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## **Definition and diagnosis of paradoxical aortic stenosis: A call for reappraisal**

**Abbreviated title:** Diagnosis of paradoxical aortic stenosis

**Tweet:** Paradoxical aortic stenosis with preserved ejection fraction: a call for reappraisal

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## Summary

Paradoxical low-flow/low-gradient severe aortic stenosis (LF/LG SAS) is currently defined in patients with an aortic valve area  $< 1 \text{ cm}^2$  and normal ( $\geq 50\%$ ) left ventricular ejection fraction by a low ( $< 40 \text{ mmHg}$ ) aortic mean pressure gradient in the presence of a stroke volume index  $\leq 35 \text{ mL/m}^2$ . The diagnosis of paradoxical LF/LG SAS requires a careful stepwise approach that minimizes the risk of overdiagnosis. By this approach, LF/LG SAS is an infrequent clinical entity, encountered in  $< 10\%$  of patients with severe aortic stenosis and preserved left ventricular ejection fraction. The outcome of paradoxical LF/LG SAS is a source of controversy. Some authors report that patients with paradoxical aortic stenosis have a dismal outcome and benefit from aortic valve replacement, whereas for others, LF/LG SAS is a more benign entity, with a prognosis that is close to that of moderate aortic stenosis. Recent data on healthy individuals and on the outcome of severe aortic stenosis suggest that the stroke volume index threshold defining low flow in severe aortic stenosis with preserved left ventricular ejection fraction should be lowered below  $28 \text{ mL/m}^2$  in men and below  $27 \text{ mL/m}^2$  in women, or below  $30 \text{ mL/m}^2$  for clinical practice simplification. When paradoxical LF/LG SAS is defined by the lowered  $30 \text{ mL/m}^2$  cut-off, its prognosis is poorer than that of high-gradient severe aortic stenosis with preserved left ventricular ejection fraction, and is favourably influenced by aortic valve replacement in selected patients. This lowered stroke volume cut-off point should reconcile divergent outcome reports and solve the controversy regarding the prognosis of this entity. Aortic valve replacement must be considered for "true" paradoxical aortic stenosis in patients presenting with symptoms related to the valve obstacle.

## Résumé

Le rétrécissement aortique serré bas-débit/bas-gradient paradoxal est actuellement défini chez les patients avec surface valvulaire aortique  $< 1 \text{ cm}^2$  et fraction d'éjection ventriculaire gauche normale par un gradient moyen aortique bas ( $< 40 \text{ mmHg}$ ) en présence d'un volume d'éjection systolique indexé  $\leq 35 \text{ mL/m}^2$ . Le diagnostic de rétrécissement aortique paradoxal nécessite une approche rigoureuse et standardisée afin de minimiser le risque de diagnostiquer cette entité par erreur. Avec cette approche, le rétrécissement aortique paradoxal est une entité clinique rare, observée dans  $< 10\%$  des cas des rétrécissements aortiques à fraction d'éjection normale. Le pronostic du rétrécissement aortique paradoxal est une source de controverses. Pour certains auteurs le rétrécissement aortique

paradoxal a un pronostic péjoratif et requiert une correction chirurgicale ou interventionnelle alors que d'autres estiment qu'il s'agit d'un pronostic plus bénin, proche de celui du rétrécissement aortique modéré. L'étude du volume d'éjection systolique aortique par échocardiographie-Doppler dans la population générale indemne de maladies cardiovasculaires, ainsi que des données de mortalité des patients atteints de sténose aortique à fraction d'éjection normale suggèrent que le bas-débit devrait être défini par des valeurs  $< 28 \text{ mL/m}^2$  chez l'homme et  $< 27 \text{ mL/m}^2$  chez la femme, ou  $< 30 \text{ mL/m}^2$  pour simplification dans la pratique clinique. Le risque de mortalité de cette entité redéfinie par le seuil de  $30 \text{ mL/m}^2$  est plus élevé que celui du rétrécissement classique à haut gradient, et chez des patients sélectionnés est réduit par le remplacement valvulaire aortique. Cette nouvelle valeur seuil pour le volume d'éjection systolique devrait réconcilier les travaux divergents et résoudre la controverse qui entoure le pronostic du rétrécissement aortique paradoxal. Le remplacement valvulaire aortique doit être discuté pour tous les patients symptomatiques atteints de rétrécissement aortique paradoxal véritable quand les symptômes sont liés à l'obstacle valvulaire.

