

## Aortic Stenosis Suspected to Be Severe Despite Low Gradients

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The American College of Cardiology/American Heart Association and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines generally recommend aortic valve replacement (AVR) in patients with severe aortic stenosis (AS) who have symptoms, have left ventricular (LV) systolic dysfunction, or undergo coronary artery bypass graft surgery or other heart surgery.<sup>1,2</sup> These guidelines propose a peak aortic jet velocity  $>4.0$  m/s, a mean transvalvular gradient  $>40$  mmHg, and an aortic valve area (AVA)  $<1.0$  cm<sup>2</sup> as the criteria to be used for the identification of severe AS. However, clinicians are often confronted with patients with discordant findings, the most frequent being the combination of a small AVA ( $<1.0$  cm<sup>2</sup>) consistent with the presence of severe AS with a low mean gradient ( $<40$  mmHg) rather indicating the presence of moderate AS. This situation raises uncertainty regarding the actual severity of the stenosis as well as the potential indication of AVR if the patient is symptomatic.

Such discordance between AVA (small) and gradient (low) is often related to the presence of low LV outflow. Indeed, given that the pressure gradient is directly related to the squared function of transvalvular flow rate, even a modest decrease in flow rate can result in an important reduction in gradient and thus lead to an underestimation of stenosis severity. Hence, a patient with bona fide severe AS may indeed present with a low gradient if cardiac output is reduced. Moreover, this low-flow, low-gradient condition may occur in the context of either a reduced (ie, classical low flow) or preserved (ie, paradoxical low flow) LV ejection fraction (LVEF; Figure 1).<sup>3,4</sup> However, such discordance may also be observed in patients with normal LVEF and cardiac output, in which case it may be attributable to measurement errors, a small body size, or previously emphasized inherent inconsistencies in the guidelines criteria.<sup>5</sup> Hence, it is most important to properly differentiate between these various entities given that they may have markedly different implications in terms of risk stratification and therapeutic management.

### Classical Low-Flow, Low-Gradient AS With Reduced LVEF

Classical low-LVEF, low-flow, low-gradient AS is generally characterized by the combination of an AVA compatible with severe stenosis (ie,  $\leq 1.0$  cm<sup>2</sup> or  $\leq 0.6$  cm<sup>2</sup>/m<sup>2</sup>), a low transvalvular gradient (ie, mean gradient  $<40$  mmHg), a low LVEF

(ie,  $\leq 50\%$ ), and a low-flow state (ie, stroke volume index  $<35$  mL/m<sup>2</sup> or cardiac index  $<3.0$  L·min<sup>-1</sup>·m<sup>-2</sup>). The main diagnostic challenge associated with this mode of presentation is that resting echocardiographic data do not distinguish between patients with true-severe AS and thus usually benefiting from AVR and patients with pseudosevere AS who may not necessarily benefit from this intervention (Figures 1 and 2). Operative risk for surgical AVR is also higher in patients with classical low-flow AS, particularly if they have no LV contractile or flow reserve,<sup>6-9</sup> and transcatheter AVR might thus prove to be a suitable alternative in their case.<sup>10</sup> Selecting the most appropriate treatment (ie, surgical versus transcatheter versus medical) requires a comprehensive assessment of both disease severity and operative risk.

### Clinical Vignette

In patients with classical low-flow, low-gradient AS, dobutamine stress echocardiography (DSE) is used to distinguish between pseudosevere AS and true-severe AS as well as to evaluate LV contractile or flow reserve (Figures 1 and 2). Table 1 and Movies in the Data Supplement show the DSE findings in 4 such patients included in the True or Pseudo Severe Aortic Stenosis (TOPAS) study.

### Assessment of LV Functional Reserve and Viability

In the context of low-flow AS, the presence of myocardial contractile reserve is generally defined as a  $\geq 20\%$  increase in stroke volume during DSE, but the term LV flow reserve would probably be more appropriate (Figure 1)<sup>2</sup> given that the increase in stroke volume induced by dobutamine may not uniquely be a marker of myocardial viability but may also be influenced by variations in the degrees of stenosis severity and afterload mismatch.

