Projected Valve Area at Normal Flow Rate Improves the Assessment of Stenosis Severity in Patients With Low-Flow, Low-Gradient Aortic Stenosis
The Multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) Study

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Background—We sought to investigate the use of a new parameter, the projected effective orifice area (EOA_{proj}) at normal transvalvular flow rate (250 mL/s), to better differentiate between truly severe (TS) and pseudo-severe (PS) aortic stenosis (AS) during dobutamine stress echocardiography (DSE). Changes in various parameters of stenosis severity have been used to differentiate between TS and PS AS during DSE. However, the magnitude of these changes lacks standardization because they are dependent on the variable magnitude of the transvalvular flow change occurring during DSE.

Methods and Results—The use of EOA_{proj} to differentiate TS from PS AS was investigated in an in vitro model and in 23 patients with low-flow AS (indexed EOA <0.6 cm²/m², left ventricular ejection fraction $\leq40\%$) undergoing DSE and subsequent aortic valve replacement. For an individual valve, EOA was plotted against transvalvular flow (Q) at each dobutamine stage, and valve compliance (VC) was derived as the slope of the regression line fitted to the EOA versus Q plot; EOA_{proj} was calculated as $EOA_{proj}=EOA_{rest}+VC\times(250-Q_{rest})$, where EOA_{rest} and Q_{rest} are the EOA and Q at rest. Classification between TS and PS was based on either response to flow increase (in vitro) or visual inspection at surgery (in vivo). EOA_{proj} was the most accurate parameter in differentiating between TS and PS both in vitro and in vivo. In vivo, 15 of 23 patients (65%) had TS and 8 of 23 (35%) had PS. The percentage of correct classification was 83% for EOA_{proj} and 91% for indexed EOA_{proj} compared with percentages of 61% to 74% for the other echocardiographic parameters usually used for this purpose.

Conclusions—EOA_{proj} provides a standardized evaluation of AS severity with DSE and improves the diagnostic accuracy for distinguishing TS and PS AS in patients with low-flow, low-gradient AS. (***Circulation.*** 2006;113:711-721.)

Key Words: aortic valve stenosis ■ echocardiography ■ hemodynamics ■ surgery ■ valves

Although patients with severe aortic stenosis (AS) and severely reduced left ventricular (LV) ejection fraction represent ≈5% of AS patients, they also represent the most controversial and challenging subset. Dobutamine stress echocardiography (DSE) has been shown to be useful to separate patients with truly severe (TS) AS and concomitant LV systolic dysfunction from those with pseudo-severe (PS) AS, in which a weakened ventricle is incapable of opening an aortic valve that is only mildly or moderately stenotic.[1–7] The distinction between these 2 subgroups is essential because patients with TS AS will generally benefit from aortic valve replacement (AVR), whereas those with PS AS may not. Several criteria have been proposed in the literature to

differentiate TS AS from PS AS, including the following: a peak DSE mean gradient >30 mm Hg, a peak DSE effective orifice area (EOA) ≤1.0 or <1.2 cm² depending on the study, and an absolute increase in EOA <0.3 cm² during DSE.[1,4,5,7] However, the changes in gradient and EOA during stress depend largely on the magnitude of flow augmentation achieved during DSE, which may vary considerably from one patient to another.[8,9] To overcome this limitation, we sought to examine whether the projected valve area (EOA_{proj}) at a normal transvalvular flow rate, a

Pseudo Severe Valve

Panel A

Panel B

SV: 20 mL
EOA: 0.57 cm^2
MG: 9 mm Hg

SV: 70 mL
EOA: 1.08 cm^2
MG: 26 mm Hg

Truly Severe Valve

Panel C

Panel D

SV: 20 mL
EOA: 0.50 cm^2
MG: 20 mm Hg

SV: 70 mL
EOA: 0.84 cm^2
MG: 42 mm Hg

Figure 1. Photograph of the valve orifice of 2 silicone-made valves recorded by a high-speed video camera at peak systole. The figure shows the example of valve with PS stenosis at low (A) and normal (B) flow rate and the example of valve with TS stenosis at low (C) and normal (D) flow rate. MG indicates mean gradient.

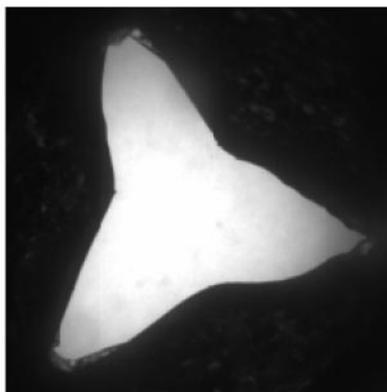new parameter, could provide additional accuracy to separate TS from PS AS.

Methods

In Vitro Study

The mock flow circulation model used for the in vitro study has been described in detail previously.[10] Briefly, this model is composed of a reservoir, a pump, an aortic valve, a compliant aortic chamber, and systemic vascular resistance. The flow is provided by a computer-controlled motor coupled to a gear pump. The flow rate is measured by an electromagnetic flowmeter (Cliniflow II, Carolina Medical Electronics), and the LV and aortic pressures are measured with Millar catheters.

With the use of this model, 8 rigid stenoses (Plexiglas plates with circular orifices of 0.80, 1.16, 1.35, 1.50, 1.60, 1.65, 1.72, and 1.80 cm^2) and 5 aortic bioprosthetic heart valves (Medtronic Mosaic 19, 21, and 23 mm and Carpentier Edwards Perimount 19 and 21 mm) were tested under a wide range of flow rates. In the case of rigid stenotic orifices, a large bioprosthetic valve (Mosaic 27 mm) was inserted immediately after the orifice to avoid any flow regurgitation during diastole. In addition, we tested 9

trileaflet valves fabricated by a new proprietary technique (developed by L.K.) using a mold of the aortic valve and a multi–silicone layer method. With the use of this technique, a variable number of silicone layers are successively applied on the mold, such that valves with 2 layers have relatively flexible leaflets, whereas valves with 10 layers have very stiff leaflets and severely reduced mobility. All orifices and valves were tested under 5 stroke volumes (SVs): 20 ± 0.7 (stage 1), 30 ± 0.9 (stage 2), 50 ± 0.7 (stage 3), 70 ± 1.1 (stage 4), and 90 ± 1.5 mL (stage 5), with an ejection time of 300 ± 22 ms. A Sonos 5500 ultrasound system (Philips Medical Imaging) was used for Doppler velocity measurements. Valves were classified as TS AS when the valve EOA was ≤1.00 cm^2 and the mean gradient was >30 mm Hg at SV ≥70 mL. According to this definition, 14 valves were classified as PS AS (total of 70 hemodynamic measurements obtained) and 8 valves as TS AS (total of 40 hemodynamic measurements obtained). Figure 1 displays typical examples of TS and PS valves at low and normal flow rates.

