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VALVULAR HEART DISEASE (V NKOMO, SECTION EDITOR)

Paradoxical Low Flow Aortic Valve Stenosis: Incidence, Evaluation, and Clinical Significance

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Abstract Paradoxical low-flow (PLF) aortic stenosis is defined by a stroke volume index <35 ml/m^2 despite the presence of preserved LV ejection fraction (≥50 %). This entity is typically characterized by pronounced LV concentric remodeling with small LV cavity, impaired LV filling, increased arterial load, and reduced LV longitudinal shortening. Patients with PLF also have a worse prognosis compared to patients with normal flow. Because of the low flow state, these patients often have a low gradient despite the presence of severe stenosis, thus leading to discordant AS grading (i.e., aortic valve area< 1.0 cm^2 but mean gradient<40 mmHg) and thus uncertainty about the indication of aortic valve replacement. Stress echocardiography and aortic valve calcium score by computed tomography may be helpful to differentiate true from pseudo severe stenosis and thereby guide therapeutic management in these patients. Aortic valve replacement improves outcomes in patients with PLF low gradient AS having evidence of severe stenosis. Transcatheter aortic valve replacement may provide an interesting alternative to surgery in these patients.

Keywords Aortic stenosis · Doppler-echocardiography · Paradoxical low-flow aortic valve stenosis

Introduction

Current ACC/AHA guidelines define severe aortic stenosis (AS) by a peak aortic jet velocity (V_{max}) ≥4 m/s, a mean gradient (MG)≥40 mmHg or an aortic valve area (AVA)≤1 cm^2 [1]. However, the co-existence of an AVA≤1 cm^2 and a MG≤40 mmHg or V_{max}≤4 m/s is frequently encountered in clinical practice [2, 3, 4••]. It is well known that this discordance between AVA (small) and MG (low) may occur in patients with severe AS and reduced left ventricular ejection fraction (LVEF). This entity is now often referred as "Classical" low-flow, low-gradient AS [5].

In patients with preserved LVEF, such discordance between echocardiographic parameters of AS severity may be related to: i) Errors in the measurement of AVA or velocity/gradient, ii) small body surface area, and iii) and "paradoxical" low-flow (PLF), i.e. the presence of a reduced stroke volume index and transvalvular flow despite a normal LVEF. PLF AS has been defined as a stroke volume indexed to body surface area<35 ml/m^2 despite a preserved LVEF (≥50 %) [2, 5]. This entity is generally characterized by more pronounced LV concentric remodeling, small LV cavity, impaired LV filling and reduced LV global longitudinal strain and it is often associated with low gradient.

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Case Presentation: Evolution from Moderate AS to Paradoxical Low-flow AS

A 66-year-old asymptomatic woman was diagnosed with moderate AS and was followed annually by Doppler-echocardiography. She had a body surface area of 1.55 m^2, a body mass index of 23 kg/m^2, mild hypercholesterolemia, no hypertension and no known coronary artery disease. As shown in Fig. 1, MG was 26 mmHg and AVA was 1.05 cm^2 at first visit, consistent with moderate AS. During the 4 years of the follow-up, AVA decreased gradually to reach 0.64 cm^2 at last follow-up while MG increases during the first two years up to 34 mmHg and then decreased down to 28 mmHg. During follow-up, the LV end-diastolic diameter decreased from 47 to 42 mm with worsening of LV concentric remodeling (relative wall thickness increased from 0.43 to 0.53). The E/E' ratio increased from 7.4 to 14.5 LV ejection decreased from 75 to 60 % but remained preserved at last follow-up. The global longitudinal strain measured by speckle tracking decreased from 18 % to 13 %. The stoke volume index decreased from 45 (i.e., normal flow) to 32 ml/m^2 (i.e., low-flow). The valvulo-arterial impedance increased from 3.0 to 4.5.

The calcium score measured by multidetector CT also went from 853 AU at baseline, consistent with moderate AS up to 1485 AU at last follow-up, consistent with severe AS. At the 4-year follow-up, the patient also developed exercise-limiting dyspnea during exercise stress echocardiography and was referred to aortic valve replacement (AVR).

