Invasive Hemodynamic Characteristics of Low Gradient Severe Aortic Stenosis Despite Preserved Ejection Fraction

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Objectives The study sought to compare echocardiographic with invasive hemodynamic data in patients with “paradoxic” aortic stenosis and in patients with conventionally defined severe aortic stenosis.

Background Controversy exists whether low gradient severe aortic stenosis despite preserved ejection fraction (“paradoxic” aortic stenosis; aortic valve area ≲1 cm², mean gradient <40 mm Hg, ejection fraction >50%), which has been mainly diagnosed by echocardiography (echo), may be largely due to mistakes in echocardiographic measurements.

Methods We compared echocardiographic and invasive hemodynamic data from 58 patients (43% male, mean age 77 ± 5 years) with “paradoxic” aortic stenosis. Data of 22 patients (45% male, mean age 73 ± 7 years) with conventionally defined severe aortic stenosis area (aortic valve area ≲1 cm², mean gradient >40 mm Hg, ejection fraction ≳50%) were also analyzed.

Results In patients with “paradoxic” aortic stenosis, orifice area by echo (0.80 ± 0.15 cm²) and catheterization showed modest agreement, whether stroke volume was measured by oxymetry (0.69 ± 0.16 cm³, bias 0.14 ± 0.17 cm³), or by thermodilution (0.85 ± 0.19 cm³, bias −0.03 ± 0.19 cm³). Mean systolic gradients were very similar (32 ± 7 mm Hg vs. 31 ± 6 mm Hg; bias −0.08 ± 7.8 mm Hg). In comparison, in patients with conventionally defined severe aortic stenosis, orifice area by echo was 0.72 ± 0.17 cm² and by catheterization 0.51 ± 0.15 cm² (oxymetry) and 0.68 ± 0.21 cm² (thermodilution), respectively, and mean systolic gradient 51 ± 10 mm Hg and 55 ± 8 mm Hg, respectively. Ejection fractions did not differ significantly in both groups. Ascending aortic diameter was significantly smaller in the “paradoxic” aortic stenosis group than in patients with conventionally defined severe aortic stenosis (28 ± 5 mm vs. 31 ± 5 mm), and energy loss index was significantly larger (0.51 ± 0.12 cm²/m² vs. 0.42 ± 0.09 cm²/m², respectively). Heart rate and mean blood pressure during echo and catheterization were not significantly different.

Conclusions Occurrence of low gradient severe aortic stenosis despite preserved ejection fraction was confirmed by invasive hemodynamics and was not the result of a systematic bias in the echo calculation of aortic orifice area. (J Am Coll Cardiol 2013;61:1799–808) © 2013 by the American College of Cardiology Foundation

Aortic stenosis is the most frequent severe valvular disease of Western countries, with a rising prevalence due to the aging population. Although pathophysiology, clinical features, and natural course have been extensively described, management recommendations are still in evolution and some clinically important questions remain unresolved. Current European and American guidelines (1,2) both recommend a valve area cutoff of 1 cm², or, indexed for body surface area, 0.6 cm²/m², and a mean pressure gradient <40 mm Hg to identify severe aortic stenosis in the presence of normal cardiac output and preserved left ventricular ejection fraction. However, several recent reports (3–7) have pointed out that there is a considerable number of patients with apparently preserved systolic left ventricular function in whom the severity of aortic stenosis appears to be severe judged by their valve orifice area (<1 cm² or 0.6 cm²/m²), but moderate (or even mild) by their transvalvular gradients.
(mean systolic gradient <40 mm Hg). The latest European guidelines therefore acknowledge that “the possible presence of severe aortic stenosis in patients with valve area <1.0 cm² and mean gradient <40 mm Hg, despite preserved LVEF, has been suggested” (1). Low gradient severe aortic stenosis despite preserved ejection fraction has sometimes been called “paradoxical.” Because both orifice area and gradients are in clinical practice usually derived from echocardiography, and especially valve area calculation by the continuity equation may be affected by several measurement errors, the occurrence of such “paradoxical” aortic stenosis has often been ascribed at least in part to errors in echocardiographic diagnosis. It was the purpose of this study to compare echocardiographic and invasive hemodynamic data in patients with “paradoxical” aortic stenosis to evaluate if this diagnosis typically is due to echocardiography (echo) measurement errors or a systematic echocardiographic bias.

