ORIGINAL RESEARCH

Delayed Time to Peak Velocity Is Useful for Detecting Severe Aortic Stenosis

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***Background*—**Time to peak velocity (TPV) is an echocardiographic variable that can be easily measured and reflects a late peaking murmur, a classic physical finding suggesting severe aortic stenosis (AS). The aim of this study was to investigate the usefulness of TPV to evaluate AS severity.

***Methods and Results*—**This study included 700 AS patients, whose aortic valve area (AVA) was <1.5 cm^2, and 200 control patients. The TPV was defined as the time from aortic valve opening to when the flow velocity across the aortic valve reaches its peak. AS severity was classified as follows: High gradient severe AS, mean pressure gradient ≥40 mm Hg and AVA index (AVAI) <0.6 cm^2/m^2; Low gradient severe AS, mean pressure gradient <40 mm Hg, AVAI <0.6 cm^2/m^2, and dimensionless index <0.25; moderate AS, mean pressure gradient <40 mm Hg, AVAI ≥0.6 cm^2/m^2. The area under the receiver operating characteristic curve of TPV to predict high gradient severe AS was 0.94 (95% CI: 0.92–0.97, P<0.001). TPV was significantly delayed in low gradient severe AS compared with moderate AS both in patients with preserved (102±13 ms versus 83±13 ms, P<0.001) and with reduced ejection fraction (110±18 ms versus 88±13 ms, P<0.001). Delayed TPV was associated with increased all-cause mortality or need for aortic valve replacement after adjustment for confounders (hazard ratio for first quartile, reference is fourth quartile: 7.31, 95% CI 4.26–12.53, P<0.001).

***Conclusions*—**TPV is useful to evaluate AS severity and predict poor prognosis of AS patients. **(*J Am Heart Assoc*. 2016;5: e003907 doi: 10.1161/JAHA.116.003907)**

Key Words: diagnosis • echocardiography • time to peak velocity • valves

Aortic stenosis (AS) is a public health issue globally.[1] It is assumed that the number of patients presenting with clinically significant AS has been increasing in developed countries,[2] and about 12% of people over 75 years of age have more than mild AS in Europe and North America.[3] Thus, its impact on public health and healthcare resources is expected to increase. Accurately diagnosing the severity of AS is not always a simple process. For example, peak flow velocity or mean pressure gradient across the aortic valve (mean PG) are important parameters used in the assessment of AS.[4] However, accurate measurement of peak flow velocity or mean PG requires parallel alignment of the Doppler ultrasound beam and accurate tracing of the velocity time integral of the continuous Doppler wave.[4] Furthermore, because of their flow dependency, peak flow velocity or mean PG cannot be applied to low flow–low gradient (LF-LG) AS, which accounts for 5% to 10% of severe AS patients with reduced ejection fraction (EF) and 10% to 25% of severe AS patients with preserved EF.[5] On the other hand, calculating aortic valve area using the Continuity equation method requires accurate left ventricular outflow tract (LVOT) diameter and flow velocity data.[4] Because the prevalence of atrial fibrillation (AF) increases with aging and its risk factors are similar to degenerative AS, both conditions frequently coexist.[6] AS is also commonly associated with conduction disease in the His bundle and the trifascicular conduction system.[7,8] Therefore, AS is frequently associated with left bundle branch block (LBBB) or need for a permanent pacemaker. Beat-to-beat variation of heart rate and stroke volume in AF may affect the accuracy of the PG and tracing the time-velocity integral. It has been reported that AS patients with AF have smaller stroke volumes (SV) and lower PG than AS patients

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without AF, even if the aortic valve area (AVA) is comparable between the groups.[9] LBBB reduces peak positive LV dp/dt and SV, and therefore, may affect the PG in AS patients.[10] Therefore, these conditions may also contribute to the difficulty in accurately diagnosing AS severity. Patients with severe AS (including asymptomatic AS,[11] high-risk AS patients,[12] and LF-LG AS[13]) may benefit from aortic valve replacement (AVR) including transcatheter aortic valve replacement; therefore, accurate diagnosis of severe AS is crucially important.[14]

Severe AS is associated with a late peaking murmur, a well-recognized physical finding.[15] Time to peak aortic valve velocity (TPV), which will reflect the late peaking murmur, and can be readily measured during routine echocardiographic examination, could be a marker for AS severity.[16] It has been reported that TPV might be useful to predict severe AS.[16] However, whether it can be applied to patients with AS and reduced EF, LBBB, AF, or LF-LG AS and whether TPV is associated with prognosis of AS patients remain unknown. Therefore, the aim of this study was to investigate the usefulness of TPV to predict severe AS in the patients with preserved EF, reduced EF, LBBB, AF, or LF-LG AS and to examine the ability of TPV to identify AS patients with poor prognosis.

Methods

Subjects

Patients with and without AS who underwent echocardiography from January 1, 2010 to December 31, 2014 at the University of Mississippi Medical Center, Jackson, MS were included in the study. The study protocol was approved by the institutional review board, and informed consent was waived because this study was conducted as a retrospective chart review protocol and all information was gathered from existing data within the organization.

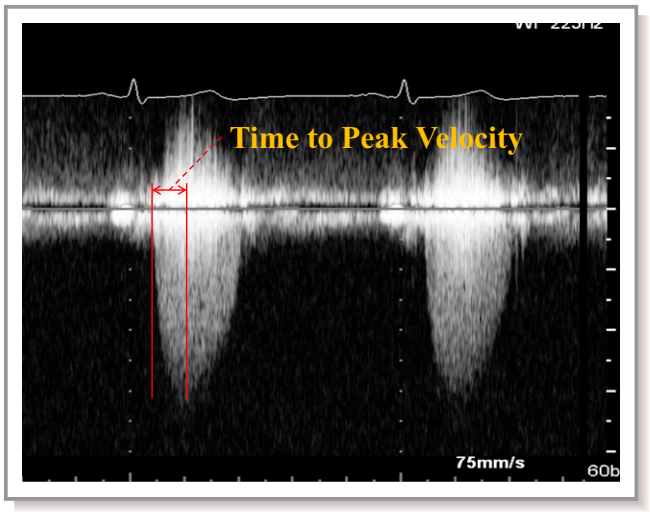

Figure 1. Measurement of time to peak velocity. Time to peak velocity was measured on the continuous-wave Doppler image across the aortic valve. Time to peak velocity was defined as from the aortic valve opening to the time when the flow velocity reaches its peak.

