Prognostic Impact of the Ratio of Acceleration Time to Ejection Time in Patients With Low Gradient Severe Aortic Stenosis and Preserved Ejection Fraction

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The clinical management of patients with low gradient severe aortic stenosis (LG-SAS) and preserved left ventricular ejection fraction (LVEF) remains challenging owing to their heterogeneity. The aim to this study was to evaluate the relation between an ejection dynamic parameter linked to AS severity and outcome, the ratio of acceleration time (AT) to ejection time (ET), in a cohort of patients with LG-SAS and preserved LVEF. Three hundred and fifty-six patients with LG-AS (defined by AVA ≤1 cm^2 and/or AVAi ≤0.6 cm^2/m^2 and mean aortic pressure gradient <40 mm Hg) and preserved LVEF ≥50% were studied. The relation between AT/ET and all-cause and cardiac mortality during follow-up was studied. Median follow-up was 41 months (interquartile range, 35 to 47 months). Median AT/ET was 0.32 (interquartile range, 0.29 to 0.36). The 5-year estimates of all-cause and cardiac mortality were respectively 57 ± 7%, 36 ± 7% for patients with AT/ET >0.36 versus 43 ± 4%, 16 ± 3% for patients with AT/ET ≤0.36 (p = 0.024 and p <0.001, respectively). After adjustment on known predictors of outcome including aortic valve replacement used as a time-dependent covariate, there was a significant increase in all-cause mortality risk for patients with AT/ET >0.36 (adjusted hazard ratio 2.04 [95% confidence interval, 1.32 to 3.13]; p = 0.001) and cardiac mortality risk (adjusted hazard ratio 2.89 [95% confidence interval, 1.54 to 5.43]; p<0.001) compared with patients with AT/ET ≤0.36. The association of AT/ET >0.36 and all-cause or cardiac mortality risk was consistent in subgroups of patients with LG-SAS and preserved EF. In conclusion, an AT/ET ratio of more than 0.36 is an independent predictor of mortality in patients with LG-SAS and preserved EF. **(Am J Cardiol 2019;124:1594−1600)**

According to current guidelines, severe aortic stenosis (SAS) is classically defined by a transvalvular mean pressure gradient (MPG) >40 mm Hg or peak aortic jet velocity >4 m/s,[1] and/or an aortic valve area (AVA) ≤1.0 cm^2 or an AVA indexed to body surface area (AVAi) ≤0.6 cm^2/m^2. However, up to 40% of patients with severe AS show discrepancies in their Doppler-echocardiographic AS parameters, the most common of which being the association of a reduced AVA but a low transvalvular gradient (<40 mm Hg).[2] In this subgroup of patients with "low gradient severe aortic stenosis" (LG-SAS), it is still a matter of debate to determine who should be considered for aortic valve replacement (AVR) and who should be treated conservatively.[3] The ratio of acceleration time (AT) to ejection time (ET) is a simple and reproducible parameter which may be used to assess native AS severity,[4] but its prognostic implications have not been specifically evaluated in patients with LG-SAS and preserved left ventricular ejection fraction (LVEF). The present study addressed this issue.

Methods

Between 2012 and 2018, 356 patients ≥18 years of age diagnosed with severe AS (defined as AVA ≤1 cm^2 and/or AVA normalized to body surface area (BSA) ≤0.6 cm^2/m^2], a low transaortic gradient (defined as mean aortic pressure gradient (MPG) <40 mm Hg) and preserved LVEF ≥50% in the echocardiography laboratories of 2 tertiary hospitals in France (Lille and Amiens) were prospectively included in the present ancillary study from a larger registry. We excluded: (1) >mild aortic and/or mitral regurgitation; (2) prosthetic valves, congenital heart disease, supravalvular or subvalvular AS, or dynamic LV outflow tract obstruction; (3) mitral stenosis; and (4) patients who refused to participate in the study. Clinical and demographic baseline characteristics were collected. The Charlson co-morbidity index, summating the patient's individual comorbidities, was calculated.[5] Coronary artery disease was defined by the presence of documented history of acute coronary syndromes, coronary artery disease previously

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confirmed by coronary angiography (reduction of normal diameter ≥50% in the left main coronary artery and ≥70% in the right coronary artery, left anterior descending coronary artery, left anterior descending coronary artery, and circumflex coronary artery), or history of coronary revascularization. The study had been approved by an independent ethic committee and was conducted in accordance with institutional policies, national legal requirements, and the revised Declaration of Helsinki. Authorization for research participation was obtained for all patients.