Methods

Patient selection. At our hospital, patients with echo findings suggestive of “paradoxical” aortic stenosis routinely underwent right and left heart catheterization with retrograde passage of the aortic valve and calculation of aortic orifice area by the Gorlin formula, besides coronary angiography. Reviewing the database of our hospital’s angiographic and echocardiographic laboratories of the years 2004 to 2008, we found 1,377 patients coded as having aortic stenosis, of whom 52% were clinically diagnosed as having severe aortic stenosis. From these, after review and eliminating cases with insufficient data, 58 consecutive patients (25 male, mean age 77 ± 5 years) were identified who: 1) had aortic stenosis with an orifice area ≤1 cm² and a mean systolic gradient ≤40 mm Hg, as well as an ejection fraction ≥50% on echocardiography; and 2) underwent hemodynamic evaluation within 7 days of echocardiographic evaluation.

These patients formed the group with “paradoxical” aortic stenosis. For comparison, data from 22 patients (10 male, mean age 73 ± 7 years) with conventionally defined severe aortic stenosis by echo (area ≤1 cm², mean gradient >40 mm Hg, ejection fraction ≥50%), were analyzed. These were patients who had also undergone invasive hemodynamic evaluation at the time of preoperative coronary angiography and had echocardiography within 7 days. All our patients were symptomatic, mostly with dyspnea, as this was a clinical prerequisite to consider them for cardiac catheterization before possible surgical therapy. All echocardiographic and invasive data were reanalyzed for the purpose of the study. Blood pressure at the time of echocardiography was taken from the closest recorded noninvasive measurement in the patient charts. Demographic and clinical characteristics of the 2 patient groups are given in Table 1.

Echocardiography. Echocardiographic measurements, including Doppler measurements, were performed according to current recommendations and guidelines (8,9) on state-of-the-art echo machines (Philips iE 33, Philips Healthcare, Hamburg, Germany, or General Electric Vivid 7, GE Healthcare, München, Germany). Care was taken to search for the highest transvalvular aortic gradients from all windows, including suprasternal and right parasternal. The pulsed-wave Doppler sample volume was aligned as well as possible with the direction of flow in the left ventricular outflow tract. For assessment of left ventricular outflow tract diameter, the parasternal long axis scan plane was systematically varied in zoom mode to avoid tangential cuts and to find the largest diameter. The diameter of the ascending aorta was calculated from parasternal long axis images at the level of the sinotubular junction, approximately 2 cm downstream of the aortic valve. Pressure gradients were calculated by the simplified Bernoulli equation. Ejection fraction was measured by biplane Simpson’s rule method. Relative wall thickness was calculated as:

\[
RWT = \frac{2 \cdot PW}{LVEDD}
\]

where PW is end-diastolic posterior wall thickness and LVEDD is end-diastolic left ventricular diameter, both measured by 2-dimensional echo in parasternal images.

Left ventricular mass was estimated by the recommended formula based on linear measurements (8) and indexed for body surface area, although this formula has not been validated for patients with aortic stenosis. All measurements were averaged from 3 sinus beats or 5 beats in atrial fibrillation. Aortic valve area was calculated by the continuity equation. Echo stroke volume was calculated by multiplying the systolic time-velocity integral from pulsed-wave Doppler recordings of the left ventricular outflow tract with the cross-sectional area of the outflow tract, calculated from its diameter at the aortic annulus level assuming circular geometry. The energy loss index was also computed, a parameter integrating pressure loss across the stenosis and post-stenotic pressure recovery (4,10). Energy loss index was calculated from the aortic valve orifice area and the ascending aortic cross-sectional area that was obtained from