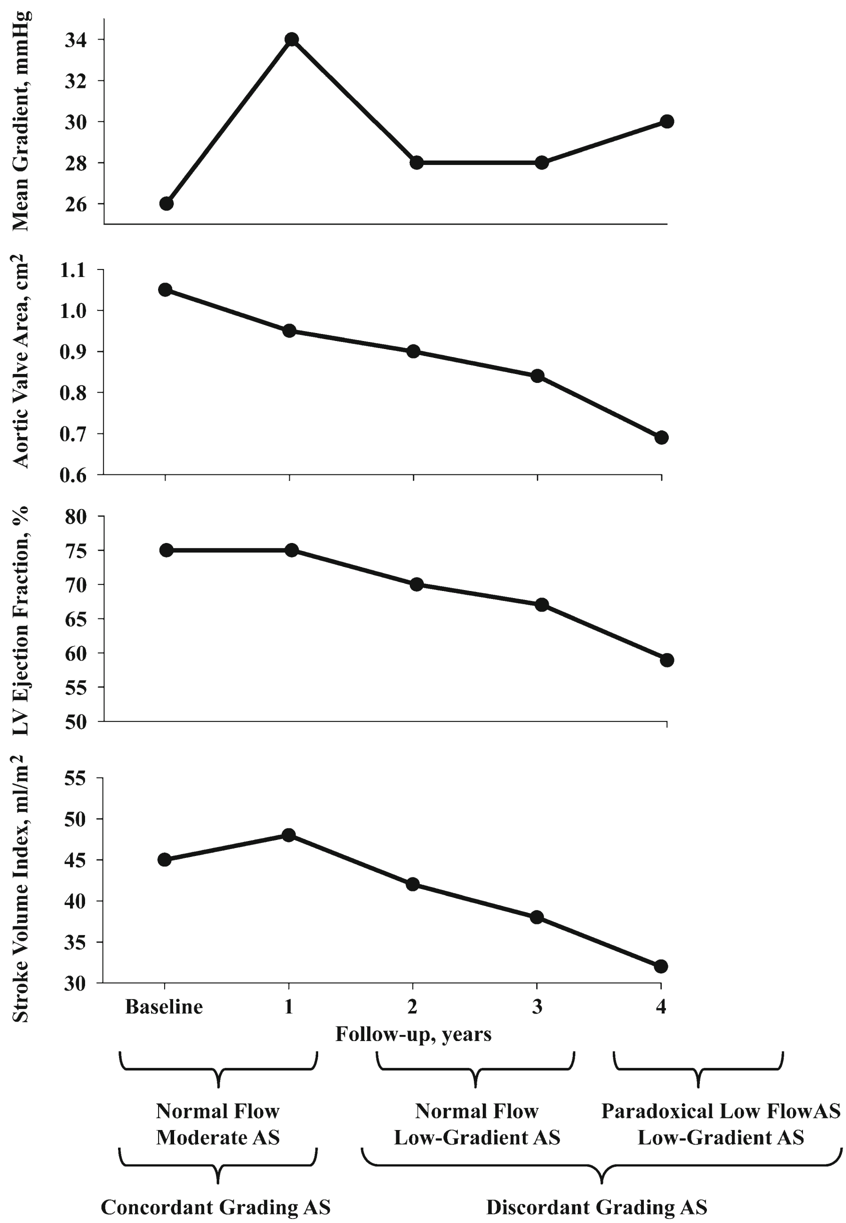

Fig. 1 Evolution of mean gradient, aortic valve area, left ventricular ejection fraction and stroke volume index in a 66-year-old woman with calcific AS

This is an interesting case where the transvalvular gradient had a biphasic evolution and never reached the threshold for severe AS (i.e., 40 mmHg) even in the late phase of the follow-up when the stenosis was severe according to AVA, indexed AVA, and CT calcium score and the patient was symptomatic. This patient went from moderate AS at baseline to PLF, low-gradient, severe AS at last follow-up. The progression of LV concentric remodeling and ensuing reduction in LV end-diastolic volume and worsening of LV diastolic and systolic function lead to a decrease in stroke volume and thus in transvalvular flow rate. This precluded the MG, a highly-flow dependent parameter, to increase during the late phase of follow-up despite the progression of the stenosis to the severe symptomatic stage.

Features and Prevalence of Paradoxical Low-flow

The PLF entity is typically defined by the presence of LV outflow (stroke volume index<35 ml/m^2) despite preserved LVEF (≥50 %) [2, 5, 6]. As illustrated in the case above, patients with PLF are characterized by pronounced concentric remodeling, small LV cavity, impaired filling, reduced arterial compliance, and increased global LV hemodynamic load, as documented by high valvulo-arterial impedance [2, 7–9]. PLF is more frequent in women and elderly people as they are more prone to develop concentric remodeling. In patients with PLF, the LVEF is typically within normal range. However, as shown by several previous studies, the LVEF grossly underestimates the extent of myocardial systolic dysfunction in presence of LV concentric remodeling [2, 7, 9, 10•, 11••, 12, 13]. Indeed, when more sensitive parameters such as mid-wall fractional shortening or global longitudinal strain are utilized, it becomes evident that myocardial systolic function is significantly impaired in these patients [2, 7–9, 14–16]. This impairment of myocardial function has been shown to be related to more advanced myocardial fibrosis located predominantly within the subendocardium [8, 14, 15].

