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REVIEW ARTICLE

Low-flow aortic stenosis and preserved left ventricular ejection fraction

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Abstract Valvular aortic stenosis (AS) is the most frequent valvular disease in developed countries. Treatment decisions in AS are mainly based upon the symptomatic status of the patient and the severity of AS. Doppler echocardiography represents the standard tool for detecting and assessing the severity of the disease. Under the same denomination of severe AS [aortic valve area (AVA) < 1 cm^2], several entities might be identified that differ in terms of trans-valvular flow rates and pressure gradients development. From a clinical standpoint, severe AS (AVA < 1 cm^2) can be subdivided into 4 flow-gradient patterns: 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). The most commonly described entity is the paradoxical low-flow, low-gradient severe AS state, in which the stroke volume is unexpectedly reduced, despite preserved left ventricular (LV) ejection fraction. In daily practice, misdiagnosing this clinical condition might lead to an inappropriate timing of follow-up with an unnecessary delay of aortic valve replacement (AVR), which may, in turn, have a negative impact on patient outcome.

Keywords Aortic stenosis · Classification · Echocardiography · Outcome

Introduction

Valvular aortic stenosis (AS) is the most frequent valvular disease in developed countries. Treatment decisions in AS are mainly based upon the symptomatic status of the patient and the severity of AS. Doppler echocardiography represents the standard tool for detecting and assessing the severity of the disease [1]. Severe AS is usually defined on the basis of an aortic valve area (AVA) <1 cm^2, a mean trans-aortic pressure gradient ≥40 mmHg and a peak aortic jet velocity >4 m/s [2]. However, discrepancies are frequently observed between the mean gradient and the valve area in a single patient [3]. In fact, given that gradients are a squared function of flow, even a modest decrease in flow may lead to an important reduction in gradient, even if the stenosis is very severe. These discrepancies are, thus, easy to understand in patients with low cardiac output secondary to reduced left ventricular (LV) ejection fraction, but also may occur in patients with apparently preserved LV ejection fraction [4]. The most commonly described entity is the paradoxical low-flow, low-gradient severe AS state, in which the stroke volume is unexpectedly reduced, despite preserved LV ejection fraction. In daily practice, misdiagnosing this clinical condition might lead to an inappropriate timing of follow-up with an unnecessary delay of aortic valve replacement (AVR), which may, in turn, have a negative impact on patient outcome [5–7].

New look into AS grading severity

Under the same denomination of severe AS (AVA < 1 cm^2), several entities might be identified that differ in terms of trans-valvular flow rates and pressure gradients development [8–11]. From a clinical standpoint, severe AS (AVA < 1 cm^2) can be subdivided into 4 flow-gradient patterns: 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

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Table 1 New aortic stenosis (AS) grading classification

Normal flow/high gradient	Normal flow/low gradient
AVA <0.6 cm^2/m^2	AVA <0.6 cm^2/m^2
SVi ≥35 ml/m^2	SVi ≥35 ml/m^2
Mean gradient ≥40 mmHg	Mean gradient <40 mmHg
Low flow/high gradient	**Low flow/low gradient**
AVA <0.6 cm^2/m^2	AVA <0.6 cm^2/m^2
SVi <35 ml/m^2	SVi <35 ml/m^2
Mean gradient ≥40 mmHg	Mean gradient <40 mmHg

as an indexed LV stroke volume <35 ml/m^2 and LG as a mean trans-aortic pressure gradient <40 mmHg [12] (Table 1). The NF/LG 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. The NF/HG pattern represents the most prevalent entity (39–72 %) and is fully consistent with the criteria proposed by the guidelines [4, 5, 12]. The LF/HG pattern accounts for 8 % of patients with severe AS [4, 12]. An indexed LV stroke volume <35 ml/m^2 in spite of preserved LV ejection fraction characterises this group. The prevalence of the LF/LG pattern, namely paradoxical LF/LG AS, seems to be lower than that initially reported. The LF/LG entity accounts for 7 % in asymptomatic patients and up to 15–35 % in symptomatic patients [4–6, 12, 13]. This pattern represents a challenging clinical entity that shares many pathophysiological and clinical similarities with heart failure and preserved LV ejection fraction.