All patients underwent a comprehensive Doppler-echocardiography study, using commercially available ultrasound systems by experienced echocardiographers. Aortic flow was recorded using continuous-wave Doppler, by imaging and nonimaging transducers, systematically in several acoustic windows (apical 5-chamber, right parasternal, suprasternal, epigastric). The highest aortic velocity was used to calculate aortic time-velocity integral and mean pressure gradient (MPG). As recommended by current guidelines,[6] wall (high-pass) filters are set at a high level and gain is decreased to optimize identification of the velocity curve from the spectrogram envelope. LV stroke volume (LV-SV) was calculated by multiplying the LV outflow tract area with the LV outflow tract time-velocity integral obtained by pulsed Doppler in the apical 5-chamber view. The LV outflow tract diameter was measured in zoomed parasternal long-axis views in early systole at the level of aortic cusp insertion (inner-to-inner edge). Aortic valve area (AVA) was calculated using the continuity equation. AVA and LV-SV were indexed to BSA. Low flow was considered if LV-SV was <35 mL/m^2.[7] Conventional echocardiographic measurements were performed according to current EACVI/ASE guidelines.[8] AT was defined as time from the start to the peak of flow through the valve by continuous-wave Doppler. ET was defined from aortic valve opening to aortic valve closure (Figure 1). Continuous-wave Doppler recordings were performed at a sweep speed of 100 mm/s. The AT/ET ratio was then calculated. Interobserver variability of AT/ET ratio has been previously reported in our institution, with an intraclass correlation coefficient at 0.90 95% confidence interval [CI] 0.78 to 0.96 and a coefficient of variation = 7.3%.[9] When patients were in sinus rhythm, 3 cardiac cycles were averaged for all measures. For patients in atrial fibrillation, 5 cardiac cycles were averaged. Echocardiograms were stored in Digital Imaging and Communications in Medicine format to allow subsequent offline analysis.

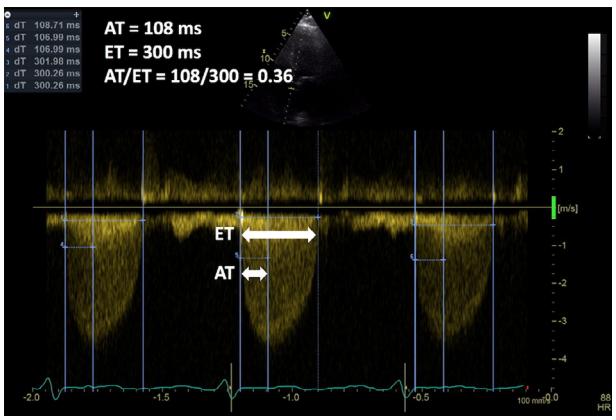

Figure 1. Systolic time interval measurement on a continuous-wave Doppler recording of transaortic flow. AT = Acceleration Time, ET = Ejection Time

After the initial medical management, treatment was conservative or surgical, as deemed appropriate by the patient's personal physician. The majority of patients were followed by clinical consultation and echocardiography in the outpatient clinics of the 2 tertiary centers. The others were followed in public hospitals or private practices by referring cardiologists working together with the tertiary centers. Information on follow-up was retrospectively obtained. Events were ascertained by direct patient interview and clinical examination and/or by repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. Medical reports and death certificates were consulted for attribution of causes of death. Eighty-four percent of patients were followed for at least 2 years or until death. The outcome variable of the study was all-cause mortality. Cardiac mortality was also studied. Clinical decisions regarding medical management and referral for surgery were made by the heart team with the approval of the patient's cardiologist in accordance with current practice guidelines.

The study population was divided in 2 groups according to AT/ET threshold of 0.36 as previously reported.[9] The relationship between baseline continuous variables and the 2 groups was explored using an unpaired two-sided Student's *t* test (for normally distributed variables) or Mann-Whitney U test (for non-normally distributed variables). Pearson chi-square test or Fisher's exact test was used to examine the association between the 2 groups and baseline categorical variables.

