Predictors of Long-Term Outcomes in Asymptomatic Patients With Severe Aortic Stenosis and Preserved Left Ventricular Systolic Function Undergoing Exercise Echocardiography

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Background—In asymptomatic patients with severe aortic stenosis and preserved left ventricular ejection fraction, we sought to assess incremental prognostic utility of exercise stress echocardiography.

Methods and Results—We studied 533 such patients (age, 66±13 years; 78% men; 31% with coronary artery disease) who underwent exercise stress echocardiography between 2001 and 2012. Clinical, echocardiographic, and exercise variables (metabolic equivalents [METs], % of age–sex–predicted METs and heart rate recovery at first minute post exercise) were recorded. The end point was all-cause mortality. The Society of Thoracic Surgeons score, left ventricular ejection fraction, mean resting aortic valve (AV) gradient, indexed AV area, METs, and heart rate recovery were 2.9±3%, 58±4%, 35±11 mm Hg, 0.47±0.1 cm^2/m^2, 7.8±3, and 26±12 bpm, respectively. Only 50% achieved >100%, whereas 26% achieved <85% age–sex–predicted METs. There were no major exercise stress echocardiography-related complications. Over 6.9±3 years, 341 (64%) underwent AV replacement (54% isolated), and there were 104 (20%) deaths. On multivariable Cox proportional hazard survival analysis, a higher Society of Thoracic Surgeons score (hazard ratio, 1.21), lower % age–sex–predicted METs (hazard ratio 1.15), and slower heart rate recovery (hazard ratio, 1.22) were associated with higher longer-term mortality, whereas AV replacement (time-dependent covariate, hazard ratio, 0.26) was associated with improved survival. The addition of % age–sex–predicted METs to the Society of Thoracic Surgeons score resulted in significant reclassification of longer-term mortality risk (integrated discrimination index, 0.07 [0.03–0.11; P<0.001).

Conclusions—In asymptomatic patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing exercise stress echocardiography, a lower % of age–sex–predicted METs and slower heart rate recovery were associated with longer-term mortality, whereas AV replacement was associated with improved survival. **(*Circ Cardiovasc Imaging*. 2016;9:e004689. DOI: 10.1161/CIRCIMAGING.116.004689.)**

Key Words: aortic valve stenosis ■ echocardiography ■ exercise ■ metabolic equivalent ■ outcome measures

Aortic stenosis (AS) is the second most common valvular heart disease in the developed world, with an increasing prevalence with an aging population.[1] Aortic valve replacement (AVR) is a class I indication in symptomatic severe AS with significant improvement in survival.[2,3] However, the management of asymptomatic patients with severe AS remains controversial. The risk of sudden death in asymptomatic patients with severe AS is low (<1% per year); however, once symptomatic, 3% of patients may die within 6 months, with an overall mortality of 50% over 2 years.[4–7] The decision to intervene on an asymptomatic patient with significant AS, therefore, requires a careful assessment of the risk–benefit ratio of AVR versus watchful waiting. However, as demonstrated in other valvular diseases, the patients' perception of their symptoms is often misleading, and patients may be more symptomatic than they realize as they may have unknowingly adjusted their exercise to meet the reduced capability.[8,9] When symptom status is a concern, stress testing can provide objective insight into functional capacity and hemodynamic responses.

See Editorial by Gillam and Marcoff
See Clinical Perspective

Previous studies have demonstrated the safety of stress testing in carefully selected asymptomatic patients with severe AS.[10,11] According to current guidelines, AVR is recommended for symptomatic patients with severe high-gradient AS who have symptoms by history or on exercise testing (class Ib). In

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addition, exercise-induced drop in systolic blood pressure is a class IIa indication for surgery in both guidelines.[2,3] However, these recommendations are based on multiple small reports with heterogeneous end points.[4,12–18] In addition, AS frequently coexists in clinical practice with occult coronary artery disease, aortic diseases, hypertensive heart disease, and other valvular or pulmonary conditions. The exact contribution of these conditions to symptoms and outcome is not always obvious, but may affect surgical decision making. Given the paucity of large-scale data, we sought to assess the predictors of long-term outcomes in asymptomatic patients with severe AS and preserved left ventricular ejection fraction (LVEF) undergoing treadmill exercise echocardiography

Methods

Study Design

This was an observational study of 533 consecutive patients with severe AS (indexed valve area 0.6 cm^2/m^2 on resting echocardiogram) who underwent exercise treadmill echocardiography at our center between January 2001 and December 2012. All patients were asymptomatic at the time of initial evaluation. The primary indications for the stress test were to elicit symptoms and to assess functional capacity and blood pressure/ischemic LV response. Patients were excluded if they were symptomatic, were unable to exercise because of other comorbidities, had more than moderate tricuspid/mitral stenosis/regurgitation, had LVEF <50%, or underwent transcatheter AVR (because of expected higher operative risk or nonsurgical candidacy). Data were prospectively entered at the time of initial encounter and manually extracted for the study, after appropriate institutional review board approval. Society of Thoracic Surgeons (STS) score and Charlson comorbidity index (as a surrogate for frailty)[19] were calculated in all patients.