An absence of flow reserve during DSE is observed in about one third of patients with classical low-flow, low-gradient AS (eg, patient No. 4, Table 1), and this situation is challenging because the degree of stenosis severity may often remain indeterminate after DSE (Figure 1), and overall the operative mortality (8%–30%) in their case is much higher than in patients exhibiting flow reserve.<sup>4</sup> Nonetheless, those who survive operation usually exhibit significant improvements in LVEF and New York Heart Association functional class as well as in long-term prognosis.<sup>6,9</sup> Hence, notwithstanding the high

Received October 24, 2013; accepted February 21, 2014.

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The Data Supplement is available at <http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.113.001375/-/DC1>.

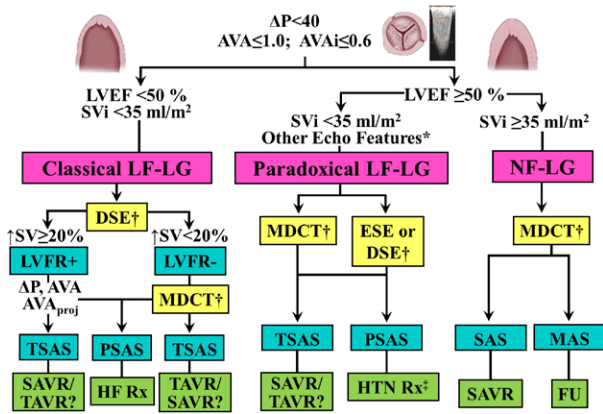
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(*Circ Cardiovasc Imaging*. 2014;7:545-551.)

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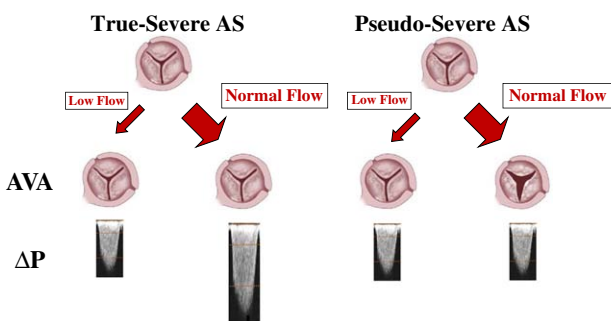
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**Figure 1.** Algorithm for the diagnostic and therapeutic management of patients with discordant aortic valve area (AVA; small)–gradient (low) findings. AVA<sub>proj</sub> indicates projected aortic valve area at normal flow rate; DSE, dobutamine stress echocardiography; ESE, exercise stress echocardiography; FU, follow-up; HF Rx, heart failure therapy; HTN Rx, antihypertensive therapy; LF-LG, low-flow, low-gradient; LVEF, left ventricular ejection fraction; LVFR, LV flow reserve; LVFR<sub>-</sub>, absence of flow reserve; LVFR<sub>+</sub>, presence of flow reserve; MAS, moderate aortic stenosis; MDCT, multidetector computed tomography; NF-LG, normal-flow, low-gradient; PSAS, pseudosevere AS; SAS, severe AS; SAVR, surgical aortic valve replacement; SV, stroke volume; SVi, stroke volume index; TAVR, transcatheter aortic valve replacement; TSAS, true-severe AS; and ΔP, mean transvalvular gradient. \*Other echocardiographic features that may be used to identify paradoxical low-flow, low-gradient AS include small LV cavity, high relative wall thickness, and reduced global longitudinal strain. †See Table 2 for the Doppler echocardiographic and MDCT parameters and criteria that can be used to differentiate true-severe from pseudosevere AS. ‡Initiation or optimization of antihypertensive therapy should be considered if blood pressure is elevated (>140/90 mm Hg), systemic arterial compliance is low (<0.6 mL·mm Hg<sup>-1</sup>·m<sup>-2</sup>), or vascular resistance is high (>2000 dyne·s·cm<sup>-2</sup>).

operative risk, the absence of flow reserve should not preclude the consideration of AVR in these patients.