Median follow-up time was obtained using the reverse Kaplan-Meier method. Event rates ±SEs of the overall population and of the 2 groups were estimated according to the Kaplan-Meier method and compared using log-rank tests. Univariate and multivariate analyses of time to events were performed using Cox proportional-hazards models. We did not use model building techniques; covariates were entered in the models which were considered of potential prognostic impact on an epidemiologic basis. Models were adjusted for age, gender, Charlson co-morbidity index (not including age), hypertension, coronary artery disease, atrial fibrillation, symptoms (New York Heart Association Class III-IV dyspnea, angina, or syncope), LVEF, low flow, aortic valve area, and AVR. The effect of AVR on outcome was analyzed as a time-dependent covariable using the entire follow-up. The proportional hazards assumption was confirmed using statistics and graphs based on the Schoenfeld residuals. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. To evaluate whether AT/ET >0.36 provides incremental prognostic value over clinical and echocardiographic variables, the differences between models were tested by calculating the overall difference in −2 log likelihood chi-square between models. We conducted subgroup analyses to determine the homogeneity of the association of AT/ET ratio and all-cause mortality. First, we estimated the effect of AT/ET on all-cause mortality in each subgroup using a Cox univariate model and then formally tested for first-order interactions entering interaction terms, separately for each subgroup. All p values are the results of two-tailed

tests. For all analyses, a p value of <0.05 was considered statically significant. Data were analyzed with R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 20.0 (IBM, Amonk, New York).

Results

Three hundred and fifty-six patients were enrolled in the present study. Patient's clinical characteristics, overall and according to AT/ET threshold of 0.36 are detailed in Table 1. Median AT/ET was 0.32 (interquartile range, 0.29 to 0.36). Seventy-five patients (21%) had a value of AT/ET >0.36. Patients with AT/ET >0.36 were similar to patients with an AT/ET ≤0.36 in terms of clinical profile (Table 1). The echocardiographic characteristics of the study population and according to AT/ET ≤ or >0.36 are detailed in Table 2. Briefly, patients with AT/ET >0.36 had lower AVA, AVAi, higher peak aortic jet velocity, and transaortic mean pressure gradient. They had a higher LV mass index but showed no other difference for LV function, volumes, or cardiac output.

During a median follow-up time of 41 months (interquartile range, 35 to 47 months), 135 patients died, 53 of

Table 1
Baseline demographic and clinical characteristics of the study patients with low gradient severe aortic stenosis according to AT/ET threshold ≤ or >0.36

Variable	All (n = 356)	AT/ET Threshold		p Value
		≤0.36 (n = 281)	>0.36 (n = 75)	
Age (y)	81.0 [74.8; 87.0]	81.0 [74.0; 87.0]	83.0 [76.5; 87.0]	0.397
Women	206 (58%)	168 (60%)	38 (51%)	0.197
Body mass index (kg/m^2)	27.3 [24.2; 31.7]	27.5 [24.1; 32.3]	26.9 [24.2; 29.4]	0.318
Body surface area (kg/m^2)	1.85 [1.69; 2.00]	1.85 [1.68; 2.02]	1.84 [1.73; 1.95]	0.737
Systolic blood pressure (mm Hg)	140 [121; 150]	140 [123; 150]	130 [120; 149]	0.098
Diastolic Blood Pressure (mm Hg)	73.0 [61.0; 80.0]	75.5 [62.2; 80.0]	70.0 [60.0; 80.0]	0.332
Heart rate (beats/min)	75.0 [66.0; 87.0]	74.0 [65.0; 86.0]	75.0 [68.0; 87.0]	0.553
Aortic stenosis-related symptoms	103 (31%)	75 (28%)	28 (38%)	0.136
History of hypertension	268 (75%)	213 (76%)	55 (73%)	0.772
Diabetes mellitus	130 (36%)	107 (38%)	23 (31%)	0.294
Dyslipidemia	189 (53%)	152 (54%)	37 (49%)	0.546
Documented coronary artery disease	112 (31.5%)	81 (29%)	31 (41%)	0.053
History of atrial fibrillation	128 (36.0%)	101 (36%)	27 (36%)	1.000
Charlson co-morbidity index	2.00 [1.00; 3.00]	2.00 [1.00; 3.00]	2.00 [1.00; 3.00]	0.926

Data are expressed as median (IQR) or number (percentage).

Dyslipidemia was considered in case of hypercholesterolemia (defined as cholesterol level greater than 200 mg/dL and/or LDL-C level greater than 100 mg/dL), hypertriglyceridemia (triglyceride level greater than 150 mg/dL) or in case of hypolipidemic treatment.