In Vivo Study

From July 2002 to November 2004, 46 patients with low-flow, low-gradient AS were recruited in the TOPAS (Truly or Pseudo-
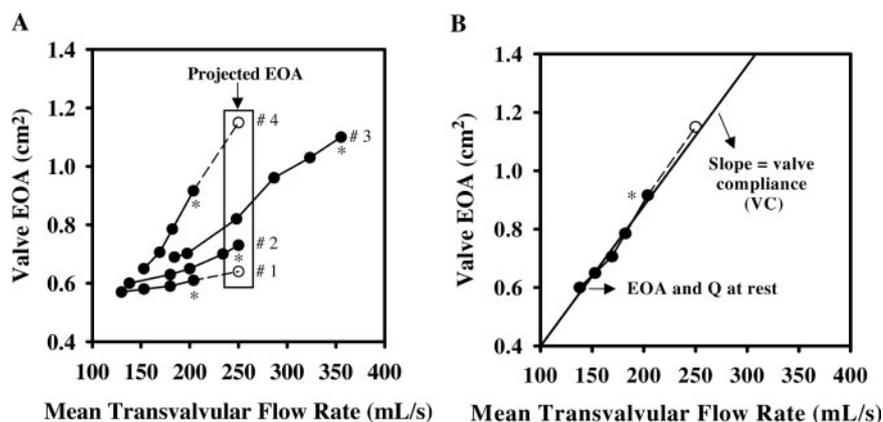
Figure 2. Concept of the EOA_{proj} in 4 different patients (A) and calculation of the projected EOA at a flow rate of 250 mL/s (B) with the use of Equation 3. *Peak valve EOA obtained during DSE.

Severe Aortic Stenosis) multicenter (Quebec Heart Institute, University of Ottawa Heart Institute, and Vienna General Hospital) prospective study. The inclusion criteria were as follows: (1) suspected severe AS defined by a valve EOA ≤ 1.2 cm^2 and an indexed valve EOA ≤ 0.6 cm^2/m^2; (2) mean gradient <40 mm Hg; and (3) moderate or severe LV systolic dysfunction, defined as a LV ejection fraction $\leq 40\%$. The EOA, mean gradient, and LV ejection fraction used for patient inclusion were obtained from the clinical Doppler echocardiographic examination. The exclusion criteria were as follows: (1) $>2+$ aortic regurgitation; (2) mitral valve disease, defined by mitral valve area <2.0 cm^2 or $>2+$ regurgitation caused by an intrinsic pathology of the valve; (3) atrial fibrillation; (4) paced rhythm; (5) unstable angina; (6) acute pulmonary edema; (7) end-stage renal disease; (8) pregnant or lactating women; and (9) unwillingness to provide informed consent.

All patients underwent DSE with the use of commercially available ultrasound systems. The dobutamine infusion protocol was designed to obtain incremental increases in flow and a steady state at each level. It consisted of 8-minute increments of 2.5 or 5 μg/kg per minute up to a maximum dosage of 20 μg/kg per minute. The predetermined end points for terminating DSE were as follows: (1) heart rate $>220-$age bpm; (2) systolic blood pressure <80 mm Hg; (3) systolic blood pressure >220 mm Hg or diastolic blood pressure >110 mm Hg; (4) significant increase in the LV outflow tract (LVOT) gradient (peak gradient >20 mm Hg); (5) ischemia detected by ECG (>5 mm of flat or downsloping ST depression); (6) complex ventricular arrhythmias; (7) rapid new atrial arrhythmias; (8) chest discomfort; and (9) maximum dose reached (20 μg/kg per minute).

The Doppler echocardiographic measurements were performed at rest and at each stage of the dobutamine protocol: 0 (baseline), 2.5, 5, 10, 15, and 20 μg/kg per minute. These measurements included SV in the LVOT calculated from the product of the LVOT velocity-time integral and cross-sectional area, mean transvalvular flow rate, peak and mean transvalvular gradients by the Bernoulli equation, valve EOA by the continuity equation, and LV ejection fraction by the Simpson method. The LVOT diameter was assumed to have remained constant during the test protocol.

Of the 46 patients recruited to date in the TOPAS study, 23 underwent AVR (18 underwent concomitant coronary artery bypass grafting). A comprehensive morphological description of the valve was performed by the surgeon at the time of operation. Care was taken to standardize the methods used by the different surgeons involved in the study. The location and degree of commissural fusion were described. The stiffness of each valve leaflet was assessed in situ with a scoring system, as follows: 0, the whole leaflet is flexible; 1, the margin and the mid part of the leaflet are flexible but the base is rigid; 2, only the free margin of the leaflet is flexible; and 3, the leaflet is completely rigid. The score of the 2 or 3 leaflets (2 for bicuspid, 3 for tricuspid) was summed to obtain the overall valve stiffness score. The overall score was then divided by the number of leaflets to obtain a per

leaflet average score. According to this visual and manual inspection of the valve, the surgeon was asked to grade the stenosis severity as nonsignificant, mild, moderate, or severe. Patients were considered to have TS AS if the valve stenosis was graded as severe and PS AS if the stenosis was considered nonsignificant, mild, or moderate. The degree of calcification was assessed by the pathologist for each valve leaflet, as follows: 0, no calcification; 1, mildly calcified (small isolated spots); 2, moderately calcified (multiple larger spots); and 3, heavily calcified (extensive thickening and calcification of all leaflets). The per leaflet average calcification score was determined by the same method as that used for the stiffness score. The surgeons and pathologists were unaware of the results of EOA_{proj}. The pathologists were also unaware of the surgeon's assessment of the leaflet stiffness score and stenosis severity.

Echocardiographic Measurements

For both the in vitro and in vivo studies, valve EOA was determined by the standard continuity equation, and mean transvalvular gradient was calculated with the use of the modified Bernoulli equation.[8,9] Some investigators have suggested that other parameters such as valve resistance or LV stroke work loss might be useful to assess the stenosis severity in patients with low-flow, low-gradient AS.[11,12] Hence, valve resistance (RES) was calculated according to the following formula[11]:

$$(1) \qquad RES = \frac{1333 \times MG}{Q}$$

where MG is the mean transvalvular gradient in mm Hg, the constant 1333 is a conversion factor allowing an expression of resistance in dyne $\cdot$ s $\cdot$ cm^{-5}, and Q is the mean transvalvular flow rate in mL/s, obtained by dividing the SV by the ejection time. The LV stroke work loss (SWL) was expressed as percentage and obtained from the following formula[9]:

$$(2) \qquad SWL = 100 \times \left(\frac{MG}{MG + SAP} \right)$$

where SAP is the systolic brachial artery pressure in mm Hg.