#### **KEYWORDS**

Aortic stenosis;

Paradoxical;

Low gradient;

Flow;

Stroke volume index

#### **MOTS CLÉS**

Sténose aortique ;

Paradoxal ;

Bas gradient ;

Débit ;

Volume d'éjection systolique indexé

*Abbreviations:* AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; LF/LG SAS, low-flow/low-gradient severe aortic stenosis; LV, left ventricular; LVEF, left ventricular ejection fraction; SV, stroke volume.

## Background

Paradoxical low-flow/low-gradient severe aortic stenosis (LF/LG SAS) is currently defined in patients with an aortic valve area (AVA)  $< 1 \text{ cm}^2$  and normal ( $\geq 50\%$ ) left ventricular ejection fraction (LVEF) by a low ( $< 40 \text{ mmHg}$ ) Doppler gradient across the aortic valve in the presence of a stroke volume (SV) index  $\leq 35 \text{ mL/m}^2$  [1-3]. The LF/LG SAS pattern is often observed in elderly women with concentric left ventricular (LV) hypertrophy, small LV cavity size, impaired ventricular filling and increased global haemodynamic load [1, 2]. Early studies reported that paradoxical LF/LG SAS was encountered in clinical practice in 15–35% of patients with severe aortic stenosis (AS) and normal LVEF [1, 2, 4], whereas in more recent patient series [5, 6], the prevalence of this entity is much lower ( $< 10\%$ ). This discrepancy reflects the excess risk of diagnosis of LF/LG SAS [2]. The prognosis of paradoxical LF/LG SAS remains a matter of debate. Some authors report that these patients incur a high mortality risk and benefit from aortic valve replacement (AVR), whereas others report a similar outcome to that of moderate AS [5, 7-12]. These divergent results suggest that some of these patients have truly severe AS, but that others have moderate AS. Whereas the current definition of low flow in paradoxical AS is arbitrarily based on a Doppler-derived SV index  $\leq 35 \text{ mL/m}^2$  [1, 3], we recently reported in healthy adults that lower normal reference values for Doppler-derived SV index are  $28 \text{ mL/m}^2$  for men and  $27 \text{ mL/m}^2$  for women [13]. These results raise the question of whether the  $35 \text{ mL/m}^2$  threshold measured by Doppler echocardiography truly delineates low flow in AS with preserved LVEF and, as proposed in a recent issue of the Archives of Cardiovascular Diseases, lead to the hypothesis that lowering the SV index cut-off for low-flow AS to  $30 \text{ mL/m}^2$  might help to resolve the controversy regarding the prognosis of paradoxical severe AS [14].

## Diagnosis of paradoxical LF/LG SAS

The diagnosis of paradoxical LF/LG SAS (Fig. 1) requires a careful stepwise approach that minimizes the risk of wrongly identifying this entity [2]. First, as elevated blood pressure can result in decreased cardiac output and Doppler gradients [15, 16], elevated blood pressure at the time of echocardiography should prompt the assessment to be repeated once blood pressure is controlled. Second, the Doppler echocardiography examination needs to be rigorous to minimize sources of error, and a suspicion of paradoxical low-flow AS should lead to echocardiography measurements being reassessed. A dimensionless index  $> 0.25$ , an acceleration time/LV ejection time ratio of the aortic

