Paradoxical Low-Flow, Low-Gradient Aortic Stenosis
New Evidence, More Questions

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Different Patterns of Flow/Gradient Aortic Stenosis

In the American Heart Association/American College of Cardiology and European Society of Cardiology/European Association of Cardiothoracic Surgery guidelines, severe aortic stenosis (AS) is defined as a peak aortic jet velocity >4.0 m/s, a mean gradient >40 mm Hg, or an aortic valve area (AVA) <1.0 cm², and it is considered a Class I indication for aortic valve replacement (AVR) if the patient has symptoms or left ventricular (LV) systolic dysfunction defined as LV ejection fraction (LVEF) <50%. However, the cardiologist is often confronted with patients with discordant echocardiographic findings, the most frequent being the combination of a small calculated AVA (<1.0 cm²) consistent with the presence of severe AS with a low mean gradient (<40 mm Hg), suggesting the presence of moderate AS. This type of discordance may raise uncertainty about the actual severity of the AS and thus about the therapeutic management, particularly if the patient is symptomatic. Such AVA-gradient discordance is often related to the presence of low LV outflow, which may, even if modest, lead to an important reduction in gradient and thus to underestimation of AS severity. A low-flow state is generally defined as a stroke volume index <35 mL/m², and it may occur not only in patients with reduced LVEF (i.e., classical low-flow) but also in those with preserved LVEF. This latter entity was first described in 2007 by Hachicha et al and was named “paradoxical” low-flow AS. Subsequently, Dumesnil et al proposed a new classification whereby patients with a priori severe AS on the basis of AVA and a preserved LVEF (i.e., >50%) are separated into 4 groups according to flow (stroke volume index <35 or ≥35 mL/m²) and gradient (<40 or ≥40 mm Hg) as follows: (1) normal-flow, high-gradient; (2) normal-flow, low-gradient (NF/LG); (3) low-flow, high-gradient; and (4) low-flow, low-gradient (LF/LG). In this issue of Circulation, Eleid et al report the characteristics, outcomes, and impact of therapy in a large series of 1704 patients stratified according to this classification. The main findings of this elegant study include the following. (1) Among patients with AVA <1.0 cm² and LVEF ≥50%, those with LF/LG have lower survival compared with patients with the other flow/gradient patterns, but, nevertheless, the outcome of these patients is markedly improved by AVR. (2) Patients with NF/LG have favourable survival with medical management, and the effect of AVR on their outcome is neutral, thereby suggesting that these patients are likely at a less advanced stage of their disease than patients with other flow/gradient patterns.

Etiology and Prevalence of Paradoxical LF/LG AS

Several factors may lead to a low-flow state in patients with preserved LVEF (Figure). As reported in the original description of paradoxical LF/LG AS and further confirmed in the present study, this entity is most frequently characterized by restrictive physiology in relation to more pronounced LV concentric remodeling, reduced LV cavity size, impaired LV filling, and reduced systemic arterial compliance. Moreover, several studies have shown that longitudinal myocardial function is often impaired in these patients, thus reemphasizing that LVEF may underestimate the extent of LV systolic dysfunction in patients with LV concentric remodeling. Hence, the cutoff value of LVEF (<50%) proposed in the guidelines to define LV systolic dysfunction and eventually recommend AVR in patients with severe AS may have to be revisited (e.g., raised to 60%), or other more sensitive parameters, such as the global LV longitudinal strain, may have to be incorporated in the evaluation.

Nonetheless, other factors may also contribute to reduced LV stroke volume and thus transvalvular gradients in these patients. In the present study, Eleid et al identified atrial fibrillation as a potential factor in which case the low flow may be attributable to impairment in intrinsic LV filling or a more rapid heart rate with a reduced LV filling time (Figure). Concomitant valvular dysfunctions, such as mitral stenosis, mitral regurgitation, or tricuspid regurgitation, are other factors that may also contribute to reduced stroke volume and thus potentially alter prognosis. Such factors should also be kept in mind when evaluating these patients given that the AS may nonetheless be severe despite the low gradient.

