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iCONCEPTS

CONCEPTS ON THE VERGE OF TRANSLATION

Stress Echocardiography to Assess Stenosis Severity and Predict Outcome in Patients With Paradoxical Low-Flow, Low-Gradient Aortic Stenosis and Preserved LVEF

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The objective of this study was to examine the value of stress-echocardiography in patients with paradoxical low-flow, low-gradient (PLFLG) aortic stenosis (AS). The projected aortic valve area (AVA_{Proj}) at a normal flow rate was calculated in 55 patients with PLFLG AS. In the subset of patients (n = 13) who underwent an aortic valve replacement within 3 months after stress echocardiography, AVA_{Proj} correlated better with the valve weight compared to traditional resting and stress echocardiographic parameters of AS severity (AVA_{Proj}: r = −0.78 vs. other parameters: r = 0.46 to 0.56). In the whole group (N = 55), 18 (33%) patients had an AVA_{Proj} >1.0 cm^2, being consistent with the presence of pseudo severe AS. The AVA_{Proj} was also superior to traditional parameters of stenosis severity for predicting outcomes (hazard ratio: 1.32/0.1 cm^2 decrease in AVA_{Proj}). In patients with PLFLG AS, the measurement of AVA_{proj} derived from stress echocardiography is helpful to determine the actual severity of the stenosis and predict risk of adverse events. (J Am Coll Cardiol Img 2013;6:175–83) © 2013 by the American College of Cardiology Foundation

We previously reported that a significant proportion of patients with severe aortic stenosis (AS) on the basis of aortic valve area (i.e., AVA <1.0 cm^2 and indexed AVA <0.6 cm^2/m^2) may have a restrictive physiology resulting in lower left ventricular (LV) outflow (i.e., stroke volume index <35 ml/m^2) and lower than expected transvalvular gradients (i.e., <40 mm Hg)

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despite the presence of a preserved LV ejection fraction (i.e., LVEF ≥50%), and this clinical entity was labeled "paradoxical low-flow, low-gradient (PLFLG) AS" (1,2). Given that transvalvular flow rate is reduced in these patients, it cannot be excluded that, as in low LVEF, low-flow, low-gradient AS, some patients may have a pseudo severe AS due to incomplete opening of a moderately stenotic valve.

The distinction between true severe (TS) versus pseudo severe (PS) AS is essential because patients with TS AS and symptoms will generally benefit from aortic valve replacement (AVR), whereas patients with PS AS may not benefit from surgical intervention and may rather need intensive medical therapy and close follow-up. As recommended in the 2012 European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines, AVR should be considered in symptomatic patients with PLFLG after careful confirmation of stenosis severity (Class IIa indication) (3). We previously reported that a new index of AS severity derived from dobutamine stress echocardiography (DSE), the projected aortic valve area (AVA_{proj}) at a normal transvalvular flow rate, is superior to traditional Doppler echocardiographic parameters (rest or peak stress gradient and AVA) to differentiate TS from PS AS and predict outcome in patients with low LVEF, low-flow, low-gradient AS (4). However, there are no published data about the utility of stress (dobutamine or exercise) echocardiography in patients with PLFLG AS. The objective of this study was to examine the diagnostic and prognostic value of stress echocardiography in patients with PLFLG AS.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVA_{Proj} = projected aortic valve area

AVR = aortic valve replacement

CI = confidence interval

DSE = dobutamine stress echocardiography

HR = hazard ratio

LV = left ventricular

LVEF = left ventricular ejection fraction

PLFLG = paradoxical low flow low gradient

PS = pseudo severe

TS = true severe

Methods

Doppler echocardiographic and clinical data were prospectively collected in 55 patients with PLFLG AS defined as an AVA ≤1 cm^2, an indexed AVA ≤0.6 cm^2/m^2, a mean gradient ≤40 mm Hg, a preserved LVEF (>50%), and stroke volume indexed to body surface area ≤35 ml/m^2. These patients were recruited in the context of 2 prospective observational studies, TOPAS (True Or Pseudo-Severe Aortic Stenosis) and EXERSA (Exercise Stress Echocardiography in Aortic Stenosis) (4,5). Exclusion criteria for these studies were as follows: 1) moderate/severe aortic or mitral regurgitation or mitral stenosis; 2) atrial fibrillation or flutter; 3) paced rhythm; 4) unstable angina; 5) acute pulmonary edema; 6) end-stage renal disease; 7) pregnant or lactating women; and 8) unwillingness to provide informed consent.