<table>
<thead>
<tr>
<th>Demographic Characteristics of Patients With Low Gradient Severe Aortic Stenosis Despite Preserved Ejection Fraction (“Paradoxic”) and With Conventionally Defined Severe Aortic Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Paradoxic” Aortic Stenosis (n = 58)</strong></td>
</tr>
<tr>
<td><strong>Age, yrs</strong></td>
</tr>
<tr>
<td><strong>Male</strong></td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
</tr>
<tr>
<td><strong>Body surface area, m²</strong></td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).
the diameter of the ascending aorta at the sinotubular junction and assuming a circular aortic cross-section:

\[ AOA = \pi \cdot AOD^2/4 \]

Then,

\[ ELI = \frac{(AVA \cdot AOA)/(AOA - AVA)}{BSA} \]

where ELI is energy loss index, AVA is aortic valve orifice area, AOA is ascending aortic cross-sectional area, and BSA is body surface area.

As an index of global afterload, valvuloarterial impedance \( Z_{va} \) was calculated (4) as

\[ Z_{va} = (SAP + \Delta P_{mn})/SVI \]

where SAP is systolic arterial pressure, \( \Delta P_{mn} \) is mean systolic transaortic gradient, and SVI is stroke volume index.

Interobserver variability (expressed as coefficient of variation, standard deviation between measurements divided by average of measurements) in our laboratory for Doppler velocity measurements is 9% and for linear measurements 8% ± 6%.

**Cardiac catheterization.** In all patients, cardiac catheterization was performed according to clinical indications and not for the purpose of research; patients gave written informed consent. Right heart catheterization was performed in standard manner with a balloon-tipped 3-way catheter inserted via the inferior vena cava. Right-sided pressures were measured and cardiac output was determined by oxymetry, using a nomogram for oxygen consumption. Additionally, cardiac output was determined by thermodilution as the average of 3 runs which were repeated until subsequent differences in cardiac output values were <10%. Left heart catheterization was performed by the Judkins technique with 7-F sheaths and 6-F catheters. Retrograde passage of the stenotic aortic valve was performed. For the analysis described herein pressure tracings of the pullback of a fluid-filled pigtail catheter from the left ventricle into the ascending aorta were used, to avoid the well-known problems of distal pressure increase and delay in the arterial pressure waveform from the femoral sheath. The electronically recorded pressure tracings from the pullback were manually traced on a digitizing tablet, and aortic pressure tracings were superimposed manually on left ventricular pressure tracings, using aortic upstroke and incisure (11) as landmarks to position the tracings; subsequently, maximal and mean pressures and ejection times were calculated electronically from the stored tracings (12).

All measurements were done in triplicate. Aortic valve area was calculated by the Gorlin equation as:

\[ AVA = \frac{SV}{ET} \]

\[ 44.3 \cdot \sqrt{\frac{\Delta P_{mn}}{H20850}} \]

where SV is stroke volume, ET is ejection time, \( \Delta P_{mn} \) is mean transvalvular gradient (mm Hg).

Systemic vascular resistance was calculated from mean arterial pressure, mean right atrial pressure and cardiac output as

\[ SVR = \frac{(BP_{mn} - RAP_{mn})}{CO} \]

where SVR is systemic vascular resistance, \( BP_{mn} \) is mean arterial pressure, \( RAP_{mn} \) is mean right atrial pressure and CO is cardiac output.

Left ventricular end-diastolic pressure was recorded at the onset of the QRS complex of the electrocardiogram. In patients in atrial fibrillation (12 of 58 in the “paradoxic” aortic stenosis group and 3 of 22 in the conventionally defined aortic stenosis group), 5 beats were averaged.

**Statistics.** Continuous parameters are given as mean ± SD. Comparisons of echo and catheterization parameters from the groups with “paradoxic” and with conventionally defined aortic stenosis were performed by unpaired, 2-tailed \( t \) test, with the significance level set at \( p < 0.05 \). Comparisons between echo parameters and invasively measured parameters were performed by paired, 2-tailed \( t \) test, with the same significance level. The relation of invasive and noninvasive values for aortic valve area and mean pressure gradients was analyzed by linear regression and the Bland-Altman difference plot. Boxplots show median and 25th and 75th percentile, as well as data minimum and maximum (whiskers).

