Dobutamine Stress Echocardiography in Low-Gradient Aortic Stenosis

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Importance: Guidelines recommend the use of dobutamine stress echocardiography (DSE) in patients with low-gradient aortic stenosis (AS) and left ventricular ejection fraction (LVEF) <50%. However, a paucity of DSE data exists when LVEF >35%.

Objective: To examine the diagnostic accuracy of DSE in patients with low-gradient AS with a wide range of LVEF and to examine the interaction between the diagnostic accuracy of DSE and LVEF.

Design, Setting, and Participants: Patients with mean gradient <40 mm Hg, aortic valve area <1.0 cm^2, and stroke volume index ≤35 mL/m^2 undergoing DSE and cardiac computer tomography (C-CT) were identified from 3 prospectively collected patient cohorts and stratified according to LVEF: LVEF<35%, LVEF 35% to 50%, and LVEF>50%.

Exposure: Dobutamine stress echocardiography and C-CT were performed on patients with low-gradient AS.

Main Outcomes and Measures: Severe AS was defined as aortic valve calcification score ≥2,000 arbitrary units (AU) among men and ≥1,200 AU for women on C-CT.

Results: Of 221 patients included in the study, 78 (35%) presented with LVEF <35%, 67 (30%) with LVEF 35% to 50%, and 76 (34%) with LVEF >50%. Mean-gradient and aortic valve peak velocity during DSE showed significant diagnostic heterogeneity between LVEF groups, being most precise when LVEF <35% (both areas under the curve [AUC] = 0.90), albeit with optimal thresholds of 30 mm Hg and 377 cm/sec and a limited diagnostic yield in patients with LVEF ≥35% (AUC = 0.67 and 0.66 in LVEF 35% to 50% and AUC = 0.65 and 0.60 in LVEF ≥50%). Using guideline thresholds led to a sensitivity/specificity of 49%/84% for all patients with LVEF <50%.

Conclusion and Relevance: While DSE is safe and leads to an increase in stroke volume in patients with low-gradient AS regardless of LVEF, the association between DSE gradients and AS severity assessed by C-CT demonstrates important heterogeneity depending on LVEF, with the highest accuracy in patients with LVEF <35%. (J Am Soc Echocardiogr 2024;37:1023-33.)

Keywords: Aortic stenosis, Low-flow low-gradient, Dobutamine stress echocardiography, Aortic valve calcification

The diagnosis of severe aortic stenosis (AS) is challenging when gradients are low. When this occurs in the presence of reduced stroke volume and left ventricular ejection (LV) fraction (LVEF) <50%, guidelines recommend the use of dobutamine stress echocardiography (DSE) to distinguish between true severe and pseudo-severe AS.[1-3] However, only a few data support an LVEF threshold of 50%

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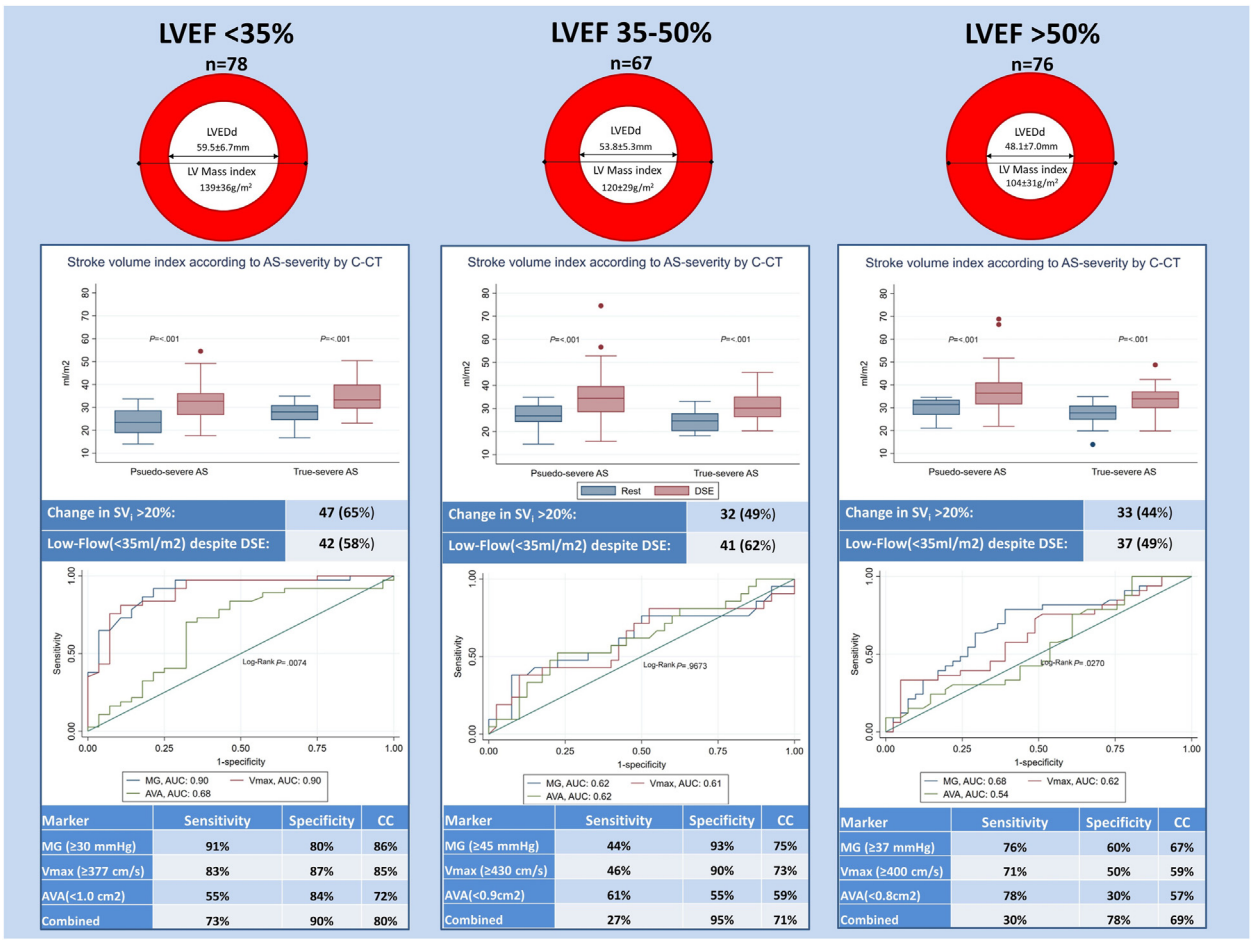