Table 2
Echocardiographic characteristics of the study patients with low gradient AS according to AT/ET threshold of 0.36

Variable	All (n = 356)	AT/ET Threshold		p Value
		≤0.36 (n = 281)	>0.36 (n = 75)	
Aortic valve				
Indexed aortic valve area (cm^2/m^2)	0.50 [0.44; 0.56]	0.51 [0.45; 0.57]	0.47 [0.42; 0.54]	0.010
Aortic valve area (cm^2)	0.93 [0.79; 1.04]	0.94 [0.81; 1.05]	0.88 [0.73; 1.00]	0.023
Peak aortic jet velocity (m/s)	3.34 [3.00; 3.75]	3.29 [2.90; 3.68]	3.70 [3.30; 3.90]	<0.001
Transaortic mean pressure gradient (mm Hg)	27.0 [21.0; 34.0]	26.0 [20.0; 33.0]	34.0 [26.5; 37.0]	<0.001
Acceleration time (AT) (msec)	97.0 [80.0; 109]	90.0 [80.0; 100]	114 [107; 126]	<0.001
Ejection time (ET) (msec)	300 [274; 321]	300 [275; 326]	299 [270; 320]	0.428
AT/ET ratio	0.32 [0.29; 0.36]	0.30 [0.28; 0.34]	0.38 [0.37; 0.40]	By design
Cardiac output and LV function				
Left ventricular ejection fraction (%)	61.0 [55.0; 65.0]	61.0 [55.0; 65.0]	61.0 [55.0; 65.0]	0.628
Left ventricular stroke volume index (mL/m^2)	36.6 [31.0; 43.0]	36.4 [30.9; 42.5]	37.5 [32.1; 47.4]	0.182
Left ventricular stroke volume index <35 mL/m^2	148 (42.2%)	121 (43.5%)	27 (37.0%)	0.382
Left ventricular mass index (g/m^2)	107 [90.0; 129]	104 [87.0; 128]	114 [93.0; 140]	0.027
Relative wall thickness	0.52 [0.43; 0.61]	0.52 [0.43; 0.61]	0.51 [0.43; 0.61]	0.769
Left ventricular end-diastolic diameter (mm)	45.0 [41.0; 50.0]	45.0 [41.0; 50.0]	46.0 [42.0; 50.0]	0.517
Left ventricular end-diastolic volume (mL)	99.5 [81.2; 124]	97.5 [82.0; 122]	110 [80.8; 135]	0.185
Other parameters				
Left atrial volume index (mL/m^2)	44.0 [34.0; 58.0]	44.0 [33.3; 57.1]	45.0 [35.9; 59.0]	0.419
Right ventricular systolic peak pressure (mm Hg)*	30.0 [25.0; 40.0]	30.0 [25.0; 40.0]	30.5 [25.0; 37.0]	0.829

Data are expressed as median (IQR) or number (percentage).

* Data available in 269 (76%) patients.