**Results**

**Patient characteristics.** Fifty-eight patients with “paradoxic” and 22 age- and gender-matched patients with conventionally defined severe aortic stenosis were studied (Table 1).

**Comparison between echo and catheterization data.** A typical example of echocardiographic and invasive data from a patient with “paradoxic” aortic stenosis is presented in Figures 1 and 2, and summary echocardiographic and catheterization data from the “paradoxic” and conventionally defined aortic stenosis patient groups are presented in Table 2 and Figures 3, 4, 5, and 6. In patients with “paradoxic” aortic stenosis, aortic valve area and mean gradients by echo and by invasive hemodynamics differed only modestly. For the invasive determination of cardiac output and stroke volume, both oxymetry and thermodilution were used. Stroke volumes measured by thermodilution were higher than stroke volumes measured by oxymetry (64 ± 18 ml/beat vs. 50 ± 14 ml/beat; \( r = 0.75 \), \( p < 0.0001 \)). Using the oxymetry stroke volumes, all patients with an aortic valve area ≤1 cm² by echo also had an area ≤1 cm²...
by catheterization. Both measurements correlated modestly, with a small overestimation of invasive measurements by echo ($r = 0.48$, bias $0.14 \pm 0.17 \text{ cm}^2$; $p < 0.001$). If thermodilution stroke volumes were used, invasively calculated valve areas were minimally larger than echo-based valve areas ($r = 0.47$, $p < 0.001$; bias $-0.03 \pm 0.19 \text{ cm}^2$, $p = 0.20$), and 6 of 58 patients in the “paradoxic” aortic stenosis group by echo and 1 of 22 patients in the conventionally defined aortic stenosis group by echo had areas $>1 \text{ cm}^2$ (Table 2, Figs. 3 and 4). Mean transaortic pressure gradients were very similar by echo and catheterization, with a nonsignificant minimal bias (Table 2, Figs. 5 and 6). The Pearson correlation coefficient of echo derived stroke volume with oxymetry derived stroke volume was $r = 0.61$, and with stroke volume measured by thermodilution $r = 0.49$ (all $p < 0.0001$) (see Table 2 for mean values). Considering only the patient group with stroke volume index $<35 \text{ ml/m}^2$ ($n = 71$), mean stroke volume by echo was $55 \pm 17 \text{ ml}$ versus mean stroke volume by oxymetry of $49 \pm 12 \text{ ml}$ ($r = 0.56$, $p < 0.0001$).

Echo stroke volumes calculated as product of systolic velocity-time integral in the left ventricular outflow tract and the outflow tract cross-section were similar, but only modestly correlated with stroke volumes calculated as the difference of end-diastolic and end-systolic left ventricular volume ($57 \pm 17 \text{ ml/beat}$ vs. $50 \pm 16 \text{ ml/beat}$, respectively; $r = 0.59$, $p < 0.0001$).

Heart rate and mean blood pressure during echo and catheterization were not significantly different.

Comparison between “paradoxic” and conventionally defined severe aortic stenosis. Comparing patients with “paradoxic” aortic stenosis to those with conventionally defined severe aortic stenosis, aortic valve areas were significantly higher in the “paradoxic” aortic stenosis group (Table 2, Figs. 3 and 4). One patient listed in our echo database as having a valve area of $1 \text{ cm}^2$ upon reanalysis had
an aortic valve area of 1.1 cm$^2$ by echo and 0.7 cm$^2$ by catheterization and was kept in the study population. Mean systolic gradients, by definition, were significantly lower in the “paradoxic” group than in the conventionally defined group (Figs. 5 and 6).

Stroke volumes tended to be lower in the “paradoxic” than in the conventionally defined severe aortic stenosis group (by echo: $48 \pm 16$ ml vs. $53 \pm 15$ ml, respectively, $p = 0.14$; by catheterization [oxymetry]: $50 \pm 15$ ml vs. $51 \pm 12$ ml, respectively, $p = 0.65$).

