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ORIGINAL RESEARCH

Prognostic Value of Exercise-Stress Echocardiography in Asymptomatic Patients With Aortic Valve Stenosis

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ABSTRACT

OBJECTIVES This study sought to evaluate the prognostic value of mean pressure gradient (MPG) increase and peak systolic pulmonary artery pressure (SPAP) measured during exercise stress echocardiography in asymptomatic patients with aortic stenosis (AS).

BACKGROUND Exercise testing is recommended in asymptomatic AS patients, but the additional value of exercise-stress echocardiography, especially the prognostic value of MPG increase and peak SPAP, is still debated.

METHODS We enrolled all consecutive patients with pure, isolated, asymptomatic AS and preserved ejection fraction ≥50% and normal SPAP (<50 mm Hg) who underwent symptom-limited exercise echocardiography at our institution. Occurrence of AS-related events (symptoms or congestive heart failure) or occurrence of aortic valve replacement was recorded.

RESULTS We enrolled 148 patients (66 ± 15 years of age; 74% males; MPG: 47 ± 13 mm Hg; SPAP: 34 ± 6 mm Hg). No complications were observed. Thirty-six patients (24%) had an abnormal exercise test result (occurrence of symptoms, fall in blood pressure, and/or ST-segment depression) and were referred for surgery. Among the 112 patients with a normal exercise test result, 38 patients (34%) had abnormal exercise echocardiography scores (MPG increase >20 mm Hg and/or SPAP at peak exercise >60 mm Hg). These 112 patients were managed conservatively. During a mean follow-up of 14 ± 8 months, an AS-related event occurred in 30 patients, and 25 patients underwent surgery. Neither MPG increase >20 mm Hg nor peak SPAP >60 mm Hg was predictive of occurrence of AS-related events or aortic valve replacement (all $p > 0.20$). In contrast, baseline AS severity was an important prognostic factor (all $p < 0.01$).

CONCLUSIONS In this observational study including 148 patients with asymptomatic AS, we confirmed and extended the importance of exercise testing for unveiling functional limitation. More importantly, neither the increase in MPG nor in SPAP at peak exercise was predictive of outcome. Our results do not support the use of these parameters in risk-stratification and clinical management of asymptomatic AS patients. (J Am Coll Cardiol Img 2018;11:787–95) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AS = aortic valve stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CAD = coronary artery disease

LVEF = left ventricular ejection fraction

MPG = mean pressure gradient

PV = peak velocity

SPAP = systolic pulmonary arterial pressure

Aortic valve stenosis (AS) is the most common valvular heart disease in Western countries (1,2). Aortic stenosis affects approximately 5% of the population older than 70 years of age, and its prevalence is due to increase dramatically with the aging of the population. Management of patients with severe AS, either symptomatic or with left ventricular systolic dysfunction, is clear, and these patients should be promptly referred for surgical or percutaneous aortic valve replacement (AVR) (Class I indication) (3,4). In contrast, management of asymptomatic severe AS remains a matter of controversy due, on one side, to the risk of sudden death without preceding symptoms and irreversible myocardial dysfunction and, on the other side, to the risk of surgery and prosthetic valve complications. Thus, identifying subsets of asymptomatic AS patients with preserved left ventricular ejection fraction (LVEF) who have the highest likelihood of developing symptoms or AS-related events over the short term and who may benefit from an early or prophylactic surgery rather than a watchful waiting is a critical clinical challenge.

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Exercise testing is strongly recommended in physically active asymptomatic AS patients and has shown both its safety and its important prognostic value (5-7). The abnormal exercise test results that show symptoms or abnormal blood pressure responses are Class I and IIa recommendations for surgery, respectively (3,4). In the last decade, exercise echocardiography has gained considerable interest. According to the current European Society of Cardiology guidelines, surgery may also be considered in patients who are at low operative risk demonstrating normal exercise performance but increased mean pressure gradient (MPG) with exercise by >20 mm Hg or systolic pulmonary hypertension (Class IIb). However, the level of evidence is low, and the use of exercise echocardiography is not mentioned in the American College of Cardiology/American Heart Association recommendations. To further improve the level of evidence, we reviewed all asymptomatic AS patients who underwent exercise echocardiography at our institution and specifically evaluated the additional prognostic value of exercise echocardiography.