flow velocity  $> 0.36$  or a mean flow rate (stroke volume/ejection time)  $> 200$  mL/s in this setting suggests that the AS is not truly severe [17-19]. The measurement of the anteroposterior LV outflow tract diameter is a common source of error, especially in the presence of calcifications and/or in patients with poor-quality echocardiographic views [2, 16]. Moreover, as the shape of the LV outflow tract is often elliptical, with an anteroposterior diameter smaller than the septal to lateral diameter [20], the AVA measured by echocardiography using the continuity equation may be underestimated. A computed tomography scan enables more precise evaluation of the geometry of the LV outflow tract [20]. Some authors proposed calculating a “hybrid” AVA by combining Doppler data and the measurement of LV outflow tract area by computed tomography scan, and have defined, using this combined method, a threshold of  $1.2 \text{ cm}^2$  for severe AS [21]. Doppler gradients are also frequently underestimated when continuous-wave Doppler is performed exclusively in the apical five-chamber view, because of frequent misalignment between the aortic flow and the Doppler beam [5, 6]. Higher peak velocities and mean gradients are obtained in about 20% of cases with right parasternal or suprasternal views, leading to the reclassification of some patients with paradoxical LF/LG SAS as high-gradient severe AS [6]. The position of the pulsed Doppler sample volume for the measurement of the LV outflow tract and velocity-time integral may also influence AVA calculation [2]. Then (third step) the cause of low flow (small LV cavity, severe mitral or tricuspid valve disease or severe right ventricular dysfunction) should be clearly identified to make the diagnosis of true severe paradoxical LF/LG SAS. The fourth step is the systematic normalization to body surface area for patients with small body surface area ( $< 1.6 \text{ cm}^2$ ) to avoid wrongly concluding severe AS in such cases on the sole basis of non-indexed AVA [16]. However, body surface area normalization should be avoided in obese patients, in whom it is associated with a risk of overestimation of the severity of the stenosis [13]. The fifth step is to measure the diameter of the ascending aorta, and in patients in whom this diameter is  $< 30$  mm, to calculate the energy loss index in order to take into account the pressure recovery phenomenon [22]. The calculation of this index allows reclassification of  $> 20\%$  of cases of paradoxical severe AS as moderate AS [23]. Finally, the sixth step is to eliminate “pseudo-severe” paradoxical LF/LG AS, which is present in 25–30% of cases [2, 16, 24, 25]. This situation can be detected by stress echocardiography (dobutamine or exercise) [24] or cardiac catheterization with nitroprusside afterload reduction [25]. Unfortunately, the performance of stress echocardiography may be difficult in elderly patients with paradoxical AS, and is non-contributive in patients who are unable to adequately

increase their cardiac output as a result of restrictive LV physiology. In our practice, we prefer to use the aortic valve calcium score by multidetector computed tomography to identify pseudo-severe AS [26, 27]. Actually, the aortic valve score, in our opinion, should be calculated systematically in this setting; it shows a close (although not perfect) correlation with the severity of the AS [26], and provides a high degree of discrimination for identifying severe AS [3, 26, 27]. Quantitatively, a score of > 2000 AU in men (positive and negative predictive values of 88% and 82%, respectively) or > 1250 AU in women (positive and negative predictive values of 93% and 79%, respectively) is a robust argument for severe AS [26]. Moreover, patients with a valve calcium score of > 3000 AU in men or > 1600 AU in women have a very high probability of severe AS (positive predictive value of 95% for both sexes) [3]. By comparison, severe AS is very unlikely when the calcium score is < 1600 AU in men or < 800 AU in women (Fig. 2) [3, 26]. In these cases, the diagnosis of severe AS should be reconsidered towards moderate AS (echocardiographic measurement errors, elliptical LV outflow tract, pseudo-severe AS, etc.). Thus, in a recent multicentre study, only 56% of patients with the echocardiography pattern of paradoxical LF/LG AS showed severe calcification according to the aortic valve calcium score [27]. This score is therefore an important criterion of the integrated diagnostic approach, but unfortunately is not a perfect method for identifying all cases of severe AS. Indeed, for patients in the grey zone (Fig. 2; about 15–20% of patients), no conclusion can be drawn and, therefore, the sole calculation of aortic valve calcium score does not always solve the problem of diagnosing paradoxical AS (Fig. 2). For example, the score may be lower in younger patients with bicuspid valves and severe AS. In difficult cases, the assessment of the anatomical AVA by planimetry using multidetector computed tomography or magnetic resonance imaging may be helpful [28-30]. When there is still doubt after this step-by-step integrative approach concerning the severity of the AS, and especially if AVR is discussed, cardiac catheterization should be performed to confirm the need for AVR [2].