Left ventricular mass index was lower in “paradoxic” aortic stenosis. Left ventricular volumes, ejection fraction, and relative wall thicknesses were not significantly different between patients with “paradoxic” and conventionally defined severe aortic stenosis. Further stratification by stroke volume index indicated a closer association of left ventricular geometry with stroke volume index than with gradient, although the differences lacked statistical significance, presumably due to low group numbers. Ascending aortic diameter was lower in “paradoxic” than in conventionally defined severe aortic stenosis patients, and energy loss index in “paradoxic” aortic stenosis was significantly higher than in conventionally defined group (Table 2); global left ventricular afterload did not differ significantly between the 2 groups.

**Discussion**

Our results show minor biases and modest agreement when comparing invasive and echo-derived aortic valve areas and mean transvalvular systolic pressure gradients (biases, $+0.14$ cm$^2$ against oxymetry-based invasive area calculation, $-0.03$ cm$^2$ against thermodilution-based invasive area calculation, and $-0.08$ mm Hg for mean pressure gradient), both in patients classified as having “paradoxic” as well as conventionally defined severe aortic stenosis. Nevertheless, with regard to the classification of stenosis severity in the paradoxic aortic stenosis group, reclassification to moderate severity according to catheterization data occurred in only 1 of 58 based on oxymetry stroke volume and in 6 of 58 (10%) based on thermodilution stroke volume. In the conventionally defined aortic stenosis group, 1 patient classified as severe aortic stenosis by echo was reclassified by thermodilution data to moderate aortic stenosis. Although the considerable individual differences of valve area between invasive and noninvasive measurements may in the individual patient lead to discrepancies in the grading of severity, our data indicate that the diagnosis of “paradoxic” stenosis is not the consequence of a systematic underestimation of aortic valve area by the continuity equation. Only few reports of invasive hemodynamics in “paradoxic” aortic stenosis have been published (6,13,14), and a systematic comparison of echo and invasive hemodynamic data to the best of our knowledge has not been undertaken.

**Pitfalls in the calculation of aortic valve area by echo and catheterization.** In the individual patient, measurement error by echo is an important concern. The highest transvalvular velocities may be missed by continuous-wave Doppler, especially if not all windows are carefully used, leading to falsely too low maximal and mean gradients. The recording of left ventricular outflow tract velocities may be affected by malposition of the sample volume (typically too far from the valve) and to angle error. The diameter of the left ventricular outflow tract may be measured incorrectly, typically too low. Other methodological limitations include
the absence of a truly flat flow velocity profile in the left ventricular outflow tract and the rather elliptic than circular cross-section of the outflow tract (15–17). A further important consideration is the nature of the effective aortic valve orifice area calculated by the continuity equation. This area is smaller than the anatomic orifice area by a variable “coefficient of contraction,” which varies with the morphology of the stenosis (18). The Gorlin equation, on the other hand, is based on the same physical relationships of orifice area, pressure, and flow rate as the Bernoulli and continuity principles used in echocardiography (19). However, in order to improve the correlation with surgical inspection of the anatomical area of the stenosed valve—the ancient gold standard—the traditional Gorlin formula incorporates a “Gorlin constant” of 44.3 for aortic stenosis, a correction factor assumed to correct for the coefficient of contraction and to account for the conversion of units (mm Hg instead of Pascal). Acceptable agreement of aortic valve area calculations from catheterization data by Gorlin formula and from echo data by continuity equation has been shown clinically and by animal experimentation (20,21). Although the discussed limitations of echo-calculated aortic valve area tend to produce falsely low areas, both underestimation (22) and overestimation (20,23) of invasively calculated aortic valve area by echo have been observed. In our data, depending on the method for determining invasive stroke volume, slight overestimation (vs. oxymetry–based catheterization data) or slight underestimation (vs. thermodilution-based catheterization data) of invasively obtained aortic valve area by echo was observed, with little effect as to the classification of severity.