AS patients

Patients who had an AVA <1.5 cm^2 by the Continuity equation method were consecutively recruited. Among the 846 patients with AVA <1.5 cm^2, a total of 146 patients with the following findings and conditions were excluded from the study: prosthetic aortic or mitral valve in place (n=14), sick sinus syndrome or atrioventricular block without pacing (n=8), LVOT obstruction (n=3), aortic coarctation (n=2), frequent premature ventricular contraction (n=2), sinus tachycardia due to hypovolemia (n=1), tachycardia due to atrial flutter (n=1), septic shock (n=3), respiratory failure (n=1), cardiac tamponade (n=1), biventricular pacing (n=2), insufficient echocardiography image quality (n=48), and lack of relevant patient clinical data (n=50). We also excluded patients both with AF and LBBB including right ventricular pacing (n=10). The remaining 700 AS patients were included in the final analysis. In this patient population, there were 79 patients with LBBB without AF (55 patients out of 79 LBBB patients were paced from the right ventricle), and 114 patients with AF without LBBB.

Patients without AS (control group)

During the same period, age-matched patients who did not have AS on echocardiography within the following categories were included in the study:

1. Patients with sinus rhythm and without LBBB with preserved EF (n=50).
2. Patients with sinus rhythm and without LBBB with reduced EF (n=50).
3. Patients with sinus rhythm and with LBBB with preserved EF (n=20).
4. Patients with sinus rhythm and with LBBB with reduced EF (n=20).
5. Patients with AF and without LBBB with preserved EF (n=30).
6. Patients with AF and without LBBB with reduced EF (n=30).

The control group consisted of 200 patients without AS.

The study protocol was approved by the Institutional Review Board of the University of Mississippi Medical Center, Jackson, MS. This study was conducted as a retrospective study and data for analysis were collected from electronic medical records.

Table 1. Patient Characteristics

Variables	Severe		Unclassified	Moderate	Control			*P* Value for No Difference[¶]
	HG	LG			Whole	PEF	REF	
No. of patients	105	101	240	254	200	100	100	N/A
Age, y	73±13	73±13	71±13	72±12	72±8	72±8	73±8	0.49
Male sex, %	54	56	55	40*†‡	59§	50	67‖	<0.001
Ethnicity, %								
White	68	68	70	63	53	57	50	
Black	30	31	30	35	46	41	50	
Other	2	1	0	2	1	2	0	
SBP, mm Hg	130±22	127±22	134±24	138±25†	132±24	134±24	130±24	0.004
DBP, mm Hg	69±13	73±13	70±15	70±14	71±14	70±15	72±14	0.54
HR, bpm	74±16	77±17	74±16	73±17	77±19	75±20	78±19	0.08
Peak PG, mm Hg	90±23	50±14*	39±15*†	29±12*†‡	7±3*†‡§	8±4	6±3	<0.001
Mean PG, mm Hg	54±13	28±8*	21±8*†	15±6*†‡	4±2*†‡§	4±2	3±2	<0.001
AVA, cm^2	0.64±0.20	0.67±0.18	0.98±0.19*†	1.31±0.13*†‡	2.52±0.58*†‡§	2.54±0.51	2.51±0.65	<0.001
AVAI, cm^2/m^2	0.33±0.09	0.36±0.11	0.49±0.08*†	0.71±0.08*†‡	1.28±0.32*†‡§	1.29±0.29	1.28±0.37	<0.001
DLI	0.21±0.06	0.21±0.04	0.34±0.07*†	0.43±0.08*†‡	0.75±0.15*†‡§	0.78±0.13	0.72±0.16	<0.001
LVEDVI, mL/m^2	72±23	80±30	65±23†	69±23†	75±30‡§	59±16	92±33‖	<0.001
LVESVI, mL/m^2	32±20	47±28*	28±18†	29±19†	44±30*‡§	23±8	65±28‖	<0.001
SVI (Tei), mL/m^2	40±12	33±13*	37±12*†	40±13†‡	32±13*‡§	37±10	27±12‖	<0.001
SVI (TVI), mL/m^2	36±10	27±9*	31±8*†	39±9*†‡	31±11*†§	35±10	28±11‖	<0.001
LVEF, %	58±14	44±17*	59±13†	60±14†	45±19*‡§	62±8	31±10‖	<0.001
LVMI, g/m^2	137±37	133±59	119±44*	118±44*†	113±40*†	94±28	133±41‖	<0.001
TPV, ms	118±17	106±17*	97±18*†	85±15*†‡	81±12*†‡§	79±11	83±14‖	<0.001

Values are mean±1 SD, or %. AVA indicates aortic valve area; AVAI, aortic valve area index; DBP, diastolic blood pressure; DLI, dimensionless index; HG, high gradient; HR, heart rate; LG, low gradient; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; N/A, not applicable; PEF, preserved ejection fraction; PG, pressure gradient; REF, reduced ejection fraction; SBP, systolic blood pressure; SVI (Tei), stroke volume index measured by Teichholz method; SVI (TVI), stroke volume index measured from time velocity integral.

*P<0.05 vs high gradient, †P<0.05 vs low gradient, ‡P<0.05 vs unclassified, §P<0.05 vs moderate, ‖P<0.05 vs control PEF. One-way analysis of variance was performed among aortic stenosis severity categories. Unpaired t test in continuous variables and χ^2 test in categorical variables were performed between Control PEF and REF.

¶P value for no difference includes both HG and LG severe aortic stenosis (AS), Unclassified AS, Moderate AS, and Whole Control group.

Echocardiography

Echocardiography was performed using an iE33 ultrasound system (Philips Medical Systems, Andover, MA). LVOT and transaortic valve blood flow velocities and gradients were derived from velocity time integrals, measured by pulsed-wave Doppler in the LVOT near the aortic valve and by continuous-wave Doppler from different (including apical 5-chamber and parasternal) views. The highest and clearest image of transaortic valve velocity was used for tracing of the time-velocity integral. LVOT diameter was measured at midsystole in the 2-dimensional parasternal long-axis view by an inner-edge-to-inner-edge method. The effective AVA was calculated with the Continuity equation. The dimensionless index (DLI) was calculated as ratio of the LVOT time-velocity integral to that of the aortic valve level.[17] Heart rate was calculated from the pulsed-wave Doppler image in the LVOT. LV structure was evaluated in the 2-dimensional parasternal long-axis view. LV end-diastolic volume, LV end-systolic volume, LVEF, and SV were calculated by Teichholz method and SV was indexed to body surface area (SVI-Tei). SV was also calculated using the time-velocity integral at the LVOT multiplied by the LVOT cross-sectional area and indexed to body surface area (SVI-TVI). LV mass (LVM) was calculated using the following equation as recommended by the European Society of Echocardiography and American Society of Echocardiography[18]: LVMI (g/m^2)=$(0.8\times\{1.04\times[(LVDd+IVSTd+PWTd)^3-(LVDd)^3]\}+0.6)$/body surface area.