By using this stepwise approach (Fig. 1), a large proportion of patients with paradoxical LF/LG SAS are reclassified as having classical high-gradient ( $\geq 40$  mmHg) severe AS or moderate AS [6, 16, 23, 24, 26]. Accordingly, Ringle et al. have reported that the use of multiple imaging windows for the assessment of the peak aortic flow velocity and the correction for pressure recovery lead to a significant reduction from 23% to 3% in the proportion of cases of paradoxical LF/LG SAS among patients with severe AS (AVA < 1 cm<sup>2</sup>) with preserved LVEF [6]. This low frequency of paradoxical

LF/LG SAS is similar to that reported by Eleid et al., who used multiple continuous Doppler views for gradient assessment in a large series of patients included at the Mayo Clinic [5]. We believe that severe paradoxical LF/LG SAS is often overdiagnosed, and that the true prevalence is < 10% of patients with severe AS and preserved LVEF. Thus, previously published series reporting a high frequency of paradoxical LF/LG SAS have presumably included, on the one hand, patients with moderate AS (in such cases severity was overestimated – for example, by underestimation of the LV outflow tract diameter or lack of correction for pressure recovery) and, on the other hand, patients with classical high-gradient severe AS falsely labelled as paradoxical severe AS (for example, underestimation of the aortic jet velocity when only the apical view is used).

Another particularly important point recently underlined is that, in elderly patients with AS and preserved LVEF, the frequency of associated cardiac amyloidosis ranges between 9% and 15% [31, 32]. Cardiac amyloidosis may be observed in true severe AS or in pseudo-severe AS (low flow related to restrictive LV physiology). The clinician should therefore systematically think of possible associated amyloidosis in patients with paradoxical AS, and discuss a diagnostic work-up that includes diphosphonate scintigraphy [32]. Indeed, associated amyloidosis must be taken into account when discussing the management of paradoxical severe AS.

### **Outcome of paradoxical LF/LG SAS**

The outcome of patients with paradoxical LF/LG SAS is a source of controversy. Some authors report that patients with paradoxical AS have a dismal outcome, and benefit from AVR [5, 7, 9, 11], whereas for others, LF/LG SAS is a more benign entity, with a prognosis that is close to that of moderate AS [8, 10, 12]. All of these studies [5, 7-12] used the 35 mL/m<sup>2</sup> SV index cut-off to define low flow, which was proposed arbitrarily in 2007 [1]. Using this SV index cut-off, our group reported in 2015 that the outcome of paradoxical LF/LG SAS was similar to that of moderate AS, and better than that of high-gradient AS [12]. Apart from errors that lead to the misclassification of some patients as having paradoxical severe AS, the controversy regarding the outcome of paradoxical severe AS may be also related to an improper SV index threshold [13, 33, 34]. Indeed, by Doppler-echocardiography healthy individuals demonstrate a median SV index of 37 mL/m<sup>2</sup> and lower reference values of 28 mL/m<sup>2</sup> in men and 27 mL/m<sup>2</sup> in women [13, 34]. This would lead, based on the 35 mL/m<sup>2</sup> cut-off, to the conclusion of “low-flow state” in almost 40% of healthy individuals, with most of these “low-flow

healthy” displaying an SV index of 30–35 mL/m<sup>2</sup> [34]. Furthermore, in patients with severe AS and preserved LVEF, we observed that an SV index < 30 mL/m<sup>2</sup> was associated with an increased mortality risk, irrespective of baseline characteristics and management type, whereas above the 30 mL/m<sup>2</sup> cut-off point, outcome was not affected by further flow stratification [34]. These data on healthy individuals [13, 33] and on the outcome of severe AS [34] suggest that the SV index threshold defining low flow in severe AS with preserved LVEF should be lowered below 28 mL/m<sup>2</sup> in men and below 27 mL/m<sup>2</sup> in women [13], or below 30 mL/m<sup>2</sup> for clinical practice simplification [34]. In a recent issue of the Archives of Cardiovascular Disease [14], we reported that when paradoxical LF/LG SAS is defined by the lowered 30 mL/m<sup>2</sup> cut-off, the prognosis of this entity is poorer than that of high-gradient severe AS with preserved LVEF, and is favourably influenced by AVR in selected patients. Irrespective of management (conservative or medical and surgical), the 5-year estimated survival was lower for LF/LG SAS compared with high-gradient AS. LF/LG SAS was associated with a 50–60% increase in mortality risk that persisted after covariate adjustment and further adjustment for AVR. The beneficial effect of AVR on mortality was observed in both groups. This lowered SV cut-off point should reconcile divergent outcome reports [5, 7-12], and help to solve the controversy regarding the prognosis of this entity. AVR must therefore be considered for “true” paradoxical AS in patients presenting with symptoms related to the valve obstacle [3]. We nevertheless acknowledge that the SV cut-off point issue might not be the sole explanation for the outcome discrepancies among observational patient series. Such outcome data are subject to confounding bias, as all prognostic factors cannot be taken into account in multivariable analyses, particularly those related to intrinsic LV impairment.