The low-flow state associated with the restrictive physiology pattern is most often associated with a low MG because the gradient is a squared function of flow. However, in cases of very severe AS and depending on the balance between AS severity and LV inotropic reserve, PLF may also be associated with a high MG (i.e., ≥ 40 mmHg) despite the low flow state. Hence the PLF entity includes patients with low gradient (i.e., MG<40 mmHg) (PLF-LG) and patients with high gradient (PLF-HG)

The prevalence of PLF AS reported in the literature varies between 17 and 38 %, whereas the range of prevalence of PLF-LG is 7-26 % and that of PLF-HG is 8-19 % (Fig. 2) [2, 7, 9, 10•, 11••, 16, 17]. The presence of PLF is important from a prognostic standpoint, regardless of the level of gradient (low or high). However, from a diagnostic standpoint, the PLF-LG subset is certainly the most challenging since the apparent discrepancy in measurements needs to be further documented before a definite diagnosis can be established.

Prognosis of Paradoxical Low-flow

Several studies have demonstrated that PLF, is associated with reduced survival compared to patients with moderate AS or patients with normal flow and high gradient AS [2, 10•, 11••, 16, 18]. In a substudy of the PARTNER-I trial [19••] and a study from the Québec-Vancouver Experience of transcatheter aortic valve replacement [20•], the presence of low-flow defined as a stroke volume index ≤35 ml/m^2 was the most powerful echocardiographic predictor of mortality and this impact was independent of the LVEF or the gradient.

As opposed to the studies mentioned above, a substudy of the SEAS trial [21], which included asymptomatic patients with preserved LVEF, reported similar prognosis in patients with low flow versus those with normal flow. However, by study design, patients with severe AS were excluded from this trial thus introducing a selection bias and some concerns have been raised about the validity of the measurements of the stoke volume measured in the LV outflow tract by Doppler in the context of this multicenter trial [22].

When analyzed collectively, previous studies suggest that patients with PLF have worse outcome compared to those with normal flow but better compared to patients with classical low flow (i.e., reduced LVEF). Among patients with PLF, those with PLF-LG appear to have worse prognosis than those with PLF-HG [11••]. Patients with PLF-LG also have worse prognosis compared to patients with moderate AS and similar levels of gradient and compared to patients with severe AS, normal flow and high gradient [2, 4••, 10•, 11••]. Some studies also reported that they have worse outcomes compared to patients with normal flow, small AVA and low gradient. The latter entity is intriguing and also raises uncertainty about the stenosis severity. This AVA-gradient discordance in the context of normal flow could be related to: i) measurement errors, ii) small body size: i.e., small AVA in a small patient may correspond to moderate AS and low gradient, iii) inconsistencies in the guidelines criteria: from a fluid-mechanics stand-point the cut-point value of AVA (1.0 cm^2) does not correspond to the MG cut-point (40 mmHg). An AVA of 1.0 cm^2 rather corresponds to 30–35 mmHg MG at a normal flow rate. The normal-flow, low-gradient entity should be differentiated from the PLF-LG entity because the latter is associated with worse prognosis [4••, 11••]. Hence, the identification of low flow, i.e., stroke volume index<35 ml/m^2 is key for risk stratification. However, from a diagnostic standpoint, both PLF-LG and normal-flow, low-gradient entities require careful confirmation of stenosis severity.