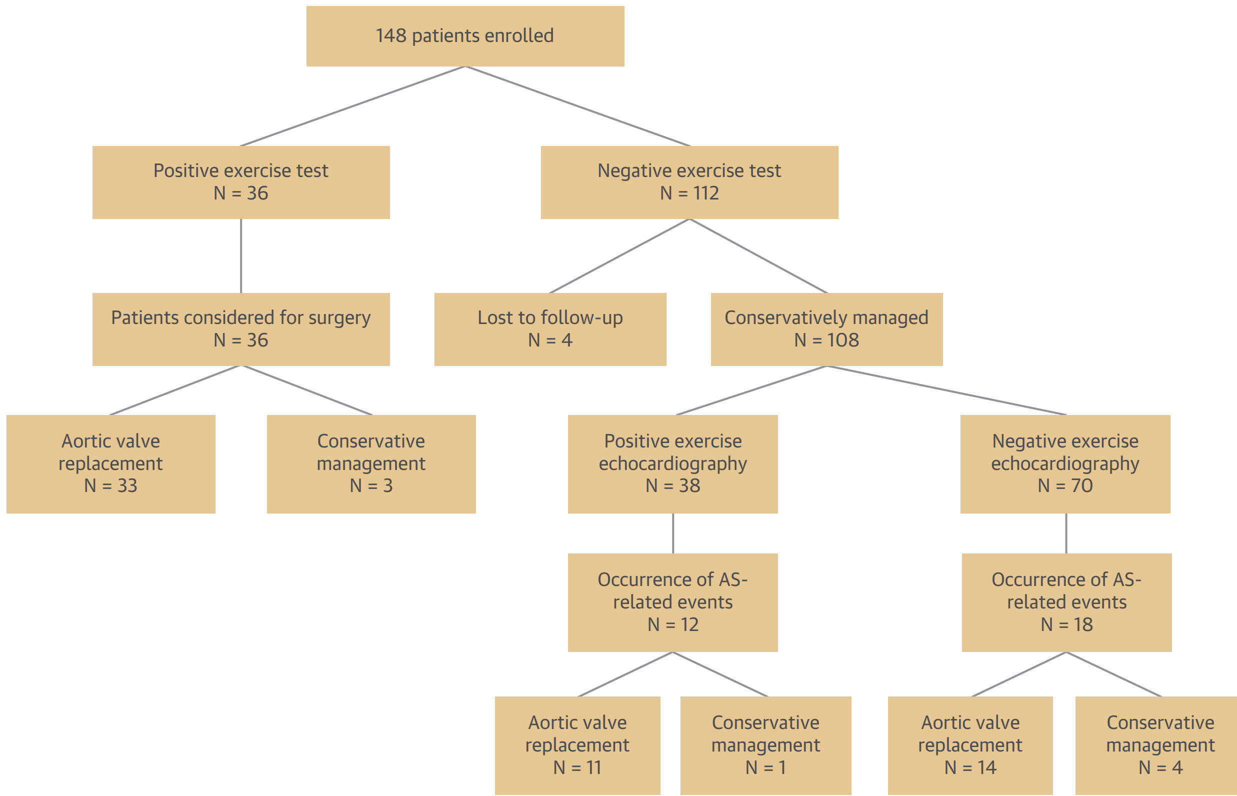
METHODS

STUDY DESIGN. We enrolled all consecutive patients with at least moderate asymptomatic AS (MPG ≥20 mm Hg) who underwent exercise echocardiography testing between January 2005 and December 2014 at our institution. Exclusion criteria were LV systolic dysfunction (LVEF <50%); congenital stenosis, except for bicuspid valve, rheumatic disease, and systolic pulmonary hypertension at rest (systolic pulmonary artery pressure [SPAP] >50 mm Hg); and associated aortic regurgitation or other valvular disease of grades ≥2 to 4. All patients underwent a comprehensive transthoracic echocardiography test at rest, followed by symptom-limited exercise echocardiography. All echocardiography procedures were performed by experienced operators using iE33 (Philips Healthcare, Andover, Massachusetts) or Vivid 7 (General Electrics, Chalfont, St. Giles, United Kingdom) ultrasonography systems. Follow-up examinations were performed by telephone interviews with the treating cardiologist, or the patients, or were collected from medical records.