Central Illustration Schematic summary for each of the three patients groups (LVEF <35%, LVEF 35%-50% and LVEF >50%) outlining; differences in left ventricular geometry, change in stroke volume during DSE according to AS severity, and Sensitivity, Specificity and Correct Classification for the detection of severe AS, for the optimal cut-off point for mean gradient, peak velocity and aortic valve area.

Abbreviations

AS = Aortic stenosis

AU = Arbitrary units

AUC = Area under the curve

AVA = Aortic valve area

AVC = Aortic valve calcification

C-CT = Cardiac computer tomography

DSE = Dobutamine stress echocardiography

LV = Left ventricular

LVEF = Left ventricular ejection fraction

SV_i = Stroke volume indexed

V_{max} = Aortic valve peak velocity

as most studies have tested DSE in patients with severely reduced LVEF. Furthermore, evidence suggests that in AS LVEF may even be considered reduced already when less than 60%,[1,4] explaining why some advocate for the fact that DSE may provide diagnostic information even when LVEF >50%.[5] However, all of these studies are limited by the lack of a clear gold standard of assessing AS severity[6,7] and have thus largely been based on prognostic data[8] rather than objective measures for AS severity per se. This poses a potential problem as DSE findings, not being blinded for the clinicians, may have influenced decision-making (e.g., referring for surgery), potentially biasing the clinical end point.[9-11] Furthermore, as recent studies have demonstrated that even moderate AS may worsen prognosis,[12] in particular when LVEF is reduced,[13] the use of prognostic data to classify AS severity may be misleading.

Aortic valve calcification (AVC) assessed by cardiac computer tomography (C-CT) has recently emerged as an additional method of determining AS severity.[2] Aortic valve calcification has been demonstrated to clearly discriminate between moderate and severe AS[14] and is associated with outcome.[15] Accordingly, the European Society of Cardiology, American Heart Association, and American College of Cardiology recommend the use of AVC to diagnose severe AS, in particular among patients with low-gradient AS.[1,2]

The purpose of this study was to examine the diagnostic accuracy of guideline recommendations for DSE in low-gradient AS in patents with a wide range of LVEF and to examine whether an interaction between the diagnostic accuracy of DSE and LVEF exists. Furthermore, we studied the safety and feasibility of DSE in patients with LVEF >50%.

METHODS

We identified patients ages ≥18 years with low-gradient AS (aortic mean gradient <40 mm Hg and aortic valve area [AVA] <1.0 cm^2)

HIGHLIGHTS

- DSE is safe in patients with low-gradient AS regardless of LVEF.
- DSE leads to an increase in stroke volume increase regardless of LVEF.
- AS severity assessed by C-CT or DSE demonstrates heterogeneity depending on LVEF.
- Highest accuracy between DSE and C-CT was seen in patients with LVEF <35%.
- Mean gradient and V_{max} exceeded AVA in diagnosing severe AS adjudicated with C-CT.

and stroke volume indexed (SV_i) ≤35 mL/m^2 from 2 prospectively collected cohorts at Quebec Heart and Lung Institute, Canada[11,16] and a prospective cohort collected at Odense University Hospital, Denmark, between 2019 and 2022. For this study, we excluded patients with missing DSE or C-CT data or with concomitant moderate or severe valvular heart disease other than AS. Patients were stratified into 3 subgroups according to LVEF (LVEF <35%, LVEF 35%-50%, and LVEF>50%) at the baseline evaluation, which included a clinical examination, transthoracic echocardiography, and DSE.

Research was performed in accordance with the Declaration of Helsinki, and informed consent was obtained according to approval by each institutional review board.

Echocardiography

Patients underwent a comprehensive transthoracic echocardiographic in accordance with guidelines.[17,18] Doppler values were calculated as the average of 3 cardiac cycles for patients with sinus rhythm and 5 cycles for atrial fibrillation. Left ventricular ejection fraction was determined by the Simpson biplane method. Left ventricular stroke volume was calculated using pulsed-wave Doppler as the product of the LV outflow area and LV outflow tract time-velocity integral and indexed for body surface area (SV_i). Low-flow state was defined as SV_i ≤35 mL/m^2. In men, LV mass index >116 g/m^2 and in women >104 g/m^2 was considered indicative of LV hypertrophy.[19]

Valvulo-arterial impedance, systemic arterial compliance, and systemic vascular resistance were calculated.[20]

Dobutamine Stress Echocardiography

A comprehensive DSE was performed in all patients. Dobutamine infusion was initiated at a dose of 5 μg/kg/min and increased every third min to a maximal dosage of 20 μg/kg/min. Dobutamine stress echocardiography was terminated early if an adverse event occurred, if the patient became symptomatic during the examination, or if a mean gradient >40 mm Hg was recorded in patients with LVEF <50%. Contractile reserve was defined as an increase in SV_i exceeding 20%. Echocardiographic measurements of aortic flow and LV were obtained at each stage. During DSE heart rate, systolic and diastolic blood pressure were recorded at each dose increment. Patients with adverse symptoms during DSE were included in the final analysis.