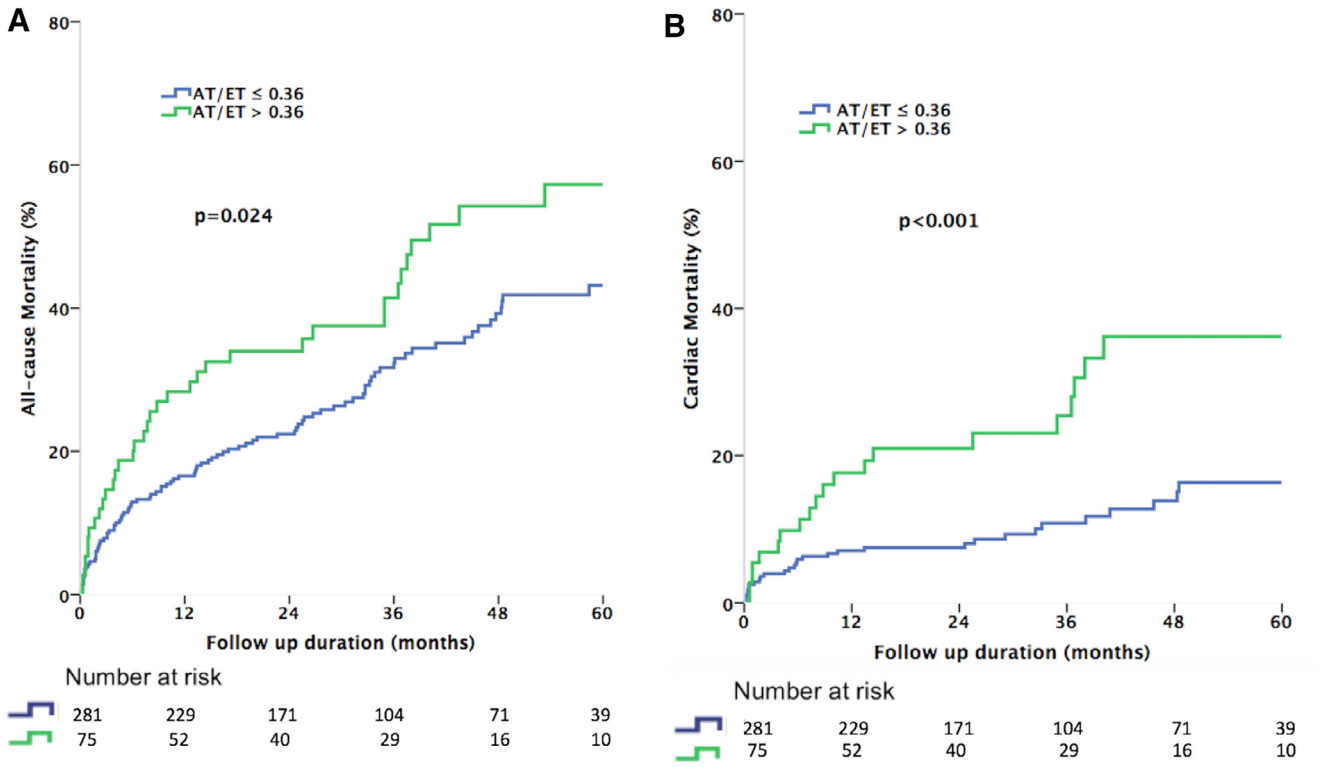

Figure 2. Kaplan-Meier estimates for all-cause (A) and cardiac (B) mortality according to AT/ET > or ≤0.36.

them from cardiac causes. AVR was performed in 116 patients (surgical AVR in 72 patients, and TAVR in 44 patients); among patients who underwent surgical AVR, 22 patients had at least 1 associated coronary artery bypass graft at the time of surgery. Overall, the 1-, 3-, and 5-year estimates of all-cause mortality were 19 ± 2%, 35 ± 3%, and 47 ± 3%. The 5-year estimate of all-cause mortality was 57 ± 7% for patients with AT/ET >0.36 and 43 ± 4% for patients with AT/ET ≤0.36 (p = 0.024, Figure 2). Overall, the 1-, 3-, and 5-year estimates of cardiac mortality were 19 ± 2%, 14 ± 2%, and 21 ± 3%. The 5-year estimate of cardiac mortality was 36 ± 7% for patients with AT/ET >0.36 and 16 ± 3% for patients with AT/ET ≤0.36 (p <0.001, Figure 2). When patients were analyzed under medical treatment (i.e., censored at the time of AVR if performed), AT/ET >0.36 remained significantly associated with an increased risk of all-cause and cardiac mortality (log-rank p = 0.009 and p = 0.002, respectively).

After adjustment for covariates of prognostic importance, AVA, low flow status, and AVR as a time-dependent covariable, the association between AT/ET >0.36 and all-cause mortality remained unchanged (adjusted hazard ratio [HR] 2.04 [95% CI, 1.32 to 3.13]; p = 0.001, Table 3, Figure 3). When replacing AT/ET >0.36 by quartiles of AT/ET (AT/ET <0.29, 0.29 to 0.32, 0.32 to 0.36, and >0.36) in this multivariate model, only patients with an AT/ET >0.36 had a significant increased risk of all-cause mortality (adjusted HR 2.44 [95% CI, 1.44 to 4.02]; p

Table 3
Results of Cox multivariate analysis: Relation between AT/ET ratio >0.36 and all-cause and cardiac mortality