All patients underwent stress echocardiography. Exercise stress echocardiography was performed in 37 patients with no or equivocal symptoms whereas DSE was performed in 18 patients who were symptomatic. The dobutamine infusion protocol consisted of 8-min increments of 2.5 or 5 μg/kg/min, starting at 2.5 μg/kg/min up to a maximum dosage of 20 μg/kg/min (4). The exercise test was a symptom-limited graded maximum bicycle exercise test, performed in the semisupine position on an ergometer table tilted to 20°, with an initial workload of 20 W to 25 W maintained for 3 min and subsequent increase in workload of 20 W to 25 W every 3 min (5). Doppler echocardiographic data were obtained at rest and at peak exercise/dobutamine stress.

The Doppler echocardiographic measurements included LV dimensions, LVEF determined by the modified biplane Simpson's method, stroke volume in the LV outflow tract, mean transvalvular flow rate (Q) by dividing stroke volume by LV ejection time, transvalvular gradients by the simplified Bernoulli equation, and AVA by the continuity equation. The LV outflow tract diameter was assumed to have remained constant during the stress test protocol. For each measurement, at least 3 cardiac cycles were averaged. The projected AVA (AVA_{proj}) was calculated, a posteriori, in each patient by the following equation, as previously described and validated (4):

$$AVA_{proj} = \frac{AVA_{peak} - AVA_{rest}}{Q_{peak} - Q_{rest}} \times (250 - Q_{rest}) + AVA_{rest}$$

where AVA_{rest} and Q_{rest} are AVA and Q at rest, and AVA_{peak} and Q_{peak} are AVA and Q measured at peak stress echocardiography. The treating cardiologists and cardiac surgeons were thus unaware of the results of $AVA_{Proj.}$

The endpoints for this study were as follows. 1) The severity of stenosis at the time of AVR as documented by macroscopic assessment of the explanted valve by the surgeon and pathologist with the use of standardized method and criteria (4); the weight of explanted valve was also measured with the use of a laboratory scale in a subset of patients. 2) The time to occurrence of the composite endpoint of death or need for AVR motivated by the development of severe AS with symptoms or LV systolic dysfunction.

Results are expressed as mean ± SD or percentages. Continuous variables were tested for distribution normality with the Shapiro-Wilk test. Differences between patient groups were analyzed with the use of the 2-sided Student *t* test for continuous variables and the chi-square test or Fisher exact test for categorical variables as appropriate. Sensitivity, specificity, and percentage of correct classification for the prediction of TS AS were determined for various cutoff values of the Doppler echocardiographic indices of stenosis severity using receiver-operating characteristic curves. Correlation between stenotic indices and valve weight was determined with the use of Pearson correlation. Differences between correlation coefficients were analyzed with the use of the Wolfe test.

Event-free survival function was obtained by Kaplan-Meier estimates. The effect of the clinical and Doppler echocardiographic variables on survival was assessed with the use of Cox proportional hazard models. A p value <0.05 was considered statistically significant. Statistical analyses were performed with the use of JMP 8.0.1 software (SAS Institute, Cary, North Carolina).

Results

Our population consisted of 35 (64%) men and 20 (36%) women with a mean age of 65 ± 13 years; prevalence of hypertension was 55%, diabetes mellitus, 18%, and chronic kidney disease, 11%. The average AVA was 0.83 ± 0.17 cm^2, and average mean gradient 27 ± 16 mm Hg (Table 1). During a mean follow-up of 1.5 ± 1.4 years, 27 (49%) patients underwent an AVR for symptomatic severe