Cardiac Computer Tomography

All patients underwent a noncontrast C-CT with a tube potential at 120 kV. Operators blinded to patient clinical and echocardiographic data performed all MDCT analyses. The aortic valve was visualized in multiple planes, and careful measurement section by section aimed to accurately distinguish contiguous calcium in coronary arteries, mitral valve annulus, or aortic wall. Aortic valve calcification score was assessed using the Agatston method and expressed in arbitrary units (AU). We defined severe AS using the sex-specific thresholds recommended by guidelines, AVC score ≥2,000 AU in male patients and ≥1,200 AU in female patients on C-CT.[1,2,21]

Dobutamine Stress Echocardiography Safety End Points

Patients undergoing DSE were safety monitored for adverse events. Adverse events during DSE were defined as new onset of complex ventricular arrhythmia, a rise in systolic blood pressure ≥200 mm Hg, a decrease in systolic blood pressure <80 mm Hg, LV outflow tract peak-flow velocity ≥2.0 m/sec, or systolic anterior motion of the mitral valve.

Statistical Analysis

Continuous variables were tested for normality with the Shapiro-Wilk test and are expressed as either mean ± SD or median and interquartile range. Differences in values between groups were tested by 1-way analysis of variance. Categorical variables are expressed as number and percentages and tested by Fisher's exact test.

Times between C-CT and DSE and AVC are presented as median and interquartile range, and differences were tested using the Kruskal-Wallis test because of non-Gaussian distribution for these variables. Correlations were obtained using Spearman rank test. For overall tests, a P value of <.05 were considered significant and 2-sided tests were used. Comparison of each method's predictive capability was performed by comparing the C statistic derived from the area under the receiver operating characteristic curves using the generalized U statistic as proposed by DeLong *et al.*[22] Statistical analysis was performed with STATA/SE V.17.0 (StataCorp.) software.

RESULTS

We identified 556 patients with low-gradient AS from the 3 cohorts and excluded all patients with missing C-CT data (n = 161) and DSE data (n = 174) leaving 221 patients (n = 150 Quebec Heart Institute, n = 71 Odense University Hospital) in this study (Supplemental Figure 1). Excluded patients were younger, more symptomatic, with less known coronary artery disease, and with more severe AS (Supplemental Table 1). Seventy-eight (35%) presented with LVEF <35%, 67 (30%) with LVEF 35% to 50%, and 76 (34%) with LVEF >50%. Dobutamine stress echocardiography and C-CT were performed within a median timespan of 12 [1; 26] days, with no difference between groups (P = .17).

Patients with LVEF >50% were more likely to be women, had less symptoms, and were less likely to have implantable electronic devices (Table 1). Severe AS, as evaluated by AVC, was present among 102 (46%) patients with no differences between groups (55% vs 37% vs 46%, LVEF <35% LVEF 35%-50%, LVEF >50% respectively, P = .10). Patients with LVEF >50% presented with higher aortic valve peak velocity (V_{max}; 304 ± 45 vs 302 ± 43 vs 324 ± 37 cm/sec, P < .01) and mean gradient (22 ± 7 vs 23 ± 7 vs 25±6 mm Hg, P = .03), despite similar AVA. Sixteen patients had a bicuspid aortic valve with an equal distribution among LVEF subgroups.

An inverse relationship was seen between LVEF and LV diameter (r = −0.65, P < .001). Patients with LVEF <35% had higher LV mass index and lower relative wall thickness than patients with LVEF >35%. These differences translated into significant differences

Table 1 Baseline characteristics

	LVEF <35% (*n* = 78)	LVEF 35%-50% (*n* = 67)	LVEF >50% (*n* = 76)	*P* value
Age, years	77 ± 8	76 ± 8	76 ± 8	.56
Sex, female	11 (14)	25 (37)	35 (46)	<.001
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	.28
Heart rate, rest, bpm	72 ± 14	75 ± 16	74 ± 12	.64
New York Heart Association class III-IV (*n* = 189)	46 (65)	26 (46)	15 (24)	<.001
Renal failure (estimated glomerular filtration rate <30; *n* = 214)	10 (13)	4 (6)	5 (7)	.24
Diabetes	31 (40)	32 (48)	22 (29)	.02
Hypertension	63 (81)	48 (72)	57 (75)	.38
Coronary artery disease	36 (46)	25 (37)	29 (38)	.65
Never smoking	31 (47)	23 (46)	31 (48)	1.00
Pacemaker or intracardiac defibrillator	24 (31)	8 (12)	15 (20)	.02
C-CT data:				
AVC in male patients, AU	2,183 [1,326; 3170]	1,634 [1,107; 2,376]	1,831 [1,441; 2,661]	.07
AVC in female patients, AU	875 [607; 1624]	1088 [632; 1989]	1067 [485; 1827]	.82
Severe AS on computed tomography	43 (55)	25 (37)	34 (45)	.10
Echocardiographic data:				
Aortic V_{max}, cm/sec	304 ± 45	302 ± 43	324 ± 37	<.001
Aortic mean gradient, mm Hg	22.3 ± 7.0	23.0 ± 7.1	25.1 ± 6.1	.03
AVA, cm^2	0.76 ± 0.13	0.77 ± 0.14	0.73 ± 0.13	.23
Dimensionless index	0.20 ± 0.04	0.23 ± 0.04	0.24 ± 0.05	<.001
LVEF, %	26 ± 6	41 ± 4	60 ± 6	<.001
Stroke volume, mL	49.3 ± 11.5	49.9 ± 10.0	54.3 ± 9.3	.01
SV_i, mL/m^2	25.6 ± 5.4	26.2 ± 4.9	28.9 ± 4.4	<.001
Interventricular septal thickness, mm (*n* = 203)	11.3 ± 2.3	11.3 ± 2.3	11.8 ± 2.5	.42
LV end-diastolic diameter, cm/m^2 (*n* = 214)	3.2 ± 0.4	2.9 ± 0.4	2.6 ± 0.4	<.001
Posterior wall thickness, mm (*n* = 204)	9.6 ± 1.8	9.8 ± 1.5	9.9 ± 2.6	.67
LV mass index, g/m^2 (*n* = 199)	139 ± 36	120 ± 29	104 ± 31	<.001
Relative wall thickness (*n* = 202)	0.33 ± 0.08	0.37 ± 0.07	0.41 ± 0.11	<.001
LV remodeling pattern (*n* = 199):				
Normal	19 (29)	23 (36)	28 (41)	
Concentric hypertrophy	9 (14)	9 (14)	8 (12)	
Concentric remodeling	0 (0)	3 (5)	19 (28)	
Eccentric hypertrophy	38 (58)	29 (45)	14 (20)	<.001