Estimation of myocardial functional reserve is generally based on changes in stroke volume or LVEF during DSE. However, the stress-induced changes in these parameters may also be affected by concomitant changes in LV geometry, chronotropy, and mitral regurgitation. Hence, a recent study<sup>11</sup> has suggested that measurements of the changes in global longitudinal myocardial strain by speckle tracking imaging during DSE might provide a more accurate assessment of LV contractile reserve than the changes in flow. In



**Figure 2.** The behavior of aortic valve area (AVA) and transvalvular gradient (ΔP) with increasing flow in true-severe versus pseudo-severe aortic stenosis (AS).

the same context, the quantification of myocardial fibrosis by cardiac magnetic resonance could potentially be useful to improve risk stratification and therapeutic decision making in patients with low-flow, low-gradient AS. Patients with either classical or paradoxical low-flow, low-gradient severe AS indeed have more extensive myocardial fibrosis than patients with normal-flow, high-gradient severe AS.<sup>12</sup> Furthermore, longitudinal myocardial shortening is also affected to a larger extent in these patients likely because of the more advanced fibrosis observed in the subendocardial layer.<sup>13</sup> Besides focal fibrosis, which can be assessed by late gadolinium enhancement cardiac magnetic resonance, it may also be important and possibly more relevant to assess diffuse fibrosis using contrast-enhanced T1 mapping techniques in these patients with low-flow, low-gradient AS.

### Assessment of Stenosis Severity: True-Severe Versus Pseudosevere AS

The evaluation of the changes in AVA and gradient during low-dose (5–20 μg·kg<sup>-1</sup>·min<sup>-1</sup>) DSE as well as quantification of valve calcification by multidetector computed tomography (MDCT) are helpful in differentiating true-severe from pseudosevere AS (Figures 1 and 2, Table 2).<sup>14–16</sup> Typically, the AVA increases significantly with increasing flow and gradients increase only slightly or do not change during DSE in pseudosevere AS (patient No. 2, Table 1), whereas small or no increases in AVA and marked increases in gradients are observed when flow is increased in true-severe AS (patient No. 1, Table 1; Figure 2). About 25% to 35% of patients with classical low-flow, low-gradient AS have pseudosevere AS.<sup>4</sup> Several DSE parameters and criteria have been proposed in the literature to differentiate pseudosevere from true-severe AS (Table 2).<sup>6,15,17</sup>

The AVA–gradient discordance observed at rest may persist during DSE in a substantial number of patients (patient No. 3, Table 1). These persistent discordances are related to the fact that all parameters of stenosis severity, including gradient and, to a lesser extent, AVA, are inherently flow dependent,<sup>18</sup> and flow augmentation achieved by dobutamine stress may vary considerably from 1 patient to another.<sup>15,18,19</sup> The AVA and gradient are therefore measured at flow conditions that differ dramatically from 1 patient to another (Table 1). To overcome this limitation, the projected AVA at a normal transvalvular flow rate is calculated (Figure 3).<sup>18,19</sup> The most discriminative cut point of projected AVA to identify true-severe AS is <1.0 cm<sup>2</sup>,<sup>18,19</sup> which is consistent with the traditional cutoff value proposed in the guidelines for severe AS.<sup>1,2</sup> However, more recent studies have suggested that higher cutoff values (ie, ≤1.2 versus ≤1.0 cm<sup>2</sup>) of peak stress AVA or projected AVA should be used to define severe AS and eventually recommend AVR in these patients (Table 2).<sup>19,20</sup> This suggestion is consistent with the concept that the increased load imposed by a moderate AS may be well tolerated by a normal ventricle but poorly by a failing ventricle.

A substantial proportion of patients with no flow reserve (ie, percent increase in stroke volume <20%) nonetheless exhibit a significant increase in mean transvalvular flow rate (ie, stroke volume/LV ejection time) during DSE because of the acceleration in heart rate and ensuing shortening in ejection time.<sup>18,19</sup> This flow rate augmentation is often sufficient to induce conclusive