Table 2. Simple Correlation and Multivariable Analysis of TPV

	Correlation		Multivariable Analysis (1)			Multivariable Analysis (2)		
Variables	Correlation Coefficient	*P* Value	B±SE*	β	*P* Value	B±SE*	B	*P* Value
Age	0.013	0.69	†			†		
Male sex	0.055	0.10	†			†		
Systolic BP	−0.042	0.25	†			†		
Diastolic BP	−0.005	0.89	†			†		
HR	−0.235	<0.001	−0.003±0.000	−0.240	<0.001	−0.003±0.000	−0.234	<0.001
AVAI	−0.476	<0.001	−0.280±0.015	−0.510	<0.001	†		
DLI	−0.488	<0.001	†			−0.506±0.027	−0.507	<0.001
LVEF	−0.092	0.006	−0.002±0.000	−0.193	<0.001	−0.002±0.000	−0.163	<0.001
SVI (Teichholz)	0.088	0.008	†			†		
SVI (TVI)	0.081	0.015	†			†		
LBBB	0.186	<0.001	0.097±0.017	0.157	<0.001	0.096±0.017	0.155	<0.001
AF	−0.185	<0.001	−0.025±0.015	−0.046	0.111	−0.028±0.015	−0.052	0.070

AF indicates atrial fibrillation; AVAI, aortic valve area index; B, regression coefficient; BP, blood pressure; DLI, dimensionless index; HR, heart rate; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; SVI, stroke volume index; β, standardized regression coefficient; TPV, time to peak velocity; TVI, time velocity integral.
*Represents 1 unit change in each variable and 1 unit change in the log-transformed TPV.
†Not included in multiple analysis.

Measurement of Time to Peak Velocity (TPV)

TPV was defined as time from aortic valve opening to when the aortic valve velocity reaches its peak by continuous-wave Doppler[16] (Figure 1). Three consecutive pulses were used for measurement and averaged value was used for analysis. Mean±SD of intraobserver and interobserver variability of TPV was 6.0±4.4 (%) (n=10) and 8.7±5.3 (%) (n=10), respectively.

Classification of the Severity of AS

Based on the American Society of Echocardiography guidelines, we classified the AS severity into the following groups[4]:

1. High gradient (HG) severe AS: aortic valve area index (AVAI) <0.6 cm^2/m^2, mean PG ≥40 mm Hg.
2. Low gradient (LG) severe AS: AVAI <0.6 cm^2/m^2, mean PG <40 mm Hg, and dimensionless index (DLI) <0.25.
3. Unclassified AS: AVAI <0.6 cm^2/m^2, mean PG <40 mm Hg, and DLI ≥0.25.
4. Moderate AS: AVAI ≥0.6 cm^2/m^2, mean PG <40 mm Hg.

Outcome

Follow-up information was obtained from patients' medical records. Outcomes were defined as (1) all-cause mortality or need for aortic valve replacement (AVR) and (2) cardiovascular mortality or need for AVR. Cardiovascular death includes death attributable to worsening of heart failure, sudden death, and fatal myocardial infarction. These were ascertained by patients' medical records or death certificates. Clinical decisions with regard to medical management and referral for surgery were made by each patient's cardiologist in accordance with current practice guidelines.

Statistical Analysis

Results are expressed as mean±SD or percentage unless otherwise specified. We used 1-way ANOVA for comparisons of continuous variables among groups, and χ^2 tests for comparisons of categorical variables among groups.

In order to find clinical predictors of TPV, correlations between TPV and other variables (ie, demographic data, hemodynamic data, and other echocardiographic data) were initially evaluated by simple linear regression. Independent predictors for TPV were obtained with use of standard multiple linear regression. We found that residuals were not normally distributed when the absolute value of TPV was used as a dependent variable; thus, we used log-transformed TPV instead of absolute TPV as a dependent variable in the multiple linear regression model. Variables with a univariate value of P <0.05 were used in the multivariable linear regression models. We did not include AVAI and DLI at the same time in the model, because of the close relationship between these variables (r=0.90, P<0.001) and possible issues with collinearity. We also did not include both SV

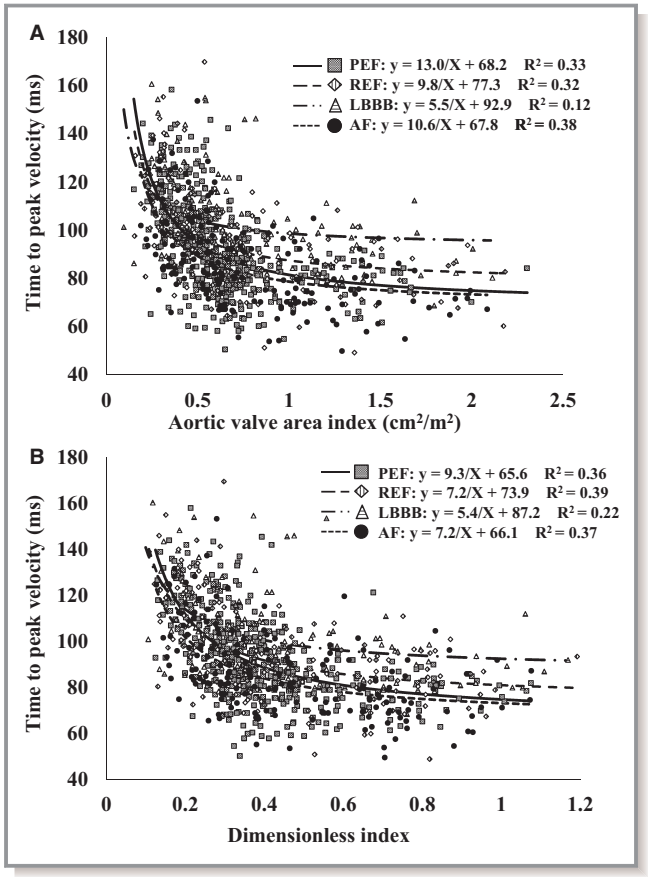

Figure 2. Scatter (A) between time to peak velocity and aortic valve area index, and (B) between time to peak velocity and dimensionless index. Time to peak velocity correlated reciprocally with aortic valve area index and dimensionless index in all subgroups. Time to peak velocity abruptly increased after aortic valve area index became smaller than 0.6 cm^2/m^2, and also after dimensionless index became smaller than 0.25. AF indicates atrial fibrillation; LBBB, left bundle branch block; PEF, preserved ejection fraction; REF, reduced ejection fraction.

indexed to body surface area calculated by Teichold method and SVI-TVI because of their collinearity with EF.

Unadjusted scatter plots were constructed between TPV and AVAI or DLI in each patient group (preserved EF and reduced EF without LBBB or AF, LBBB without AF, AF without LBBB). An approximation curve was estimated using the following equation and least squares approximation: TPV=a/AVAI+b or TPV=a/DLI+b.