Rest and Stress Echocardiographic Data

All patients underwent a comprehensive echocardiogram with commercially available instruments (Philips Medical Systems, NA, Bothell, WA; General Electric Medical Systems, Milwaukee, WI; and Siemens Medical Solutions, Inc, Malvern, PA) as a part of a standard clinical diagnostic evaluation. Indexed measurements (including LV mass) and diastolic function were obtained according to guidelines.[20–22] We used a semiquantitative 5-point scale (none-severe) to stratify valvular regurgitation, along with right ventricular systolic pressure.[23] Quantitative parameters related to AS (including stroke volume index) were measured, as described.[24] LV outflow tract diameter was measured on parasternal long-axis views. Pulsed-wave and continuous-wave Doppler were used to record peak velocities across the LV outflow tract and AV, respectively, in different views. AV area was calculated using the continuity equation and subsequently indexed.

Subsequently, patients underwent treadmill echocardiography using Bruce, modified Bruce, Cornell, or Naughton protocols, as considered appropriate. Patients were instructed to hold their medications on the day of the test. The stress test was terminated because of symptoms and not at achievement of a prespecified target heart rate. Standard measurements were made at rest, at 1-minute intervals, and for ≥6 minutes in recovery. Maximal predicted heart rate (220−age), %-predicted maximal heart rate, heart rate recovery (HRR; drop in heart rate from peak to 1-minute post exercise[25]), and number of metabolic equivalents (METs) achieved were recorded. To calculate the expected METs based on age and sex, we used Veterans Affairs cohort formula in men (predicted METs=18−[0.15×age])[26] and St. James Take Heart Project formula (predicted METs=14.7−[0.13×age]) in women,[27] as they have been previously demonstrated to best predict outcomes in respective sexes.[28] We subsequently calculated the following ratio: (METs achieved/age–sex expected METs)×100. Chronotropic Response Index was calculated using the following formula: (peak HR–resting HR)/(220−age−resting HR).[29] In addition, Duke treadmill score was calculated[30]

Immediately after exercise, peak-stress echocardiographic images were acquired, according to guidelines,[31] and the following parameters were assessed: regional wall motion abnormalities for evaluation of ischemia and peak right ventricular systolic pressure. Poststress AV gradients were recorded, where available. We acquired all data from the standard windows (parasternal and apical). However, when the resting suprasternal gradients were much higher than apical gradients, suprasternal gradients were also recorded, after all standard views were obtained. Major (death, sustained ventricular or atrial arrhythmias associated with severe symptoms, hemodynamic compromise, or need for cardioversion) and minor complications (decrease in blood pressure, transient symptoms, or nonsustained arrhythmias) were recorded.

Surgical Details

Cardiac surgical procedures were categorized as follows: (1) isolated AVR, (2) AVR and coronary artery bypass grafting, and (3) AVR and ascending aorta repair or replacement±coronary artery bypass grafting. Time to surgery was recorded. The primary indications for surgery included (1) abnormalities on stress testing (abnormal blood pressure/ischemic LV response to stress and symptomatic functional capacity impairment) or development of symptoms during follow-up. The primary reasons to not operate were as follows: no stress abnormalities (normal BP response and no ischemia) and lack of symptoms at stress testing. In addition, these nonoperated patients were evaluated periodically at our institution to confirm lack of symptom development. There were no patients who had noncardiac comorbidities precluding referral to AVR. Decision to undergo AVR was made by the evaluating cardiologist and cardiothoracic surgeon.

Follow-Up

All-cause mortality was the primary outcome. Death was confirmed by querying nationally available databases, inspection of the death certificate, or verified with a family member. In addition, we further identified patients with a noncardiac (eg, malignancy, cirrhosis, and primary pulmonary/neurological cause) cause of death. The duration of follow-up ranged from the initial stress echocardiogram to October 2014.

Statistical Analysis

Continuous variables are expressed as mean±SD and median with interquartile range and compared using Analysis of Variance (ANOVA) (for normally distributed variables) or Mann–Whitney *U* test (for non-normally distributed variables). Categorical data are expressed as percentage and compared using χ^2. To assess outcomes, Cox proportional hazards analysis was performed. For multivariable analysis, we created a parsimonious model in which prespecified variables, known to be associated with adverse outcomes in AS patients, were considered. Even though STS score was developed to predict perioperative mortality, we chose to include STS score in longer-term survival analyses as it represents a composite of various predictors that are known to be associated with outcomes in AS patients.[24] AVR was included as a time-dependent covariate in Cox survival analysis. For each patient undergoing AVR, the analysis time was modeled so that only the person-time after AVR was included in surgical group. Hazard ratios with 95% confidence intervals were calculated. Cumulative proportion of events as a function over time was obtained by Kaplan–Meier method and compared using log-rank test or Generalized Wilcoxon test, as appropriate. We also assessed the reclassification of longer-term mortality risk using category-free integrated discrimination index. Discriminative ability of various survival models was compared using the C statistic.[32] Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, IL), Stata version 10.0 (StataCorp, College Station, TX), and R 3.0.3 (R foundation for Statistical Computing, Vienna, Austria). A $P<0.05$ was considered significant.