Table 1. Baseline Patient Characteristics

Variable	Whole Cohort (N = 55)	No Event (n = 24)	AVR or Death (n = 31)	p Value
Clinical data				
Age, yrs	65 ± 13	64 ± 15	66 ± 11	0.44
Male	35 (64)	14 (58)	21 (68)	0.47
Body surface area, m^2	1.84 ± 0.24	1.82 ± 0.26	1.85 ± 0.23	0.60
Symptoms	18 (33)	9 (38)	9 (29)	0.51
Systolic blood pressure, mm Hg	139 ± 24	132 ± 22	145 ± 25	0.06
Diastolic blood pressure, mm Hg	79 ± 14	76 ± 10	81 ± 16	0.23
Hypertension	30 (55)	15 (63)	15 (48)	0.30
Obesity	14 (25)	7 (29)	7 (23)	0.58
Diabetes mellitus	10 (18)	6 (25)	4 (13)	0.25
Dyslipidemia	32 (58)	17 (71)	15 (48)	0.09
Chronic kidney disease	6 (11)	1 (4)	5 (16)	0.14
Doppler echocardiographic data				
Aortic valve morphology (bicuspid/tricuspid/unevaluable)	17/36/2	9/15/0	8/21/2	0.44
LVEF, %	62 ± 7	61 ± 7	62 ± 7	0.84
Peak SE LVEF, %	72 ± 10	72 ± 8	73 ± 11	0.67
SV index, ml/m^2	32 ± 3	32 ± 3	32 ± 3	0.80
Peak SE SV index, ml/m^2	39 ± 10	39 ± 7	39 ± 11	0.98
Δ SV index, ml/m^2	7 ± 8	7 ± 7	6 ± 10	0.86
Rest flow rate, ml/s	197 ± 46	195 ± 32	198 ± 29	0.78
Peak SE flow rate, ml/s	289 ± 84	281 ± 83	295 ± 86	0.57
Δ Flow rate, ml/s	92 ± 78	86 ± 74	96 ± 82	0.95
Rest mean gradient, mm Hg	27 ± 16	23 ± 11	28 ± 10	0.08
Peak SE mean gradient, mm Hg	40 ± 16	33 ± 15	45 ± 15	0.006
Rest AVA, cm^2	0.83 ± 0.17	0.88 ± 0.21	0.80 ± 0.17	0.13
Peak SE AVA, cm^2	1.01 ± 0.32	1.09 ± 0.36	0.94 ± 0.27	0.07
AVA_{proj}, cm^2	0.95 ± 0.24	1.04 ± 0.24	0.88 ± 0.22	0.01
Indexed AVA_{proj}, cm^2/m^2	0.53 ± 0.15	0.59 ± 0.16	0.48 ± 0.12	0.007
Rest Z_{va}, mm Hg·ml^{-1}·m^2	5.1 ± 1.1	4.8 ± 0.9	5.4 ± 1.0	0.05
Peak SE Z_{va}, mm Hg·ml^{-1}	5.7 ± 1.9	5.0 ± 1.3	6.1 ± 2.1	0.04

Values are mean ± SD or n (%). Delta (Δ) indicates absolute difference between peak stress and rest data.
AVA = aortic valve area; AVA_{Proj} = projected aortic valve area; AVR = aortic valve replacement; LVEF = left ventricular ejection fraction; SE = stress echocardiography; SV = stroke volume; Z_{va} = valvuloarterial impedance.