**Table 1. Cases of Patients with Low-Flow, Low-Gradient Aortic Stenosis**

| Parameters   | Patient No. 1 |         | Patient No. 2 |         | Patient No. 3 |         | Patient No. 4 |         | Patient No. 5 |         |
|--|---------------|---------|---------------|---------|---------------|---------|---------------|---------|---------------|---------|
|  | Rest          | Stress* | Rest          | Stress* | Rest          | Stress* | Rest          | Stress* | Rest          | Stress* |
| Stroke volume, mL                                  | 50            | 73      | 34            | 46      | 40            | 53      | 51            | 57      | 42            | 52      |
| LV ejection fraction, %                            | 40            | 50      | 15            | 25      | 25            | 35      | 25            | 30      | 60            | 70      |
| Peak/mean gradient, mm Hg                          | 49/29         | 92/52   | 18/12         | 21/13   | 33/21         | 54/32   | 46/27         | 52/30   | 51/29         | 94/57   |
| Aortic valve area, cm <sup>2</sup>                 | 0.77          | 0.75    | 0.85          | 1.2     | 0.70          | 0.85    | 0.80          | 0.80    | 0.70          | 0.77    |
| Projected aortic valve area, cm <sup>2</sup>       | ...           | ...     | ...           | ...     | ...           | 0.96    | ...           | ...     | ...           | ...     |
| Aortic valve calcium load, AU†                     | ...           | ...     | ...           | ...     | ...           | ...     | 2010          | ...     | 1900          | ...     |
| Aortic valve calcium density, AU/cm <sup>2</sup> † | ...           | ...     | ...           | ...     | ...           | ...     | 528           | ...     | 605           | ...     |
| LV flow reserve                                    | ...           | Yes     | ...           | Yes     | ...           | Yes     | ...           | No      | ...           | Yes     |
| True-severe stenosis                               | ...           | Yes     | ...           | No      | ...           | Yes     | Yes‡          | ...     | Yes‡          | Yes     |
| Movies in the Data Supplement                      | No. 1         | No. 2   | ...           | ...     | ...           | ...     | No. 3         | No. 4   | No. 5, 6, 7   | ...     |

LV indicates left ventricular.

\*Dobutamine stress echocardiography.

†Measured by multidetector computed tomography.

‡Determined by multidetector computed tomography.

changes in AVA and gradient and to calculate the projected AVA, therefore allowing confirmation of stenosis severity. However, in  $\approx 10\%$  to  $20\%$  of patients with classical low-flow, low-gradient AS, the increase in mean flow rate induced by DSE is not sufficient to obtain conclusive DSE results.

Quantification of valve calcification by MDCT may be useful to distinguish true-severe from pseudosevere AS in the patients who have no significant increase in flow rate with DSE and in whom this diagnostic test thus remains inconclusive with regard to stenosis severity (eg, patient No. 4, Table 1; Figures 1 and 4). This flow-independent imaging modality may also be used in patients with significant flow reserve but who have ambiguous or discordant results at DSE. Aortic valve calcification is assessed using the Agatston method by

taking care to exclude contiguous calcium in coronary arteries, mitral valve annulus, or aortic wall (Figure 4).<sup>14,16</sup> Recent studies suggest that lower cut point values of aortic valve calcium score should be used in women than in men to identify severe AS (Table 2).<sup>14</sup> This sex difference persists even after indexing the aortic valve calcium score for the aortic annulus cross-sectional area.<sup>14</sup>

### Therapeutic Management

The 2014 American College of Cardiology guidelines<sup>1</sup> provide a class IIa (level of evidence C) recommendation for AVR in symptomatic patients with classical low-LVEF, low-flow, low-gradient AS with a DSE that shows a mean gradient  $\geq 40$  mmHg and with an AVA  $\leq 1.0$  cm<sup>2</sup> at any dobutamine dose. The 2012 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines<sup>2</sup> support the utilization of AVR (class IIa; level of evidence C) in the subset of patients with LV flow reserve on DSE. Hence, patients with flow reserve and evidence of true-severe AS on DSE should be considered for surgical AVR, and coronary artery bypass graft surgery should be performed concomitantly in the patients with clinical indications for revascularization (Figure 1). Transcatheter AVR may be considered in patients with severe concomitant comorbidities.

Recent studies<sup>19,20</sup> suggest that in pseudosevere AS, survival under medical treatment is better than in true-severe AS and comparable with that of patients with LV systolic dysfunction and no evidence of valve disease. Hence, patients with flow reserve and pseudosevere AS should probably be managed with heart failure therapy and should be followed closely (Figure 1). Failure of medical therapy could, however, be attributable to inability of the failing ventricle to tolerate the hemodynamic burden imposed by the moderate stenosis or to progression of the stenosis to the severe stage during follow-up, in which case AVR should be reconsidered.