Further, stenotic orifice areas calculated by either the Gorlin equation or the continuity equation have both been shown in vitro and in vivo to vary with flow rates (23–25), particularly at low flow rates. The reasons include the effects of downstream vortices at low flow rates, viscous effects, and incomplete cusp opening of stenotic valves at low flow. Such effects may also have affected our data. However, in our “paradoxic” aortic stenosis group stroke volume index was $26 \pm 8 \text{ ml/m}^2/\text{min}$ and volume flow rate (stroke volume divided by ejection time) $158 \pm 26 \text{ ml/s}$. At such flow rates, flow-mediated reduction in effective orifice areas in the in vivo conditions prediction of the anatomic (geometric) orifice area becomes unreliable.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>“Paradoxic” Aortic Stenosis (n = 58)</th>
<th>Conventionally Defined Severe Aortic Stenosis (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Echo</td>
<td>Catheterization</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg</td>
<td>98 ± 11</td>
<td>98 ± 15</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>76 ± 16</td>
<td>76 ± 15</td>
</tr>
<tr>
<td>Mean systolic transvalvular gradient, mm Hg</td>
<td>32 ± 7</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>Peak systolic transvalvular gradient, mm Hg</td>
<td>52 ± 12</td>
<td></td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.80 ± 0.15</td>
<td>0.69 ± 0.16†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.85 ± 0.19</td>
</tr>
<tr>
<td>Aortic valve area index, cm²/m²</td>
<td>0.43 ± 0.08</td>
<td>0.37 ± 0.08†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.46 ± 0.09</td>
</tr>
<tr>
<td>End-diastolic volume index, ml/m²</td>
<td>40 ± 13</td>
<td>44 ± 11</td>
</tr>
<tr>
<td>End-systolic volume index, ml/m²</td>
<td>14 ± 6</td>
<td>16 ± 6</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>65 ± 7</td>
<td>65 ± 7</td>
</tr>
<tr>
<td>Stroke volume, ml/beat</td>
<td>48 ± 16</td>
<td>50 ± 15†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63 ± 18‡</td>
</tr>
<tr>
<td>Stroke volume index ml/beat/m²</td>
<td>26 ± 8</td>
<td>27 ± 7†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34 ± 9§</td>
</tr>
<tr>
<td>Systemic vascular resistance, mm Hg - min/l</td>
<td>2,140 ± 662</td>
<td>2,188 ± 766</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>18 ± 6</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>126 ± 27</td>
<td>143 ± 34§</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.56 ± 0.12</td>
<td>0.59 ± 0.09</td>
</tr>
<tr>
<td>Aortic diameter, mm</td>
<td>28 ± 5</td>
<td>31 ± 5§</td>
</tr>
<tr>
<td>Global left ventricular afterload, mm Hg/ml/beat/m²</td>
<td>7.54 ± 2.52</td>
<td>7.14 ± 1.93</td>
</tr>
<tr>
<td>Energy loss index, cm²/m²</td>
<td>0.51 ± 0.12</td>
<td>0.42 ± 0.09*</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *p < 0.01 for comparison between “paradoxic” and conventionally defined severe stenosis. †Based on oxymetry. ‡p < 0.01 for comparison of echocardiography and catheterization based parameters. §p < 0.05. Based on thermodilution. LVEDP = left ventricular end-diastolic pressure.
Hence, pitfalls exist for both methods, and as evaluation nowadays is primarily performed by echo, “paradoxic” data before acceptance should always prompt a critical review of echo findings, and, if necessary, clarification by other imaging modalities or invasive hemodynamic assessment.