Pathophysiology

The present 4 flow-gradient patterns hold different physiopathology and cardiac adaptation. The NF/LG entity is characterised by a mild degree of LV remodelling, a preserved LV longitudinal myocardial function, resulting in lower brain natriuretic peptide (BNP) level and Monin's risk score [score = (peak velocity (m/s) × 2) + (natural logarithm of B-type natriuretic peptide × 1.5) + 1.5 (if female sex)], normal or mildly elevated global LV afterload, as estimated by the valvulo-arterial impedance (Zva), and less severe AS [12, 14]. When compared with the NF/LG group, although the LV longitudinal function is preserved, the global LV afterload, the BNP release and the degree of LV hypertrophy are higher in the NF/HG group. Furthermore, patients with NF/HG seem to have more severe AS, suggesting a longer exposition to this progressive disease. The LF/HG pattern is characterised by a high BNP level and Monin's risk score, an increased global LV afterload and a significant reduction in LV longitudinal function [13]. Of note, the LV ejection fraction is a crude estimate of the LV systolic function. The LV ejection fraction is influenced by both intrinsic myocardial function and the 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 a left ventricle with normal geometry may be abnormal for a left ventricle 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 LF/LG pattern is associated with more pronounced LV concentric remodelling, smaller LV cavity, increased global LV afterload (Zva), intrinsic myocardial dysfunction and more myocardial fibrosis [12, 13, 15]. Of note, the double load (valvular + vascular) imposes on the LV results from outflow obstruction (AS) and reduces systemic arterial compliance (vascular disease) due to the concomitant presence of systemic atherosclerosis, hypertension and/or diabetes in these patients. The chronically increased global LV afterload plays a direct detrimental effect on the LV systolic function with a progressive decrease in the LV stroke volume due to a restrictive physiology—impaired LV filling—because of a smaller LV cavity size and ongoing intrinsic myocardial impairment.

Assessment of disease severity: pitfalls and differential diagnosis

The accurate assessment of the haemodynamic severity of AS is vital. In daily practice, the assessment of AS severity should integrate the flow-gradient pattern to the classic measurement of the AVA. As a general rule, a low trans-valvular gradient (<40 mmHg) or velocity (<4 m/s) does not exclude 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. Potential causes of discordance between AVA and gradient in patients with preserved LV ejection fraction include: (a) measurement errors; (b) small body size; (c) paradoxical low-flow AS; and (d) 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 the LV outflow tract and/or misplacement of the 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 Simpson's method (volumetric method to measure LV ejection fractions 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 the 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 the erroneous estimation of AS severity. Fourth, in some cases, discrepancy in the gradient–valve area relationship may be related to inconsistencies in current guidelines. A harmonisation of the definition of severe AS may reclassify some of these patients with "severe" AS as "moderate" AS. When one combines the current prospective clinical data with earlier haemodynamic 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 [17, 18]. Hence, a meticulous differential diagnosis is of utmost importance when a diagnosis of LF/LG AS is being made (Table 2).

Table 2 Stepwise approach to the differential diagnosis of low flow/low gradient (LF/LG) aortic stenosis (AS) and preserved left ventricular (LV) ejection fraction (>50 %)