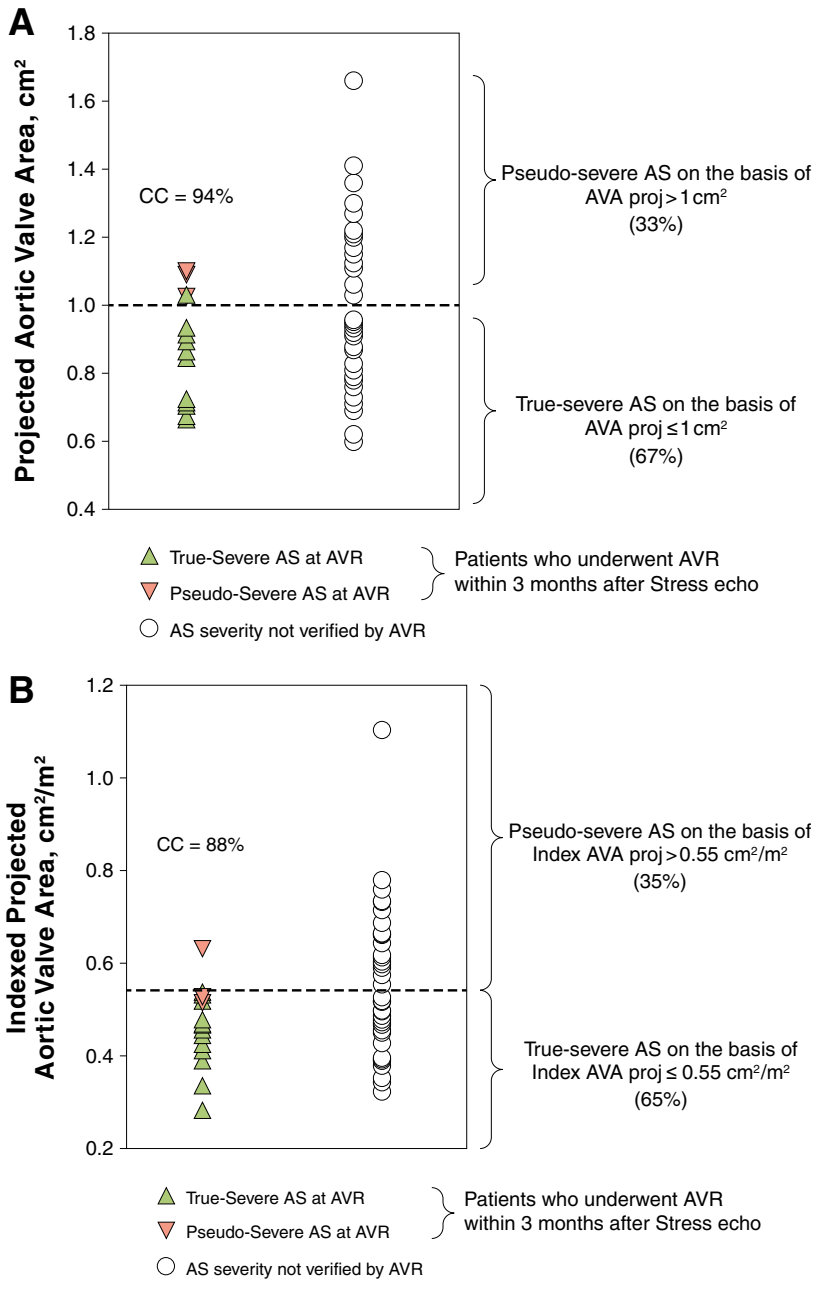

Figure 1. Accuracy of Stress Echocardiographic Parameters to Differentiate True Severe From Pseudo Severe Aortic Stenosis

(A) Projected aortic valve area (AVA_{Proj}) at normal flow rate. **(B)** Indexed AVA_{Proj} at normal flow rate.

AS, and 4 (7%) patients died: 1 had a sudden cardiac death, 1 died of acute pulmonary edema, 1 died of end-stage heart failure, and 1 died of noncardiovascular cause.

Among the 37 patients who underwent exercise stress echocardiography, the maximum workload achieved by the patients was 119 ± 94 W (range 44 to 480 W). Among the 18 patients who underwent DSE, the dose of dobutamine at termination of stress test was 20 μg/kg/min in 7 patients, 15 μg/kg/min in 4 patients, and 10 μg/kg/min in 7 patients. No adverse effects occurred during stress echocardiography, and all patients had an increase in mean transvalvular flow rate >15% (range +30 to 274 ml/s; i.e., +17% to 157%), thus allowing the calculation of AVA_{proj} (4).

Among the 27 patients treated surgically, 16 had an AVR within the 3 months after stress