REST ECHOCARDIOGRAPHY. Severity of AS was assessed based on peak velocity (PV), MPG, and aortic valve area (AVA), calculated using the continuity equation, as recommended (8). Severe AS was defined by an AVA of <0.6 cm^2/m^2, a PV of >4 m/s, or an MPG of >40 mm Hg. Left ventricle mass was calculated using the Devereux formula and indexed to body surface area; LV hypertrophy was defined by an LV mass index >95 g/m^2 in women and >115 g/m^2 in men (9). LVEF was assessed visually or using the modified biplane Simpson's method. Systolic pulmonary artery pressure was estimated based on the modified Bernoulli equation using continuous wave Doppler.

EXERCISE-STRESS ECHOCARDIOGRAPHY. Patients performed exercise-stress echocardiography in a semisupine position on a bicycle ergometer under blood pressure (BP) measurement and continuous 12-lead electrocardiographic monitoring. Workload was increased every 1, 2, or 3 min by 20/30 W, depending on age and physical ability. At each stage, LV systolic function, occurrence of LV wall motion abnormalities, MPG, and SPAP were measured using echocardiography. Criteria for positivity of the exercise test result and of the echocardiographic part of the test (presented below) were analyzed independently. A positive exercise test result was defined by the occurrence of symptoms (dyspnea, angina, or syncope), the fall in systolic BP or rise <20 mm Hg, ST-segment depression ≥2 mm or sustained ventricular arrhythmia. A positive echocardiographic stress result was defined as an exercise-induced MPG increase >20 mm Hg, a peak SPAP >60 mm Hg, an impaired LVEF, or the occurrence of left wall motion abnormalities (LWMA). Patients with a positive

FIGURE 1 **Flow Chart**



Flow chart describes the clinical management of the study population who underwent exercise-stress echocardiography.

exercise test result were considered for valve replacement as were those who developed LV dysfunction or LWMA during exercise. The remaining population was managed conservatively.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD, median (25th to 75th percentile), or number of patients (percent). Quantitative variables were compared using Student's *t*-test or the Wilcoxon rank-sum test as appropriate. Categorical variables were compared using the Fisher exact test. Correlations between quantitative variables were assessed using the Spearman test. Event-free survival (composite endpoint of AS-related events defined as the need for AVR [occurrence of congestive heart failure or new onset of symptoms, i.e., dyspnea, angina or syncope]) within 2 years after the exercise and echocardiography results were assessed, using the Kaplan-Meier method. Same analyses were also performed for occurrence of aortic valve replacement. Comparison of event-free survival according to rest or exercise echocardiographic parameters was performed by means of log-rank test. Cox proportional hazard analyses were used to evaluate the predictive value of rest or exercise echocardiographic parameters for event-free survival in univariate analysis and after adjustment for age, sex, and LVEF. Statistical analyses were performed using JMP9 software (SAS Institute, Cary, North Carolina) for Macintosh (Apple, Cupertino, California). All tests were 2-sided. A p value of <0.05 was considered significant.

RESULTS

BASELINE CHARACTERISTICS. Between January 2005 and December 2014, 148 patients fit the inclusion and exclusion criteria and were considered in the present study (Figure 1). Baseline clinical and echocardiographic characteristics of the population are presented in Table 1. Briefly, 110 patients (74%) were male, and the mean age was 66 ± 15 years. Most of the patients were in sinus rhythm (n = 141; 95%). History of coronary artery disease was present in 30 patients (21%). Mean pressure gradient was 47 ± 13 mm Hg; mean AVA was 0.97 ± 0.23 cm^2; and 119 patients

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TABLE 1 Clinical, Hemodynamic, and Echocardiographic Characteristics of the Overall Population and According to Exercise Test Results