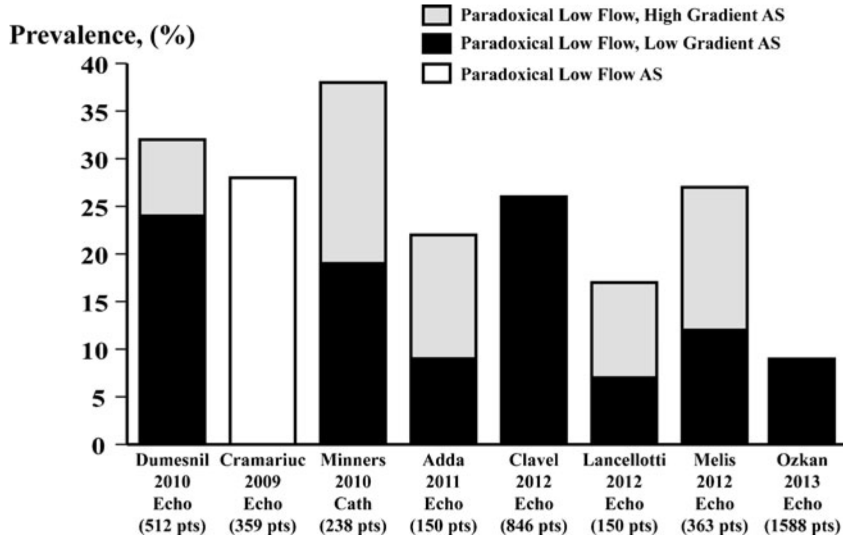

Fig. 2 Prevalence of paradoxical low flow AS (i.e., LVEF≥50 % and stroke volume index ≤35 ml/m^2/m^{2*}) with low mean gradient (i.e., <40 mmHg) or high mean gradient (i.e., ≥40 mmHg) in study populations with preserved LVEF and a priori "severe" AS on the basis of aortic valve area (≤1 cm^2) indexed aortic valve area (≤0.6 cm^2/m^2) and/or energy loss index (≤0.55 cm^2/m^2). *In the study by Cramariuc et al [7], stroke volume was indexed to a 2.7 power of height and low flow was defined by a stroke volume index≤22 ml/m$^{2.7}$

Differentiating True versus Pseudo Severe Stenosis in Patients with Paradoxical Low-flow, Llow-gradient

Patients with PLF-LG are, by definition, in low flow state and so, as patients with depressed LVEF and "classical" low flow, low-gradient, the stenosis severity and thus the therapeutic management often remains undetermined at the outset of the resting echocardiographic exam. Indeed, in patients with classical or paradoxical low flow, it is often difficult to differentiate patients with a true severe stenosis who will generally benefit of AVR from those with pseudo-severe AS, in whom the flow is too low to completely open a valve that is only moderately stenotic. In these patients the reduction in LV outflow may be more related to concomitant hypertension, coronary artery disease, and ensuing alteration of LV geometry and function rather than to the AS-related pressure overload, per se. Few data are available regarding the outcome of these patients but it may be better to first manage them with aggressive medical therapy rather than AVR.

It is thus important to differentiate true versus pseudo severe stenosis to guide therapeutic management in patients with PLF-LG [23]. In a recent multicenter study, we showed that stress echocardiography is helpful to confirm stenosis severity in patients with PLF-LG. In this study, exercise stress was utilized in patients with no or equivocal symptoms and dobutamine stress in symptomatic patients [24••]. We used the projected AVA at normal flow rate to assess stenosis severity. This parameter was previously proposed and validated in the context of low LVEF, low-flow, low gradient AS [25, 26]. Given that all stenotic parameters are inherently flow-dependent and that the flow response to stress varies extensively from one patient to the other, discordances between AVA and MG (i.e., AVA≤1 and MG<40 or vice versa AVA>1 and MG≥40) often persist or appear at peak stress echocardiographic exam. The projected AVA at normal flow rate allows the echocardiographer to standardize the results of AVA according to flow and thereby to reconcile discrepancies in the parameters of stenosis severity. Using the projected AVA at normal flow rate, it was possible to separate true from pseudo severe AS in 51 patients with PLF-LG with a percentage of correct classification of 94 % and 30 % of these patients had a pseudo-severe AS defined as a projected AVA> 1.0 cm^2 [24••]. This prevalence is similar to what has been reported in patients with classical low-flow, low-gradient AS [27, 28].

Dobutamine stress echocardiography should be used with caution in patients with PLF-LG, and particularly those having a severe restrictive LV pattern. A low-dose protocol starting at 2.5 and up to a maximum of 20 μg/kg/min should be used and close monitoring of blood pressure, electrocardiogram, and LV outflow tract velocity should be performed. In these patients with PLF-LG AS, some investigators also proposed to use nitroprusside vasodilation to induce flow increase (by decreasing arterial hemodynamic load) and confirm stenosis severity in the catheterization laboratory [29•, 30]. Further studies are needed to confirm safety and accuracy of this approach.