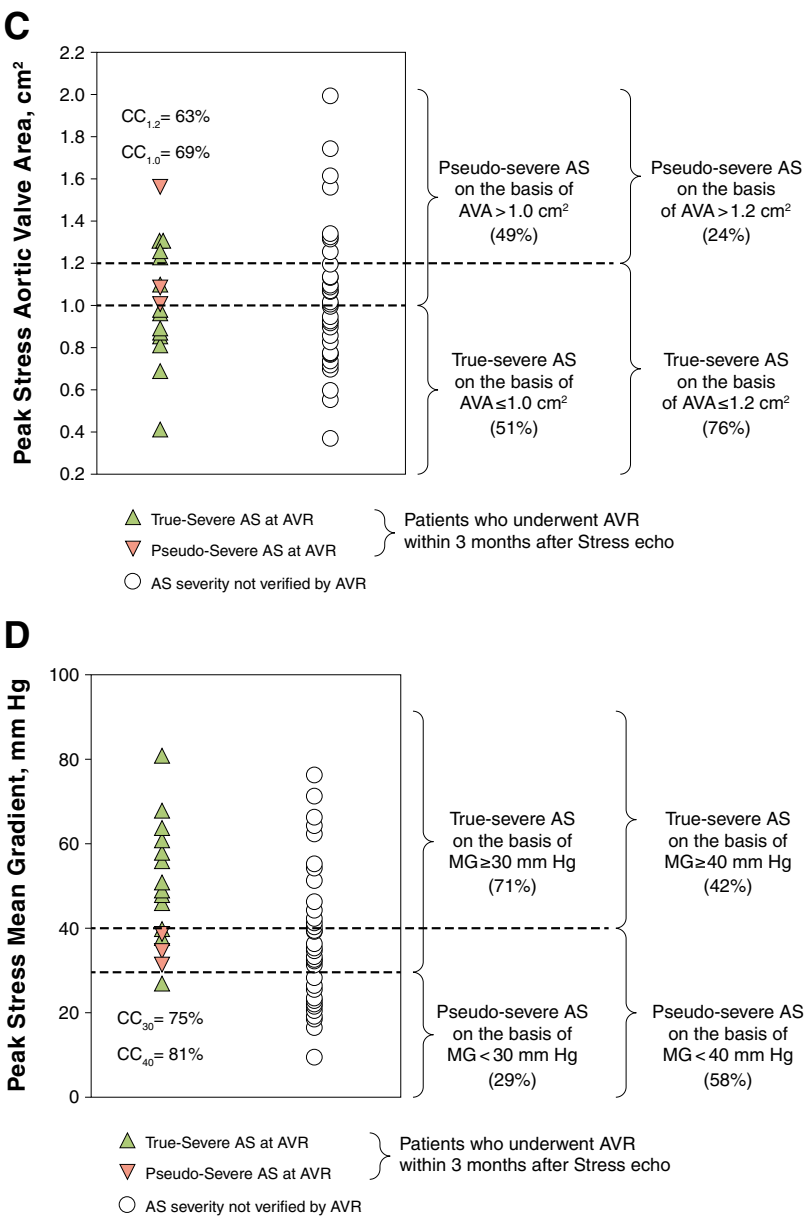

Figure 1. Continued

(C) Peak stress AVA. **(D)** Peak stress gradient. AS = aortic stenosis; AVR = aortic valve replacement; CC = correct classification; echo = echocardiography; MG = mean gradient.

echocardiography. The valves explanted from these 16 patients were evaluated for AS severity by the cardiac surgeon and the pathologist, and 13 of them were weighted.

Among the 16 explanted valves, 13 (81%) were considered as TS AS, and 3 (19%) as PS AS. Among the stress Doppler echocardiographic parameters of stenosis severity, AVA_{proj} or indexed AVA_{proj} had the best accuracy to differentiate TS versus PS AS in this subset (Fig. 1). An AVA_{proj} ≤ 1 cm^2 was the best cutoff value to predict TS AS with an area under the receiver-operating characteristic curve of 0.99, a sensitivity of 92%, a specificity of 100%, and a percentage of correct classification of 94% (Fig. 1). The best cutoff for indexed AVA_{proj} was ≤ 0.55 cm^2/m^2 (sensitivity of 100%, specificity of 67%, and percentage of correct classification of 88%). Moreover, AVA_{proj} or indexed AVA_{proj} correlated better (Wolfe p values <0.05) with the weight of the explanted valve ($r > 0.78$;