In the series reported by Eleid et al, low gradient was present in 24% of patients, with only 3% having LF/LG and 21% having NF/LG. The prevalence of paradoxical LF/LG is thus much lower than reported in numerous previous studies (7–24%). and such discrepancy might be attributable to several factors, including differences in baseline characteristics of study populations and, in particular, AS severity, symptomatic
status and prevalence of comorbidities, and concomitant valvular disease. Noteworthy, patients with concomitant valvular disease were excluded from the present study, but they were included in some previous studies. As emphasized previously,1 technical issues and, in particular, the determination of stroke volume are also of crucial importance when evaluating patients with low-gradient severe AS. Hence, it cannot be excluded that some previous studies might have overestimated the prevalence of paradoxical LF/LG as a result of a tendency to underestimate the stroke volume. Conversely, the very low prevalence of LF/LG reported in the present study (3%), even when compared with that observed in previous catheterization studies (13–16%),3,10 raises the possibility that there could have been a tendency to overestimate the stroke volume. Closer examination of the data indeed shows that, if one multiplies the LV end-diastolic volume derived from the mean value for LV end-diastolic dimension by the mean value for ejection fraction, the extrapolated value for stroke volume in the NF/LG group is 62 mL rather than the reported 82 mL value for the Doppler measurement. Hence, stroke volume may well have been overestimated in some patients with low gradient, thus resulting in an underestimation of the prevalence of LF/LG. These observations underline that the error in the measurement of stroke volume may go in both directions; the most frequent is probably an underestimation as emphasized in several previous studies,3 but an overestimation can also occur as may have been the case in the present study.6 They also highlight the importance of independently corroborating the measurement of Doppler stroke volume by other methods (e.g., 2- or 3-dimensional volumetric methods or confrontation with estimated ejection fraction, as illustrated above). Conversely, we concur with the authors that, for the measure of Doppler stroke volume, the LV outflow tract diameter should be measured preferably at the insertion of the aortic valve cusps rather than at 5 to 10 mm below the aortic annulus. Indeed, the cross-sectional shape is more circular at the former level, and the measurements are likely to be more reproducible because of the more easily identifiable anatomical landmarks. Positioning of the pulse-wave Doppler sample volume is also crucial to an accurate measurement of stroke volume. A sample volume position too low in the LV outflow tract or too lateral toward the anterior mitral leaflet may lead to underestimation of flow velocity and thus of stroke volume, whereas a position too close to the valve or to the septum may lead to overestimation.

Also, one cannot exclude the possibility of a selection bias given that patients with LF/LG are probably less likely to be referred to quaternary care centers, such as the Mayo Clinic, because of an underestimation of severity in association with their low gradient. Finally, regardless of the prevalence of LF/LG, which may vary from one population to the other and one practice to the other, this entity needs to be promptly and properly identified to provide optimal therapeutic management to these higher-risk patients.

**Outcome of Paradoxical LF/LG AS**

In the present study,4 patients with LF/LG had a 3.2-fold increase in the risk of mortality compared with NF/LG when treated medically. This study confirms, in a large series including both asymptomatic and symptomatic patients, the results obtained by Lancellotti et al7 in a prospective study of asymptomatic patients. In both studies, patients with paradoxical LF/LG had the worst outcome among the 4 flow/gradient groups, whereas those with NF/LG had the best outcome. Furthermore, patients with paradoxical LF/LG also had worse outcomes compared with those with normal-flow, high-gradient.

Several studies have demonstrated that low flow defined as stroke volume index <35 mL/m² is a powerful predictor of mortality independently of LVEF or gradient, and this negative effect was observed in patients treated medically as well as in those undergoing AVR.3,4,10,11,12 These findings emphasize that flow matters and that the stroke volume index, a parameter that is measured routinely in the echocardiographic examination, should be systematically incorporated in the assessment and risk stratification of patients with AS.

**Impact of AVR on Outcome of Paradoxical LF/LG AS**

There were concerns initially that patients with LF/LG may not benefit from AVR because these patients may be at a too advanced stage of their disease with potentially irreversible myocardial fibrosis and dysfunction.3 However, there is now a growing amount of evidence supporting that AVR improves outcome in most patients with paradoxical LF/LG severe AS, and the results of this study6 performed in a large series of patients with adjustment for treatment and survival biases further reinforce this level of evidence. These new findings provide strong support for the new recommendation included in the 2012 European Society of Cardiology/European Association of Cardiothoracic Surgery guidelines,2 which proposes a Class IIa indication for AVR in patients with LF/LG and evidence of severe AS.

A recent post hoc analysis of the PARTNER-I (for Placement of Aortic Transcatheter Valve) trial also revealed that non-operative patients (Cohort B) with paradoxical LF/LG AS undergoing transcatheter AVR have markedly improved survival compared with those undergoing conservative management.11 Furthermore, high-risk patients (Cohort A) with paradoxical LF/LG AS had better 1-year survival with...
transcatheter AVR compared with surgical AVR. Additional studies are needed to determine whether transcatheter AVR should be preferred to surgical AVR in such patients.