		Exercise Test			Negative Exercise Test		
	Overall (N = 148)	Positive Results (n = 36)	Negative Results (n = 112)	p Value	Positive Exercise Echocardiography Results (n = 38)	Negative Exercise Echocardiography Results (n = 70)	p Value
Male	110 (74)	24 (60)	86 (80)	0.02	28 (74)	58 (83)	0.33
Age, yrs	67 ± 13	67 ± 14	67 ± 12	0.79	67 ± 14	67 ± 11	0.65
History of coronary artery disease	30 (21)	6 (16)	24 (23)	0.34	9 (25)	15 (22)	0.81
Atrial fibrillation	18 (12)	6 (15)	12 (11)	0.4	5 (13)	7 (10)	0.75
Pacemaker	2 (1)	0 (0)	2 (2)	1	1 (3)	1 (2)	1
Chronic respiratory failure	8 (6)	1 (3)	7 (7)	0.68	3 (8)	4 (6)	0.69
Diabetes mellitus	20 (14)	7 (18)	13 (13)	0.28	5 (14)	8 (12)	0.76
BMI, kg/m^2	26 ± 4	24 ± 3	26 ± 4	0.001	25 ± 3	27 ± 5	0.12
Echocardiography at rest							
Pressure gradient, mm Hg	47 ± 13	52 ± 13	45 ± 13	0.0008	48 ± 15	43 ± 11	0.07
Peak velocity, m/s	4.3 ± 0.6	4.7 ± 0.5	4.2 ± 0.6	<0.0001	4.4 ± 0.7	4.1 ± 0.5	0.02
Aortic valve area, cm^2	0.97 ± 0.23	0.88 ± 0.17	1 ± 0.23	0.001	0.99 ± 0.26	1.01 ± 0.22	0.72
Indexed aortic valve area, cm^2/m^2	0.52 ± 0.11	0.49 ± 0.08	0.53 ± 0.12	0.03	0.53 ± 0.12	0.52 ± 0.11	0.7
Left ventricular hypertrophy	93 (70)	27 (73)	66 (69)	0.83	26 (79)	40 (64)	0.17
LVEF, %	70 ± 9	69 ± 8	70 ± 9	0.55	70 ± 9	70 ± 9	0.78
SPAP, mm Hg	34 ± 6	35 ± 5	34 ± 6	0.11	35 ± 6	33 ± 6	0.14
Exercise echocardiography							
Percent predicted heart rate	83 ± 11	84 ± 11	83 ± 12	0.64	84 ± 11	83 ± 12	0.56
Mean gradient at peak exercise, mm Hg	59 ± 18	67 ± 19	56 ± 17	0.0004	65 ± 20	52 ± 13	0.0005
Gradient variation, mm Hg	13 ± 10	15 ± 12	12 ± 9	0.05	16 ± 10	9 ± 7	0.0006
Gradient variation >20 mm Hg	23 (17)	8 (22)	15 (15)	0.18	15 (41)	0 (0)	NA
SPAP variation, mm Hg	21 ± 11	23 ± 11	20 ± 11	0.38	28 ± 8	14 ± 8	<0.0001
SPAP >60 mm Hg at peak exercise	37 (25)	12 (30)	25 (23)	0.19	25 (66)	0 (0)	NA

Values are n (%) or mean ± SD.
BMI = body mass index; LVEF = left ventricular ejection fraction; NA = not applicable; SPAP = systolic pulmonary artery pressure.