Results

In the study sample, despite being considered apparently asymptomatic, only 265 (50%) patients achieved >100% of age–sex–predicted METs, whereas 129 (24%) achieved between 85% and 100% and 139 (26%) achieved <85% age–sex–predicted METs. There were no deaths, syncope, significant atrial/ventricular arrhythmias, or acute coronary syndromes precipitated by the stress test. Six patients (1%) had nonsustained ventricular tachycardia during stress that spontaneously resolved. Baseline clinical and rest–stress echocardiographic characteristics of the study sample, as a whole and divided into those who achieved ≥85% versus <85% age-predicted METs, are shown in Tables 1 and 2. Mean AV gradient at peak-stress was 44±12 mm Hg (data available in only 281 patients). Of these, only 48 (17%) patients had an abnormal increase (≥20 mm Hg) in mean AV gradient at peak-stress.[14,15]

During follow-up, 341 (64%) patients underwent surgery, with distribution as follows: 185 (54%) isolated AVR, 121 (35%) AVR+coronary artery bypass grafting, and 35 (10%) AVR+aortic replacement±coronary artery bypass grafting. The primary indications for surgery included (1) abnormalities noted on stress testing (abnormal blood pressure/ischemic LV response to stress and symptomatic functional capacity impairment, n=151; 44%) or development of overt symptoms during follow-up (n=190; 56%). The median duration between stress test and AV surgery was 147 (25–571) days, and patients with an abnormal stress test (n=151) underwent surgery within 60 days of the stress test. There were no deaths between stress test and AVR.

Of the 192 patients who did not undergo surgery, none had symptoms or abnormal findings (abnormal blood pressure/ischemia) during stress test and were perceived to be asymptomatic during follow-up, with the vast majority (n=133 or 69%) achieving ≥85% age–sex–predicted METs (mean METs 8.7±2.5). There were 59 (31%) remaining patients who achieved <85% age–sex–predicted METs (mean METs 6.5±2) but did not undergo surgery at the discretion of the evaluating cardiologist, primarily because of perceived lack of symptoms during follow-up. There were no patients who had noncardiac comorbidities precluding referral to AVR. No patient had follow-up stress echocardiograms.

Table 1. Clinical and Demographic Characteristics of the Study Sample

Variable	Total Population (n=533)	Age–Sex–Predicted METs ≥85% (n=394)	Age–Sex–Predicted METs <85% (n=139)	*P* Value
Age, y	66±13	66±13	65±13	0.11
Male sex, n (%)	415 (78)	309 (78)	106 (76)	0.34
Body mass index, kg/m^2	28±5	28±5	28±5	0.44
Hypertension, n (%)	369 (69)	275 (70)	94 (68)	0.63
Hyperlipidemia, n (%)	365 (69)	269 (68)	96 (69)	0.48
Diabetes mellitus, n (%)	84 (16)	60 (15)	24 (17)	0.57
Previous stroke, n (%)	28 (5)	20 (5)	8 (6)	0.45
Smoking history, n (%)	370 (49)	205 (52)	76 (54)	0.34
Obstructive coronary artery disease, n (%)	165 (31)	123 (32)	42 (30)	0.46
Atrial fibrillation, n (%)	59 (11)	41 (11)	18 (13)	0.26
Previous cardiac surgery, n (%)	90 (17)	62 (16)	28 (20)	0.15
Pacemaker, n (%)	35 (7)	28 (7)	7 (7)	0.89
STS score	2.94±3	3.00±4	2.9±3	0.44
Charlson comorbidity Index	2.62±1.5	2.61±1.5	2.66±1.6	0.76
B-blockers, n (%)	209 (41)	147 (38)	62 (47)	0.20
ACE-inhibitors, n (%)	183 (36)	136 (36)	47 (37)	0.73
Aspirin, n (%)	302 (59)	225 (57)	77 (55)	0.34
Statins, n (%)	286 (56)	216 (56)	70 (53)	0.20
Glomerular filtration rate, mL/min per 1.73 m^2	88±34	87±32	90±41	0.34

P values reflect comparison between subgroups. ACE indicates angiotensin-converting enzyme; METs, metabolic equivalents; and STS, Society of Thoracic Surgeons.

Outcomes

During a mean follow up of 6.9±3.3 years, 104 (20%) patients died. Of these, 15 had a documented noncardiac death. Only 3 patients died within 30 days after AVR; and at 1 year, there were an additional 9 deaths. Data on univariable Cox Proportional Hazard analysis for longer-term all-cause mortality are shown in the Table I in the Data Supplement. In the subgroup of 281 patients who had peak-stress mean AV gradient reported, the presence of an abnormal (≥20 mm Hg) increase was not associated with longer-term mortality (hazard ratio [HR] 1.12 [0.87–1.76]; *P*=0.4]).