Unfortunately, stress echocardiography may not be feasible or not conclusive (i.e., no increase in flow rate) in all patients with PLF-LG and so an alternative diagnostic test is needed to corroborate AS severity and guide therapeutic management in these cases. To this effect, aortic valve calcification measured by multi-detector CT has been shown to correlate well with hemodynamic markers of AS severity [31]. However, a recent study showed that women reach similar AS severity as men for lower aortic valve calcium loads, even after normalization for body surface area and aortic annulus size [32]. Thus, for diagnostic purposes, the cut-point of aortic valve calcium score to identify severe AS should be lower for women compared to men. In a recent study using multidetector computed tomography scanners, we proposed to use aortic valve calcification score≥1274 AU in women and≥2065 AU in men to confirm the presence of severe AS [33••]. Area under the ROC curve were >0.90 and sensitivity, specificity, positive predictive value and negative predictive value for these cutpoints were >80 %.

In the case presented above, the patient underwent exercise stress echocardiography at 4-year follow-up and the projected aortic valve area at normal flow rate (AVA_{proj}) was calculated using the following equation:

$$AVA_{proj} = \frac{AVA_{peak} - AVA_{rest}}{Q_{peak} - Q_{rest}}(250 - Q_{rest}) + AVA_{rest}$$

where AVA_{rest} and Q_{rest} are aortic valve area and transvalvular flow rate at rest; AVA_{peak} and Q_{peak} are AVA and Q at peak stress.

The projected AVA was: 0.83 cm^2 and the indexed projected AVA=0.54 cm^2/m^2, thus confirming the presence of severe stenosis. The patient also had an aortic valve calcification of 1485 AU, which again is consistent with severe AS. Moreover, the patient developed dyspnea during the exercise test. She underwent aortic valve replacement within the next month and had a good evolution with regression of LV concentric remodeling, normalization of flow, and regression of symptoms.

Stress echocardiography and CT may thus be used to corroborate AS severity in patients with PLF-LG AS. Patients with evidence of true-severe AS should undergo surgical or transcatheter AVR depending on comorbidities and those with pseudo-severe AS should probably be first managed with medical therapy and followed very closely [5].

Impact of Therapy in Patients with Paradoxical Low-Flow AS

Patients with PLF are often at more advanced stage of the disease and thus initially, there were concerns that these patients may not improve following AVR owing to potentially irreversible myocardial damage. However, several studies have now demonstrated that the prognosis of patients with PLF, including those with PLF-LG, is markedly improved by AVR [2, 4••, 10•, 16, 18]. Clavel et al. reported that surgical AVR (SAVR) is associated with a two-fold decrease in mortality compared to medical therapy after adjusting for differences in baseline characteristics between surgically and medically treated patients [10•]. In the PARTNER-I trial, patients with PLF-LG had much better survival with transcatheter AVR (TAVR) compared to medical therapy in the inoperable patients (Cohort B) [19••]. And interestingly in the patients with high operative risk (Cohort A), patients with PLF-LG had significantly better survival at 6 months compared to SAVR. The difference was no longer significant thereafter [19••]. The potential superiority of TAVR over SAVR in these patients might be explained by the lower procedural mortality and the lower incidence of prosthesis-patient mismatch. However, further studies are necessary to determine the optimal type of therapy in patients with PLF.

In the 2012 guidelines of the ESC-EACTS [34], PLF-LG is recognized as an important entity that requires special attention and more data about the impact of therapy on the outcome of these patients. Furthermore, the guidelines include a class IIa recommendation for AVR in patients with PLF-LG after careful confirmation of stenosis severity. Several studies published after the publication of these guidelines have provided compelling data confirming that AVR is beneficial in these patients [10•, 19••, 35•]. Moreover, other studies [24••, 33••] have assessed and validated stress echo and aortic valve calcium scoring by CT to corroborate the stenosis severity in these patients.

Conclusion

Discordance between AVA (small) and MG (low) in the context of normal LVEF is a conundrum often encountered during Doppler-echocardiographic evaluation of patients with AS. Paradoxical low flow is one of the possible causes of such discordance. Patients with PLF have worse prognosis compared to patients with normal flow and therefore the stroke volume index should be systematically incorporated in the risk stratification process of patients with AS. The patients with PLF-LG represent the most challenging entity from both a diagnostic and therapeutic standpoint because the stenosis severity and the potential benefit of AVR often remain uncertain following resting echocardiography. Stress echo and CT may be useful to confirm stenosis severity and guide therapeutic management. AVR improves outcomes in patients with PLF-LG and evidence of severe AS. TAVR may provide a valid alternative to SAVR in these patients.

Compliance with Ethics Guidelines

Conflict of Interest Marie-Annick Clavel declares that she has no conflict of interest.

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Jean G. Dumesnil declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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