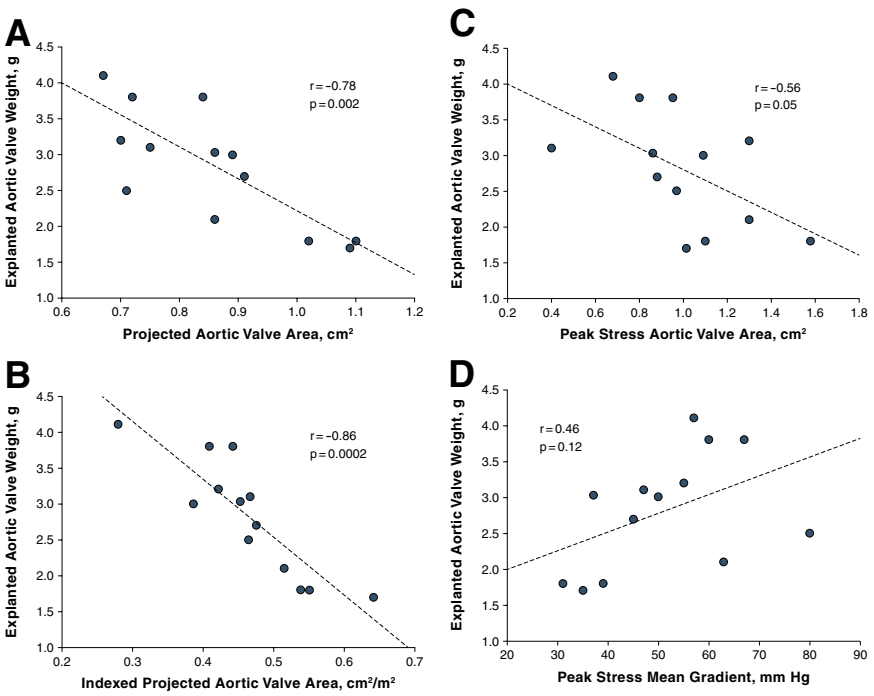

Figure 2. Correlation Between Stress Echocardiographic Parameters and Weight of Valve Explanted at Time of Valve Replacement Surgery

(A) Projected aortic valve area (AVA) at normal flow rate. **(B)** Indexed projected AVA at normal flow rate. **(C)** Peak stress AVA. **(D)** Peak stress gradient.

p = 0.002) (Fig. 2) compared to the traditional stress echocardiographic indices of stenosis severity ($r \leq 0.56$; $p \geq 0.05$). In the whole study group (n = 55), 18 (33%) patients had an $AVA_{proj} \geq 1.0$ cm^2, and 19 (35%) had an indexed $AVA_{proj} \geq 0.55$ cm^2/m^2, which is consistent with the presence of PS AS (Figs. 1A and 1B).

The AVA_{proj} (hazard ratio [HR]: 1.25/0.1 cm^2 decrease in AVA_{proj}; 95% confidence interval [CI]: 1.06 to 1.48; p = 0.008) and indexed AVA_{proj} (HR: 1.55/0.1 cm^2/cm^2 decrease in indexed AVA_{proj}; 95% CI: 1.16 to 2.12; p = 0.002) predicted the risk of events, whereas the other stress echocardiographic parameters generally used to differentiate TS versus PS AS did not (Table 2, Fig. 3). After adjustment for age and sex, lower AVA_{proj} (HR: 1.32/0.1 cm^2 decrease in AVA_{proj}; 95% CI: 1.10 to 1.60; p = 0.002) or lower indexed AVA_{proj} (HR: 1.59/0.1 cm^2 decrease in indexed AVA_{proj}; 95% CI: 1.18 to 2.22; p = 0.002) remained predictors of higher risk of events (Table 2, Fig. 3).

Discussion

The main finding of this study is that the measurement of AVA_{proj} by stress echocardiography allows accurate discrimination of TS versus PS AS in patients with PLFLG AS. On this basis, this study revealed that approximately 30% of these patients have a PS AS, which is consistent with what has been reported in patients with classical (i.e., low-LVEF) low-flow, low-gradient AS (4). Although they have preserved LVEF, patients with paradoxical low-flow have transvalvular flow rates that are as low as patients with low-LVEF, low-flow, low gradient AS (4). That likely explains why the prevalence of PS AS is similar in patients with paradoxical low-flow AS versus patients with classical low-flow AS.

Low-flow, low-gradient AS is a highly challenging condition in terms of diagnosis and therapeutic management. The presence of a low-flow state in the setting of a preserved LVEF may considerably complicate assessment of stenosis severity and therapeutic decision making. Indeed, although these patients with paradoxical low-flow, low-gradient often have similar or worse AVA at rest compared to patients with normal flow, their gradient is much lower than expected because of the low flow across the valve. The clinical presentation of these patients may thus be highly insidious because, on the basis of the