The data on multivariable Cox Proportional Hazard analysis for longer-term all-cause mortality are shown in Table 3. They demonstrate that higher STS score (for every 1% increase: HR, 1.21), lower % age–sex–predicted METs (for every 10% decrease: HR, 1.15), and slower HRR (for every 10 bpm slower recovery: HR, 1.22) were associated with higher longer-term mortality, whereas AV surgery (time-dependent covariate: HR, 0.26) was associated with improved survival. Neither quadratic nor cubic transformations of age–sex–predicted METs, HRR, or STS score were significant predictors of mortality when forced into Cox model that already included these variables in a nontransformed form. The C statistic of the clinical model (STS score, resting mean AV gradient, LVEF, and right ventricular systolic pressure) to predict long-term mortality was 0.61 (0.54–0.71). Addition of % age–sex–predicted METs and AV surgery sequentially increased the C statistic to 0.68 (0.60–0.81) and 0.76 (0.65–0.82; both *P*=0.001). Similarly, addition of % age–sex–predicted METs to the STS score resulted in significant reclassification of longer-term mortality risk (integrated discrimination index, 0.07 [0.03–0.11]; *P*<0.001).

The proportion of long-term deaths in the subgroup achieving <85% of age–sex–predicted METs was significantly higher than those achieving ≥85% (45 [32%] versus 59 [15%]; *P*<0.001). The Kaplan–Meier curves are shown in Figure 1.

Table 2. Rest and Postexercise Echocardiographic Data in the Study Sample

Variable	Total Population (n=533)	Age–Sex–Predicted METs ≥85% (n=394)	Age–Sex–Predicted METs <85% (n=139)	*P* Value
Resting echocardiography				
LV ejection fraction, %	58±4	58±4	57±5	0.12
Indexed LVESD, cm/m^2	1.4±0.3	1.4±0.3	1.4±0.3	0.72
Indexed LV mass, g/m^2	117±36	117±35	118±39	0.33
Indexed left atrial dimension, cm/m^2	2.0±0.4	2.0±0.4	2.0±0.4	0.99
Diastolic dysfunction				
Abnormal relaxation	485 (91%)	362 (92%)	123 (88%)	0.54
Pseudonormal	46 (9%)	31 (5%)	15 (11%)	
Restrictive filling	2(0.4%)	1(0.3%)	1(1%)	
Bicuspid aortic valve	123 (23%)	93 (24%)	30 (22%)	0.79
Peak velocity, m/s	3.8±2	3.8±2	3.9±2	0.49
Mean AV gradient, mm Hg	35±11	35±11	36±12	0.51
AV area, cm^2, continuity	0.79±0.2	0.79±0.2	0.77±0.2	0.14
Indexed AV area, cm^2/m^2, continuity	0.47±0.1	0.47±0.1	0.46±0.1	0.13
Stroke volume index, mL/m^2	40±9	40±9	39±9	0.14
Stroke volume index <35 mL/m^2	211 (40%)	152 (39%)	64 (42%)	0.12
Aortic regurgitation, n (%)				
None	123 (23)	86 (22)	37 (27)	0.12
Mild	257 (48)	187 (49)	70(50)	
Moderate	101 (19)	80 (20)	21 (15)	
Moderate-severe	40 (8)	30 (8)	10 (7)	
Severe	12 (2)	11 (3)	1 (0.7)	
Resting RVSP, mm Hg	33±10	33±9	32±10	0.34
Resting RVSP ≥50 mm Hg	19 (4%)	12 (3%)	7 (5%)	0.20
Exercise echocardiography				
Resting systolic blood pressure, mm Hg	137±18	137±18	137±20	0.79
Resting heart rate, bpm	68±13	68±13	68±12	0.74
Peak rate-pressure product	23065±5677	23767±5389	21060±6009	<0.001
Peak rate-pressure product >20 000	382 (72%)	305 (77%)	77 (55%)	<0.001
Peak systolic blood pressure, mm Hg	168±25	170±23	161±28	<0.001
Peak heart rate, bpm	137±23	139±23	131±24	<0.001
% maximum predicted heart rate	88±13	90±12	83±13	<0.001
Chronotropic reserve index	0.79±0.2	0.83±0.2	0.68±0.2	<0.001
Maximum METs	7.8±3	8.6±2	5.5±2	0.007
Total exercise time, s	451±161	501±144	307±112	<0.001
Heart rate recovery, bpm	26±12	27±12	22±11	0.01
Symptoms at peak-stress, n (%)				
General fatigue	433 (81)	332 (84)	101 (73)	
Dyspnea	42 (8)	27 (7)	15 (11)	0.03
Angina	16 (3)	11 (3)	5 (4)	

(*Continued*)

Table 2. Continued

Variable	Total Population (n=533)	Age–Sex–Predicted METs ≥85% (n=394)	Age–Sex–Predicted METs <85% (n=139)	*P* Value
Abnormal BP response	31 (6)	19 (5)	12 (9)	
Dizziness	3 (0.6)	2 (0.5)	1 (0.7)	
Arrhythmias	8 (1)	5 (4)	3 (2)	
Duke treadmill score, n (%)				
>5	272 (51)	208 (53)	64 (46)	0.03
Between −10 and 5	174 (33)	132 (34)	42 (30)	
<−10	14 (2)	6 (1)	8 (6)	
Uninterpretable	73 (14)	48 (12)	25 (18)	
No. of ischemic LV territories, n (%)				
None	473 (89)	351 (89)	122 (88)	0.34
1	48 (9)	35 (9)	13 (9)	
2	8 (2)	5 (1)	3 (2)	
3	4 (0.8)	3 (0.8)	1 (0.7)	
Poststress RVSP	48±21	48±22	49±21	0.34
Poststress RVSP ≥60 mm Hg, n (%)	32 (6)	21(5)	11 (8)	0.24

P values reflect comparison between subgroups. AV indicates aortic valve; BP, blood pressure; LV, left ventricle; LVESD, left ventricular end-systolic dimension; METs, metabolic equivalents; and RVSP, right ventricular systolic pressure.