Calculation of the EOA_{proj}

The classification of AS severity based on the peak EOA may be limited by the fact that this parameter is not measured at the same flow rate in all patients. Figure 2A shows the change in EOA obtained in 4 selected patients during the different stages of the dobutamine protocol. As can be appreciated, the peak flow rate achieved during DSE as well as the slope of the EOA-flow relationship varies considerably from one patient to another. To overcome this limitation, we derived the EOA_{proj}, ie, what the EOA would be at a standardized flow rate. This flow rate was arbitrarily chosen to be 250 mL/s because it approximately corresponds to the mean value of the flow rates observed in AS
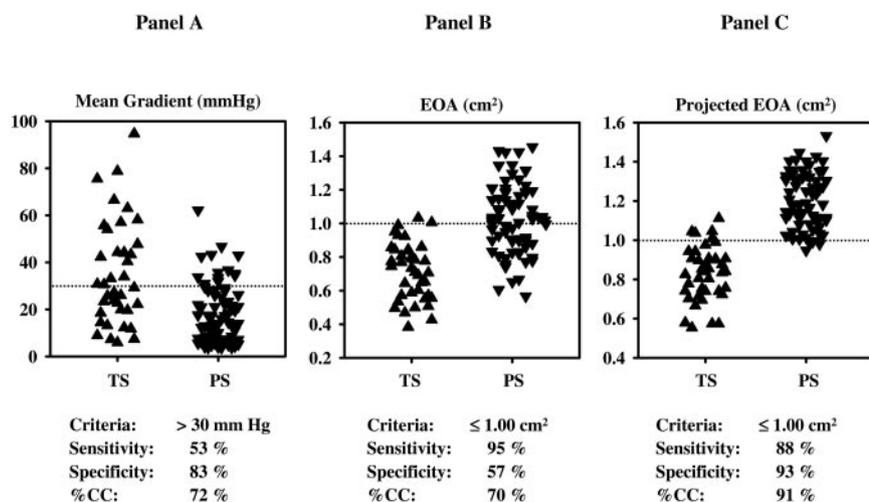
Figure 3. Distribution of mean gradient (A), EOA (B), and EOA_{proj} (C) in the TS and PS groups for the valves tested in vitro.

patients with normal LV function.[8,13] Hence, the EOA_{proj} at a standardized flow of 250 mL/s was calculated as follows

$$(3) \qquad EOA_{proj} = EOA_{rest} + VC \times (250 - Q_{rest})$$

where EOA_{rest} and Q_{rest} are the EOA and Q at rest and VC is the valve compliance corresponding to the slope of the EOA-flow relationship (Figure 2B) and representing the rate of change in EOA in relation to the increase in flow during stress. Sensu stricto, compliance is a change in area (or volume) per change in pressure. In this study we used the term *valve compliance* to describe the relationship of valve opening with the change in transvalvular flow rate.

The same method was used to determine the EOA_{proj} in the in vitro study. For each valve, EOA was plotted against mean transvalvular flow rate at each of the 5 flow stages. To reproduce the clinical situation in which there is wide interindividual variability in the resting flow rate as well as the magnitude of flow increase during DSE, the EOA-Q curve fitting and the calculation of the EOA_{proj} (Equation 3) were performed in the 5 following situations, ie, by including only data from (1) stages 1 and 2 (simulating the situation of a patient with a SV of 20 mL at rest increasing up to 30 mL on DSE); (2) stages 1, 2, and 3 (increase in SV from 20 to 50 mL); (3) stages 2 and 3 (increase in SV from 30 to 50 mL); (4) stages 2, 3, and 4 (increase in SV from 30 to 70 mL); and (5) stages 3, 4, and 5 (increase in SV from 50 to 90 mL). This provided 5 measurements of EOA_{proj} for each of the 22 valves, corresponding to 5 potential clinical scenarios.

Statistical Analysis

Differences between TS and PS groups for baseline and operative variables were tested for statistical significance by Student t, χ^2, or Fisher exact tests as appropriate. A 2-way ANOVA for repeated measures was used to evaluate the effect of DSE and the effect of group (TS versus PS) on Doppler echocardiographic variables. A probability value <0.05 was considered significant.

Results

In Vitro Study

From the in vitro protocol, SV was increased from 20 to 90 mL, and mean flow rate increased from 83 to 307 mL/s. As a result, mean gradient increased on average by 38 ± 52 mm Hg ($543 \pm 182\%$), valve EOA increased by 0.37 ± 0.71 cm^2 ($57 \pm 92\%$), valve resistance increased by 75 ± 79 dyne $\cdot$ s $\cdot$ cm^{-5} ($73 \pm 86\%$), and stroke work loss increased by $20 \pm 8\%$ ($333 \pm 160\%$). As previously described, the valves were classi-fied as truly stenotic (TS) when the valve EOA was ≤ 1.00 cm^2 and the mean gradient >30 mm Hg at a SV ≥ 70 mL. With the

use of this definition, mean gradient (Figure 3A) and EOA (Figure 3B) obtained from the 22 valves with the use of the 5 simulated clinical flow situations (n=110) discriminated poorly between TS and PS AS. In contrast, the EOA_{proj} (Figure 3C) provided a much better separation between the TS and PS AS groups, independent of the simulated clinical flow situation. The sensitivity, specificity, and percentage of correct classification (%CC) for the identification of TS AS was 53%, 83%, and, 72% for mean gradient >30 mm Hg; 95%, 57%, and 70% for EOA ≤ 1.0 cm^2; and 88%, 93%, and 91% for EOA_{proj} ≤ 1.0 cm^2. Figure 4 shows the comparison of the performance of the different parameters and criteria that have been previously proposed in the literature to distinguish TS from PS AS. When these criteria are used separately or in combination, as suggested in previous studies,[4,5,7] the %CC ranges between 48% and 85%, whereas it is 91% when an EOA_{proj} ≤ 1.0 cm^2 is used as the discriminating criterion.

In Vivo Study

Baseline clinical data are presented in Table 1. Patients who underwent AVR were significantly younger than nonoperated patients. There were no other significant differences between the operated and nonoperated groups with regard to baseline clinical data. Among the 23 operated patients, the surgeon considered the severity of the valve stenosis to be only moderate in 8 patients, and these patients were thus classified as having PS AS. The other 15 patients were considered to have TS AS. In the TS AS group, 87% of the patients had an average leaflet stiffness score of 3, and 13% had a score of 2; in the PS AS group, 50% of patients had a score of 2, and 50% of patients had a score of 1 (Table 2). Patients with TS AS also had a higher average leaflet calcification score. The proportion of patients with a bicuspid valve was low and was identical (13%) in both groups (Table 2). Patients with TS AS had slightly larger ($P=0.047$) body surface area than patients with PS AS (Table 1). Otherwise, there were no significant differences between the TS and PS AS groups with regard to the baseline clinical data.