The ability of TPV to predict HG severe AS defined as above was examined in different patient groups by receiver operating characteristic (ROC) curves, and areas under the curve were evaluated. In all of the ROC analyses, we excluded the LG severe AS and Unclassified AS patients because there may be uncertainty about the severity of AS in these groups. Thus, these ROC analyses show HG severe AS versus the combination of moderate AS and controls. In patients with LG severe AS with preserved EF or reduced EF who did not have LBBB or AF, TPV was compared to the patients with moderate AS or without AS without LBBB or AF.

The ability of TPV to predict events was examined in (1) the whole group, and also in (2) the combined group of unclassified AS and moderate AS patients. In both of the longitudinal analyses, patients with LBBB or AF were excluded. There were 512 AS patients who were eligible for the longitudinal study. One hundred ten of these patients had no documented follow-up; therefore, the remaining 402 patients were included in the analysis. Patients without follow-up (n=110) were older and more likely to be female than those with follow-up (n=402). However, mean PG, AVAI, AVA, and DLI were comparable between the 2 groups. Mean follow-up duration was 535±529 days. Probabilities of event-free survival were evaluated by Kaplan–Meier survival curves for the groups of TPV quartiles (TPV quartile 1 corresponds to highest and quartile 4 to lowest TPV) and compared by a 2-sided log-rank test. The impact of TPV on event-free survival was assessed with Cox proportional hazards models in univariate and multivariable analyses. Age, sex, ethnicity, and variables with a univariate value of $P<0.05$ other than indicators for AS severity were incorporated into the baseline multivariable model (Model 1). Then, we additionally examined 3 models including: Model 2: Model 1+AVAI, Model 3: Model 1+mean PG, and Model 4: Model 1+DLI to investigate whether TPV has the ability to provide additive prognostic information beyond that of conventional AS severity indicators. Ethnicity was categorized into 3 groups: white, black, and "other races" including Hispanic, Asian, and multiethnicity because the numbers of these groups were very small. All statistical analyses were performed with STATA version 14 (STATA Corp, College Station, TX).

Results

Baseline Characteristics

The baseline characteristics of the 700 AS patients and 200 patients without AS (controls) are shown in Table 1. TPV was delayed in accordance with AS severity, and there were significant differences in TPV between groups: TPV in HG severe AS (118±17 ms), LG severe AS (106±17 ms), unclassified AS (97±18 ms), moderate AS patients (85±15 ms), and control group (81±12 ms) ($P<0.001$).

Clinical Determinants of TPV

In simple linear regression, log-transformed TPV was significantly correlated with heart rate ($r=-0.235$, $P<0.001$), AVAI ($r=-0.476$, $P<0.001$), DLI ($r=-0.488$, $P<0.001$), LVEF ($r=-0.092$, $P=0.006$), SVI-Tei ($r=0.088$, $P=0.008$), SVI-TVI ($r=0.081$, $P=0.015$), LBBB ($r=0.186$, $P<0.001$), and

AF (r=−0.185, P<0.001) (Table 2). Figure 2 shows the unadjusted scatter plot between TPV and AVAI (Figure 2A), and between TPV and DLI (Figure 2B). The approximation curves were shown for each group. TPV was reciprocally correlated with AVAI and DLI, and rapidly increased after AVAI became smaller than 0.6 cm^2/m^2, and also after DLI became smaller than 0.25. Multiple linear regression revealed heart rate, LVEF, LBBB, and AVAI or DLI were independent predictors of log-transformed TPV. SVI had a very weak correlation with TPV and was excluded from multivariable analysis due to its collinearity with LVEF. AVAI and DLI were the strongest predictors of TPV in multivariable analyses followed by heart rate.

TPV to Predict HG Severe AS

Findings of the ROC analysis are presented in Figure 3. The areas under the ROC curves of TPV to predict HG severe AS were 0.94 in the whole group (P<0.001), 0.96 in the preserved EF group (P<0.001), 0.98 in the reduced EF group (P<0.001), 0.90 in the LBBB group, and 0.96 (P<0.001) in the AF group. The best cutoff value of TPV and its sensitivity, specificity, and positive and negative predictive values in each group are 99 ms (0.86, 0.89, 0.63, 0.96, respectively) in the whole group, 96 ms (0.89, 0.88, 0.70, 0.96, respectively) in the preserved EF group, 108 ms (0.85, 0.97, 0.85, 0.97, respectively) in the reduced EF group, 117 ms (0.78, 0.92, 0.58, 0.97, respectively) in the LBBB group, and 93 ms (0.92, 0.89, 0.55, 0.99, respectively) in the AF group.

TPV in LG Severe AS With Preserved EF or Reduced EF Patients

TPV in patients with LG severe AS (n=27), moderate AS (n=174), and without AS (n=50) who have preserved EF and without AF or LBBB are shown in Figure 4A. TPV was