A significantly lower proportion of patients who underwent AVR versus those who did not die (44 [13%] versus 60 [31%]; *P*<0.001). The Kaplan–Meier curves, for AVR versus no AVR, are shown in Figure 2.

Table 3. Multivariable Cox Proportional Hazard Survival Analysis for Longer-Term All-Cause Mortality in the Study Sample

Variable	Hazard Ratio	*P* Value
Society of Thoracic Surgeons Score (for every 1% increase)	1.21 (1.11–1.32)	<0.001
% age–sex–predicted METs achieved (for every 10% decrease)	1.15 (1.06–1.25)	0.001
Heart rate recovery (for every 10 bpm slower recovery)	1.22 (1.04–1.43)	0.004
Aortic valve surgery (time-dependent covariate analysis)	0.26 (0.16–0.41)	<0.001

MET indicates metabolic equivalent.

The following potential predictors were considered for the analysis: Society of Thoracic Surgeons Score, peak rate-pressure product, indexed LV mass, resting mean aortic valve gradient, moderate or more than moderate resting aortic regurgitation, % age–sex–predicted METs, heart rate recovery, ischemic left ventricular response to stress, resting right ventricular systolic pressure, aortic valve surgery. Because not all patients had peak-stress mean aortic valve gradients measured, the variable of increase in aortic valve gradient between stress and rest was not included in final the multivariable model. Because the Society of Thoracic Surgeon score was entered in multivariable analysis, its individual predictors were not entered into the model. Because of collinearity, only % age–sex–predicted METs achieved (and not absolute METs or chronotropic response index), aortic valve gradient (and not stroke volume index), resting right ventricular systolic pressure (and not postexercise right ventricular systolic pressure) and the Society of Thoracic Surgeon score (and not Charlson comorbidity index) were entered into the model. Results were similar if these variables were substituted in the model.

We subsequently created 4 subgroups, divided on basis of achieving ≥85% age–sex–predicted METs and subsequent AVR versus no AVR. The proportion of deaths in these 4 subgroups was significantly different (*P*<0.001), as follows: (1) achieved METs ≥85%, AVR (25/261 [10%]), (2) achieved METs <85%, AVR (19/80 [24%]), (3) achieved METs ≥85% of predicted, no AVR (34/133 [26%]) and achieved METs <85%, no AVR (26/59 [44%]), and (4). The Kaplan–Meier curves are shown in Figure 3. The longer-term survival in patients with impaired exercise capacity who underwent AVR reached a level similar to those with preserved exercise capacity who did not undergo AVR. On the contrary, in this study sample of asymptomatic severe AS patients, AVR was associated with improved survival, even in the absence of preserved exercise capacity. Of note, only 1 patient in subgroup 4 was subsequently found to have a noncardiac cause of death.

Multivariable Cox proportional hazard survival analysis in a subgroup of the study sample (severe AS without documented obstructive coronary artery disease, n=368, number of deaths=65) revealed similar results (all *P*<0.01) as follows: STS score (for every 1% increase: HR, 1.15 [1.04–1.28]), % age–sex–predicted METs (for every 10% decrease: HR, 1.12 [1.05–1.22]), HRR (for every 10 bpm slower recovery: HR, 1.23 [1.07–1.49]), and aortic valve surgery (time-dependent covariate: HR, 0.20 [0.12–0.35]).

The results of multivariable Cox Proportional Hazard Survival analysis, for the secondary outcome of deaths (total n=85, censoring, but not including documented noncardiac deaths) were similar (all *P*<0.01) as follows: STS score (for every 1% increase: HR, 1.23 [1.13–1.34]), % age–sex–predicted METs (for every 10% decrease, HR, 1.16 [1.07–1.26]), HRR (for every 10 bpm slower recovery: HR, 1.20

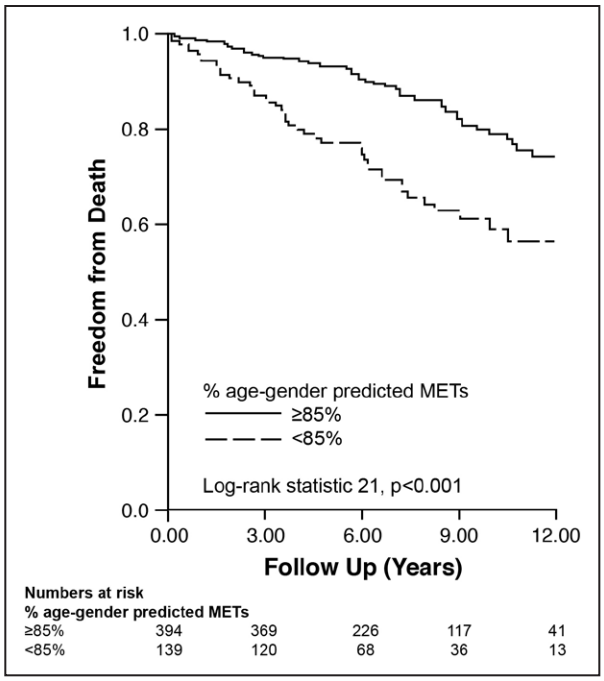

Figure 1. Kaplan–Meier curves of the study sample, based on % age–sex–predicted metabolic equivalents (METs) achieved.