Numbers in parentheses represent available data.

in LV geometry with eccentric hypertrophy being the most common pattern among patients with LVEF <35% and patients with LVEF 35% to 50% and normal geometry in patients with LVEF >50% ($P < .001$). All patients had $SV_i < 35$ mL/m^2, but a higher resting SV_i was present in patients with LVEF >50% (26±5 vs 26 ± 5 vs 29±4 mL/m^2, $P < .01$; Table 1, Central Illustration).

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography was performed without adverse symptoms in 215 (97%) patients but was discontinued prematurely in 6 patients due to adverse symptoms ($n = 1$ systolic blood pressure >200 mm Hg, $n = 1$ angina, $n = 1$ dyspnea = 1, $n = 3$ other discomfort) being most common among patients with LVEF >50% (0% vs 2% vs 9%, $P = .04$, LVEF <35%; LVEF 35%-50%, and LVEF >50%, respectively). In contrast no ventricular arrhythmia during DSE were seen in patients with LVEF >50%, while 8 patients with LVEF <50% experienced complex ventricular arrhythmia during DSE (Table 2).

While stroke volume increased similarly during DSE in all LVEF subgroups, irrespective of AS severity (Supplemental Figure 2), at the end of DSE, 56% ($n = 120$) had low stroke volume (<35 mL/m^2) and 55% ($n = 109$) had low flow rate (<250 mL/sec), evenly split between subgroups (Table 3). Patients with reduced LVEF had the highest proportion with contractile reserve (65% vs 49% vs 44%, $P = .03$; Table 3). Despite similar systemic vascular resistance and valvuloarterial impedance during baseline and DSE, patients with LVEF >35% experienced lower systemic arterial compliance than those with LVEF <35% both at baseline and during DSE (0.56 ± 0.21 vs 0.48 ± 0.17 vs 0.50 ± 0.14 mL/m^2/mm Hg, $P = .02$, LVEF <35%, LVEF 35%-50%, LVEF>50%, respectively).

Table 2 Safety parameters during DSE

	LVEF <35% (*n* = 78)	LVEF 35-50% (*n* = 67)	LVEF >50% (*n* = 76)	*P* value
Max systolic BP during DSE, mm Hg*	133 ± 27	141 ± 21	149 ± 23	<.001
Systolic BP during max DSE dose, mm Hg*	130 ± 27	134 ± 21	142 ± 23	.03
Systolic BP <80 mm Hg*	0 (0)	0 (0)	1 (1)	.38
Systolic BP >200 mm Hg*	1 (1)	0 (0)	2 (3)	.40
DSE stopped because of adverse symptoms	0 (.0)	1 (2)	5 (7)	.03
Chest pain	1 (1)	2 (3)	2 (3)	.76
Ischemia on electrocardiogram	0 (0)	0 (0)	0 (0)	.99
Newly onset supraventricular tachycardia	1 (1)	1 (2)	1 (1)	.99
Complex ventricular arrhythmia	4 (5)	4 (6)	0 (0)	.11

BP, Blood pressure.
*Data available in *n* = 143.

Classifying Severe AS in the Entire Cohort

Receiver operating characteristic curves for DSE-derived mean gradient, V_{max} and AVA are provided in Figure 1. *C* statistics for the mean gradient (area under the curve [AUC] = 0.73) were nonsignificantly higher than V_{max} (AUC = 0.70) but significantly higher than AVA (AUC = 0.61; *P* = .01; Figure 1), with differences remaining nonsignificant in a direct comparison between mean gradient and V_{max} after including AVA in both models (AUC = 0.74 vs 0.72, *P* = .12).

The identified optimal cutoff points for discriminating between severe and pseudo-severe-AS during DSE were 34 mm Hg (mean gradient), 389 cm/s (V_{max}), and 0.9 cm^2 (AVA) with a sensitivity and specificity of 75%/64% versus 70%/63% versus 57%/59%, respectively. Applying any of the guideline-specific thresholds, mean gradient >40 mm Hg, V_{max}>400 cm/sec, or AVA<1.0 cm^2, leads to a sensitivity/specificity of 49%/78% versus 64%/66%, versus 78%/40%, respectively (Supplemental Table 2). Combining guideline recommendations for AVA and either mean gradient or V_{max} led to a

