BRIEF RESEARCH COMMUNICATIONS

Utility of Doppler Systolic Timing Intervals in Discriminating "True" Severe from "Pseudo-Severe" Stenosis in Classical Low-Flow Low-Gradient Aortic Stenosis

Classical low-flow low-gradient aortic stenosis (CLFLGAS) accounts for 5% to 10% of aortic stenosis (AS) cases and is defined by a left ventricular (LV) ejection fraction <50%, aortic valve area (AVA) <1.0 cm^2, and mean gradient (MG) <40 mm Hg.[1] These patients either have true severe AS (TSAS) and therefore aortic valve (AV) replacement should lead to LV functional recovery, or they have pseudo-severe AS (PSAS), that is, mild-moderate AS, an underlying primary cardiomyopathy, and are instead managed with heart failure therapy.[2,3] Low-dose dobutamine stress echocardiography (LDDSE) is recommended for discriminating TSAS from PSAS.[1-3] However, a considerable proportion of patients remain "indeterminate" due to limited flow augmentation. Although AV calcium score (AVCS) by multislice computed tomography is advocated as the final arbitrator, significant gray zones exist between the proposed cutoffs, and there is increasing recognition that leaflet fibrosis also contributes to valvular stenosis.[4,5] While the projected AVA is another intuitive solution, it is still limited by the need for a >15% increase in flow for valve compliance calculations to be reliable.[6] The acceleration (AT) to ejection (ET) time ratio (AT:ET) has been demonstrated to be a simple angle-independent index for grading native AS severity but has been primarily studied in heterogenous cohorts of AS patients.[7] The value of AT:ET to discriminate between TSAS and PSAS specifically in CLFLGAS has not been fully explored.

All LDDSEs performed for assessment of CLFLGAS in 4 tertiary echocardiography laboratories over a 5-year period were reviewed. True severe AS was diagnosed if the AS peak velocity increased to ≥4.0 $msec^{-1}$ and/or MG increased to ≥30 to 40 mm Hg at peak dose of dobutamine (provided that AVA remained <1.0 cm^2). Pseudo-severe AS was confirmed if AVA exceeded 1.0 cm^2 (or increased by >0.2 cm^2 with no change in gradients). An increase in stroke volume ≥20% indicated the presence of flow reserve. Rest and peak ATs were measured from the onset of flow to the peak of the AS continuous-wave Doppler signal, and ETs were measured from the onset to the end of systolic flow.

We identified 41 CLFLGAS patients with LDDSEs undertaken for differentiation between TSAS and PSAS. Two patients had "indeterminate" AS severity at the end of the protocol. Three cases were excluded due to suboptimal spectral Doppler assessments. Thirty-six patients achieved a final diagnosis of TSAS (n = 22) or PSAS (n = 14; Table 1).[1] Table 2 summarizes the Doppler hemodynamic parameters at baseline and peak dose. Median resting AV peak velocities (TSAS 3.4 $msec^{-1}$ [interquartile range (IQR), 3.1-3.5 $msec^{-1}$] vs PSAS 2.9 $msec^{-1}$ [2.7-3.2 $msec^{-1}$], P = .001) and MG (TSAS, 27.5 mm Hg [23.5- 30.5 mm Hg] vs PSAS, 19.3 mm Hg [16.1-23.5 mm Hg], P = .001) were statistically different but nondiscriminatory. Baseline AVA was similar in both groups (TSAS, 0.75 cm^2 [0.64-0.83 cm^2] vs PSAS, 0.82 cm^2 [0.69-0.94 cm^2], P = .119). Flow reserve was present in 13/22 (59.1%) of TSAS and 12/14 (85.7%) of PSAS patients (%stroke volume increase: TSAS, 21.7% [12.8-33.4%] vs PSAS, 38.3% [28.0-55.3%]; P = .006). Valve resistance (R) and percentage of LV stroke work loss (%LVSWL) were also significantly different (R: TSAS, 194.8 dynes.s.cm^{-5} [169.0-227.8 dynes.s.cm^{-5}] vs PSAS, 146.9 dynes.s.cm^{-5} [133.8-166.1 dynes.s.cm^{-5}], P = .003; %LVSWL: TSAS, 19.3% [15.9%-22.8%] vs PSAS, 13.9 [10.3%-16.3%], P = .007), but neither reached their thresholds for severe AS.

Compared with patients with PSAS, patients with TSAS exhibited longer resting ATs (TSAS, 115. 8 msec [110.0-124.0 msec] vs PSAS 93.3 msec [88.0-97.7 msec], P < .001) and higher AT:ET (TSAS, 0.40 [0.38-0.42] vs PSAS, 0.31 [0.30-0.33], P < .001). Receiver operating characteristic analysis demonstrated that a resting AT:ET ratio >0.35 would differentiate TSAS from PSAS with 100% sensitivity, 85.7% specificity, and positive and negative predictive values of 91.7% and 100%, respectively. This separation persisted at peak dose for both AT (TSAS, 94.0 msec [90.5-100.0 msec] vs PSAS, 72.9 msec [60.6-81.7 msec], P < .001) and AT:ET (TSAS, 0.38 [0.37-0.40] vs PSAS, 0.29 [0.28-0.32], P < .001). The combination of resting and peak AT:ET >0.35 further differentiated TSAS from PSAS with 90.9% sensitivity, 92.9% specificity, positive predictive value 95.2%, negative predictive value 86.7%, and a likelihood ratio (+) of 12.73. While AT alone may also have predictive value, it could be less dependable as systolic timing intervals are heart rate dependent. Using AT:ET allows correction for this variable.