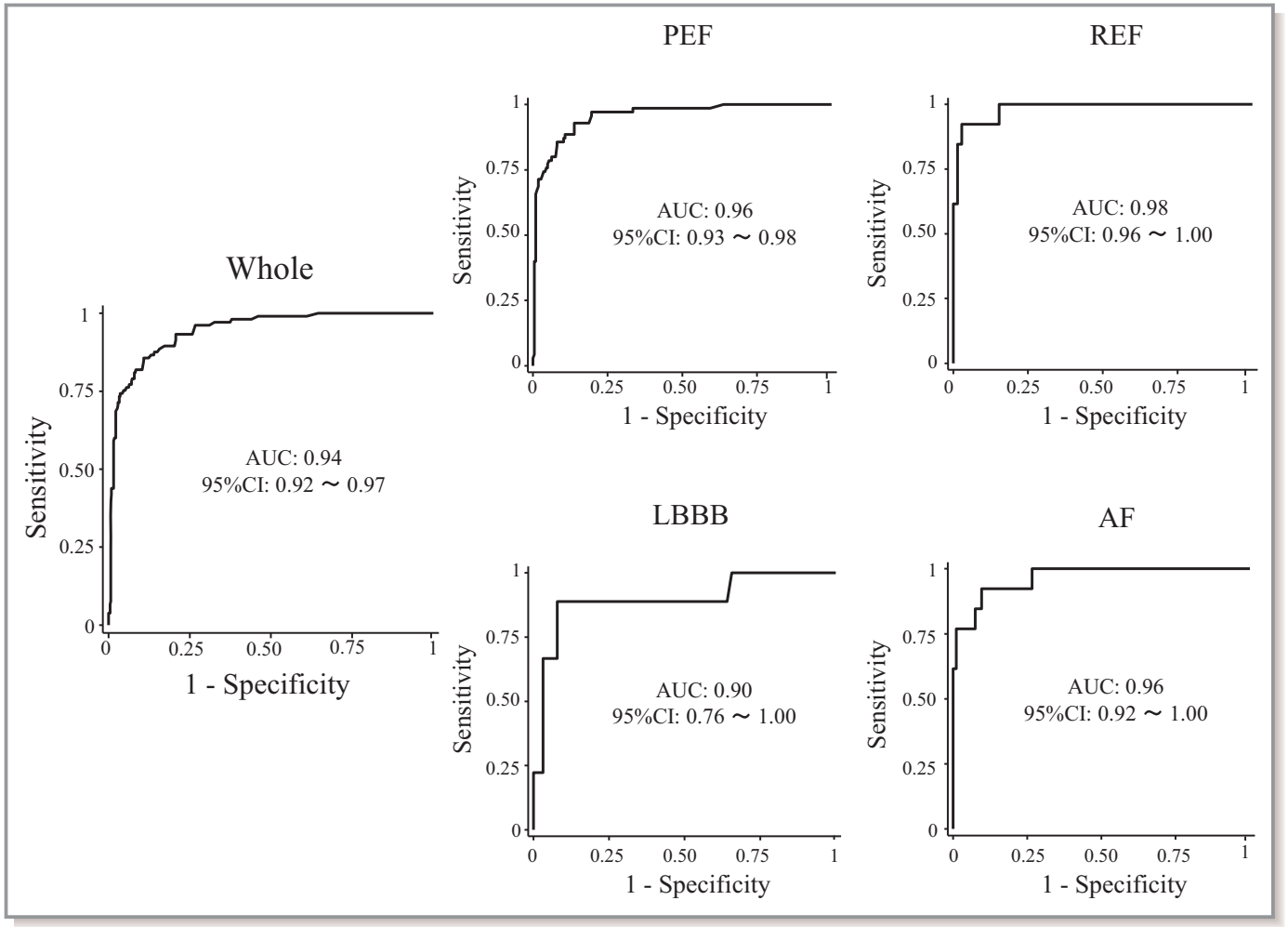

Figure 3. Receiver operating characteristic curve to predict high gradient severe aortic stenosis patients. Areas under the curves were significantly larger than 0.5 and show the good ability of time to peak velocity to predict high gradient severe aortic stenosis in each group of patients. AF indicates atrial fibrillation; AUC, area under the curve; LBBB, left bundle branch block; PEF, preserved ejection fraction; REF, reduced ejection fraction.

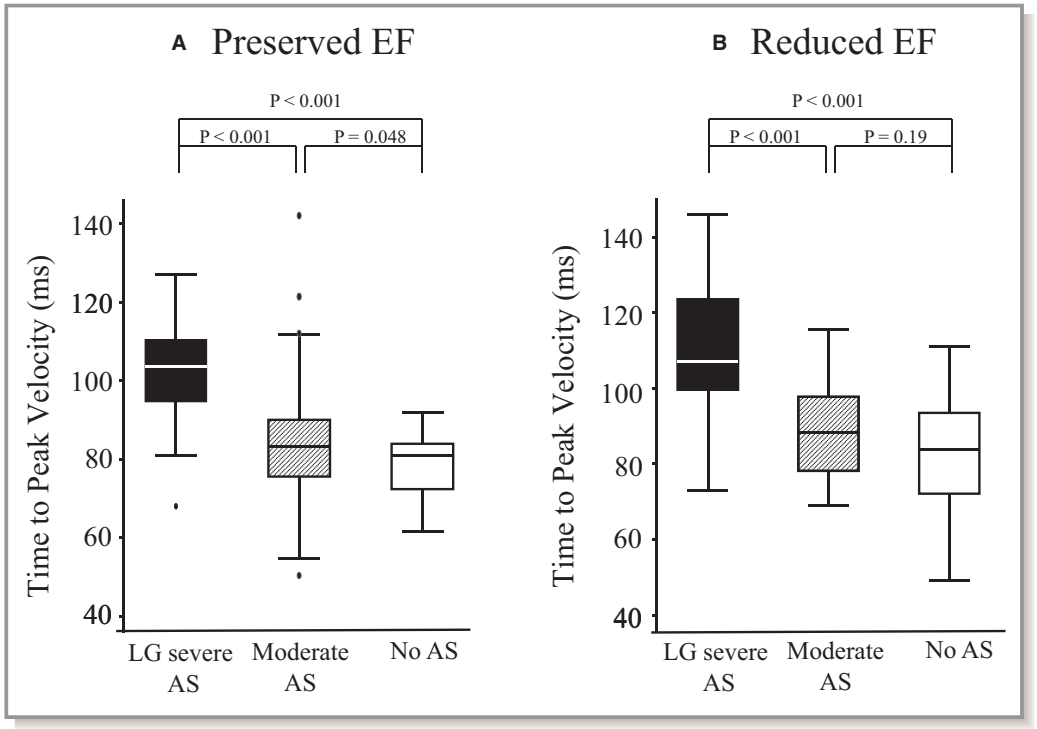

Figure 4. Time to peak velocity in LG severe aortic stenosis with preserved or reduced ejection fraction patients. Time to peak velocity was significantly delayed in LG severe AS patients compared with moderate or without AS patients with preserved EF (A) or reduced EF (B). The black dots on the box plot indicate less than first quartile−1.5×interquartile range, or more than third quartile+1.5×interquartile range. AS indicates aortic stenosis; EF, ejection fraction; LG, low gradient.

significantly longer in patients with LG severe AS (102±13 ms) compared with those with moderate AS (83±13 ms) or without AS (79±8 ms) (P<0.001). TPV in patients with LG severe AS (n=32), moderate AS (n=21), and without AS (n=50) who have reduced EF and without AF or LBBB are shown in Figure 4B. TPV was significantly longer in patients with LG severe AS (110±18 ms) compared with those with moderate AS (88±13 ms) or without AS (83±14 ms) (P<0.001).

