Paradoxical Low-Flow, Low-Gradient Aortic Stenosis:

New Evidence, More Questions

Running title: Pibarot et al.; Paradoxical Low-Flow AS

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Different Patterns of Flow/Gradient AS

In the American Heart Association (AHA) / American College of Cardiology (ACC) and European Society of Cardiology (ESC) / European Association of Cardiothoracic Surgery (EACTS) guidelines, severe aortic stenosis (AS) is defined as a peak aortic jet velocity >4.0 m/s, a mean gradient >40 mmHg, and/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 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 mmHg) suggesting the presence of moderate AS. This type of discordance may raise uncertainty about the actual severity of the stenosis 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 stenosis 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< or ≥35 ml/m²) and gradient (< or ≥ 40 mmHg) as follows: 1) Normal-Flow, High Gradient (NF/HG); 2) Normal-Flow, Low-Gradient (NF/LG); 3) Low-Flow, High-Gradient (LF/HG); and 4) Low-Flow, Low-Gradient (LF/LG). In this issue of the journal, Eleid et al. report the characteristics, outcomes,
and impact of therapy in a large series of 1704 patients stratified according to this classification.\textsuperscript{6} The main findings of this elegant study are: 1) Among patients with AVA<1.0 cm\textsuperscript{2} and LVEF $\geq 50\%$, those with LF/LG have lower survival compared to 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 impact 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 Low-Flow, Low-Gradient AS**

Several factors may lead to a low flow state in patients with preserved LVEF (Figure 1). As reported in the original description of paradoxical LF/LG AS\textsuperscript{4} and further confirmed in the present study,\textsuperscript{6} 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\textsuperscript{3,7-9} have shown that longitudinal myocardial function is often impaired in these patients, thus re-emphasizing that LVEF may underestimate the extent of LV systolic dysfunction in patients with LV concentric remodeling. Hence, the cut-off 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 re-visited (e.g. raised to 60\%) and/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,\textsuperscript{6} Eleid et al. also identified atrial fibrillation as a potential factor in which case the low flow may be due to impairment in intrinsic LV filling and/or a more rapid heart rate with a reduced LV filling time (Figure 1). 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 very severe despite the low gradient.

In the series reported by Eleid et al., \(^6\) LG 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%)\(^3,4,7,9\) and such discrepancy might be due to several factors including differences in baseline characteristics of study populations, and, in particular, in stenosis severity, symptomatic status and prevalence of comorbidities and concomitant valvular disease. Noteworthy, patients with concomitant valvular disease were excluded from the present study, whereas they were included in some previous studies. As previously emphasized\(^3\), 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 due to a tendency to underestimate the stroke volume. Conversely, the very low prevalence of LF/LG reported in the present study (3%), even when compared to 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. And 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 SV in the NF/LG group is 62 ml rather than the reported 82 ml value for the Doppler measurement. Hence, SV may well have been overestimated in some patients with LG 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 but an overestimation can also occur as may have been the case in the present study. They also underline the importance of independently corroborating the measurement of Doppler stroke volume by other methods (e.g. 2D or 3D volumetric methods or confrontation with estimated EF, as illustrated above). On the other hand, we concur with the authors that, for the measure of Doppler stroke volume, the LV outflow tract diameter should be preferably measured at the insertion of the aortic valve cusps rather than at 5-10 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 owing to 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 due to an underestimation of severity in association with their low gradient. And 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 in order to provide optimal therapeutic management to these higher-risk patients.

**Outcome of Paradoxical Low-Flow, Low-Gradient AS**

In the present study, patients with LF/LG had a 3.2-fold increase in the risk of mortality compared to NF/LG, when treated medically. This study confirms, in a large series including
both asymptomatic and symptomatic patients, the results obtained by Lancellotti et al. in a prospective study of asymptomatic patients.\textsuperscript{7} 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 to those with NF-HG.

Several studies have demonstrated that low-flow defined as stroke volume index<35 ml/m\textsuperscript{2} is a powerful predictor of mortality independently of LVEF or gradient, and this negative impact was observed in patients treated medically as well as in those undergoing AVR.\textsuperscript{3,4,9,11,12} These findings emphasize that flow matters and that the stroke volume index, a parameter that is measured routinely in the echocardiographic exam, should be systematically incorporated in the assessment and risk stratification of patients with AS.

**Impact of Aortic Valve Replacement on Outcome of Paradoxical Low-Flow, Low-Gradient AS**

There were initially concerns 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.\textsuperscript{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 study\textsuperscript{6} 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 to the new recommendation included in the 2012 ESC/EACTS guidelines,\textsuperscript{2} which proposes a Class IIa indication for AVR in patients with LF/LG and evidence of severe stenosis.

A recent post-hoc analysis of the PARTNER-I trial also revealed that non-operable patients (Cohort B) undergoing transcatheter AVR (TAVR) have markedly improved survival
compared to those undergoing conservative management.\textsuperscript{11} Furthermore, high-risk patients (Cohort A) with LF/LG AS had better 1-year survival with TAVR compared to surgical AVR (SAVR). Further studies are needed to determine if TAVR should be preferred to SAVR in such patients.

New Questions and Perspectives

Challenges in the Management of Paradoxical LF/LG AS

Patients with paradoxical LF/LG often have abnormal reduced arterial compliance and/or increased vascular resistance.\textsuperscript{4,6,9} 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 echocardiographic exam in patients with LF/LG and anti-hypertensive 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 stenosis may thus be “pseudo-severe”. Recent studies revealed that about 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).\textsuperscript{3,13} These studies also suggest that exercise or dobutamine stress echocardiography or aortic valve calcium scoring by CT may be helpful to differentiate true vs. pseudo- severe stenosis in patients with LF/LG.\textsuperscript{3,13} Further studies including 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\textsuperscript{3,5,7,9,11,13,14} including those of the present study\textsuperscript{6}
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 vs. 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, anti-hypertensive therapy should be instituted or optimized. Further studies are needed in order to determine 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: **a)** 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; **b)** 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 around 30-35 mmHg rather than the 40 mmHg cut-point given in the guidelines; **c)** Patients with arrhythmia and/or prolonged LV ejection time: these patients may have a reduced mean transvalvular flow rate and thus a lower gradient for a given AVA (Figure 1). Hence, the vast majority of patients with NF/LG have non-severe AS, which may explain why they generally have better outcomes and less benefit with AVR compared to 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 b) and c) 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,6,7,9 these 2 studies5,14 have used an indexed AVA<0.6 cm²/m² instead of an AVA<1.0 cm² as inclusion criteria, therefore excluding patients having a LG due to small body size (i.e. Category a).

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 CT quantification of aortic valve calcification should be performed to corroborate stenosis severity and guide therapeutic management.

Conclusion

As highlighted in the study of 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.5 and further validated by the present study should be systematically incorporated in the interpretation of the echocardiographic exam 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. And 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 stenosis severity may be underestimated due to the low gradient and AVR may therefore be underutilized.

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**References:**


**Figure Legend:**

**Figure 1.** Factors Contributing to Low-Flow Sate in Patients with Aortic Stenosis and Preserved LV ejection fraction.
Pronounced Concentric Remodeling

Impaired Diastolic Filling

Impaired Longitudinal systolic function

Atrial Fibrillation

Mitral Regurgitation

Mitral Stenosis

Tricuspid Regurgitation

\[ \uparrow \text{LV ejection time} \]

Reduced Forward Stroke Volume

Reduced Transvalvular flow rate

Low-Flow, Low gradient AS with Preserved LVEF