Change in Flow During DSE

The DSE was well tolerated in all patients, and the reasons for terminating DSE are described in Table 3. The resting values
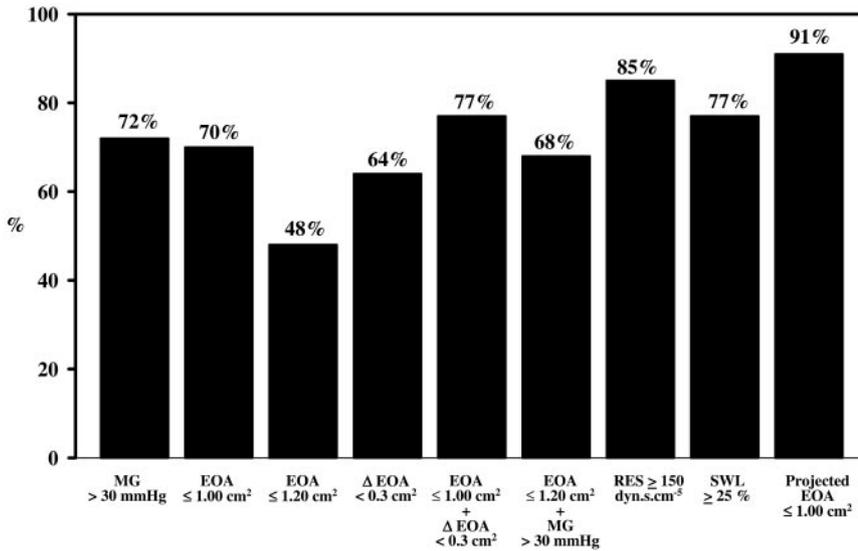
Percentage of Correct Classification

Figure 4. Comparison of the %CC observed with the use of different criteria to differentiate TS from PS stenosis in the valves tested in vitro. ΔEOA indicates absolute increase in EOA; MG, mean gradient; RES, valvular resistance; and SWL, stroke work loss.

of mean gradient (21±8 mm Hg), valve EOA (0.86±0.19 cm²), and LV ejection fraction (28±9%) were similar to those of other series reported previously in the literature.[4,5] On average, there was a significant increase in LV ejection fraction (8±6%), SV (14±10 mL), cardiac output (2.42±1.35 L/min), and mean transvalvular flow rate (79±44 mL/s) during DSE ($P<0.001$ for all variables). The peak transvalvular flow rate obtained during DSE varied extensively (138 to 445 mL/s) depending on the patient. There were no significant differences between operated and nonop-

erated patients or between TS and PS AS patients with regard to the rest, stress, or increase in flow rate during DSE.

Comparison of Indices of Stenosis Severity in Nonoperated and Operated Patients

All Doppler echocardiographic indices of stenosis severity varied significantly ($P<0.001$) with DSE in nonoperated, operated TS, and operated PS groups (Table 4). On average, stress values of mean gradient and stroke work loss were significantly higher in the operated group than in the nonoperated group. However, these differences were

TABLE 1. Baseline Clinical Data in the 46 Patients With Low-Flow AS

		Operated				
Variable	Nonoperated (n=23)	All Patients (n=23)	PS AS (n=8)	TS AS (n=15)	P, Nonoperated vs Operated	P, TS vs PS AS
Age, y	76±8	68±11*	66±13	69±10	0.018	NS
Female	7 (30)	6 (26)	3 (38)	3 (20)	NS	NS
Body surface area, m²	1.78±0.20	1.88±0.19	1.78±0.14	1.94±0.19†	NS	0.047
NYHA functional class						
II	7 (30)	8 (35)	2 (25)	6 (40)	NS	NS
III	10 (43)	15 (65)	6 (75)	9 (60)	NS	NS
Smoking	3 (13)	3 (13)	1 (13)	2 (13)	NS	NS
Coronary artery disease	18 (78)	20 (87)	5 (63)	15 (100)	NS	NS
1 vessel	9 (39)	4 (17)	1 (13)	3 (20)	NS	NS
2 vessels	2 (9)	4 (17)	2 (25)	2 (13)	NS	NS
3 vessels	7 (30)	12 (52)	2 (25)	10 (67)	NS	NS
Hypertension	19 (83)	13 (57)	4 (50)	9 (60)	NS	NS
Diabetes mellitus	7 (30)	9 (39)	1 (13)	8 (53)	NS	NS
Renal failure	7 (30)	5 (22)	2 (25)	3 (20)	NS	NS
Chronic lung disease	8 (35)	8 (35)	3 (38)	5 (33)	NS	NS
Previous myocardial infarction	17 (74)	13 (57)	3 (38)	10 (67)	NS	NS
History of CABG	8 (35)	8 (35)	2 (25)	6 (40)	NS	NS

Data are number of patients (%).
*Significant ($P<0.05$) difference between nonoperated vs operated groups.
†Significant difference between TS AS and PS AS groups.

TABLE 2. Operative and Pathological Data in the 23 Patients Who Underwent AVR

Variable	All Operated Patients (n=23)	PS AS (n=8)	TS AS (n=15)	*P*, TS vs PS AS
Congenital bicuspid	3 (13)	1 (13)	2 (13)	NS
Per leaflet average calcification score				0.025
0	1 (4)	1 (13)	0 (0)	
1	3 (13)	3 (38)	0 (0)*	
2	7 (30)	2 (25)	5 (33)	
3	12 (52)	2 (25)	10 (67)	
Per leaflet average stiffness score				<0.001
1	5 (22)	4 (50)	0 (0)*	
2	5 (22)	4 (50)	2 (13)	
3	13 (57)	0 (0)	13 (87)*	

Data are number of patients (%).
*Significant difference between TS AS and PS AS groups.

no longer significant when corrected for type I error (Table 4). The projected EOA and indexed projected EOA were significantly lower in the operated group, and these differences remained significant after correction for type I error. Among operated patients, rest and stress values of indexed EOA were significantly lower and stress values of mean gradient and LV stroke work loss were significantly higher in the TS than in the PS AS group (Table 4). However, the differences for mean gradient and stroke work loss were not significant after correction for type I error. There was no significant difference for the rest or stress values of EOA (unindexed), peak gradient, and valve resistance between the 2 groups. The EOA_{proj} and indexed EOA_{proj} were significantly lower in the TS AS group. Given that the EOA_{proj} was derived from regression modeling, the estimate of error for the calculated EOA_{proj} was 0.03 ± 0.01 cm^2.