Patients with no flow reserve represent the most challenging group with regard to therapeutic management, but AVR should nonetheless be contemplated in those with evidence

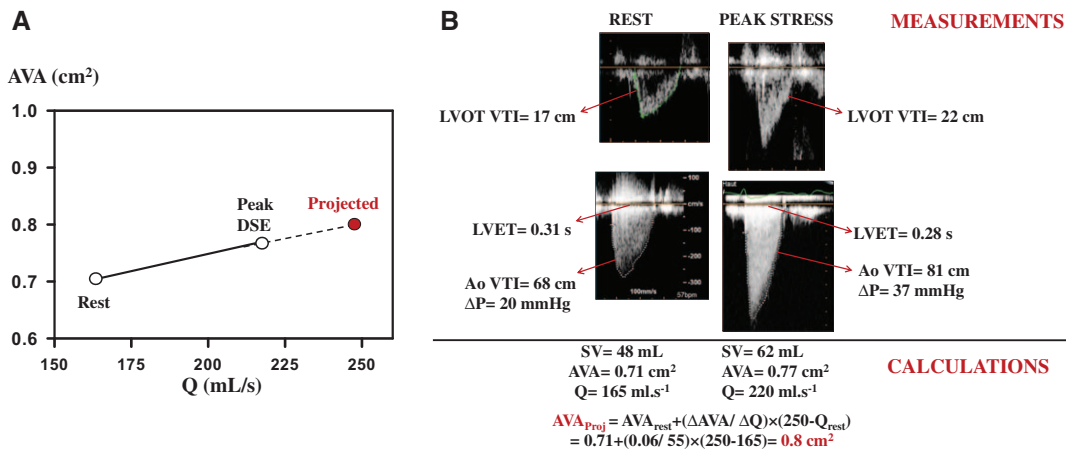
**Table 2. Cut Point Values of Dobutamine Stress Echocardiography and Multidetector Computed Tomography Parameters to Identify True-Severe Aortic Stenosis**

| Parameter  | Cut Point            |
|--|----------------------|
| Dobutamine stress echocardiography                 |                      |
| Peak stress mean gradient, mm Hg                   | $\geq 30$ – $40^*$   |
| Peak stress AVA, cm <sup>2</sup>                   | $\leq 1.0$ – $1.2^*$ |
| Absolute increase in AVA, cm <sup>2</sup>          | $< 0.3$              |
| Projected AVA at normal flow rate, cm <sup>2</sup> | $\leq 1.0$ – $1.2^*$ |
| Multidetector computed tomography                  |                      |
| Aortic valve calcium load, AU                      |                      |
| Women  | $> 1300^\ddagger$    |
| Men  | $> 2100^\ddagger$    |
| Aortic valve calcium density, AU/cm <sup>2</sup>   |                      |
| Women  | $> 290^\ddagger$     |
| Men  | $> 500^\ddagger$     |

AVA indicates aortic valve area.

\*The cut point values of peak stress gradient, peak stress AVA, and projected AVA vary depending on the studies.

†These cut point values correspond to the values proposed by Clavel et al<sup>14</sup> and rounded to the closest hundred.



**Figure 3.** Method to calculate the projected aortic valve area ( $AVA_{Proj}$ ) at normal flow rate from the dobutamine stress echocardiographic (DSE) measurements. **A**, Values of AVA as a function of mean transvalvular flow rate at rest and peak stress. The red circle shows the  $AVA_{Proj}$  at a normal flow rate of 250 mL/s. **B**, How to calculate the  $AVA_{Proj}$  from the DSE measurements in an illustrative patient with low-flow, low-gradient and persisting AVA–gradient discordance at DSE is shown.  $AVA_{Rest}$  and  $Q_{Rest}$  are the AVA and Q at rest, and  $\Delta AVA$  and  $\Delta Q$  are the absolute increases in AVA and Q during DSE. Ao indicates aortic; LVET, left ventricular ejection time; LVOT, LV outflow tract; Q, mean transvalvular flow rate; SV, stroke volume; and VTI, velocity–time integral.

of true-severe AS on MDCT (Figures 1 and 4).<sup>16,19</sup> Given that operative risk for open heart surgery is generally high in the absence of flow reserve, surgical AVR, however, received a class IIb (level of evidence C) recommendation in the 2012 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines.<sup>2</sup> Transcatheter AVR may eventually prove to be an interesting alternative to surgical AVR in these patients, but this hypothesis needs to be corroborated by future studies.<sup>10,21</sup>