## Conclusions

Paradoxical LF/LG SAS accounts for probably < 10% of patients with severe AS and preserved LVEF. The diagnosis must be based on a rigorous stepwise approach that minimizes the risk of overdiagnosis (Fig. 1). In our opinion, the definition of paradoxical LF/LG SAS should be modified with regards to the SV index threshold, which should be < 30 mL/m<sup>2</sup>. Based on this new definition of low-flow threshold using Doppler echocardiography, paradoxical AS displays a uniformly poor prognosis, and is favourably influenced by AVR in selected patients.

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### **Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this manuscript.

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## Figure legends

**Figure 1.** Diagnostic algorithm for paradoxical severe aortic stenosis. 2D: two-dimensional; 3D: three-dimensional; AS: aortic stenosis; AU: Agatston units; AVA: aortic valve area; BP: blood pressure; BSA: body surface area; ELI: energy loss index; LV: left ventricular; LVOT: left ventricular outflow tract; MDCT: multidetector computed tomography; MR: mitral regurgitation; MRI: magnetic resonance imaging; MS: mitral stenosis; RV: right ventricular; SAS: severe aortic stenosis; SV: stroke volume; TR: tricuspid regurgitation; TVI: time-velocity integral; VSD: ventricular septal defect.

**Figure 2.** Relation of aortic valve calcium score to aortic stenosis severity [3, 26, 27]. AU: Agatston units; MDCT: multidetector computed tomography.

<sup>a</sup> Threshold of 1350 AU according to [27].

<sup>b</sup> Possibility of severe aortic stenosis with “low calcium score” in young patients with bicuspid aortic valves and no or mild/moderate calcifications.

<sup>c</sup> Thresholds according to [3].

## Suspicion of paradoxical severe aortic stenosis

### Step 1 :

Check BP

### High BP :

- Repeat echo after BP control

### Step 2 :

Check echomeasurements

- LVOT diameter and TVI  
- Aortic jet velocity - multiple windows approach  
- Confirmation of low SV index (Teichholz, 2D, 3D)

### Step 3 :

Cause of low-flow

- Concentric LV remodelling  
- Severe MS/MR or TR  
- Large VSD  
- Severe RV dysfunction

### Step 4 :

Calculate AVA/BSA

$> 0.6 \text{ cm}^2/\text{m}^2$  : conclude to moderate AS

### Step 5 :

Sinotubular diameter

If  $< 30\text{mm}$  : calculate ELI  
ELI  $> 0.6 \text{ cm}^2/\text{m}^2$  : conclude to moderate AS

### MDCT aortic valve calcium score\*\*\*

- severe AS :  $> 2,000$  AU in men,  $> 1,250$  AU in women  
- Moderate AS :  $< 1,600$  AU in men,  $< 800$  AU in women

### Step 6 :

Confirm AS severity

### Low-dose dobutamine echo

(When MDCT not available or calcium score in "grey zone") : to identify pseudo-severe AS (if flow reserve)

### Persistent doubt

- Anatomical AVA by MDCT or MRI  
- Cardiac catheterization

**True severe paradoxical SAS**

## MDCT aortic valve calcium score. Probability of severe aortic stenosis

### High probability :

> 2,000 AU in men  
> 1,250 AU in women\*

### Very high probability\*\*\* :

> 3,000 AU in men  
> 1,600 AU in women

### Grey zone :

1,600 - 2,000 AU in men  
800 - 1,250 AU in women

### Low probability\*\* :

< 1,600 AU in men  
< 800 AU in women