The Ability of TPV to Predict Events

During the follow-up period, 154 events 40 all cause deaths including 16 cardiovascular deaths, and 114 AVRs) were recorded. Kaplan–Meier analysis showed patients with delayed TPV had a significant increase in all-cause mortality or need for AVR (Figure 5A: hazard ratio 5.89, 95% CI 3.53–9.81 in first quartile versus fourth quartile, P<0.001), as well as cardiovascular mortality or need for AVR (Figure 5B: hazard ratio 13.8, 95% CI 6.64–28.9 in first quartile versus fourth quartile, P<0.001) than those with a shorter TPV. Even after we excluded both HG and LG severe AS patients, patients with a longer TPV still had higher rates of both all-cause mortality or need for AVR (Figure 5C: hazard ratio 2.36 95% CI 1.09–5.10 in first quartile versus fourth quartile, P<0.05) and cardiovascular mortality or need for AVR (Figure 5D: hazard ratio 7.23, 95% CI 2.46–21.3 in first quartile versus fourth quartile, P<0.01) than those with a shorter TPV. In univariate Cox proportional hazards regression models, the following variables were shown to predict both end points (Table 3): heart rate, LVEF, LVMI, AVAI, mean PG, and DLI. After adjustment for age, male sex, ethnicity, heart rate, LVEF, and LVMI, the TPV remained a significant predictor of both all-cause mortality or need for AVR (Table 4: hazard ratio 7.31, 95% CI 4.26–12.53 in first quartile versus fourth quartile, P<0.001), and cardiovascular mortality or need for AVR (Table 5: hazard ratio 17.2, 95% CI 8.05–36.74 in first quartile versus fourth quartile, P<0.001) in these patients. Furthermore, after we additionally adjusted for conventional AS severity indicators (AVAI, mean PG, and DLI), TPV still consistently remained a significant predictor of both all-cause mortality or need for AVR (Table 4: hazard ratio 2.03, 95% CI 1.03–3.99 in first quartile versus fourth quartile, P=0.039), and cardiovascular mortality or need for AVR (Table 5: hazard ratio 3.38, 95% CI 1.41–8.13 in first quartile versus fourth quartile, P=0.006).

Discussion

The main findings of the present study are that (1) TPV can precisely predict HG severe AS regardless of preserved or reduced EF, LBBB, or AF; (2) AVAI or DLI, HR, LVEF, and LBBB

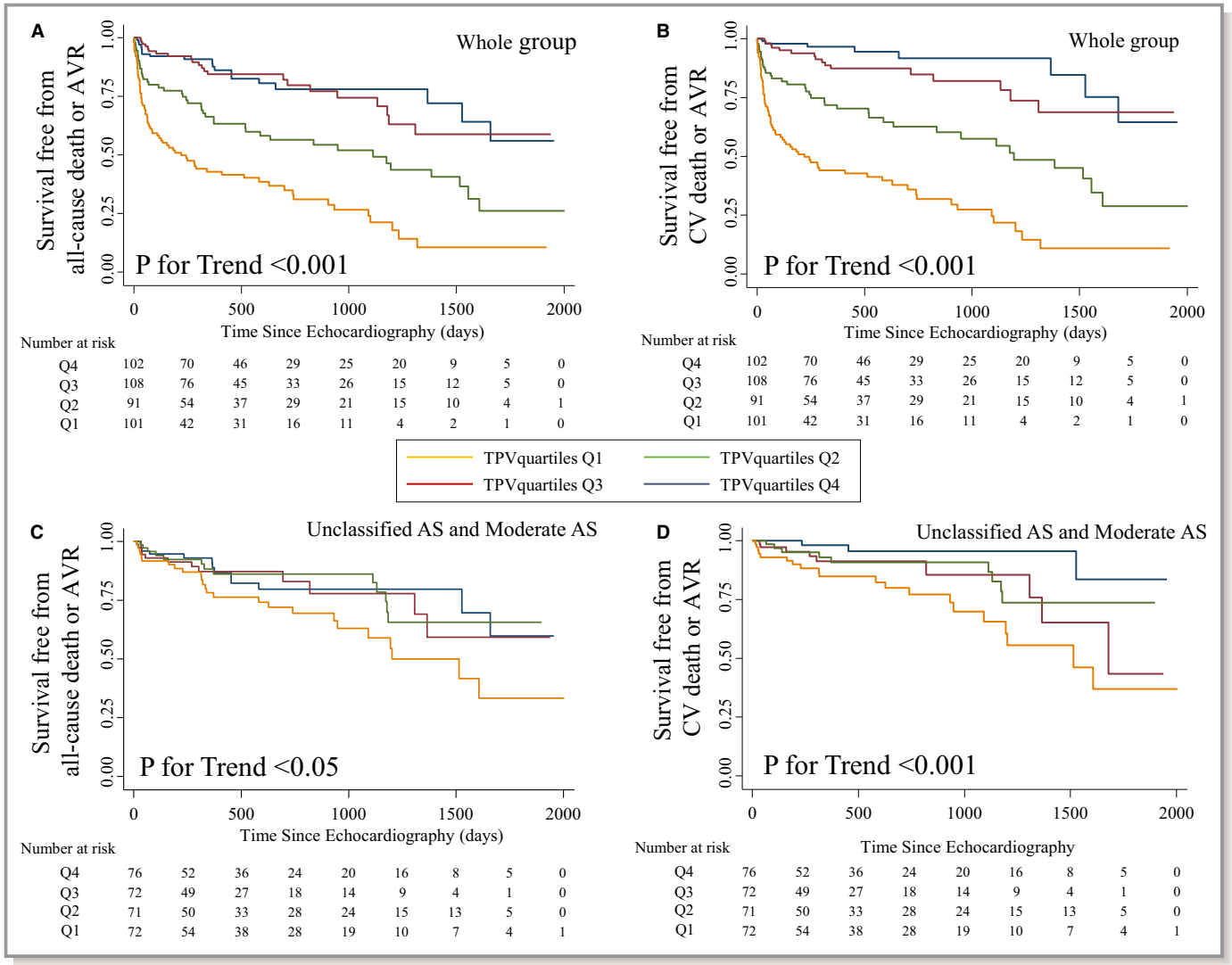

Figure 5. Time to peak velocity and prognosis in aortic stenosis patients. TPV quartile 1 (Q1) corresponds to highest and quartile 4 (Q4) to lowest TPV. In the patients with more than moderate AS without LBBB or AF, those with delayed TPV had poorer survival free from all-cause mortality or need for AVR (A), and also had poorer survival free from cardiovascular mortality or need for aortic valve replacement (B) than those with shorter TPV. Similarly, in the patients with unclassified AS and moderate AS without LBBB or AF, those with delayed TPV had poorer survival free from all-cause mortality or need for AVR (C), and also had poorer survival free from cardiovascular mortality or need for AVR (D) than those with shorter time to peak velocity. AF indicates atrial fibrillation; AS, aortic stenosis; AVR, aortic valve replacement; CV, cardiovascular; LBBB, left bundle branch block; TPV, time to peak velocity.

are independent determinants of TPV; (3) TPV is longer in patients with LG severe AS irrespective of their systolic function; and (4) a longer TPV is associated with a poor prognosis in patients with more than moderate AS, and also in a combined group of unclassified and moderate AS patients.