**New Questions and Perspectives**

**Challenges in the Management of Paradoxical LF/LG AS**

Patients with paradoxical LF/LG often have reduced arterial compliance and/or increased vascular resistance. However, because of the low-flow state, the blood pressure may tend to be pseudo-normalized similarly to what occurs with the transvalvular gradient, and, as a consequence, the presence and severity of hypertension may be underestimated. Hence, arterial compliance and resistance should be systematically calculated at the time of the echocardiographic examination in patients with LF/LG, and antihypertensive therapy should be optimized accordingly.

Furthermore, in patients with paradoxical LF/LG AS, the transvalvular flow may not be high enough to fully open a valve that is only moderately stenotic, and the AVA may thus be "pseudo-severe." Recent studies revealed that approximately one-third of patients with paradoxical LF/LG AS have pseudo-severe AS, and this proportion is similar to what has been reported in patients with classical LF/LG (i.e., with low LVEF). These studies also suggest that dobutamine stress echocardiography or aortic valve calcium scoring by computed tomography may be helpful to differentiate true versus pseudo-severe AS in patients with LF/LG. Additional studies including a larger number of patients are nonetheless needed to further validate the emerging role of these diagnostic tests in the context of paradoxical LF/LG AS.

The data published in the literature, including those of the present study, suggest that symptomatic patients with paradoxical LF/LG and evidence of severe AS should undergo AVR, whereas asymptomatic patients should probably be treated conservatively and followed closely. Regardless of the therapeutic decision described above (AVR versus conservative), patients with paradoxical LF/LG should be systematically screened for the presence of abnormal arterial hemodynamics, and, depending on the results of this screening, antihypertensive therapy should be instituted or optimized. Additional studies are needed to determine the most appropriate therapy in patients with pseudo-severe AS who remain symptomatic and still have an increased ventricular load despite optimal medical treatment.

**NF/LG AS: A Heterogeneous Entity**

The NF/LG AS entity constitutes a heterogeneous group comprising the following: (1) patients with a small body size: a small AVA in a small patient may indeed correspond to moderate AS and be associated with a low gradient; (2) patients with discordant AVA-gradient findings related to inconsistencies in the guidelines criteria: from a fluid mechanic standpoint, the cut-point value of AVA of 1.0 cm² proposed in the guidelines to define severe AS corresponds to a mean gradient ~30 to 35 mm Hg rather than the 40 mm Hg cut-point given in the guidelines; and (3) patients with arrhythmia or prolonged LV ejection time: these patients may have a reduced mean transvalvular flow rate and thus a lower gradient for a given AVA and stroke volume (Figure). Hence, the majority of patients with NF/LG have nonsevere AS, which may explain why they generally have better outcomes and less benefit with AVR compared with patients with other flow/gradient patterns.

However, one cannot exclude that a proportion of the patients with NF/LG, and particularly of those included in categories 2 and 3 mentioned above, have true severe AS and may thus benefit from AVR. To this effect, Dumesnil et al and Ozkan et al reported that patients with NF/LG treated medically have poor outcomes and that AVR is associated with improved survival in both LF/LG and NF/LG AS. As opposed to other studies, these 2 studies have used an indexed AVA <0.6 cm²/m² instead of an AVA <1.0 cm² as inclusion criteria, therefore excluding patients having a low gradient attributable to a small body size (i.e., category 1).

Hence, when analyzed collectively, these findings suggest that, in symptomatic patients with NF/LG and indexed AVA <0.6 cm²/m², additional tests, such as dobutamine stress echocardiography or computed tomography quantification of aortic valve calcification, should be performed to corroborate AS severity and guide therapeutic management.

**Conclusion**

As highlighted in the study by Eleid et al published in this issue of Circulation, flow is most important from a prognostic standpoint, whereas the gradient is most important from a diagnostic standpoint. Hence, the flow/gradient classification initially proposed by Dumesnil et al and further validated by the present study should be systematically incorporated in the interpretation of the echocardiographic examination and the prognostication of patients with AS and preserved LVEF. The gradient is always included in the echocardiographic report of such patients, and the finding of a high gradient has an important weight in the decision to refer the patient to surgery. However, it is now well established that a low gradient does not exclude the presence of severe AS and the need for AVR in patients with small AVA and preserved LVEF. Furthermore, the stroke volume index, a marker of LV pump function, which is routinely measured for the calculation of AVA, is generally not reported in the echocardiographic or catheterization reports. With the large and compelling evidence that has now been published, it is time to systematically report the stroke volume index and the presence of low flow (<35 mL/m²) and to classify patients according to their flow/gradient pattern. In this regard, particular attention should be paid to patients with paradoxical LF/LG AS given that they have poor outcomes under medical therapy and that their AS severity may be underestimated because of the low gradient, and AVR may therefore be underutilized.

**Disclosures**

Dr Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research, Ottawa, Ontario, Canada. Dr Dumesnil reports no conflicts.

**References**


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