Table 3 DSE parameters

	LVEF <35% (*n* = 78)	LVEF 35%-50% (*n* = 67)	LVEF >50% (*n* = 76)	*P* value
Hemodynamic data				
Systolic BP, rest, mm Hg (*n* = 202)	123 ± 21	129 ± 18	137 ± 21	<.001
Diastolic BP, rest, mm Hg (*n* = 202)	72 ± 12	71 ± 10	75 ± 13	.08
Systolic BP during max DSE dose, mm Hg (*n* = 143)	130 ± 27	134 ± 21	142 ± 23	.03
Diastolic BP during max DSE dose, mm Hg (*n* = 143)	67 ± 14	67 ± 13	69 ± 12	.68
BP change, mm Hg (*n* = 143)	10 ± 23	9 ± 22	9 ± 20	.97
Max heart rate during DSE, bpm (*n* = 140)	93 ± 18	103 ± 25	103 ± 24	.08
Change in heart rate, bpm (*n* = 92)	25 ± 20	21 ± 15	24 ± 19	.78
Zva, rest, mm Hg/mL/m^2 (*n* = 209)	5.85 ± 1.47	6.00 ± 1.27	5.76 ± 1.17	.55

(*Continued*)

Table 3 (*Continued*)

	LVEF <35% (*n* = 78)	LVEF 35%-50% (*n* = 67)	LVEF >50% (*n* = 76)	*P* value
Zva, DSE, mm Hg/mL/m^2 (*n* = 142)	5.01 ± 1.41	5.48 ± 1.45	5.38 ± 1.28	.24
Zva, difference, mm Hg/mL/m^2 (*n* = 142)	1.12 ± 0.95	1.10 ± 0.73	0.93 ± 0.63	.39
Systemic arterial compliance, rest (units) (*n* = 209)	0.56 ± 0.21	0.48 ± 0.17	0.50 ± 0.14	.02
Systemic arterial compliance, DSE (units) (*n* = 142)	0.60 ± 0.21	0.50 ± 0.17	0.51 ± 0.18	.02
Systemic arterial compliance, difference (units) (*n* = 142)	0.17 ± 0.11	0.12 ± 0.12	0.11 ± 0.10	.02
SVR, rest, mm Hg/L/min (*n* = 138)	1,239 ± 451	1,241 ± 395	1,221 ± 380	.97
SVR, DSE, mm Hg/L/min (*n* = 122)	1,209 ± 562	1,269 ± 389	1,228 ± 375	.85
SVR, difference, mm Hg/L/min (*n* = 122)	173 ± 177	199 ± 164	144 ± 131	.28
SV, DSE, mL (*n* = 213)	64.6 ± 15.5	63.3 ± 16.4	65.6 ± 15.6	.68
Low SV (<35 mL/m^2) despite DSE (*n* = 213)	42 (58)	41 (62)	37 (49)	.29
Change in SV, mL (*n* = 213)	14.7 ± 11.5	13.1 ± 12.5	11.5 ± 11.8	.28
Change in SV_i >20% (*n* = 213)	47 (65)	32 (49)	33 (44)	.03
Flow rate, DSE, mL/sec (*n* = 200)	247 ± 53	262 ± 69	263 ± 64	.23
Low flow rate (<250 mL/sec) despite DSE (*n* = 200)	35 (55)	34 (56)	40 (53)	.96
Aortic V_{max}, DSE, cm/sec (*n* = 212)	377 ± 55	378 ± 58	405 ± 47	<.001
Change in V_{max}, cm/sec (*n* = 212)	70 ± 35	76 ± 39	82 ± 33	.14
Aortic mean radient, DSE, mm Hg	32.7 ± 10.1	34.2 ± 11.5	38.7 ± 9.9	<.001
Change in mean gradient, mm Hg	10.6 ± 5.7	11.6 ± 6.7	13.7 ± 6.5	.01
AVA, DSE, cm^2 (*n* = 203)	0.94 ± 0.28	0.97 ± 0.33	0.91 ± 0.21	.52
Change in AVA, cm^2 (*n* = 203)	0.19 ± 0.23	0.21 ± 0.30	0.19 ± 0.15	.86
DSE dimensionless index (*n* = 201)	0.24 ± 0.05	0.28 ± 0.06	0.30 ± 0.07	<.001

BP, Blood pressure; *SV*, stroke volume; *SVR*, systemic vascular resistance; *Zva*, valvuloarterial impedance.
Numbers in parentheses represent available data.

sensitivity and specificity of 54%/77% for all patients with LVEF <50%. We tested sensitivity and specificity and optimal cutoff points in the subset of patients with contractile reserve with consistent findings in both mean gradient and V_{max} but the optimal cutoff of AVA was <1.0 cm^2 (Supplemental Table 3).

Classifying Severe AS According to LVEF Subgroups

Comparing the ability of DSE variables to predict severe AS demonstrated significant heterogeneity between LVEF subgroups. Aortic valve area displayed uniform optimal cutoff between LVEF subgroups (1.0 cm^2 vs 0.9 cm^2 vs 0.8 cm^2, LVEF <35%, LVEF 35%-50%,