Diagnosing AS severity is quite important because more and more patients develop AS with aging and patients with severe AS could benefit from surgical AVR or transcatheter aortic valve replacement.[19,20] Indications for transcatheter aortic valve replacement have been extended to those who were not previously candidates for surgical AVR due to other comorbidities and higher surgical risk.[20,21] On the other hand, asymptomatic AS patients also may benefit from AVR.[22] The event rate of surgery or cardiac death in 5 years of asymptomatic severe AS patients is high.[23] Thus, accurate assessment of AS severity in asymptomatic AS patients is very important. Furthermore, there are many aged patients with comorbidities such as chronic obstructive pulmonary disease, obesity, coronary heart disease, or cerebrovascular disease and concomitant AS, and it may be hard to determine whether the symptoms come from AS or these other comorbid conditions. However, there are some difficulties in accurately diagnosing AS severity using current standard methods.[4] Our results suggest that TPV may be able to

Table 3. Univariate Analysis (Cox Proportional Hazard Regression Models)

	All-Cause Mortality or Need for AVR			Cardiovascular Mortality or Need for AVR		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (1 SD)	1.08	0.92 to 1.27	0.34	1.07	0.90 to 1.28	0.45
Male sex	1.33	0.97 to 1.83	0.075	1.46	1.03 to 2.07	0.032
Black*	0.90	0.64 to 1.26	0.53	0.85	0.58 to 1.23	0.39
BMI (1 SD)	0.84	0.71 to 1.00	0.056	0.94	0.78 to 1.13	0.51
SBP (1 SD)	0.99	0.83 to 1.18	0.91	0.96	0.79 to 1.17	0.68
DBP (1 SD)	1.06	0.90 to 1.27	0.48	1.07	0.88 to 1.29	0.50
Heart rate (1 SD)	1.28	1.10 to 1.49	0.001	1.20	1.01 to 1.42	0.037
LVEF (1 SD)	0.77	0.66 to 0.89	0.001	0.73	0.62 to 0.87	<0.001
LVMI (1 SD)	1.27	1.10 to 1.45	0.001	1.29	1.11 to 1.49	0.001
AVAI (1 SD)	0.44	0.37 to 0.53	<0.001	0.35	0.29 to 0.42	<0.001
Mean PG (1 SD)	2.27	2.01 to 2.57	<0.001	2.56	2.25 to 2.92	<0.001
DLI (1 SD)	0.38	0.32 to 0.45	<0.001	0.29	0.24 to 0.36	<0.001

HRs represent a 1 SD change in each continuous variable. AVAI indicates aortic valve area index; AVR, aortic valve replacement; BMI, body mass index; DBP, diastolic blood pressure; DLI, dimensionless index; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PG, pressure gradient; SBP, systolic blood pressure.
*Reference is white.

precisely predict HG severe AS in 700 AS patients with several conditions including both preserved and reduced EF, AF, or LBBB. TPV was also significantly delayed in patients with LG severe AS in comparison with moderate AS regardless of EF. Thus, TPV may be useful in several conditions frequently seen in daily clinical settings.

In this study, we classified those with AVAI <0.6 cm/m^2, but mean PG <40 mm Hg, and DLI >0.25 into "unclassified AS." AVAI, mean PG, and DLI of patients of this category are medium between severe AS and moderate AS. Surprisingly, the number of patients categorized into unclassified AS was 34% of all AS patients in this study, and will be frequently encountered in daily clinical practice. In the combined population of unclassified AS and moderate AS (those it may be difficult to judge its prognosis by conventional methods), TPV was associated with poor prognosis. Therefore, TPV may be helpful in evaluating prognosis in AS patients, which may be difficult using conventional methods. Of note, in the current study, among whole groups, even after adjustment for traditional AS severity indicators including AVAI, mean PG and DLI, TPV was still significantly associated with poor prognosis. This time we did not include all of these indicators in the model at the same time due to collinearity. However, even if we included these 3 variables at the same time, TPV still was significantly associated with both end points. Thus, TPV also may be able to provide additive information on conventional methods.

The intra- and interobserver variabilities of TPV were 6% and 8.7% in this study. Thus, the reproducibility of TPV is good. TPV can be measured easily by continuous wave Doppler and will not be significantly affected by Doppler angle. As peak flow velocity and pressure gradients across the aortic valve are dependent on flow rate (ie, on SV or SVI), these conventional variables are of limited usefulness in patients with LF-LG AS.

Table 4. Multivariable Analysis: All-Cause Mortality or AVR

	Model 1			Model 2			Model 3			Model 4		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
TPV quartile 1	7.31	4.26 to 12.53	<0.001	3.32	1.78 to 6.20	<0.001	2.41	1.29 to 4.50	0.005	2.68	1.43 to 5.03	0.002
TPV quartile 2	2.97	1.72 to 5.12	<0.001	1.88	1.06 to 3.34	0.032	1.86	1.06 to 3.25	0.031	1.73	0.97 to 3.07	0.062
TPV quartile 3	1.30	0.70 to 2.40	0.411	1.07	0.57 to 1.99	0.841	0.93	0.50 to 1.73	0.820	1.02	0.55 to 1.90	0.954
TPV quartile 4	1.0 (reference)			1.0 (reference)			1.0 (reference)			1.0 (reference)		

TPV quartile 1 corresponds to highest and quartile 4 to lowest TPV. Model 1: adjusted for age, sex, and race, heart rate, LV ejection fraction, and LV mass index. Model 2: Model 1+AVAI, Model 3: Model 1+mean PG, Model 4: Model 1+DLI. AVAI indicates aortic valve area index; AVR, aortic valve replacement; DLI, dimensionless index; HR, hazard ratio; LV, left ventricular; PG, pressure gradient; TPV, time to peak velocity.

Table 5. Multivariable Analysis: Cardiovascular Death or AVR

	Model 1			Model 2			Model 3			Model 4		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
TPV quartile 1	17.2	8.05 to 36.74	<0.001	5.81	2.54 to 13.30	<0.001	4.99	2.19 to 11.38	<0.001	4.19	1.81 to 9.71	0.001
TPV quartile 2	6.11	2.83 to 13.18	<0.001	3.28	1.49 to 7.25	0.003	3.58	1.64 to 7.81	0.001	2.84	1.28 to 6.29	0.010
TPV quartile 3	2.22	0.95 to 5.21	0.066	1.70	0.72 to 4.00	0.225	1.53	0.65 to 3.61	0.328	1.57	0.67 to 3.72	0.300
TPV quartile 4	1.0 (reference)			1.0 (reference)			1.0 (reference)			1.0 (reference)		

TPV quartile 1 corresponds to highest and quartile 4 to lowest TPV. Model 1: adjusted for age, sex, race, heart rate, LV ejection fraction, LV mass index. Model 2: Model 1+AVAI, Model 3: Model 1+mean PG, Model 4: Model 1+DLI. AVAI indicates aortic valve area index; AVR, aortic valve replacement; DLI, dimensionless index; HR, hazard ratio; LV, left ventricular; PG, pressure gradient; TPV, time to peak velocity.