Performance of Indices of Stenosis Severity to Differentiate TS AS From PS AS

Figure 5 displays an important overlap between TS and PS groups for the stress values of mean gradient (Figure 5A), EOA (Figure 5B), and absolute increase in EOA (Figure 5C) during DSE. The %CC was 74% when a stress gradient >30 mm Hg was used as the criterion to identify TS AS and 65% when a stress EOA ≤ 1.0 cm^2 was used. An absolute increase in EOA <0.3 cm^2 had a very low

specificity (13%) to identify TS AS, with a %CC of 61%. Most importantly, there was less overlap between the 2 groups when the EOA_{proj} was used, and the %CC increased to 83% when an $EOA_{proj} \leq 1.0$ cm^2 was used as the criterion to identify TS AS (Figure 5D). This performance was further improved by indexing the EOA_{proj} to body surface area. The most discriminative threshold to separate the 2 groups was an indexed EOA_{proj} of ≤ 0.55 cm^2/m^2, which provided a %CC of 91% (Figure 5E). Importantly, the measurement of valve compliance and thus the EOA_{proj} may be unreliable when there is only a minimal or no increase in transvalvular flow during DSE. In our study the increase in flow rate obtained with DSE ranged between 14 and 178 mL/s (11% and 93% in relative terms). Three patients had <15% increase in flow rate with DSE. If these patients were excluded, %CC for indexed EOA_{proj} increased to 95% with only 1 patient misclassified (Figure 5F). Figure 6 summarizes the result of the performance of the different criteria that have been used in the literature to differentiate TS from PS AS. When these criteria were used separately or in combination, %CC ranged between 61% and 74% compared with 91% when the indexed EOA_{proj} was used. In addition, EOA_{proj} and indexed EOA_{proj} correlated well with the leaflet stiffness score ($r=0.62$ and $r=0.71$, respectively). In contrast, the correlation coefficients between the standard indices of stenosis severity and

TABLE 3. Reasons for Terminating DSE

Variable	Nonoperated (n=23)	Operated All Patients (n=23)	PS AS (n=8)	TS AS (n=15)	*P*, Nonoperated vs Operated	*P*, TS vs PS AS
Maximal dose reached (20 μg/kg per minute)	15 (65)	16 (70)	6 (75)	10 (67)	NS	NS
Heart rate >220− age bpm	3 (13)	3 (13)	1 (13)	2 (13)	NS	NS
Systolic blood pressure <80 mm Hg	0 (0)	1 (4)	0 (0)	1 (7)	NS	NS
Ventricular arrhythmias	4 (17)	2 (9)	1 (13)	1 (7)	NS	NS
Chest discomfort	1 (4)	1 (4)	0 (0)	1 (7)	NS	NS

Data are number of patients (%).

TABLE 4. Doppler Echocardiographic Indices of Stenosis Severity

Variable	Nonoperated (n=23)	Operated — All Patients (n=23)	PS AS (n=8)	TS AS (n=15)	P, Nonoperated vs Operated	P, TS vs PS AS
Valve EOA, cm^2						
Rest	0.91±0.18	0.81±0.18	0.89±0.18	0.76±0.17	NS	NS: 0.09
DSE	1.13±0.18‡	0.98±0.22‡	1.08±0.20‡	0.92±0.22‡		
Indexed valve EOA, cm^2/m^2						
Rest	0.52±0.10	0.43±0.10	0.50±0.09	0.39±0.08†	NS	0.003
DSE	0.64±0.12‡	0.52±0.11‡	0.60±0.08‡	0.47±0.10‡†		(0.02)
Peak gradient, mm Hg						
Rest	31±11	42±13	38±18	44±10	NS: 0.06	NS
DSE	45±17‡	66±24‡	58±28‡	70±22‡		
Mean gradient, mm Hg						
Rest	17±5	25±8	22±10	27±7	0.025	0.04
DSE	24±8‡	37±12‡*	31±12‡	41±11‡†	(NS)	(NS)
Valve resistance, dyne·s·cm^{-5}						
Rest	125±32	177±59	148±53	192±58	NS: 0.08	NS: 0.07
DSE	142±37‡	207±66‡	175±57‡	224±66‡		
Stroke work loss, %						
Rest	12±4	18±5	16±7	19±5	0.04	0.03
DSE	16±5‡	24±7‡*	21±5‡	26±7‡†	(NS)	(NS)
EOA$_{proj}$, cm^2	1.14±0.16	0.92±0.15*	1.03±0.16	0.87±0.11†	<0.001 (0.006)	0.007 (0.05)
Indexed EOA$_{proj}$, cm^2/m^2	0.65±0.14	0.49±0.09*	0.58±0.07	0.45±0.06†	<0.001 (0.007)	<0.001 (0.006)

Mean±SD values of Doppler echocardiographic variables measured at rest as well as the peak values obtained during DSE are shown. *P* values between parentheses represent the values corrected for type I error, obtained by multiplying the *P* value by the number (8) of variables included in this comparison. *P* values were indicated when <0.1.

*Significant (*P*<0.05) difference between nonoperated vs operated groups.

†Significant difference between TS AS and PS AS groups.

‡Significant difference between DSE and rest (all *P* values were <0.001).

the leaflet stiffness score were much lower (0.22 to 0.41). Among these indices, the best correlations were obtained with the stress values of mean gradient ($r=0.41$), EOA ($r=0.37$), and resistance ($r=0.36$).
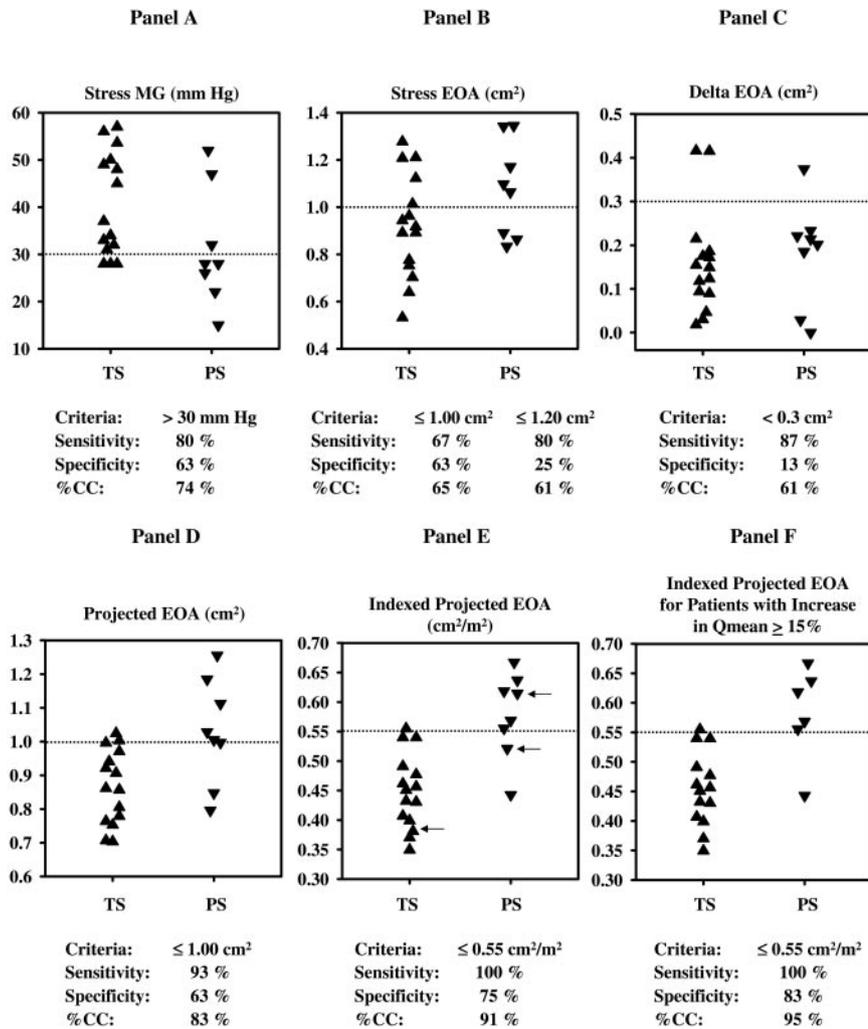
Discussion