### Paradoxical Low-Flow, Low-Gradient AS With Normal LVEF

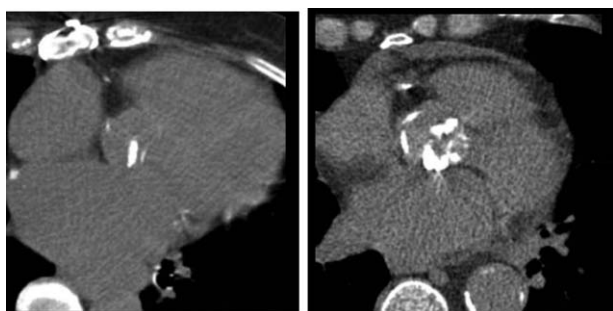
#### Clinical Presentation

Recent studies have revealed that low-flow, low-gradient severe AS may also occur in patients with preserved LVEF.<sup>3,22</sup> Such patients with severe AS on the basis of AVA (ie, <1.0 cm<sup>2</sup> and indexed AVA <0.6 cm<sup>2</sup>/m<sup>2</sup>) have usually developed more pronounced LV concentric remodeling, resulting in

a restrictive physiology, leading to a reduction in LV flow output (ie, stroke volume index <35 mL/m<sup>2</sup>) and lower than expected transvalvular gradients (ie, <40 mmHg) despite the presence of a preserved LVEF (ie, ≥50%). Because of the relatively unexpected association of a low output with a normal LVEF, this clinical entity was named paradoxical low-flow, low-gradient AS (Figure 1),<sup>3,22</sup> and Table 1 (patient No. 5) shows an example of such cases. The reported prevalence of this entity comprised between 5% and 25%, and it has been shown to increase with older age, female sex, and concomitant presence of systemic arterial hypertension, metabolic syndrome, or diabetes mellitus.<sup>4</sup> LV systolic function, which appears normal when uniquely examining the LVEF, is in fact substantially reduced when considering global LV longitudinal strain.<sup>23,24</sup> Other factors that may also contribute to the reduction of the transvalvular flow rate and thus of the gradient in AS patients with preserved LVEF include reduced arterial compliance, mitral regurgitation, mitral stenosis, tricuspid regurgitation, and atrial fibrillation.<sup>3,25,26</sup> Hence, because of its particular mode of presentation, the paradoxical low-flow, low-gradient entity is often misdiagnosed, which may lead to underestimation of stenosis severity and symptoms and therefore underutilization or inappropriate delay of AVR.

#### Assessment of Stenosis Severity

The main pitfall associated with the echocardiographic diagnosis of paradoxical low-flow, low-gradient AS is an error in the calculation of the stroke volume because of inaccurate measurement of LV outflow tract diameter or misplacement of pulsed-wave Doppler sample volume.<sup>4</sup> Indeed, an underestimation of stroke volume may lead to the erroneous conclusion that the patient has paradoxical low-flow, low-gradient severe AS, whereas, in fact, he or she has a moderate AS with normal flow. Conversely, an overestimation of stroke volume may lead to the misidentification and underestimation of the prevalence of the entity. Hence, when paradoxical low-flow AS is suspected, particular attention should be given to the measurement of the LV outflow tract cross-sectional area, which is often



**Figure 4.** Assessment of aortic valve calcification by multidetector computed tomography. **Left**, Patient with pseudosevere AS with moderate aortic valve calcification score (1034 AU) and density (280 AU/cm<sup>2</sup>). **Right**, Patient with true-severe AS with high aortic valve calcification score (4682 AU) and density (1491 AU/cm<sup>2</sup>). Courtesy of Drs Marie-Annick Clavel and Maurice Enriquez-Sarano, Mayo Clinic, Rochester, MN. Authorization for this adaptation has been obtained from both the owner of the copyright in the original work and the owner of copyright in the translation or adaptation.

underestimated because of its elliptical shape. To limit this potential error, the LV outflow tract diameter should preferably be measured at the base of the aortic valve cusps rather than 5 to 10 mm below the aortic annulus. Furthermore, the measurements of LV geometry and function should be reviewed with the expectation of finding: (1) typical echocardiographic features characterizing this entity (ie, pronounced concentric remodeling, small LV cavity size, reduced global longitudinal strain etc), and (2) consistency among Doppler stroke volume, LV end-diastolic volume, and LVEF. It is also important to identify other potential causes of low flow such as concomitant mitral regurgitation, tricuspid regurgitation, or atrial fibrillation. If these conditions are present, the antegrade stroke volume may be reduced despite the absence of some of the typical features of paradoxical low-flow gradient described above.

