

Grading aortic stenosis severity when the flow modifies the gradient/valve area correlation

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Valvular aortic stenosis (AS) is the most frequent valvular disease in developed countries. The diagnosis of AS is classically confirmed by echocardiography, the standard tool for detecting and assessing the severity of the disease (1). Nevertheless, assessment of AS severity is still challenging. Severe AS is usually defined as mean gradient >40 mmHg, aortic valve area (AVA) <1 cm² and peak aortic jet velocity >4.0 m/s (2). However, discrepancies are frequently observed between the mean gradient and the valve area in a single patient (3). These discrepancies are easy to understand in patients with low cardiac output secondary to reduced LV ejection fraction, but also may occur in patients with apparently preserved LV function (4). In daily practice, they may potentially lead to an underestimation of stenosis and symptom severity and thus to inappropriate delay of aortic valve replacement (AVR), which may, in turn, have a negative impact on patient outcome (5-7). In this issue of Cardiovascular Diagnosis and Therapy, OZKAN has elegantly reviewed the concept of low gradient AS in patients with preserved LV function (8).

New aortic stenosis grading classification

Recently, several authors have reported that under the same denomination of severe AS (AVA <1 cm²), several entities may be identified which differ in terms of transvalvular flow rates and pressure gradients develop (9-11). The first to underline the importance of integrating the valve-gradient relationship to the flow pattern was the group of Pibarot *et al.* (5), whereas Miners *et al.* (3) were the first to clearly show the inconsistencies for grading the severity of AS and to propose with Dumesnil *et al.* (6) the new classification of

AS. In patients with an AVA <1 cm², four flow-gradient AS categories can be identified: normal flow/low gradient (NF/LG), normal flow/high gradient (NF/HG), low flow/high gradient (LF/HG) and low flow/low gradient (LF/LG). LF is defined as an indexed LV stroke volume <35 mL/m² and LG as a mean trans-aortic pressure gradient <40 mmHg (12).

Normal flow-low gradient

This pattern is observed in 31-38% of patients and seems to identify a group of patients with a less severe degree of AS-inherent inconsistency contained in the guidelines-or who has been exposed to the disease for a shorter period of time. This entity is characterized by a preserved LV longitudinal myocardial function, resulting in lower BNP level and Monin's risk score (12,13). The prognosis of these patients seems to be relatively preserved as compared with the other categories.

Normal flow-high gradient

This pattern represents the most prevalent entity (39-72%) and is fully consistent with the criteria proposed by the guidelines (4,5,12). When compared with NF/LG group, although the LV longitudinal function is preserved, the BNP is higher and the cardiac event-free survival rate of NF/HG is reduced. Furthermore, patients with NF/HG seem to have more severe AS suggesting a longer exposition to this progressive disease. When symptomatic, these patients are classically referred for AVR, whereas when asymptomatic, the management of these patients underlines the need for optimized risk stratification.

Low flow-high gradient

This pattern accounts for 8% of patients with severe AS (4,12). It is characterized by an indexed LV stroke volume $<35 \text{ mL/m}^2$ in spite of preserved LV ejection fraction, a high BNP level and Monin's risk score and a significant reduction in LV longitudinal function (14). Of note, LV ejection fraction is a crude estimate of LV systolic function. LV ejection fraction is influenced by both intrinsic myocardial function and LV cavity geometry. Hence, for a similar extent of intrinsic myocardial shortening, the LV ejection fraction will tend to increase in relation to the extent of LV concentric remodelling. The LV ejection fraction may therefore markedly underestimate the extent of myocardial impairment in the presence of LV concentric remodelling such as is generally the case in AS patients. Hence, what is normal for an LV with normal geometry may be abnormal for a LV with concentric remodelling. Moreover, the reduction in LV output (related to intrinsic myocardial dysfunction and significant LV remodelling) may, in turn, result in lower than expected trans-valvular gradients. The outcome of these patients is nearly identical to patients with NF/HG. When symptomatic, these patients tend to have a better survival if treated surgically.

Low flow-low gradient

The prevalence of LF/LG pattern seems to be lower than what initially reported. This entity accounts for 7% in asymptomatic patients and up to 15-35% in symptomatic patients (4-6,12,14). This pattern, namely paradoxical low-flow AS, represents a challenging clinical entity that has been recently emphasized. It is associated with more pronounced LV concentric remodelling, smaller LV cavity, increased global LV afterload, intrinsic myocardial dysfunction, myocardial fibrosis and a dismal prognosis (12,15). In asymptomatic patients, we have shown that the likelihood of remaining alive without AVR at 3 years was 5-fold lower than for the NF/LG pattern and 4.3-fold higher than in the NF/HG group (12). This clinical entity is often misdiagnosed, which may lead to an underestimation of AS severity and thereby to underutilization or inappropriate delay of surgery. It is important to recognize this entity in order not to deny surgery to a symptomatic patient with small AVA and LG.