A resting AT:ET > 0.35 was able to accurately discriminate TSAS from PSAS in CLFLGAS. An AT:ET > 0.35 also retained good discriminatory power at peak dose, implying that this index may be a useful flow-independent marker for assessment of AS severity. The main limitations of this study include its retrospective nature and the small number of patients. In addition, the diagnosis of TSAS or PSAS was based on LDDSE criteria, which are observational and historical. Corroborative support from the AV calcium score by multislice computed tomography or prospective validation of these findings in a larger cohort matched to clinical outcomes would have been ideal but was not available for this population Therefore, the results of this study are largely hypothesis generating but appear consistent with the literature to date, albeit in mixed phenotypes of AS.

In conclusion, AT:ET is a simple and reliable Doppler index that may offer incremental diagnostic value for the assessment of CLFLGAS patients. Further studies are warranted to verify its place in the integrated approach for grading AS severity.

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Conflicts of Interest: None.

Table 1 Baseline characteristics

	TSAS (*n* = 22)	PSAS (*n* = 14)	*P* value
Age, years	77 ± 8	76 ± 9	.987
Gender, female	7 (31.8)	4 (28.6)	.837
History of smoking	8 (42.1)	8 (61.5)	.280
Known coronary artery disease	10 (50)	11 (78.6)	.092
Systemic hypertension	16 (80)	9 (64.3)	.307
Diabetes mellitus	11 (55)	10 (71.4)	.332
Chronic renal failure	7 (35)	7 (50)	.382
Previous myocardial infarction	9 (45)	8 (57.1)	.486
Previous coronary artery bypass grafting	6 (30)	6 (42.9)	.440
Previous percutaneous coronary intervention	4 (20)	5 (35.7)	.307
Systolic blood pressure, mm Hg	118 ± 22	125 ± 25	.358
Diastolic blood pressure, mm Hg	66 ± 16	66 ± 11	.759
Resting heart rate, bpm	74 ± 13	69 ± 12	.205
LV ejection fraction, %	29.5 (22.8, 35.8)	33.5 (29.3, 37.3)	.283

Data are expressed as mean ± SD or median (IQR) for continuous variables and compared using the Mann-Whitney *U* test. Categorical variables are expressed as *n* (%) and compared using the Pearson chi-square analysis.

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Table 2 Dobutamine stress echocardiography hemodynamic parameters

	TSAS (*n* = 22)	PSAS (*n* = 14)	ROC AUC	*P* value
Baseline				
AV peak velocity, rest, $msec^{-1}$	3.4 (3.1, 3.5)	2.9 (2.7, 3.2)	0.823	.001
AV MG, rest, mm Hg	27.5 (23.5, 30.5)	19.3 (16.1, 23.5)	0.838	.001
DVI (Doppler velocity index)	0.20 (0.19, 0.22)	0.22 (0.20, 0.25)	0.302	.048
AVA, rest, cm^2	0.75 (0.64, 0.83)	0.82 (0.69, 0.94)	0.344	.119
AT, rest, msec	115.8 (110.0, 124.0)	93.3 (88.0, 97.7)	0.942	<.001
AT:ET, rest	0.40 (0.38, 0.42)	0.31 (0.30, 0.33)	0.932	<.001
Valve R, $dynes.s.cm^{-5}$	194.8 (169.0, 227.8)	146.9 (133.8, 166.1)	0.799	.003
%LVSWL	19.3 (15.9, 22.8)	13.9 (10.3, 16.3)	0.769	.007
Peak				
AV peak velocity, peak, $msec^{-1}$	4.2 (4.0, 4.3)	3.3 (3.0, 3.9)	0.909	<.001
AV MG, peak, mm Hg	42.4 (39.2, 43.0)	23.7 (20.5, 33.6)	0.912	<.001
AVA, peak, cm^2	0.84 (0.75, 0.94)	1.29 (1.05, 1.35)	0.091	<.001
Projected AVA, cm^2	0.82 (0.77, 0.90)	1.06 (1.02, 1.16)	1.000	<.001
AT, peak, msec	94.0 (90.5, 100.0)	72.9 (60.6, 81.7)	0.869	<.001
AT:ET, peak	0.38 (0.37, 0.40)	0.29 (0.28, 0.32)	0.935	<.001

AUC, Area under the ROC curve; *ROC*, receiver operating characteristic.
Data are expressed as median (IQR).

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