[1.03–1.41]), and aortic valve surgery (time-dependent covariate: HR, 0.26 [0.17–0.41]).

Discussion

In the current study, we evaluated patients with severe AS and preserved LVEF undergoing stress echocardiography as a part of symptom evaluation and risk stratification. AVR was associated with improved longer-term survival, whereas a higher STS score, lower % age–sex–predicted METs achieved, and slower HRR were associated with increased longer-term mortality. Also, addition of % of age–sex–predicted METs significantly improved reclassification of longer-term mortality risk. By further dividing the patients into different subgroups based on exercise capacity, we also demonstrate that patients who did not reach 85% of age–sex–predicted METs were more than twice as likely to die versus those who did, despite similar baseline characteristics. An important observation of the current study was that, despite the fact that patients were considered asymptomatic, only half achieved 100% of age–sex–predicted METs. We also demonstrate that the outcomes of patients who achieved <85%–predicted METs followed by AVR were similar to those achieving >85% METs, but not undergoing AVR during follow-up. On the contrary, the small proportion of patients who did not achieve 85%–predicted METs and who did not undergo AVR had the highest mortality. Therefore, assessment of functional capacity on exercise testing can be an objective way of identifying at-risk patients who could potentially benefit from intervention, before onset of overt symptoms. This is true, especially in the setting where other factors that could impact exercise capacity and general medical condition (eg, obesity, pulmonary, and musculoskeletal comorbidities) are not an influence. This study examined a population with mixed cardiovascular disease where AS was the predominant presenting clinical problem, rather than selecting a population of those with isolated AS without other cardiac comorbidities. This is more representative of the real-life clinical scenario of AS that rarely exists as a solitary cardiac issue, especially in older patients. However, the findings were similar when patients with documented coronary artery disease were excluded.

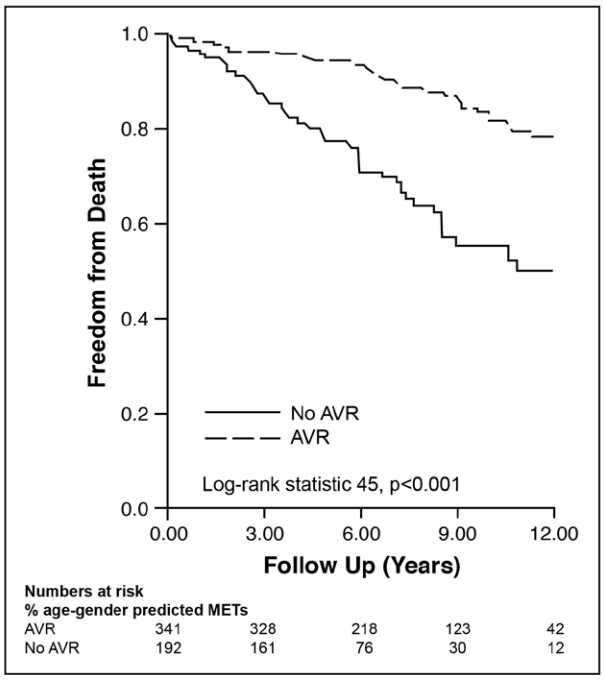

Figure 2. Kaplan–Meier curves of the study sample, based on aortic valve replacement (AVR) vs no AVR during follow-up. METs indicate metabolic equivalents.

A recent meta-analysis compiled data on 491 patients with asymptomatic severe AS from 7 previously published studies (sample sizes ranged from 30 to 125 patients).[12–18,33] In this report, there were no complications during or after stress testing. The authors reported that at 1 year post stress, there were no sudden deaths in patients with normal stress test and 5% in those with an abnormal test. Overall, 21% with normal stress tests had adverse events versus 66% with an abnormal stress test (odds ratio, 0.12 [0.07–0.21]; $P<0.001$). However, among these 7 studies, there was significant heterogeneity in the stress protocol used, with 3 studies reporting graded bicycle ergometry, 3 reporting different treadmill testing, and 1 reporting dobutamine stress echocardiography. Also, there was significant heterogeneity in definition of cardiac end points and follow-up ranged from 11 to 36 months. Thus, the current study represents the largest experience of asymptomatic patients with documented severe AS and preserved LVEF who underwent the same type of stress testing (treadmill exercise). Furthermore, the hard outcome of death was the only end point, and the duration of follow-up was significantly longer than any of the previous reports.