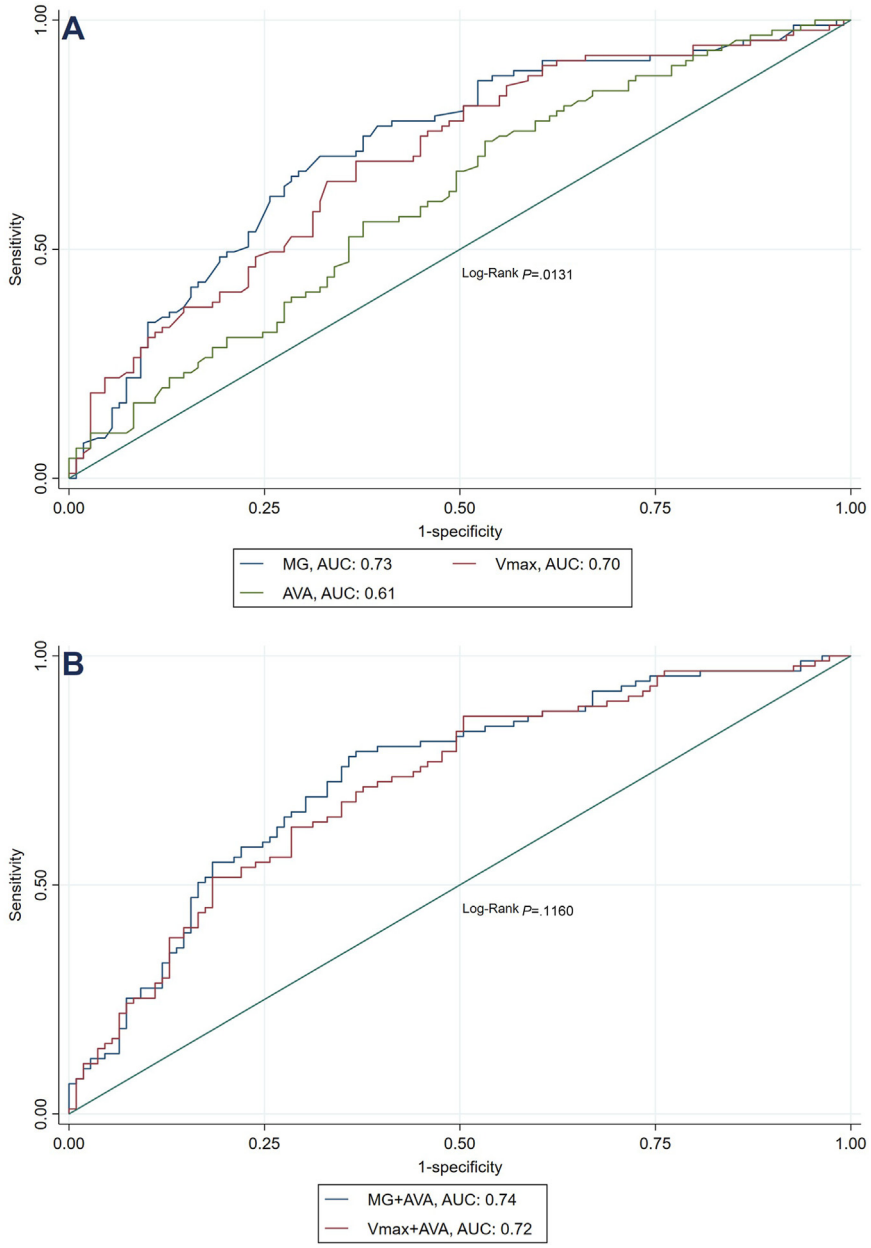

Figure 1 Receiver-operating characteristic to identify severe AS in the entire cohort of 221 patients with low-gradient AS (mean gradient <40 mm Hg and AVA <1.0 cm^2) and SV_i ≤35 mL/m^2 according to **(A)** mean gradient, peak velocity and AVA and **(B)** combination of mean gradient + AVA and peak velocity + AVA against computed tomography AVC. *MG*, Mean gradient, .

LVEF>50%, respectively) with similar *C* statistics (AUC = 0.68 vs AUC = 0.62 vs AUC = 0.54, *P* = .36, LVEF <35, LVEF 35%-50%, LVEF>50%, respectively; Figure 2). In contrast, the association of both mean gradient and V_{max} with AS severity was more accurate in the LVEF <35% group (mean gradient: AUC = 0.90 vs 0.67 vs 0.65, *P* = .0007; V_{max}: AUC = 0.90 vs 0.66 vs 0.60, *P* = .0001; Figure 2), with different optimal cutoff points (30 vs 45 vs 37 mm Hg and 377 vs 430 vs 400 cm/sec, LVEF <35%, LVEF 35%-50%, LVEF >50%, respectively; Figure 3).

Using guideline thresholds for both AVA and either mean gradient or V_{max} led to a sensitivity and specificity of 54%/93% vs 41%/78% vs 64%/63%, LVEF<35%, LVEF 35%-50%, LVEF>50%, respectively (Supplemental Table 4 and Supplemental Figure 3). For all patients with LVEF <50%, the sensitivity and specificity were 50% and 84% (Supplemental Table 2).

In LVEF subgroups, optimal cutoff points were similar regardless of including center, number of valvular leaflets, or flow state during DSE.

DISCUSSION

In this study with prospectively enrolled patients with low-gradient AS undergoing DSE we demonstrate 4 novel findings. (1) DSE is safe with few patients experiencing dobutamine-associated complications

