difficulty in selecting those in this group who indeed have severe AS and
eventually benefit from valve replacement. In this context, it must be kept in mind that it remains totally unknown how many patients in such a population might have pseudosevere AS (see preceding text). Whether dobutamine echocardiography can also be helpful in this setting remains to be shown. That we are dealing with small, stiff ventricles with normal ejection fraction—in contrast to LFLG AS with poor LVEF—makes that at least questionable.

**How to deal currently with “PLFLG severe AS.”** The subset of AS patients who present with a small AVA but low gradient despite preserved LVEF remains definitely challenging. Although such patients might indeed have severe AS, other reasons for this combination such as underestimation of transaortic flow by Doppler echocardiography, inconsistency of grading criteria, and small body size must be carefully excluded. This might require—in addition to more detailed echocardiographic measurements—additional diagnostic tools such as magnetic resonance imaging and catheterization. Because such patients are typically elderly with hypertension and other comorbidities, the evaluation remains difficult even after confirmation of hemodynamic data. Left ventricular hypertrophy and fibrosis as well as symptoms or elevation of neurohormones might also be due to hypertensive heart disease and not help to re-assure severe AS. Furthermore, it remains unclear how to exclude pseudosevere AS, and the severity of valve calcification might currently be the only clue in this context (16). Thus, PLFLG AS is associated with poor outcome in patients with the characteristics of the presented study population. How to select those patients who definitely have severe AS and who are most likely to benefit from surgery, however, still needs to be better defined.

**References**


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