The objective of DSE is, ideally, to normalize the cardiac output of patients with low-flow AS and reassess the indices of stenosis severity at normal-flow conditions. The values of these indices obtained during DSE are then compared with the criteria recommended in the guidelines to determine the stenosis severity.[14] However, as illustrated by the results of the present study, this approach is limited because many patients do not reach the normal range of resting flow rate under DSE, whereas others exhibit flow levels that exceed normal values at rest and are more similar to those observed during exercise. To this effect, it should be emphasized that peak transvalvular flow rate achieved during DSE in this study varied dramatically from 138 mL/s, which is below the normal resting flow rate, to 445 mL/s, which is comparable to the flow rate during strenuous exercise. This variability of flow response to DSE may be due to multiple factors including the degree of impairment of LV contractile

reserve, the chronotropic response to DSE, the use of medication (ie, β-blocker therapy), and the AS severity itself.[15,16] Moreover, in a significant proportion of patients in this study (30%), the DSE had to be stopped before the maximal dose was reached because of the occurrence of symptoms, arrhythmias, or hemodynamic abnormalities, thus limiting the increase in flow rate achieved during the test.

Usefulness of EOA$_{proj}$ to Assess Stenosis Severity

The main limitation of the indices used in previous studies[1,3,4,5,7] to discriminate TS from PS AS is that they are all dependent on the magnitude of flow increase achieved during DSE, which is highly variable between patients. Thus, stenotic indices may be measured at flow conditions that differ dramatically from one patient to another. The major finding of the present study is to propose a new stenotic index that is much less influenced by flow, thus providing a comparison between patients and a valuable and accurate index for interpreting the DSE results within the framework of the American College of Cardiology/American Heart Association guidelines.[14]

Accordingly, both the in vitro and in vivo results of the present study clearly show that the EOA$_{proj}$ is superior to

Panel A

Stress MG (mm Hg)

Criteria: > 30 mm Hg
Sensitivity: 80 %
Specificity: 63 %
%CC: 74 %

Panel B

Stress EOA (cm²)

Criteria: ≤ 1.00 cm²   ≤ 1.20 cm²
Sensitivity: 67 %   80 %
Specificity: 63 %   25 %
%CC: 65 %   61 %

Panel C

Delta EOA (cm²)

Criteria: < 0.3 cm²
Sensitivity: 87 %
Specificity: 13 %
%CC: 61 %

Panel D

Projected EOA (cm²)

Criteria: ≤ 1.00 cm²
Sensitivity: 93 %
Specificity: 63 %
%CC: 83 %

Panel E

Indexed Projected EOA (cm²/m²)

Criteria: ≤ 0.55 cm²/m²
Sensitivity: 100 %
Specificity: 75 %
%CC: 91 %

Panel F

Indexed Projected EOA for Patients with Increase in Qmean ≥ 15%

Criteria: ≤ 0.55 cm²/m²
Sensitivity: 100 %
Specificity: 83 %
%CC: 95 %

Figure 5. Comparison of the performance of stress mean gradient (MG) (A), stress EOA (B), absolute increase in EOA (ΔEOA) (C), EOA_{proj} (D), indexed EOA_{proj} (E), and indexed EOA_{proj} in the subgroup of patients with a relative increase in mean flow rate (Q_{mean}) ≥15% (F) to differentiate TS from PS stenosis in 23 operated patients with low-flow aortic stenosis. The arrows in E indicate the 3 patients who had <15% increase in Q_{mean} with dobutamine stress.

other conventional indices of stenosis severity to differentiate TS from PS AS. In addition, the performance of this parameter is also further improved by indexing to the patient's body surface area. This finding is consistent with the results of previous studies that emphasize the impor-

tance of indexing EOA for body surface area to take into account the cardiac output requirements of the patient under normal resting conditions and to better predict the impact of the stenosis on LV afterload and clinical outcomes.[17–19] In the present study an indexed EOA_{proj}

Percentage of Correct Classification
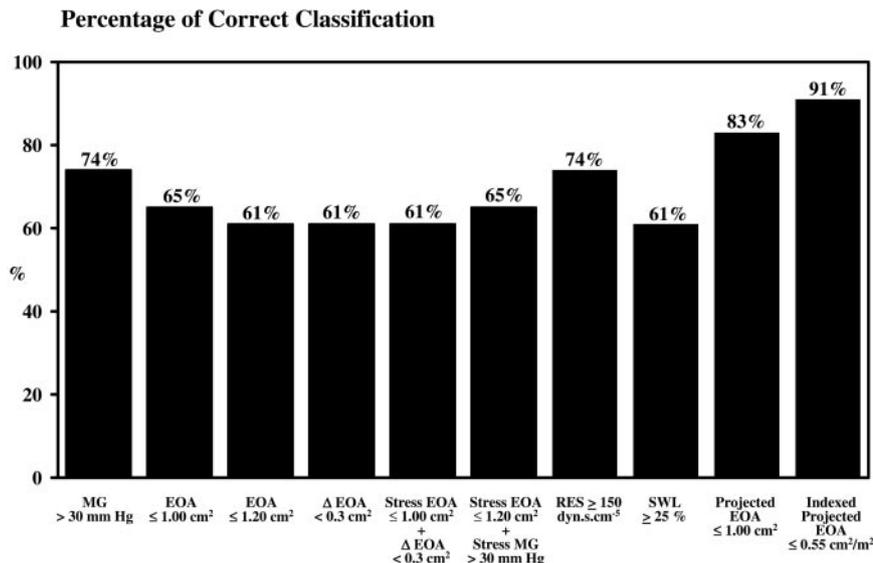
Figure 6. Comparison of the %CC observed with the use of different criteria to differentiate TS from PS aortic stenosis in the 23 operated patients with low-flow AS. Abbreviations are as defined in Figure 4 legend.

$\leq$0.55 cm^2/m^2 was found to be the best criterion to discriminate TS AS from PS AS. In our study all patients confirmed as having TS AS at the time of surgery were classified correctly with the use of the indexed EOA$_{proj}$ (sensitivity of 100%), whereas 2 patients considered to have PS AS on the basis of the surgical findings were also classified as having TS AS (specificity 75%). Importantly, 1 of these 2 misclassified patients had only an 11% increase in flow rate during DSE, which may have precluded a reliable estimation of the valve compliance and thus of the EOA$_{proj}$.