Some of the previous smaller reports have suggested that an exercise-induced increase in mean AV gradient >20 mm Hg was associated with worse composite outcomes of need for AVR or death.[14,15] In these reports, need for AVR was used as a part of a composite end point, rather than only the hard end

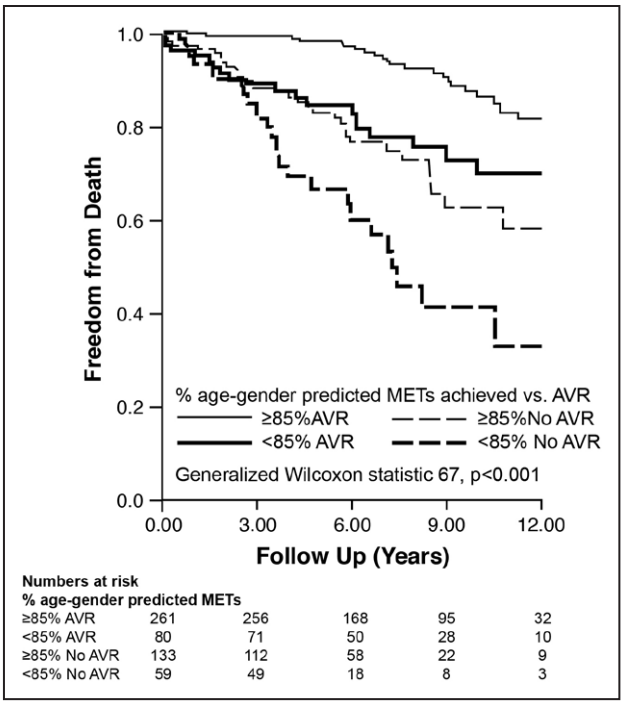

Figure 3. Kaplan–Meier curves of the study sample divided into 4 subgroups, based on aortic valve replacement (AVR) vs no AVR and %-age–sex–predicted metabolic equivalents (METs) <85% or ≥85%.

point of mortality. Furthermore, unlike the current study, measures such as age–sex–predicted METs and HRR were not included in survival analysis. Based on the current results, it is very likely that the prognostic information these exercise variables (METs and HRR) provide outweighs the effect of valve severity on hard outcome of death. Indeed, in previous reports of asymptomatic patients with other valvular diseases undergoing stress echocardiography, lower achieved METs and reduced HRR had a much stronger association with death than variables measured on stress echocardiography.[8,9,25] Our study also suggests that exercise capacity is a much stronger predictor of survival than exercise-induced hypotension/ischemia.

To the best of our knowledge, ours is one of the largest studies to investigate the significance of clinical, echocardiographic, and exercise variables in predicting mortality in asymptomatic patients with severe AS. We also report the incremental prognostic utility of an abnormal HRR after exercise in the current population, similar to that in other cardiovascular disease states. HRR is a result of vagal tone activation, and reduced HRR, reflecting blunted parasympathetic activity, has been linked to increased mortality.[25,34] Indeed, in our study, patients with an abnormal HRR were almost twice as likely to have adverse events as those with a normal HRR. Based on the current results, one can argue that in asymptomatic patients with severe AS, for the purposes of risk stratification and decision on surgical timing, a simple inexpensive exercise stress test might serve as a potential alternative to the more expensive stress echocardiography, as the stress echocardiographic variables do not significantly provide incremental prognostic value. However, the current results are only hypothesis generating and the results need to be prospectively validated, hopefully in a multicenter format. Also, in current clinical practice, a substantial proportion of AS patients present with mixed disease (ie, concomitant multivalve disease±coronary artery disease). Hence, there still seems to be potential utility of evaluating for LV ischemic response, right ventricular systolic pressure, and concomitant mitral/tricuspid valve characteristics.

Limitations

This is a retrospective observational study from a tertiary referral center and therefore not free of referral bias. The results of the stress test were available to the treating cardiologist and surgeon, further adding to the bias. We only included asymptomatic patients with severe AS and preserved LVEF. Hence, our data are not generalizable to all patients with AS. However, this has inherently helped us to focus on a population in whom uncertainties exist about optimal timing of surgical management. We included patients over a broad time-frame, and not all imaging data (AV gradients on peak-stress echocardiography[14,15] or AV calcium scoring on computed tomography) were available in all patients. Also, exercise capacity is the output of overall function of cardiovascular, respiratory, and musculoskeletal systems. Other possible causes of impaired exercise capacity could have played an important role in predicting outcomes in these patients. We did not report frailty index[35] in the current study as the various components of this index were not uniformly recorded at the time these patients were evaluated. However, all patients were considered appropriate to undergo stress testing. As a surrogate for frailty, we do report Charlson comorbidity index.[19] A previous report has demonstrated a strong association between these 2 indices in older hospitalized patients.[36] We report all-cause mortality as the primary end point, as opposed to cardiac mortality. However, on secondary outcomes analysis, where documented noncardiac deaths were excluded, the results were similar. Also, it has been demonstrated that all-cause mortality is more objective than cardiac mortality.[37] Finally, the primary intent of the study was to demonstrate incremental prognostic utility of exercise capacity on standard clinical variables, rather than developing a predictive model. Hence, model calibration was not performed.