Discordance between gradient and valve area

Potential causes of discordance between AVA and

gradient in patients with preserved LV ejection fraction include (I) measurement errors; (II) small body size; (III) paradoxical low flow AS; and (IV) inconsistent grading related to intrinsic discrepancies in guidelines criteria (4,6,7,10,11). First of all, patients with small body size and LV dimensions may exhibit a lower trans-valvular pressure gradient because of a lower albeit normal stroke volume. Secondly, the stroke volume and therefore the AVA may be underestimated because of underestimation of LV outflow tract and/or misplacement of pulsed-wave Doppler sample volume. Several methods can be used to corroborate the Doppler-echocardiographic measurements of stroke volume and AVA. For example, in the absence of significant mitral regurgitation, the stroke volume can easily be estimated by the Simpson's method (volumetric method to measure LV ejection fraction and volumes). If the stroke volume measured by these independent methods is consistent with the stroke volume measured in the LV outflow tract, one can be reassured about the accuracy of the measurement of stroke volume. Third, paradoxical LF/LG represents a new entity in which the LF state results from both LV concentric remodelling and reduced subendocardial longitudinal function. This outlines the absence of erroneous estimation of AS severity. Fourth, in some cases, discrepancy in gradient-valve area relationship may be related to inconsistencies in current guidelines. A harmonization of the definition of severe AS may reclassify some of these patients with "severe" AS into "moderate" AS. When one combines the current prospective clinical data with earlier hemodynamic echo and invasive data, it seems that a gradient of 40 mmHg fits more with a valve area of 0.8 cm^2 whereas a valve area of 1 cm^2 relates to a mean gradient of 26 mmHg (3,6,16). Furthermore, when there is a discordance between the valve area (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 (BNP, Calcium score by multislice computed tomography, exercise/dobutamine stress echocardiography) may be required to confirm disease severity and guide therapeutic management.

Clinical implications and management

In daily practice, the assessment of AS severity should integrate the flow-gradient pattern to the classic measurement of AVA. As a general rule, a low trans-valvular gradient ($<40 \text{ mmHg}$) or velocity ($<4 \text{ m/s}$) does not exclude

Table 1 Main studies on outcome in patients with paradoxical low-flow and/or low gradient AS

	Patients' characteristics	Number of patients	AS Category	Outcome
Hachicha <i>et al.</i> (5)	Retrospective Symptomatic and asymptomatic	512	LF AS 181 (35%) 80 AVR	Poorer outcome compared to normal flow AS, especially if medically treated
Barasch <i>et al.</i> (17)	Retrospective + Prospective Asymptomatic	215	LF AS 47 (22%) 15 AVR	Patients with a mean gradient <30 mmHg are less frequently referred to surgery and have higher mortality
Dumesnil <i>et al.</i> (6)	Retrospective Symptomatic and asymptomatic	512	LF/LG AS 123 (24%) 44 AVR	Tended to have a poorer outcome when treated medically
Jander <i>et al.</i> (7)	Prospective Asymptomatic	1,525	LG AS 435 (29%) 252 AVR	LF/LG AS patients have an outcome similar to patients with moderate AS
Tarantini <i>et al.</i> (16)	Retrospective Symptomatic	102	LF/LG AS 102 (100%) 73 AVR	AVR was associated with significant improvement in long-term survival and functional status
Lancellotti <i>et al.</i> (12)	Prospective Asymptomatic Normal exercise test	150	LF/LG AS 11 (7%)	The LF/LG pattern was associated with the poorer outcome

AS, aortic stenosis; AVR, aortic valve replacement; LF, low flow; LG, low gradient

the presence of a severe AS in patients with small AVA and preserved LV ejection fraction. In addition, a preserved LV ejection fraction (>50%) does not exclude the presence of myocardial systolic dysfunction and low trans-valvular flow in AS. Patients with NF/LG AS classically have no or minimal subendocardial dysfunction and a relatively preserved outcome. In this NF/LG category, indication for AVR should be restricted to patients in whom symptoms can clearly be attributed to AS. In the NF/HG category, AVR (surgical or percutaneous) is the only therapy to significantly improve both survival and symptoms. When asymptomatic, individual risk stratification can help identify patients who may benefit from early surgery. In the other categories, the LF state represents a witness of intrinsic myocardial dysfunction and a more advanced disease process. Symptomatic patients with LF/HG should also benefit from prompt AVR. When asymptomatic, individual risk stratification should also be encouraged. Exercise echocardiography may be of interest by unmasking patients with limited valve compliance and/or exhausted LV contractile reserve (17,18). Paradoxical LF/LG conveys a poor outcome even in asymptomatic patients. In this category, though the benefit of surgery is not proven, AVR may probably be beneficial in selected symptomatic patients (7,19,20) (Table 1). In clinical practice, ascertaining this entity is challenging. Before considering surgery,

symptoms should be matched to the severity of AS. In low risk patients, AVR may be advocated. In high-risk patients, additional outcome studies are needed to determine the most appropriate modality and timing of treatment.

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