In contrast, stress EOA had a markedly lower performance than EOA$_{proj}$ and indexed EOA$_{proj}$ in differentiating TS and PS AS both in vitro and in vivo. On the one hand, patients with low-flow AS often do not reach the normal range of resting flow rate under DSE, and, as a consequence, the stress EOA may remain <1.0 cm^2, although the valve is only mildly or moderately stenotic. This misclassification of stenosis severity may lead to the decision to operate on a patient with only a mild/moderate AS. On the other hand, the flow rate may exceed the normal resting values in some patients, and this may lead to the erroneous conclusion that the stenosis is not severe and that surgery is not indicated. As a consequence, a patient with TS AS may be treated conservatively with an expected adverse impact on clinical outcome. Moreover, the combination of the stress EOA with stress gradient or absolute increase in EOA did not improve the ability to differentiate TS and PS AS. When analyzed collectively, our data therefore suggest that only EOA$_{proj}$ and indexed EOA$_{proj}$ would have provided a more precise surgical indication.

We selected a standardized value of flow rate of 250 mL/s on the basis of data reported in previous studies of patients with AS and normal LV function to calculate the EOA$_{proj}$.[8,13] However, the value of flow rate selected to do this projection was not critical as long as the same value was used for all patients. If we had used another value of flow rate (eg, 240 or 230 mL/s instead of 250 mL/s) to calculate the EOA$_{proj}$, the best discriminative threshold values to separate TS and PS AS would have been different, but the %CC would have remained the same.

Definition and Prevalence of PS AS
The prevalence of PS AS (35%) observed in our study may appear higher than that reported in previous studies.[4,7] However, the prevalence is dependent on the definition used. In our study we used the surgeon's assessment of the valve at the time of operation, whereas previous studies have classified patients on the basis of indices measured by Doppler echocardiography or cardiac catheterization before operation. Using the criteria proposed by Monin et al[4] (stress EOA $\leq$1.00 cm^2 and absolute increase in EOA <0.3 cm^2), we would classify 3 of 23 patients (13%) as having PS AS, similar to the 5% of patients classified as PS AS in their series. Similarly, our prevalence of PS AS would be 13% (3/23) with the use of the criteria proposed by Nishimura et al[7] (stress EOA $\leq$1.20 cm^2 and stress mean gradient >30 mm Hg), comparable to the 24%

prevalence observed in their series. It is possible that the prevalence of PS AS may have been underestimated in previous studies because the definition of PS AS has been based on conventional Doppler echo indices, which demonstrated a relatively low performance to differentiate PS from TS AS in both our in vitro and in vivo studies. In contrast, the results of the present study demonstrate that an indexed EOA$_{proj}$ >0.55 cm^2/m^2 or EOA$_{proj}$ >1.0 cm^2 can be used with a high level of confidence to identify PS AS. It should nonetheless be acknowledged that EOA$_{proj}$ may also underestimate the prevalence of PS AS, given that 3 patients considered to have PS AS on the basis of surgical findings were classified as having TS AS on the basis of EOA$_{proj}$ $\leq$1.0 cm^2 and 2 patients were misclassified on the basis of an indexed EOA$_{proj}$ $\leq$0.55 cm^2/m^2).

Management of Patients With PS AS
The optimal management of the patients identified as having PS AS is unclear. An EOA$_{proj}$ between 1.0 and 1.5 cm^2 is theoretically an indicator of a moderately stenotic valve. However, this EOA$_{proj}$ may not impart an absolute contraindication to AVR or mandate a conservative approach in patients with low-flow AS. It is well known that the failing ventricle is extremely sensitive to any increase in afterload. In this regard, moderate patient-prosthesis mismatch, equivalent to moderate AS in terms of LV hemodynamic burden, has no significant impact on short-term postoperative mortality in patients with preserved LV systolic function but a major impact on mortality in patients with poor ventricular function.[19] Similarly, moderate AS may be well tolerated by a ventricle with normal systolic function but be poorly tolerated in the setting of a failing ventricle. In the study of Monin et al,[4] there was a 50% mortality within 2 years in the 6 patients considered to have PS AS and managed conservatively. Nishimura et al[7] also reported a 63% short-term mortality in 11 patients with PS AS managed medically. It is possible that relief of valvular obstruction, even if only moderate by conventional criteria, may have beneficial effects on morbidity and mortality in these patients. Further study in a larger population of PS AS patients with longer follow-up is warranted to determine the optimal management of these patients and evaluate whether the same surgical criteria should be used in patients with LV dysfunction as used in patients with normal LV function.

Study Limitations
The main limitation of the in vivo study is the reference method used to confirm the severity of the valve stenosis. It may be difficult for the surgeon to accurately assess the hemodynamic severity, especially in borderline cases of moderate/severe stenosis. Although an effort was made to standardize the methodology among the different surgeons involved in the study, one cannot exclude that some valves may have been misclassified. Unfortunately, there is no alternative reference method available to determine the "actual" stenosis severity in vivo. The determination of stenosis severity by catheterization or by more sophisticated technologies, such as magnetic resonance imaging,

would have faced the same limitations as Doppler echocardiography, which are that all indices of stenosis severity, including valve EOA, transvalvular gradient, valve resistance, and LV stroke work loss, vary with flow rate[8,9,20] and that there is variability in the resting and stress transvalvular flow rates among patients with low-flow AS. Significant differences in the average leaflet stiffness score and leaflet calcification score was observed between the TS and PS AS groups and provides supporting evidence for the surgeon's assessment of the severity of the valve stenosis. More importantly, it was possible to determine the actual severity of the stenosis in the in vitro study, and the results were consistent with those of the in vivo study. The consistency between the in vitro and in vivo results confirms the superiority of the EOA_{proj} to differentiate TS from PS AS. Moreover, it should be emphasized that the surgeons were unaware of the EOA_{proj} at the time of surgery and their surgical assessment. The surgical diagnosis of the stenosis severity was formulated independent of EOA_{proj}, and the excellent agreement between the 2 gives further evidence to the robustness of this proposed index as a measure of the "actual" AS severity. These compelling data provide a strong impetus for a future "interventional" study to confirm the usefulness of the projected EOA for the therapeutic management of patients with low-flow AS.

The EOA-flow relationship was linear in our patients, and therefore EOA_{proj} was determined with the use of a linear regression equation (see Equation 3). Previous studies have demonstrated a linear relationship between EOA and flow, supporting the approach used in the present study.[9,21,22] However, it may be difficult or impossible to obtain a reliable estimate of valve compliance and thus the EOA_{proj} in patients having minimal or no increase in transvalvular flow rate during DSE. In this situation, it may not be possible to determine the stenosis severity. This potential limitation also applies to currently used stenotic indices. However, this phenomenon appears to occur in only a small minority of patients because only 13% of patients (3/23) had an increase in transvalvular flow rate $<15\%$ during DSE.