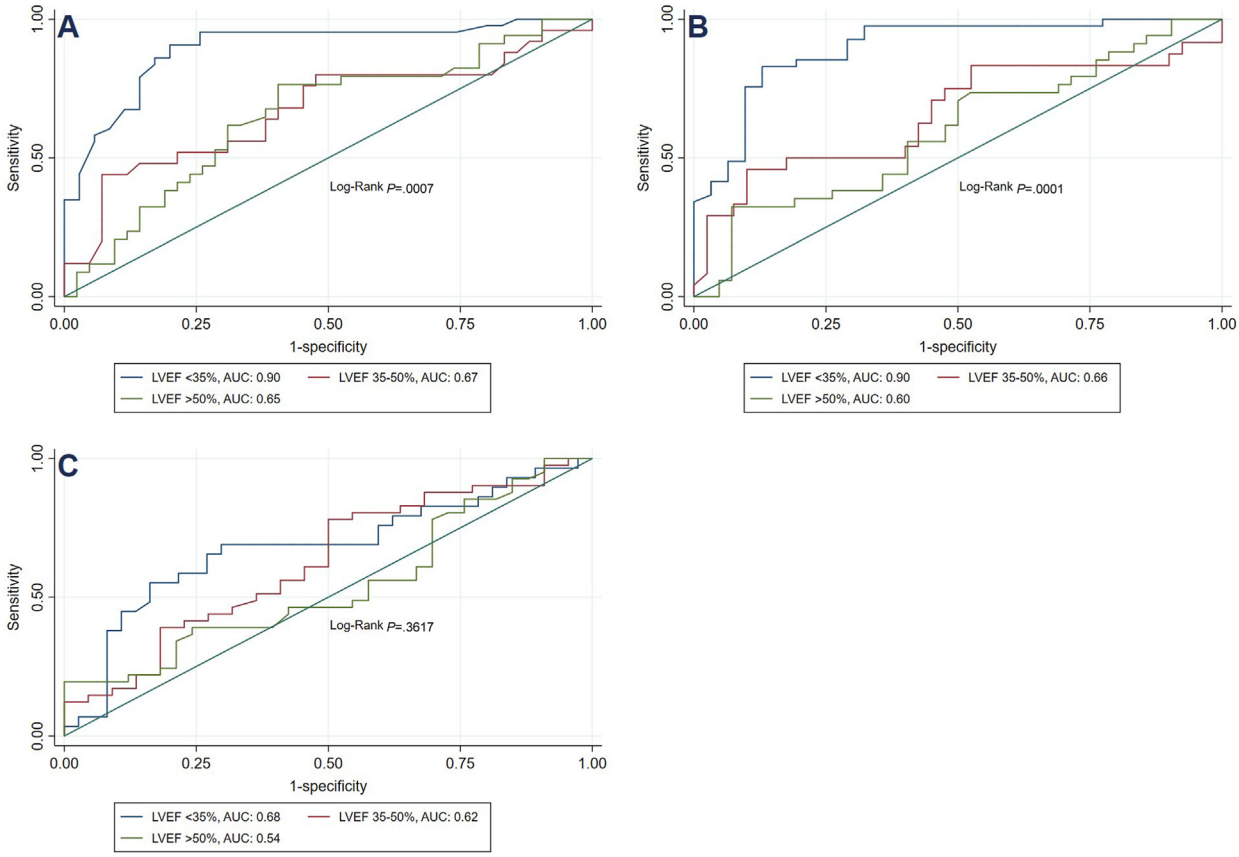

Figure 2 Receiver-operating characteristic to identify severe AS in LVEF subgroups: LVEF <35%, 35%-50%, and >50%, respectively, according to **(A)** mean gradient, (**B**) peak velocity, and **(C)** AVA against computed tomography AVC.

in patients with reduced as well as preserved LVEF. (2) DSE generally led to an increase in stroke volume in patients with low-gradient AS regardless of baseline LVEF. (3) The transvalvular mean gradient and transvalvular peak-velocity during DSE outperformed AVA in diagnosing severe AS adjudicated with C-CT AVC score. However, mean gradient was associated with a lower sensitivity but higher specificity than V_{max}. Utilizing the guideline recommendations of combining transvalvular gradients with AVA resulted in a specific but nonsensitive discrimination between severe and pseudo-severe AS in patients with LVEF <50%, highlighting that a large proportion of patients with high AVC are labeled as pseudo-severe AS based on DSE findings. This suggests that there is a discrepancy between the guideline-recommended thresholds of DSE and computed tomography indices of severe AS. (4) Although AVA during DSE provided modest but similar information regardless of LVEF, with a rather uniform optimal cutoff of 0.9 cm^2, both transvalvular mean gradient and peak velocity demonstrated important heterogeneity with outstanding discrimination in patients with LVEF <35%, while this was only modest in those with LVEF >35%. In addition, the optimal discriminatory threshold was markedly different between LVEF groups with a mean gradient 30 mm Hg being the best cutoff in patients with LVEF <35% and 40 mm Hg in those with LVEF>35%. The latter suggests that discrepancies exist between guideline-proposed thresholds for DSE and computed tomography in the assessment of severe AS and reduced LVEF.

	LVEF subgroups		
DSE parameter	LVEF <35%	LVEF 35-50%	LVEF >50%
MG(mmHg)	≥30	≥45	≥37
Vmax (cm/sec)	≥377	≥430	≥400
AVA (cm^2)	<1.0	<0.9	<0.8

Figure 3 Summary table of optimal cutoff points for severe AS according to LVEF subgroups. Summary table of identified optimal cutoff points during DSE for mean gradient, peak velocity, and AVA, according to LVEF subgroup; LVEF <35%, 35%-50% and >50%, respectively. *MG*, Mean gradient.

LOW-GRADIENT AS AND DSE IN CURRENT GUIDELINES

According to current guidelines, the use of DSE is recommended to help distinguish between moderate and severe AS when LVEF <50% and stroke volume is reduced. This strategy has been recommended since deFilippi and colleagues suggested it in 1995,[23] and Monin *et al.*[9,10] subsequently demonstrated that contractile reserve by DSE associated with outcome in patients with LVEF <35%. However, the prognostic impact of contractile reserve by DSE has since been challenged[24,25] and may not apply patients undergoing transcatheter aortic valve implantation.[26]