		All-cause mortality		Cardiac mortality	
		Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Multivariate analysis	AT/ET >0.36	2.04 (1.32, 3.13)	0.001	2.89 (1.54, 5.43)	<0.001
	Age	1.04 (1.02, 1.07)	0.001	1.03 (0.99, 1.07)	0.195
	Aortic valve replacement	0.21 (0.12, 0.36)	<0.001	0.44 (0.21, 0.9)	0.025
	Male gender	0.99 (0.63, 1.54)	0.953	1.51 (0.73, 3.12)	0.271
	Hypertension	1.09 (0.69, 1.71)	0.722	1.36 (0.64, 2.88)	0.428
	Documented coronary artery disease	0.71 (0.47, 1.06)	0.09	0.51 (0.26, 1)	0.050
	Charlson co-morbidity index	1.15 (1.06, 1.25)	<0.001	1.07 (0.94, 1.23)	0.305
	Atrial fibrillation	1.47 (1.01, 2.13)	0.045	2.18 (1.17, 4.06)	0.014
	Aortic stenosis-related symptoms	0.99 (0.67, 1.48)	0.990	1.04 (0.57, 1.92)	0.89
	Left ventricular ejection fraction	0.99 (0.96, 1.01)	0.322	0.99 (0.95, 1.03)	0.494
	Stroke volume index <35 mL/m^2	1.43 (0.96, 2.13)	0.077	0.97 (0.49, 1.92)	0.936
	Aortic valve area (per 0.1 cm^2 increment)	0.89 (0.79, 1)	0.053	0.8 (0.66, 0.98)	0.027

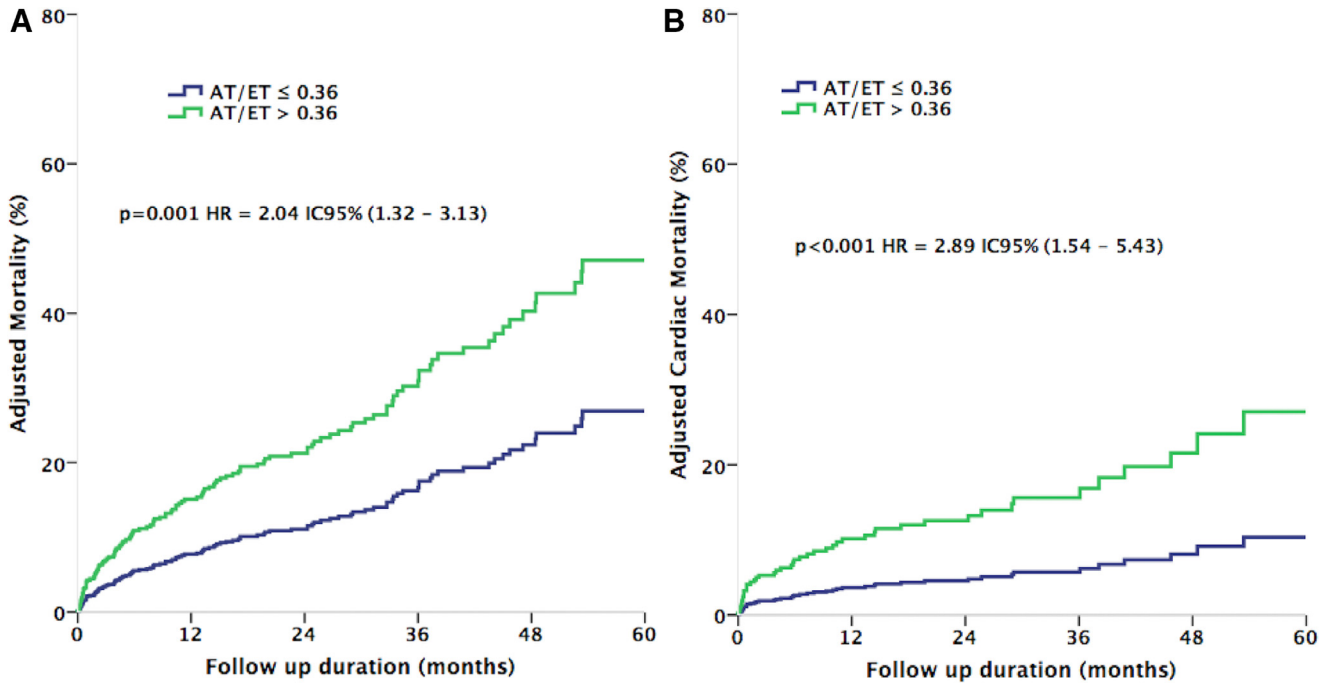

Figure 3. Cumulative hazard of all-cause (A) and cardiac (B) mortality according to AT/ET > or ≤0.36.