1) Index AVA to BSA, particularly in small patients (<0.6 cm^2/m^2)
2) Search for other findings of LF/LG AS
   a. Doppler velocity ratio <0.25
   b. Calculate the valulo-arterial impedance (Zva >4.5 mmHg/ml/m^2)
   c. Measure the global longitudinal strain (GLS <16 %)
   d. Evaluate the relative wall thickness (>0.5)
   e. Confirm the small LV cavity size (end-diastolic volume index <55 ml/m^2)
3) Validate stroke volume measurement
   a. Corroborate the LV ejection fraction obtained by Dumesnil's method (Doppler-derived stroke volume/end-diastolic volume derived from Teichholz's formula) and Simpson's method [9]
   b. Use other imaging modalities to assess stroke volume
      i. 3D echocardiography
      ii. Cardiac magnetic resonance
4) Measure BNP level (increased value)
5) Measure the calcium score by multislice computed tomography (increased value)
6) Evaluate the changes in pressure gradients and AVA during stress echocardiography (increase in pressure gradient in relation to the increase in stroke volume without significant change in AVA)
7) Invasive measurements

AVA = aortic valve area; Zva = sum of the systolic arterial pressure and the mean trans-valvular pressure gradient divided by the stroke volume index, it represents the global load (valvular + vascular) imposed on the LV and identifies poor outcome in severe AS patients

Clinical outcome and management

Patients with NF/LG AS classically have no or minimal subendocardial dysfunction and a relatively preserved outcome [12, 19, 20]. 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 (Table 3). The outcome of the LF/HG patients is nearly identical to patients with NF/HG. When symptomatic, these patients have a better survival if treated surgically. Hence, symptomatic patients with LF/HG should benefit from prompt AVR. When asymptomatic, individual risk stratification should also be encouraged. Stress 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 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 underutilisation or inappropriate delay of surgery [19]. It is important to recognise this entity in order not to deny surgery to a symptomatic patient with small AVA and LG. Indeed, in this category, though the benefit of surgery is not proven, AVR may probably be beneficial in selected symptomatic patients [7, 20–23]. Of note, the current 2006 American College of Cardiology/

Table 3 Main studies on outcome in patients with paradoxical LF and/or LG AS

	Patients' characteristics	Number of patients	AS category	Outcome
Hachicha et al. [5]	Retrospective Symptomatic Asymptomatic	512	LF AS 181 (35 %) 80 AVR	Poorer outcome compared to normal-flow AS, especially if medically treated
Dumesnil et al. [6]	Retrospective Symptomatic Asymptomatic	512	LF/LG AS 123 (24 %) 44 AVR	Tended to have a poorer outcome when treated medically
Jander et al. [7]	Prospective Asymptomatic	1,525	LG AS 435 (29 %) 252 AVR	LF/LG AS patients have an outcome similar to patients with moderate AS
Lancellotti et al. [12]	Prospective Asymptomatic Normal exercise test	150	LF/LG AS 11 (7 %)	The LF/LG pattern was associated with the poorer outcome
Herrmann et al. [15]	Prospective LGE CMR	86	LF/LG AS 11 (13 %)	LG is associated with higher degree of fibrosis and a poorer outcome
Clavel et al. [18]	Prospective stress echocardiography	55	37 (67 %) Projected AVA <1 cm^2	Stress echo can predict the severity of AS and the risk of adverse events
Mehrotra et al. [20]	Retrospective + Asymptomatic Symptomatic	183	LF/LG AS 38 (20 %)	LF/LG AS exhibited marked concentric remodelling and poor long-term survival
Clavel et al. [21]	Prospective case match study	187 187 187	LF/LG AS HG AS Moderate AS	LF/LG AS patients have a poorer outcome than patients with moderate AS. AVR improved survival in LF/LG and HG AS, but not in moderate AS
Tarantini et al. [22]	Retrospective Symptomatic	102	LF/LG AS 102 (100 %) 73 AVR	AVR was associated with significant improvement in long-term survival and functional status
Barasch et al. [23]	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

AS aortic stenosis, *AVR* aortic valve replacement, *LF* low flow, *LG* low gradient, *HG* high gradient

American Heart Association (ACC/AHA) guidelines do not contain any specific recommendations for the management of LF/LG AS [2]. Conversely, in the recent 2012 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines, AVR should be considered (class IIa) in symptomatic patients with LF/LG AS and preserved LV ejection fraction only after careful confirmation of severe AS [24].

Conflict of interest None related to this manuscript.

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