Table 2. Predictors of Combined Endpoint Aortic Valve Replacement or Death

		Univariate Analysis		Multivariate Analysis			
				Model 1		Model 2	
Variables	Increment Category	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	+1 yr	1.02 (0.99–1.05)	0.18	1.03 (1.00–1.06)	0.08	1.02 (0.99–1.05)	0.15
Sex	Male	1.36 (0.64–3.07)	0.542	—	0.48	—	0.96
Diabetes mellitus	Yes	1.62 (0.46–4.40)	0.41	—	—	—	—
Chronic kidney failure	Yes	2.35 (0.79–5.72)	0.12	—	—	—	—
Rest LVEF	+5%	0.99 (0.77–1.23)	0.92	—	—	—	—
Peak SE LVEF	+5%	1.02 (0.86–1.22)	0.82	—	—	—	—
Δ LVEF	+5%	1.03 (0.84–1.29)	0.73	—	—	—	—
Rest SV Index	+1 ml/m^2	1.03 (0.94–1.15)	0.54	—	—	—	—
Peak SE SV Index	+1 ml/m^2	1.02 (0.97–1.07)	0.45	—	—	—	—
Δ SV Index	+1 ml/m^2	1.02 (0.96–1.07)	0.57	—	—	—	—
Rest mean gradient	+5 mm Hg	1.13 (0.99–1.28)	0.08	—	—	—	—
Peak SE mean gradient	+5 mm Hg	1.13 (1.03–1.25)	0.02	—	—	—	—
Rest AVA	−0.1 cm^2	1.12 (0.95–1.34)	0.16	—	—	—	—
Peak SE AVA	−0.1 cm^2	1.08 (0.96–1.23)	0.22	—	—	—	—
AVA_{Proj}	−0.1 cm^2	1.25 (1.06–1.48)	0.008	1.32 (1.10–1.60)	0.002	—	—
Indexed AVA_{Proj}	−0.1 cm^2/m^2	1.55 (1.16–2.12)	0.002	—	—	1.59 (1.18–2.22)	0.002

Delta (Δ) indicates absolute difference between peak stress and rest data.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

"pseudonormalized" gradient, the stenosis severity may be underestimated. Conversely, as in patients with low-LVEF, low-flow, low-gradient AS, the AVA may overestimate stenosis severity in some patients because of the low flow.

Several studies have demonstrated the usefulness of the measurement of the gradient and AVA during a low-dose DSE to corroborate stenosis severity in patients with classical low-flow, low-gradient AS and reduced LVEF. The major limitation of the peak stress gradient or AVA is that they are dependent on flow rate, which may vary extensively from one patient to another (4). We have previously reported that AVA_{proj} can mitigate for important interindividual variability in transvalvular flow response during DSE, and result in improved diagnostic accuracy compared to traditional DSE parameters for distinguishing TS from PS AS in patients with classical low-flow, low-gradient AS and reduced LVEF (4). In the present study, we demonstrate, for the first time to our knowledge, that the AVA_{proj} measured by stress echocardiography with the use of the simplified method (4) is superior to other traditional stress echocardiographic parameters (peak stress gradient and AVA) to identify TS AS and predict outcomes in patients with paradoxical low-flow AS.

The explanation for this superiority of the AVA_{proj} may be that, as opposed to all other stenotic indices, AVA_{proj} is standardized for flow rate. This is an important advantage given that flow rate may vary considerably from one patient to another during stress echocardiography. Indeed, patients with reduced or preserved LVEF low-flow AS may not reach the normal range of resting flow rate under stress echocardiography, and as a consequence, their peak stress gradient may remain below 40 mm Hg although the valve is severely stenotic or their peak stress AVA may remain below 1.0 cm^2 although their stenosis is only moderate. Conversely, the flow rate may exceed the normal resting values, so that the peak stress gradient may increase above 40 mm Hg despite the presence of a moderate stenosis. The AVA_{proj} may be helpful to reconcile these discordances and better assess the true severity of the stenosis.

Although DSE was well tolerated in the patients included in this study, this test should be used with caution, using a low-dose protocol with progressive increase in dosage and close monitoring of blood pressure, electrocardiogram, and LV outflow tract velocity. Patients with paradoxical low-flow AS indeed often have a pronounced LV concentric remodeling with small cavity and impaired LV filling, and thus, they may be at risk for deterioration of hemodynamic status under dobutamine stress. The feasibility and safety of DSE and exercise stress echocardiography will need to be evaluated in a larger series of patients with PLFLG AS. For patients in whom exercise stress echo is not