TPV was also weakly correlated with SVI, and may be slightly affected by SVI (Table 2, Data S1, Figure S1). Hence, SVI should be considered when assessing AS severity by TPV. In the current study, TPV was also associated with heart rate, LVEF, and LBBB. Therefore, these conditions will need to be considered when applying TPV in clinical settings.

To our knowledge, only one previous study examined the relationship between the TPV and AS severity.[16] Acceleration time of aortic flow, an equivalent measurement to TPV, has been used to evaluate prosthetic valve function;[24] however, we are not aware of other studies evaluating these measures in native aortic valves. This study showed that TPV could predict AVA <1.0 cm^2 or AVA <1.5 cm^2 accurately in patients with preserved EF and without LBBB or AF patients, consistent with our findings. However, this study was relatively small (87 AS patients) and they did not include patients with reduced EF, LBBB, or AF. Furthermore, this study did not assess longitudinal outcome. In the current study, we included 700 AS patients, and without excluding those with reduced EF, AF, or LBBB. Also, we examined the relationship between TPV and events. Thus, our study extended the findings to those with several cardiac conditions that are frequently encountered in clinical practice, and also provided new information about the usefulness of TPV to predict prognosis in AS.

Our study has a few limitations that should be considered. First, this study was conducted as a retrospective study and patients' information was not blinded to investigators. Second, 110 of 512 patients were not able to be followed in our survival analysis; however, those without follow-up had a comparable AS severity compared with those with follow-up. Third, patients with LG severe AS with reduced EF may have included patients with "pseudosevere AS."[25] The prevalence of pseudosevere AS in patients with LF-LG AS with reduced EF is reported to be between 20% and 30%.[26,27] In order to address this issue, dobutamine infusion would be required,[28] which was beyond the scope of our study.

Strengths of our study include large sample sizes and inclusion of AS patients with reduced EF, AF, or LBBB. As shown in the present study, AS is frequently associated with reduced EF, AF, and LBBB including right ventricular pacing (about 25% of AS patients in this study had either AF or LBBB); therefore, our study covered a wide spectrum of AS patients frequently seen in clinical practice.

Conclusions

TPV, which can be readily measured noninvasively, reliably predicted HG severe AS regardless of EF, LBBB, and AF status. A longer TPV was associated with a poorer prognosis in patients with unclassified or moderate AS. TPV may be a useful parameter to diagnose severe AS, as well as to predict poor prognosis, especially in patients in whom conventional methods cannot be applicable.

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Disclosures

None.

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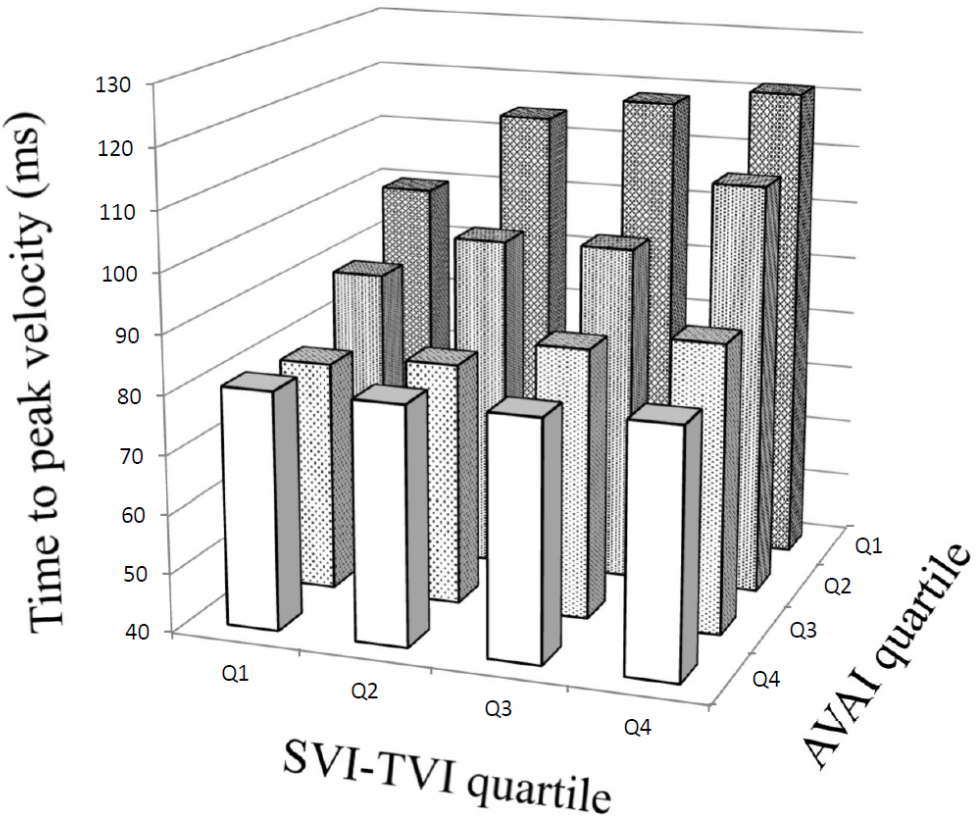
SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

We examined the relationships among TPV, SVI-TVI and AVAI in whole group. In this analysis, patients were divided into SVI-TVI quartiles and AVAI quartiles, then structured 3 dimensional graph (x axis: AVAI quartiles, y axis: SVI-TVI quartiles, z axis: TPV).

Figure S1.



	SVI-TVI	Q1	Q2	Q3	Q4	p value
AVAI						
Q1		100±16	114±20*	118±15*	121±18*	<0.001
Q2		89±10*	97±16*	97±15*	110±21*†#	<0.001
Q3		79±15*	81±13*†	86±14*†	89±17*†	0.08
Q4		80±14*†	80±14*†	81±13*†	82±11*†	N.S.
p value		<0.001	<0.001	<0.001	<0.001	

*: $p < 0.05$ vs AVAI Q1, †: $p < 0.05$ vs AVAI Q2

*: $p < 0.05$ vs SVI-TVI Q1, †: $p < 0.05$ vs SVI-TVI Q2, #: $p < 0.05$ vs SVI-TVI Q3

Supplemental Figure Legend:

Figure S1. The figure shows the relationships among TPV, AVAI, and SVI-TVI. AVAI quartile 1 (Q1) corresponds to smallest and quartile 4 (Q4) to largest AVAI. SVI-TVI quartile 1 (Q1) corresponds to smallest and quartile 4 (Q4) to largest SVI-TVI. TPV was delayed in accordance with AVAI in each SVI-TVI quartile. There were some differences in TPV among SVI-TVI quartiles in smaller AVAI quartiles. AVAI: aortic valve area index, SVI: stroke volume index, TPV: time to peak velocity.