

Editorial

Low Gradient Severe Aortic Stenosis With Preserved Ejection Fraction: Don't Forget the Flow!

Estenosis aórtica grave con bajo gradiente y fracción de eyección preservada: no olvidemos el flujo

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INTRODUCTION

In *Revista Española de Cardiología*, González-Cánovas et al.¹ reported the results of a study that examined whether severe aortic stenosis (AS) with low-gradient and preserved ejection fraction is a real phenomenon or whether it corresponds to an error in measurement. As they appropriately emphasize in their introduction, most cardiologists now recognize that this mode of presentation is frequently encountered during echocardiographic examinations. Also, several studies have reported that this entity is a more advanced form of the disease and has a worse prognosis. In contrast, a recent prospective study suggested that prognosis in these cases is similar to moderate AS and that this subcategory of patients probably reflects an error in classification. To answer this question, González-Cánovas et al.¹ examined 63 patients with paradoxical low-gradient AS and found that aortic valve area (AVA) measured by 3-dimensional (3D) aortic valve planimetry was congruent with that obtained by trans-thoracic echocardiography (TTE) using the continuity equation; the presence of severe AS was confirmed in 85% of patients. They hence concluded that paradoxical low-gradient severe AS is a real entity. These results are important and we would like to make a few observations so that these results may be interpreted in the right context.

DEFINITION OF LOW GRADIENT AORTIC VALVE STENOSIS: DON'T FORGET THE FLOW

In the original description of this condition,^{2,3} the low gradient was deemed to be due to a decrease in flow in relation to a marked increase in global hemodynamic load, more severe left ventricular (LV) concentric remodeling, a small LV cavity, a restrictive physiology, and a decrease in intrinsic LV function despite a normal ejection fraction. Hence, low flow was considered to be an integral component of this entity.^{2,3} Since outcome data showed that these patients had worse prognosis than the classical form of

AS,^{3–5} these patients were also considered to be at a more advanced stage of the disease. However, it later became evident that there was yet another subgroup of patients with severe AS who had low gradient that could be attributed to inherent inconsistencies in the criteria's guidelines.^{3,6} Indeed, theoretical models have shown that a patient with normal transvalvular flow rate and an effective orifice area of 1.0 cm² should be expected to have a mean gradient of around 30 mmHg to 35 mmHg rather than the cutoff value of 40 mmHg given in the guidelines. Conspicuously, the degree of AS and global hemodynamic load in these patients with low gradient but normal flow was less severe than in patients with both low gradient and low flow; also, these patients did not present the characteristics of more severe LV concentric remodeling, small LV cavity, and restrictive physiology observed in patients with low flow. Hence, it became apparent that patients with severe AS could be divided into 4 subgroups according to flow and gradient and that there was a clear distinction to be made between low-flow, low-gradient AS and normal-flow, low-gradient AS with regards to severity and prognosis.³ Subsequently, Lancellotti et al.⁷ confirmed that low-flow, low-gradient AS and normal-flow, low-gradient AS were indeed 2 very distinct entities; since the former entity had the worst prognosis amongst the 4 subgroups and could thus be considered to be at a more advanced stage of the disease, whereas the latter had the best prognosis and was thus likely to have the less advanced form of severe AS. The study by Jander et al.,⁸ emerging from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, did not make this distinction when they concluded that prognosis in low-gradient AS is similar to moderate AS and they did not account for body surface area. Moreover, the SEAS trial followed asymptomatic low-risk patients with mild or moderate AS at the onset of the study, and on average, the patients they identified as having developed low-gradient severe AS did not exhibit the features of severe LV concentric remodeling, small LV cavity, and restrictive physiology typically observed in patients with paradoxical low-flow AS. As recently discussed,^{9,10} the finding of low-gradient severe AS in these cases could rather be due to 1 or more of the following: a) influence of body size; b) measurement errors, and c) inconsistent grading due to intrinsic discrepancies in guidelines criteria.⁶ This interpretation is further supported by the results of a previous substudy from the SEAS trial, whereby, in the same cohort of patients, Cramariuc et al.¹¹ identified only 100 patients with

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low-flow AS whereas Jander et al.⁸ identified more than twice that number of patients (ie, 223 patients) with low-flow AS. The results from the Jander et al. trial were, however, based on the stroke volume measured by Doppler in the LV outflow tract whereas Cramariuc et al. utilized a volumetric method based on the Teicholz formula. Also, the patients reported by Cramariuc et al.¹¹ typically exhibited the restrictive features usually associated with paradoxical low-flow AS but this was not the case in the 223 patients reported by Jander et al. A possible explanation for this discrepancy is that many of the patients in the latter study could have had an underestimation of stroke volume resulting in overestimation of AS severity due to an error in measurement. Hence, these observations further underline the importance of making a meticulous differential diagnosis when seeing a patient with low-flow, low-gradient severe AS despite a preserved LV ejection fraction, and in particular, to validate the stroke volume measurements and to search for other features usually associated with paradoxical low-flow AS (ie, small LV with restrictive physiology, unequivocally high valvulo-arterial impedance, and so on).¹⁰