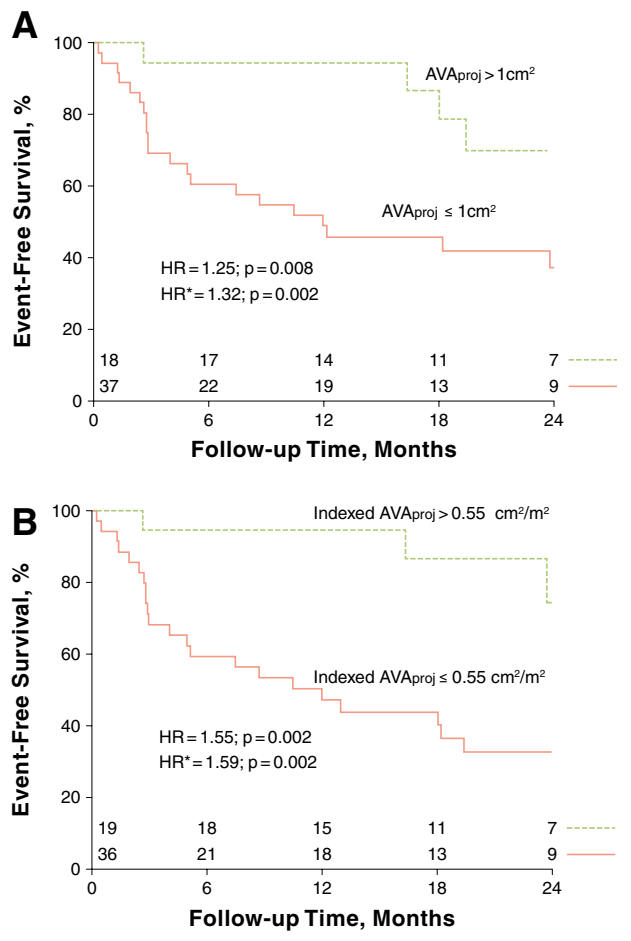

Figure 3. Event-Free Survival According to AVA_{Proj}

Event-free survival according to **(A)** projected aortic valve area (AVA_{Proj}) at normal flow rate and **(B)** indexed AVA_{proj} during stress echocardiography. *Hazard ratio (HR) adjusted for age and sex.

feasible or inconclusive, one may envision other imaging modalities such as quantification of aortic valve calcification by multislice computed tomography (CT) to confirm stenosis severity in these patients. Computed tomography has been shown to accurately differentiate TS from PS AS in patients with classical low-flow AS (6). Further studies are needed to assess the usefulness of CT calcium scoring in the subset of patients with paradoxical low-flow AS. Patients with PLFLG AS with evidence of TS AS at stress echocardiography or CT should undergo AVR or transcatheter aortic valve implantation. Several studies have reported that patients with PLFLG AS have worse outcomes compared to patients with normal-flow high-gradient AS (2), and that AVR improves survival in these patients (1).

The presence of PS AS should not necessarily be interpreted as equivalent to mild disease and good prognosis. These patients often have moderate AS plus moderate/severe hypertension, which impose a high hemodynamic burden on the left ventricle. That may in turn worsen the LV concentric remodeling, the myocardial fibrosis, the impairment of diastolic filling, and pump function. Optimization of antihypertensive therapy and close monitoring of valve hemodynamic and LV function should be considered in these patients. Also, it should be kept in mind that failure of medical therapy could also be due to a worsening of AS severity during follow-up, in which case AVR should be reconsidered. Further studies are needed to establish what is the most appropriate therapeutic management for patients with PLFLG AS having evidence of PS AS.

Study limitations. The most important limitation of this study is the small number of patients, and further studies in larger number of patients are needed to confirm the utility of AVA_{proj} to confirm stenosis severity in PLFLG AS. Nevertheless, this is the first study, to our knowledge, to establish the feasibility, safety, and utility of stress echocardiography in the context of patients with PLFLG AS. Interestingly, the results that we found in this subset of patients were highly consistent with those that we previously reported in patients with classical low-flow, low-gradient AS (4).

Conclusions

This study reports that AVA_{proj} measured by stress echocardiography better predicts the actual stenosis severity and clinical outcome of patients with PLFLG AS. Thus, AVA_{proj} may help in therapeutic decision making in this challenging group of patients by providing a more accurate surgical indication. The risk-benefit ratio of stress echocardiography in this context, however, needs to be better established in larger series of patients before it can be advocated for routine clinical utilization.

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Key Words: aortic stenosis ■ dobutamine stress echocardiography ■ exercise stress echocardiography ■ low-flow aortic stenosis.