Characteristics of “paradoxic” aortic stenosis. Several studies have identified a group of patients in whom echocardiographic data indicated “paradoxically” low transaortic gradients despite severe aortic stenosis according to orifice area calculation and a preserved left ventricular ejection fraction (3–7). As possible contributing factors to this hemodynamic constellation, small ventricular volumes, concentric left ventricular hypertrophy, reduced longitudinal left ventricular function, increased systemic arterial resistance, and others have been proposed (26–28). The prognosis of these patients with “paradoxic” aortic stenosis remains unclear at present. Studies including mainly low stroke volume index patients indicate a worse survival than of patients with high gradient severe aortic stenosis (4,6,7), while a study including mainly patients with normal stroke volume index did not indicate impaired prognosis (29). It is possible that the category “paradoxic (severe) aortic stenosis” encompasses at least 2 prognostically different patient groups, 1 with normal or high stroke volume that is prognostically similar to moderate aortic stenosis, and 1 that represents more advanced myocardial impairment and presents with low stroke volume (30). In Table 3, the data from all our patients are stratified according to both mean gradient and stroke volume index. As expected, proportionally more patients in the “paradoxic” aortic stenosis group had a stroke volume index than in the conventionally defined aortic stenosis group (although the difference was nonsignificant in our modest sized groups). This underlines the contribution of low stroke volume to the pathophysiology of “paradoxic” aortic stenosis. Nevertheless, most patients (18 of 22) with conventionally defined aortic stenosis (i.e., high gradient) also had low stroke volume index, and diastolic left ventricular volumes and relative wall thicknesses in these patients were closer to the values in the low flow/low gradient group than to those in the 2 high-flow groups. This indicates that many patients with severe aortic stenosis have low stroke volumes despite
preserved ejection fraction, even if the gradients are well within the conventional definition of severe stenosis, and confirms earlier observations (30). Our data also confirm earlier findings (4) of a higher proportion of females in the low stroke volume groups as opposed to the high stroke volume groups (Table 3, Online Table 1).

Stratification using invasively obtained stroke volume index data showed a very similar distribution of patients (Online Table 1).

Pibarot and Dumesnil from Québec have emphasized the role of hypertension and ventriculoarterial coupling in this scenario (30,31). Ventriculoarterial coupling denotes the
combined pressure-volume relationship of ventricle and systemic circulation during ejection. Hypertension and elevated systemic resistance to aortic ejection are frequent in patients with aortic stenosis and create a “second stenosis” in series with the valvular aortic stenosis. The elevated afterload reduces stroke volume, and thus leads to a relatively low transvalvular gradient. The implication is that stroke volume, and hence gradients, would be higher if systemic resistance were lower.

In our study, energy loss index, a relatively flow-independent measure of severity of aortic stenosis based on morphology (10), was higher in the “paradoxic” aortic stenosis group than in the conventionally defined severe aortic stenosis group, and lowest in the group with low stroke volume index and high gradient (see Table 3). Because of the inverse relation between total energy loss and energy loss index, this indicates that in our patients with “paradoxic” aortic stenosis, average energy loss was less than in those with conventionally defined aortic stenosis. Thus, in terms of the energy loss concept, the group with “paradoxic” aortic stenosis had in fact functionally less severe stenosis than the group with conventionally defined severe aortic stenosis, which is also in line with the fact that aortic valve area was significantly larger in the “paradoxic” group than in the conventionally defined group. This seems to contradict the retrospective analysis of Hachicha et al. (4), where aortic stenosis patients with “paradoxical low flow” had lower energy loss index values than those with “normal flow.” However, Hachicha et al. used the term “paradoxical” to describe severe aortic stenosis with low stroke volume index despite preserved ejection fraction, while in the present manuscript it denotes low gradient despite preserved ejection fraction. Therefore, their selection of patients with “paradoxical aortic stenosis” was different from ours.

However, their “paradoxical low flow” group had in fact significantly lower average aortic valve areas than their “normal flow” group, opposite to findings in our conventionally defined severe aortic stenosis patients, and this difference, reflecting different patient selection, probably explains the divergent findings.

Although not statistically significant in our modestly sized groups, left ventricular mass index was higher in the conventionally defined severe aortic stenosis group. This confirms that overall there was a higher degree of obstruction, in accordance with lower valve areas, higher gradients, and lower energy loss index in this group than in the “paradoxic” aortic stenosis group.

**Study limitations.** The agreement between echo and catheterization data was no more than modest. This in part was due to not simultaneous echo and catheterization measurements; however, mean blood pressures and heart rates did not differ significantly between the 2 examinations, and patients in unstable conditions were not included. Further, only a limited range of aortic valve areas was considered. Fluid filled catheters were used for pressure measurements, with the catheter across the stenotic orifice during left ventricular pressure tracings, both of which can introduce minor inaccuracies. Finally, our study, which was cross-sectional at the time point of evaluation for planned surgery, by design did not provide insight into prognosis of different types of aortic stenosis.

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