<0.001) compared with patients in the first quartile (AT/ET <0.29). Adjusted all-cause mortality was similar in the other quartiles (AT/ET 0.29 to 0.32 and 0.32 to 0.36) compared with patients in the first quartile (p = 0.204 and p = 0.369, respectively). Replacing AVA by MPG or aortic peak velocity in this multivariate model did not alter the strength of the relationship between AT/ET >0.36 and all-cause mortality (adjusted HR 1.92 [95% CI, 1.26 to 2.92]; p = 0.002, and adjusted HR 1.93 [95% CI, 1.27 to 2.94]; p = 0.002, respectively). AT/ET >0.36 provided incremental prognostic value over clinical and echocardiographic variables (Figure 4). Similar results were found for cardiac mortality (adjusted HR 2.89 [95% CI, 1.54 to 5.43], Table 3, Figure 3).

The association of AT/ET >0.36 and all-cause mortality risk was consistent in subgroups of patients with LG-AS (Figure 5). There were no significant interactions between AT/ET >0.36 and any of the subgroups.

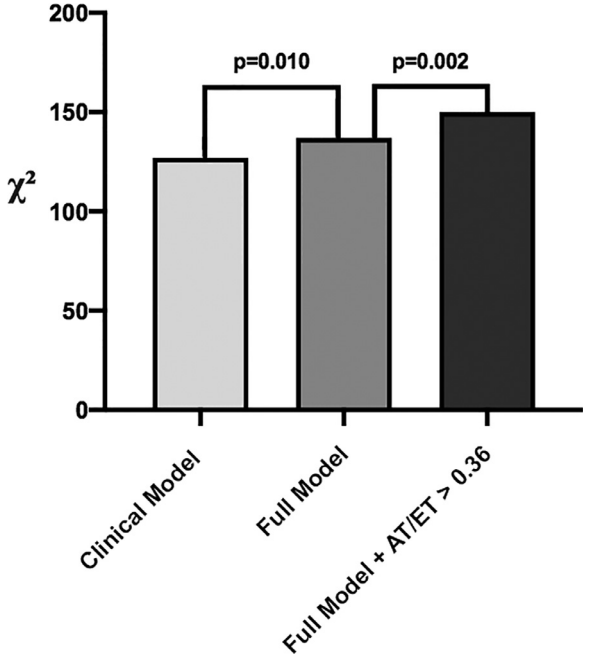

Figure 4. Incremental prognostic value of AT/ET >0.36 over clinical and echocardiographic data.

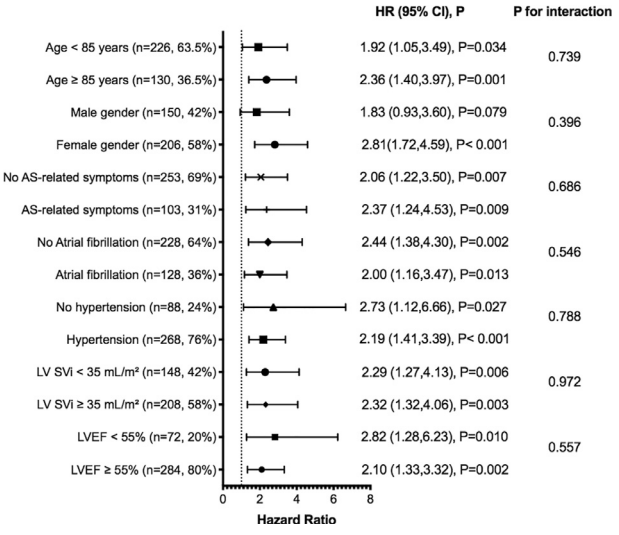

Figure 5. Hazard ratio and 95% confidence interval for risk of all-cause mortality associated with AT/ET >0.36 in subgroups of patients with LG-AS and preserved EF.

Discussion

In the present study based on patients with low gradient SAS and preserved LVEF managed in clinical routine practice, we observed that an increase of AT/ET >0.36 is associated with worse outcome. Accordingly, patients with AT/ET >0.36 experienced a significant increase of the risk of all-cause and cardiac mortality during follow-up after adjustment on known predictors of outcome including AVR used as a time-dependent covariate compared with patients with AT/ET ≤0.36. Hence, these results demonstrate the interest of assessing AT/ET in routine echocardiographic practice to identify patients with a poor outcome who may derive benefit from AVR among the challenging group of patients with LG-SAS and preserved EF.