Conclusion

The EOA_{proj} can correct for important interindividual variability in the flow response to DSE and thus allow an assessment of AS severity under similar flow conditions. This new index has the potential to improve the diagnostic accuracy of DSE to distinguish TS from PS AS in patients with low-flow, low-gradient AS.

Acknowledgments

Disclosures

References

1. deFilippi CR, Willett DL, Brickner E, Appleton CP, Yancy CW, Eichhorn EJ, Grayburn PA. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol*. 1995;75:191–194.

2. Roger VL. Left ventricular function in aortic stenosis: a clinical review. *J Heart Valve Dis*. 1995;4(suppl II):S230–S235.

3. Monin JL, Monchi M, Gest V, Duval-Moulin AM, Dubois-Range JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients. *J Am Coll Cardiol*. 2001;37: 2101–2107.

4. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*. 2003;108:319–324.

5. Schwammenthal E, Vered Z, Moshkowitz Y, Rabinowitz B, Ziskind Z, Smolinski AK, Feinberg MS. Dobutamine echocardiography in patients with aortic stenosis and left ventricular dysfunction: predicting outcome as a function of management strategy. *Chest*. 2001; 119:1766–1777.

6. Grayburn PA, Eichhorn EJ. Dobutamine challenge for low-gradient aortic stenosis. *Circulation*. 2002;106:763–765.

7. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation*. 2002;106:809–813.

8. Blais C, Pibarot P, Dumesnil JG, Garcia D, Chen D, Durand LG. Comparison of valve resistance with effective orifice area regarding flow dependence. *Am J Cardiol*. 2001;1:45–52.

9. Burwash IG, Hay KM, Chan KL. Hemodynamic stability of valve area, valve resistance and stroke work loss in aortic stenosis: a comparative analysis. *J Am Soc Echocardiogr*. 2002;15:814–822.

10. Garcia D, Pibarot P, Landry C, Allard A, Chayer B, Dumesnil JG, Durand LG. Estimation of aortic valve effective orifice area by Doppler echocardiography: effects of valve inflow shape and flow rate. *J Am Soc Echocardiogr*. 2004;17:756–765.

11. Cannon JD, Zile MR, Crawford FA, Carabello BA. Aortic valve resistance as an adjunct to the Gorlin formula in assessing the severity of aortic stenosis in symptomatic patients. *J Am Coll Cardiol*. 1992; 20:1517–1523.

12. Bermejo J, Odreman R, Feijoo J, Moreno MM, Gomez-Moreno P, Garcia-Fernandez MA. Clinical efficacy of Doppler-echocardiographic indices of aortic valve stenosis: a comparative test-based analysis of outcome. *J Am Coll Cardiol*. 2003;41:142–151.

13. Bermejo J, Rojo-Alvarez JL, Antoranz JC, Abel M, Burwash IG, Yotti R, Moreno M, Garcia-Fernandez MA, Lehmann KG, Otto CM. Estimation of the end of ejection in aortic stenosis: an unreported source of error in the invasive assessment of severity. *Circulation*. 2004;110: 1114–1120.

14. Bonow RO, Carabello BA, de Leon ACJr, Edmunds LH Jr, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol*. 1998;32:1486–1588.

15. Otto CM, Pearlman AS, Kraft CD, Miyake-Hull CY, Burwash IG, Gardner CJ. Physiologic changes with maximal exercise in asymptomatic valvular aortic stenosis assessed by Doppler echocardiography. *J Am Coll Cardiol*. 1992;20:1160–1167.

16. Kadem L, Pibarot P, Dumesnil JG, Mouret F, Garitey V, Durand LG, Rieu R. Independent contribution of the left ventricular ejection time to the mean gradient in aortic stenosis. *J Heart Valve Dis*. 2002;11: 615–623.

17. Rahimtoola SH. Perspective on valvular heart disease: an update. *J Am Coll Cardiol*. 1989;14:1–23.
18. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. *J Am Coll Cardiol*. 2000;36:1131–1141.
19. Blais C, Dumesnil JG, Baillot R, Simard S, Doyle D, Pibarot P. Impact of prosthesis-patient mismatch on short-term mortality after aortic valve replacement. *Circulation*. 2003;108:983–988.
20. Mascherbauer J, Schima H, Rosenhek R, Czerny M, Maurer G, Baumgartner H. Value and limitations of aortic valve resistance with particular consideration of low flow-low gradient aortic stenosis: an in vitro study. *Eur Heart J*. 2004;25:787–793.
21. Burwash IG, Forbes AD, Sadahiro M, Verrier ED, Pearlman AS, Thomas R, Kraft C, Otto CM. Echocardiographic volume flow and stenosis severity measures with changing flow rate in aortic stenosis. *Am J Physiol*. 1993;265:H1734–H1743.
22. Das P, Rimington H, Smeeton N, Chambers J. Determinants of symptoms and exercise capacity in aortic stenosis: a comparison of resting haemodynamics and valve compliance during dobutamine stress. *Eur Heart J*. 2003;24:1254–1263.

CLINICAL PERSPECTIVE

Dobutamine stress echocardiography (DSE) has been used in patients with low-flow, low-gradient aortic stenosis (AS) to distinguish truly severe (TS) AS from pseudo-severe (PS) AS. However, traditional stenotic indices used to discriminate TS from PS AS are limited by their dependence on the magnitude of flow increase achieved during DSE, which is highly variable between patients. As a consequence, these indices may be measured at dramatically different flow conditions from one patient to another. In this study we have proposed a new stenotic index that is standardized for flow, thus providing a measure of AS severity that can be compared between patients and accurately interpret the results of DSE within the framework of the American College of Cardiology/American Heart Association guidelines. For an individual patient, valve effective orifice area (EOA) was plotted against transvalvular flow (Q) at each dobutamine stage and the projected EOA (EOA_{proj}) at normal flow rate, 250 mL/s, derived from the slope of the linear regression equation fitted to the EOA versus Q plot [$EOA_{proj}=EOA_{rest}+VC(250-Q_{rest})$, where VC is the valve compliance or slope of the linear relationship]. TS AS and PS AS were correctly classified in 83% of low-flow, low-gradient AS patients when an $EOA_{proj} \leq 1.0$ cm^2 was used to identify TS AS, compared with 61% to 74% of patients with the use of the traditional indices. The performance was further improved by indexing EOA_{proj} to the patient's body surface area (91% correctly classified with the use of $EOA_{proj} \leq 0.55$ cm^2/m^2). Thus, EOA_{proj} provides a more standardized assessment of AS severity and improves the diagnostic accuracy of DSE for distinguishing TS and PS AS in patients with low-flow, low-gradient AS.