In line with these studies, we concordantly demonstrate that approximately two-thirds of patients with LVEF <35% had contractile reserve but as a novel finding show a lower rate of contractile reserve among patients with LVEF >35%. Although this could counterintuitively be interpreted as patients with higher baseline LVEF having a poorer ability to increase their contractile state, we speculate this rather reflects differences in LV geometry and baseline SV_i between groups. While reduced stroke volume in patients with LVEF <35% is the consequence of poor contractility, patients with LVEF >50% predominantly have a reduced stroke volume due to concentric LV remodeling that leads to small cavities and impeding normal stroke volume despite preserved LVEF.[27] Accordingly, the presence of smaller cavities combined with a higher baseline SVi in patients with LVEF >50% may defy an SV_i increase >20% as a criterion for contractile reserve. Thus, caution should be taken when interpreting contractile reserve without regard to LVEF. This may pose a potential problem as guidelines recommend the use of DSE in patients with LVEF <50%, while DSE and contractile reserve have mainly been studied in patients with LVEF <35%.[6-11]

CARDIAC COMPUTER TOMOGRAPHY RECOMMENDATIONS IN CURRENT GUIDELINES

A potential limitation of DSE is that AS severity may be challenging to grade when flow does not increase during DSE. In this setting, Cueff and colleagues[28] demonstrated that C-CT-derived AVC was able to distinguish severe from nonsevere AS when LVEF was <40%.[28] Current guidelines recommend the use of AVC as a tool to differentiate between moderate and severe AS in patients with low-gradient AS without contractile reserve on DSE or when LVEF >50%. It is thus interesting that among patients with LVEF <50% and severe AS ascertained by C-CT, 23% were labeled as having pseudo-severe AS by DSE.

These discrepancies imply that a diagnosis of severe AS is more likely if we use C-CT-assessed AVC rather than DSE data. Thus, patients with LVEF <35% and contractile reserve are less likely to be labeled as severe AS, based solely on DSE response, than patients without contractile reserve where determination of AS severity relies on AVC. As a consequence, it seems that while current DSE recommended thresholds are rather specific, they are also nonsensitive when compared to C-CT. This naturally raises the question of why the current thresholds have been chosen. While most DSE studies in low-gradient AS have used the same thresholds for AS severity as in normal flow, confirmation of AS severity has solely been based on either patient outcome or surgeons' evaluation during surgery as indicators of AS severity.[9,10] In these studies, the decision of surgery was not blinded for DSE response, and as no gold standard for severe AS existed, outcome was chosen as the indicator for AS severity. The latter may pose a particular problem as it recently has become evident that even moderate AS may influence outcome in patients with LVEF <50%,[13] with potential benefits from AVR in this subset of patients.[29] To our knowledge, our study is the first to compare the response of DSE with AS severity ascertained by C-CT. Accordingly, it is interesting that while AVA demonstrated a rather identical cutoff between LVEF subgroups, both transvalvular mean gradient and peak velocity showed higher accuracy in patients with LVEF <35% with optimal cutoff points of 30 mmHg for transvalvular mean gradient and 377 cm/sec for peak velocity.

These findings are in accordance with a previous paper by Nishimura and colleagues[30] reporting that under DSE, an invasively measured gradient of <30 mm Hg correlated with severe AS. In line with this, Annabi *et al.*[31] demonstrated that lowering the cutoff point for transvalvular mean gradient to either 35 mm Hg or 30 mm Hg improved the diagnostic accuracy of DSE.

A possible explanation for our finding could be that despite dobutamine raising stroke volume in most patients, almost half still experience a low-flow condition after dobutamine infusion, suggesting that a lower gradient would be expected than during normal flow. Thus, contractile reserve during DSE does not entail a normalization of flow per se and gradients corresponding with a normal flow may not always be achieved. Furthermore, while dobutamine has a positive inotropic effect on the heart stimulating β1-receptors, the effects on the α-receptors may also alter vascular resistance, changing the ventriculoarterial coupling and eventually lowering the transvalvular gradients.[32] Suggestive of this, we demonstrated different systemic arterial compliance between LVEF groups. Finally it is also possible that inconsistencies exist between gradients and AVA as a consequence of discrepancies also described in patients with normal systolic LV function.[33]

While DSE has the advantage over C-CT in radiation exposure and a functional hemodynamic assessment of AS severity, our findings suggest that the use of DSE to determine AS severity should be limited to patients with LVEF <35% and a mean gradient threshold of 30 mm Hg rather than 40 mm Hg should be preferred, while in patients with LVEF >35% DSE may have limited value in the diagnosis of severe AS.

Study Limitations

Assessment of AS severity is challenging with no clear gold standard. In this study, we used C-CT-assessed AVC as the reference for adjudication of AS severity. Different concerns can been raised regarding this choice as (1) AVC does not quantify fibrotic tissue, which might play an important role in the development of low-gradient AS,[14,34] or in bicuspid valves; (2) the current thresholds are derived from patients with concordant AS and have not been validated in low-gradient AS patients, and (3) reproducibility of AVC may be challenging. However, the Agatston method is a well-established marker of anatomic severity that has been demonstrated to correlate with valve severity on explanted valves,[34] AS hemodynamic severity measured by Doppler echocardiography,[28,35] and clinical outcomes.[15,36]

In our study, the measurement of AVC was done separately in each institution but was standardized between centers and demonstrated excellent reproducibility. And while the sensitivity and specificity of AVC in detecting severe AS have been described to be in the range of 85% to 90%, the use of invasive hemodynamic measurements by catheterization could have provided further ascertainment of AS severity.

CONCLUSION

The use of DSE is safe and led to an increase in stroke volume in patients with low-gradient AS regardless of baseline LVEF. However, the association between DSE gradients and AS severity assessed by C-CT demonstrates important heterogeneity, with highest accuracy in patients with LVEF <35% but limited diagnostic yield when LVEF≥ 35% and with different optimal diagnostic thresholds.

REVIEW STATEMENT

Given her role as JASE Editor-in-Chief, Patricia A. Pellikka, MD, had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Kian Keong Poh, MBBChir.

CONFLICTS OF INTEREST

None

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SUPPLEMENTARY DATA

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