Management of patients with LG-SAS and preserved EF still represents a challenge mainly due to the heterogeneity of this specific population.[10] Among these patients, the identification of those who would take benefit of surgical or percutaneous AVR is of particular importance.[11–13] Considering the currently available published data, it becomes clear that among patients with LG-AS and preserved EF, careful evaluation is needed to differentiate patients with "true-severe" AS that lead to discuss AVR from patient with pseudo-severe AS, actually moderate AS that should be managed conservatively.[14] Use of multimodality imaging permits to improve risk stratification.[15,16] Measurement of the degree of aortic valve calcification (AVC) using multidetector computed tomography (MDCT) is an accurate, flow-independent method to assess AS severity including LG-AS.[17] Stroke volume assessment by MDCT and Doppler data may be considered to avoid misclassifications in patients with LG-SAS due to the elliptical shape of the LVOT.[18] Recent data have suggested that calculation of projected AVA derived from preload or dobutamine/exercise stress echocardiography may be useful to predict adverse events in patients with LG-AS and preserved EF.[19,20] However, access to multimodality imaging is not widely open and calculation of projected AVA may be cumbersome in daily clinical practice. Beyond conventional indices of AS severity, new echocardiographic parameters, easy-to-measure and reproducible, are needed to guide routine practice.

The AT/ET ratio reflecting ejection dynamics through the valve is a convenient, angle-independent, and reproducible parameter. Landmark AS studies introduced before the emergence of two-dimensional echocardiography have shown that moderate AS has fast up-stroke and slow down-stroke; in contrast, severe calcified AS has slower up-stroke resulting in an aortic flow with rounded contour. Rapid early-systolic opening of normal the aortic valve on Doppler spectrograms is replaced by a slow end-systolic opening of the stenotic aortic valve.[21] However, although guidelines suggest that the aortic waveform shape could be useful to assess severity of native AS, until recently a few attention had been given to ejection dynamics parameters in the setting of these patients. We have recently shown that prolonged AT/ET is a valuable parameter to predict mortality in unselected patients with at least moderate AS, with a prognostic cut-off value of 0.36.[9] Sato et al have recently shown that prolonged time between left ventricular and aortic systolic pressure peaks measured by left cardiac catheterization is associated with SAS according to aortic valve calcification scoring, including a subgroup of patients with LG-SAS.[22] To the best of our knowledge, no study has specifically studied the relation between AT/ET ratio and outcome in patients with LG-SAS and preserved EF. In the present study, we observed that patients with LG-SAS and an AT/ET >0.36 had a 2-fold increase of all-cause mortality and nearly 3-fold increase of cardiac mortality compared with patients with AT/ET ≤0.36. Interestingly, the AT/ET ratio performed well in subgroups of patients with LG-SAS and preserved EF, with no interaction between its prognostic power and gender, low flow status (defined by a stroke volume index <35 mL/m^2), presence of AS-related symptoms, hypertension, or atrial fibrillation.

AT/ET measurement is probably less angle-dependent than Doppler velocities. Hatle et al demonstrated that AT/ET well correlates with peak pressure gradient obtained by catheterism.[23] Interestingly, in Hatle's report, some AS patients had an underestimation of peak pressure gradient compared with cardiac catheterism, but had a prolonged AT/ET ratio, suggesting that AT/ET may be effectively measured if the maximal velocity cannot be obtained by Doppler. However, as AS assessment primarily relies on the highest aortic jet velocity and gradients, we recommend to measure AT/ET on the corresponding acoustic window.

Our study has several limitations. Although echocardiograms were prospectively collected, follow-up data were obtained retrospectively; hence, our study presents inherent limitations of this type of analysis. The specific indications for surgery during follow-up were not collected in our database. However, diagnosis and follow-up were performed by cardiologists with expertise in valvular disease, and the surgical decisions were made by the heart team with the approval of the patients' physicians in accordance with current practice guidelines. Although it has been previously shown that assessing aortic valve calcification by multidetector computed tomography was of interest to stratify risk of patients with AS, this information was not available in our study.

In conclusion, our study shows that AT/ET ratio is independently predictive of all-cause and cardiac mortality in patients with LG-SAS and preserved left ventricular ejection fraction and permits to identify a high-risk subgroup of patients with a very poor outcome.

Disclosures

The authors declare that they have no conflicts of interest concerning this article.

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