If the existence of paradoxical low-flow, low-gradient AS is confirmed, then it is important to rule out the presence of a pseudosevere stenosis. Indeed, given that transvalvular flow rate is reduced in these patients, it cannot be excluded that the AVA may be pseudosevere, that is, that the flow may not be high enough to fully open a valve that is only moderately stenotic, such as described above in the patients with reduced LVEF (Figure 2). Exercise or dobutamine stress echocardiography may be useful in patients with paradoxical low-flow, low-gradient AS (patient No. 5, Table 1) to assess the response of AVA and gradient with increasing flow and to calculate the projected AVA (Figures 2 and 3).<sup>27</sup> According to a recent study,<sup>27</sup> one third of these patients have pseudosevere stenosis, which is similar to what has been reported in patients with classical low-flow, low-gradient AS. DSE should not be used in patients with severe LV restrictive physiology.

The measurement of aortic valve calcification load and density by MDCT (Table 2 and Figures 1 and 4) may also be used to corroborate stenosis severity in patients with paradoxical low-flow, low-gradient AS, particularly in those in whom stress echocardiography is not feasible or inconclusive (patient No. 5, Table 1).<sup>14</sup> Evidently, further studies are needed to confirm the clinical usefulness of stress echocardiography and MDCT in this challenging subset of patients.

### Therapeutic Management

The recent guidelines<sup>1,2</sup> have recognized that paradoxical low-flow, low-gradient AS is an important new entity that requires further investigation, particularly with regard to the impact of AVR; moreover, a class IIa (level of evidence C) indication for AVR has been included providing that stenosis severity is carefully confirmed by a comprehensive evaluation (Figure 1) and that the clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms. Several studies<sup>10,14,26-31</sup> published recently provide further support for this recommendation.

Paradoxical low-flow AS is associated with several factors (ie, pronounced concentric remodeling, myocardial fibrosis, impaired myocardial function, etc.) that may increase the operative risk.<sup>12,22</sup> Furthermore, given that they often have smaller aortic annulus and root sizes,<sup>3</sup> patients with paradoxical low-flow, low-gradient AS may have increased risk for prosthesis-patient mismatch after surgical AVR, which may, in turn, negatively impact their postoperative outcomes.

Hence, as in patients with classical low-flow, low-gradient AS, transcatheter AVR may also provide a valuable alternative to surgical AVR in patients with paradoxical low-flow, low-gradient AS (Figure 1). To this effect, a recent substudy of the Placement of Aortic Transcatheter Valves (PARTNER) trial revealed that patients with paradoxical low-flow, low-gradient AS seem to have better short-term survival with transcatheter AVR compared with surgical AVR.<sup>10</sup>

Finally, because of the low-flow state, the presence and severity of arterial hypertension may be underestimated in these patients.<sup>4</sup> Blood pressure as well as arterial compliance and vascular resistance should thus be systematically measured at the time of echocardiographic examination,<sup>3</sup> and optimization of antihypertensive therapy should be considered, regardless of whether the patient is to be treated conservatively or with surgical or transcatheter valve replacement (Figure 1).

### Normal-Flow, Low-Gradient AS

An important proportion of patients with preserved LVEF and normal flow (stroke volume index >35 mL/m<sup>2</sup>) nonetheless have a low gradient despite a small AVA (Figure 1). The AVA-gradient discordance in such patients may be because of the following:

1. Measurement errors: Although the stroke volume index is within normal range in these patients, the stroke volume and thus the AVA may still be underestimated in some patients. Hence, the first step, in case of apparent discordances, should be the corroboration of the measurement of the Doppler stroke volume. Multiwindow interrogation with continuous-wave Doppler is also key to ensure accurate measurement of peak aortic jet velocity and gradient.
2. Small body size: A small AVA in a small patient may correspond to moderate AS and be associated with a low gradient. This situation can simply be ruled out by calculating the indexed AVA. A value >0.6 cm<sup>2</sup>/m<sup>2</sup> indicates the presence of moderate AS.
3. Inherent inconsistencies in the guidelines criteria: From a fluid mechanic standpoint and if LV flow is normal, the cut point value of AVA of 1.0 cm<sup>2</sup> proposed in the guidelines to define severe AS corresponds more precisely to a mean gradient around 30 to 35 mmHg rather than to the 40 mmHg cut point given in the guidelines.<sup>5</sup>
4. Prolonged LV ejection time: Patients with prolonged LV ejection time may have a reduced mean transvalvular flow rate (ie, stroke volume/LV ejection time) and thus a lower gradient for a given AVA and stroke volume.<sup>32</sup>