Conclusions

In patients with severe AS and preserved LVEF, considered asymptomatic at the time of stress echocardiography, we demonstrate that only 50% achieved 100% of age–sex–predicted METs. Exercise stress test provides significant reclassification of longer-term mortality risk, with higher achieved % of age–sex–predicted METs associated with longer survival. Patients with severe AS who are presumed to be asymptomatic, but subsequently demonstrate impaired exercise capacity (and free of additional orthopedic/pulmonary comorbidities) may benefit from earlier AVR, which is associated with improved survival. The current data are hypothesis generating and need to be validated prospectively.

Disclosures

Dr Gillinov reports the following conflicts: speakers' bureau for Atricure, Edwards, Medtronic and St. Jude's Medical. He also reports

equity stake in Pleuraflow. Dr Sabik is a consultant for Medtronic and Sorin. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

In 533 patients with severe aortic stenosis and preserved left ventricular ejection fraction (age, 66±13 years; 78% men; 31% with coronary artery disease) who underwent exercise stress echocardiography, only 50% achieved >100%, whereas 26% achieved <85% age–sex–predicted metabolic equivalents, despite being deemed asymptomatic. There were no major stress test-related complications. Over 6.9±3 years, 341 (64%) underwent aortic valve replacement (54% isolated), and 104 (20%) died. On multivariable Cox proportional hazard survival analysis, a higher Society of Thoracic Surgeons score (hazard ratio, 1.21), lower % age–sex–predicted metabolic equivalents (hazard ratio 1.15), and slower heart rate recovery (hazard ratio 1.22) were associated with higher longer-term mortality, whereas aortic valve replacement (time-dependent covariate: hazard ratio, 0.26) was associated with improved survival. The addition of % age–sex–predicted metabolic equivalents to the Society of Thoracic Surgeons score resulted in significant reclassification of longer-term mortality risk (integrated discrimination index, 0.07 [0.03–0.11]; $P<0.001$). These data support the use of stress echocardiography in patients with severe aortic stenosis who present themselves as being asymptomatic.

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Predictors of Long-Term Outcomes in Asymptomatic Patients With Severe Aortic Stenosis and Preserved Left Ventricular Systolic Function Undergoing Exercise Echocardiography

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Supplemental Material

Supplemental Table. Univariable Cox Proportional Hazards Survival Analysis for all-cause mortality in the Study Sample

Variable	Hazard ratio	p-value
Baseline clinical and resting echocardiographic variables		
Age (for 10-year increase)	1.65 [1.35-2.01]	<0.001
Female gender	1.74 [0.95-3.17]	0.21
Body mass index (for every 10 unit increase)	1.20 [0.83-1.77]	0.34
Hypertension	1.32 [0.98-1.79]	0.19
Hyperlipidemia	1.08 [0.76-1.55]	0.74
Diabetes mellitus	1.22 [0.62-2.12]	0.69
Atrial fibrillation	2.19 [1.45-3.30]	<0.001
Obstructive coronary artery disease	1.45 [0.97-2.16]	0.11
Stroke	1.74 [0.90-3.33}	0.22
Smoking	1.32 [0.91-1.85]	0.29
Prior cardiac surgery	1.21 [0.72-2.04]	0.49
Society of Thoracic Surgeons Score (for every 1 % increase)	1.22 [1.13-1.32]	<0.001
Charlson comorbidity index (for every unit increase)	1.56 [1.38-1.77]	<0.001
Glomerular filtration rate (for every 10 unit decrease)	1.14 [1.051-1.23]	0.001
Indexed left ventricular end-systolic dimension (for every 1 cm/m2 increase)	1.23 [0.73-2.14]	0.54
Indexed left ventricular mass (for every 10 g/m2 increase)	1.001 [0.95-1.07]	0.84
Left ventricular ejection fraction (for every % increase)	0.97 [0.93-1.01]	0.19
Left ventricular diastolic dysfunction	1.66 [0.90-2.74]	0.39
Mean aortic valve gradient	1.07 [0.89-128]	0.48
Stroke volume index	0.99 [0.97-1.01]	0.42
≥ Moderate aortic regurgitation	1.28 [1.05-1.50]	0.03
Right ventricular systolic pressure	1.04 [0.99-1.05]	0.14
Post-stress echocardiography variables		
Maximum METs achieved (for every unit decrease)	1.33 [1.23-1.44]	<0.001
% Age-gender predicted METs achieved (for every 10% decrease)	1.17 [1.08-1.27]	<0.001
Chronotropic response index	0.22 [0.09-0.52]	<0.001
Heart rate recovery (for every 10 beat slower recovery)	1.73 [1.45-2.08]	<0.001
Blood pressure drop during stress	1.62 [0.61-4.56]	0.33
Post-stress right ventricular systolic pressure	1.03 [0.96-1.06]	0.47
>20 mm Hg Change in mean aortic valve gradient between stress and rest (data available in 281 patients)	1.12 [0.87-1.76]	0.44
Number of ischemic territories (0-3)	1.1 [0.87-1.69]	0.34
Surgical variables		
Aortic valve surgery (time dependent covariate analysis)	0.28 [0.19-0.42]	<0.001
Type of cardiac surgery performed (isolated AVR vs. combination procedures)	1.14 [0.69-1.37]	0.33
Duration between stress test and aortic valve surgery	1.04 [0.67-1.76]	0.73

METs=metabolic equivalents, AVR=aortic valve replacement