CONCORDANT VS DISCORDANT PATIENTS

The distinction between low-flow and normal-flow, low-gradient AS was not made in the study by González-Cánovas et al.¹ but this would not affect the relevance of the results since the primary objective of these authors was essentially to determine the extent to which measurement errors of AVA could contribute to the apparent discrepancy between AVA and gradient. In this context, it is interesting to note that the 52 (85%) patients with concordant findings between TTE and 3D transesophageal echocardiography (3D-TEE) had an average value for stroke volume index=31.6 (9.8) mL/m² (Table 1 of the study¹) well below the threshold of 35 mL/m² utilized to identify patients with low-flow AS^{2,3,5,7,12} as well as an average LV dimension (41.9 [5.4] mm) consistent with a small LV cavity and a restrictive physiology. Hence, most of these patients likely had the bona fide paradoxical low-flow, low-gradient form of severe AS and the results of the study confirm that they were properly identified. Such a finding is comforting since these patients have been shown to be at a more advanced stage of their disease and to have a definitely worse prognosis if treated medically. Unfortunately, due to the low gradient and potential misinterpretation of the data, they may be erroneously deemed as having a prognosis similar to moderate AS up to the extent that they might be inappropriately denied operation even if symptomatic.

In contrast and as underlined by the authors, most of the patients with discordant findings had an AVA between 0.8 cm and 1.0 cm² on TTE and their average values for AVA were significantly higher than in the patients with concordant findings (AVA by TTE=0.86 (0.08) vs 0.72 (0.16) cm²; *P*=.024 and AVA by 3D-TEE=1.08 (0.05) vs 0.69 (0.15) cm²; *P*=.0001). Moreover, their LV dimensions were much larger than in the concordant patients (51.6 [9.3] vs 41.9 [5.4]; *P*=.0001) and their average SV index (38.3 [9.8] mL/m²) was consistent with normal flow. Hence, on the basis of flow and gradient, most of these patients likely had the mildest form of severe AS and the apparent discrepancy between AVA and gradient in their case is not likely to be due to low flow but rather due to 1 or more of the aforementioned factors ie, variations in body size, measurement errors, or the intrinsic discrepancies in the guideline criteria.^{3,6} These results emphasize that, in the absence of low flow and the other factors usually associated with this entity ie, higher valvulo-arterial impedance,¹³ small LV, and restrictive physiology, it becomes important to corroborate the true severity and actual repercussions of the AS by other means such as AVA 3D, computed tomography scan, calcium score, exercise testing etc. Indeed, some

of these patients are likely to have borderline severity and a relatively good prognosis if asymptomatic.

ANATOMIC VS EFFECTIVE ORIFICE AREA

The mean difference between AVA by TTE and AVA by 3D-TEE was very small with similar classification in 85% of cases. There was, however, only gross agreement with regards to individual values. This should however be of no surprise since, as pointed out by the authors, measurement of AVA by 3D-TEE is a planimetry of the anatomic area of the valve whereas the AVA by TTE measured by the continuity equation is a measure of the effective or physiological area occupied by flow. Theoretically, and if there are no measurement errors, the effective orifice area should always be smaller than the anatomic area but in varying proportions depending on the shape of the valve and the geometry of the orifice. Hence, *in vitro* studies have shown that the ratio between the 2, called the contraction coefficient, may vary between 0.6 and 1.0. *In vivo*, the anatomic area measured by planimetry may, however, be underestimated in heavily calcified valves due to shadowing and loss of spatial resolution and, as mentioned, temporal resolution might also be an issue. It is interesting to note in this context that the AVA by 3D-TEE was clearly higher than the AVA by TTE in the discordant patients where the disease was less severe and who were thus likely to have less calcified valves. The observed differences between AVA by 3D-TEE and AVA by TTE could thus be real and physiologically, these patients could thus still have severe AS since it is the effective orifice area and not the anatomic area that determines increased burden supported by the ventricle.¹⁴

CONCLUSIONS

González-Cánovas et al.¹ are to be commended for a well-conceived study that further confirms that paradoxical low-flow, low-gradient severe AS despite preserved ejection fraction is a real and relatively frequent entity in patients with degenerative AS. Indeed, the prevalence of low-gradient severe AS in their series was 24.9% and, as outlined, the great majority of concordant patients, which represented 22% of their cohort, are likely to have had bona fide paradoxical low-flow, low-gradient AS. These results are thus highly consistent with the 10% to 25% prevalence for paradoxical low-flow, low-gradient AS reported in the literature.¹⁰ Proper recognition is important, given that these patients have a much poorer prognosis if treated medically and that misdiagnosis may lead to underutilization or inappropriate delay in surgery.^{2–5} The current 2006 American College of Cardiology/American Heart Association guidelines¹⁵ do not contain any specific recommendation for the management of these patients, given that this is a new entity first described in 2007.² The more recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines,¹² however, have a class IIa recommendation stating that “Aortic valve replacement should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) AS with normal ejection fraction only after careful confirmation of severe AS”. This recommendation recognizes the clinical relevance of the entity, emphasizing that it represents an important diagnostic challenge with regards to accuracy of measurements. Hence, when there is a discordance between the AVA (in the severe range) and the gradient (in the moderate range) in patients with preserved LV ejection fraction, a more comprehensive Doppler echocardiographic evaluation and potentially other diagnostic tests (exercise, stress echocardiography, computed tomography, magnetic resonance imaging, plasma natriuretic peptides, and invasive studies) may be required to confirm disease severity and guide therapeutic management.¹⁰

CONFLICTS OF INTEREST

None declared.

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