Hence, patients presenting with a normal-flow, low-gradient AS pattern are a highly heterogeneous group. From the above considerations, it also follows that, depending on populations, an important proportion of them may not in fact have severe AS, which may, in turn, explain why they generally have better outcomes compared with patients with paradoxical low-flow, low-gradient or those with normal-flow, high-gradient AS.<sup>24,26,31</sup> However, given the various causes, particularly those in categories 3 and 4 outlined above, an important subset of these patients may nonetheless have true-severe AS and thus benefit from AVR.<sup>14,22,30</sup> When analyzed collectively, these findings

suggest that in symptomatic patients with normal-flow, low-gradient, and small indexed AVA ( $<0.6 \text{ cm}^2/\text{m}^2$ ), additional tests such as MDCT quantification of aortic valve calcification should be performed to corroborate stenosis severity and guide therapeutic management (Figures 1 and 4). To this effect, a recent study revealed that, according to aortic valve calcium load (Table 2), approximately 50% of these patients have severe AS and may thus benefit from AVR.<sup>14</sup> On the contrary, patients with normal-flow, low-gradient AS and no evidence of severe stenosis on MDCT should likely have a standard clinical and echocardiographic follow-up.

### Conclusions

AS suspected to be severe on the basis of a small AVA but associated with a low gradient represents a highly challenging and heterogeneous entity that includes patients with classical (ie, low LVEF) low-flow AS, patients with paradoxical (preserved LVEF) low-flow AS, as well as patients with measurement errors, small body size, and discordances because of inconsistencies in the guidelines criteria. A particular effort should be made to rule out measurement errors in these patients with discordant AVA–gradient findings. Patients with reduced flow (ie, stroke volume index  $<35 \text{ mL}/\text{m}^2$ ) should receive particular attention because they generally have worse prognoses and often have pseudonormalization of their transvalvular gradients and systemic blood pressure, which may be insidious because it can lead to underestimations of both AS and hypertension severity. These patients can thus benefit from further investigations (stress echocardiography and aortic valve calcium scoring by MDCT) to confirm the stenosis severity and the need for AVR. Among patients with normal flow, those who are asymptomatic should be managed conservatively, whereas those who are symptomatic and have a small indexed AVA may need further diagnostic tests to clarify the stenosis severity and the indication for AVR.

### Acknowledgments

Dr Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research, Ottawa, Canada. The research program of Dr Pibarot is funded by research grants (No. MOP 126072 and 114997) from Canadian Institutes of Health Research.

### Disclosures

None.

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KEY WORDS: aortic valve stenosis ■ echocardiography, Doppler ■ echocardiography, stress ■ multidetector computed tomography

## Aortic Stenosis Suspected to Be Severe Despite Low Gradients

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*Circ Cardiovasc Imaging.* 2014;7:545-551  
doi: 10.1161/CIRCIMAGING.113.001375

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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## VIDEO LEGENDS

**Video #1.** Apical 4-chamber views of the left ventricle at rest for Patient #1.

**Video #2.** Apical 4-chamber views of the left ventricle during dobutamine stress echocardiography for Patient #1.

LV ejection fraction (40 to 50%) and stroke volume (50 to 73 mL) increased with dobutamine (Video #2) compared to rest (Video #1) this patient thus has significant flow reserve.

**Video #3.** Apical 4-chamber views of the left ventricle at rest for Patient #4.

**Video #4.** Apical 4-chamber views of the left ventricle during dobutamine stress echocardiography for Patient #4.

There was no significant increase in LV ejection fraction (25 to 30%) and stroke volume (51 to 57 mL) with dobutamine (Video #4) compared to rest (Video #3); this patient has thus no flow reserve.

**Video #5.** Parasternal long-axis view of for Patient #5.

This video reveals pronounced concentric remodeling of the left ventricle with very small cavity size (LV end-diastolic volume: 79 mL) and preserved LV ejection fraction (60%).

Despite the normal LV ejection fraction, the stroke volume is reduced (42 mL) in this patient. The aortic valve appears thickened, calcified and, has restricted opening. This patient has paradoxical low-flow, low-gradient, severe AS.

**Video #6.** Parasternal short-axis view of for Patient #5.

This video shows pronounced concentric remodeling of the left ventricle with very small cavity size and preserved LV ejection fraction.

**Video #7.** Parasternal short-axis view of for Patient #5.

The aortic valve appears thickened, calcified and, has restricted opening.