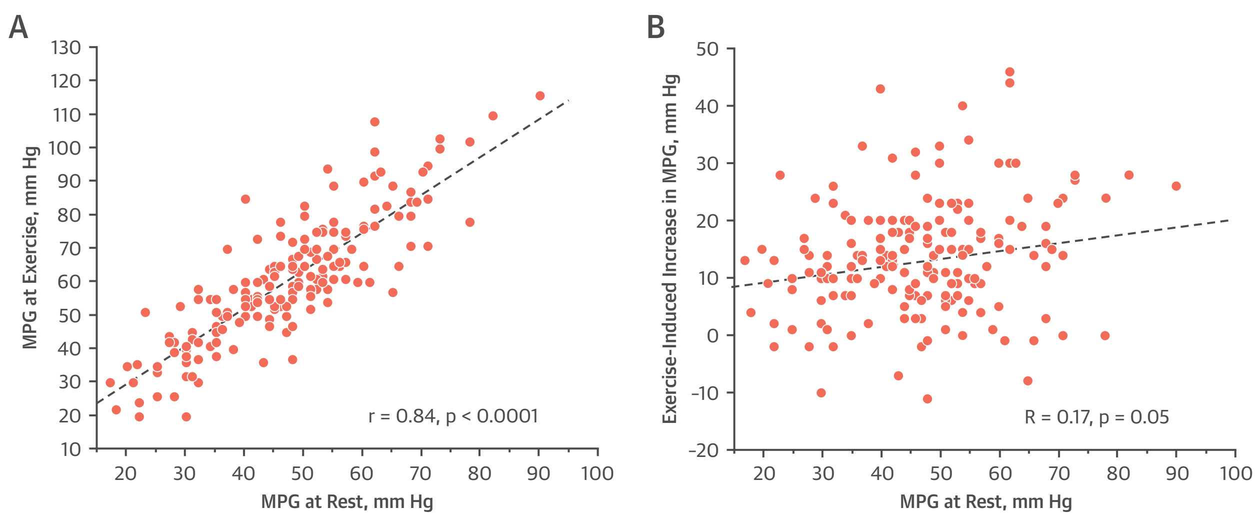
(80%) presented with severe AS. Mean SPAP at rest was 34 ± 6 mm Hg.

SYMPTOM-LIMITED EXERCISE ECHOCARDIOGRAPHY. No complication related to the test was observed. Main reasons for stopping the test were fatigue in 76 patients (51%), dyspnea in 32 (22%), and achievement of the maximal predicted heart rate in 20 patients (14%). Most of the patients achieved a satisfactory exercise test rate (83 ± 11% of the maximal predicted heart rate). Mean pressure gradient at peak exercise, measurable in 138 patients (93%), was 59 ± 18 mm Hg. Exercise-induced MPG increase was 13 ± 10 mm Hg, and 23 patients (17%) had an exercise-induced increase in MPG of >20 mm Hg. SPAP at peak exercise could be measured in 87 patients (59%), and 37 patients (25%) had an SPAP of >60 mm Hg at peak exercise.

Thirty-six patients (24%) had a positive (abnormal) exercise test result. Reasons for positivity of the exercise test results were occurrence of symptoms in 29 patients (81%), fall in BP or no BP increase for 16 patients (44%), and/or occurrence of ST-segment depression in 19 patients (53%). Isolated ST-segment depression was observed in only 2 patients. Comparison between patients with positive and those with negative exercise testing results are presented in Table 1. Patients with a positive exercise testing were more frequently female than male (40% vs. 20%, respectively; p = 0.02) and less overweight (24 ± 3 kg/m^2 vs. 26 ± 4 kg/m^2, respectively; p = 0.001) and presented with more severe AS (0.88 ± 0.17 cm^2 vs. 1.00 ± 0.23 cm^2, respectively; p = 0.001). Interestingly, MPG at peak exercise (67 ± 19 mm Hg vs. 56 ± 17 mm Hg, respectively; p = 0.0004) and MPG changes during exercise (+15 ± 12 mm Hg vs. +12 ± 9 mm Hg, respectively; p = 0.05) were also higher. No differences were observed in terms of SPAP changes (+23 ± 11 mm Hg vs. +20 ± 11 mm Hg, respectively; p = 0.38) or rate of SPAP >60 mm Hg at peak exercise (30% vs. 23%, respectively; p = 0.19).

Among the 112 patients with a negative exercise test result (86 male; mean 67 ± 14 years of age), 38 patients (34%) had a positive exercise echocardiography outcome. Reasons for the positivity of the exercise echocardiography results were exercise-induced increase in MPG of >20 mm Hg in

FIGURE 2 **Correlations Between Rest and Exercise-Stress Echocardiographic Parameters**



Correlation between mean pressure gradient at rest and **(A)** mean pressure gradient at peak exercise and **(B)** changes in mean pressure during exercise. MPG = mean pressure gradient.

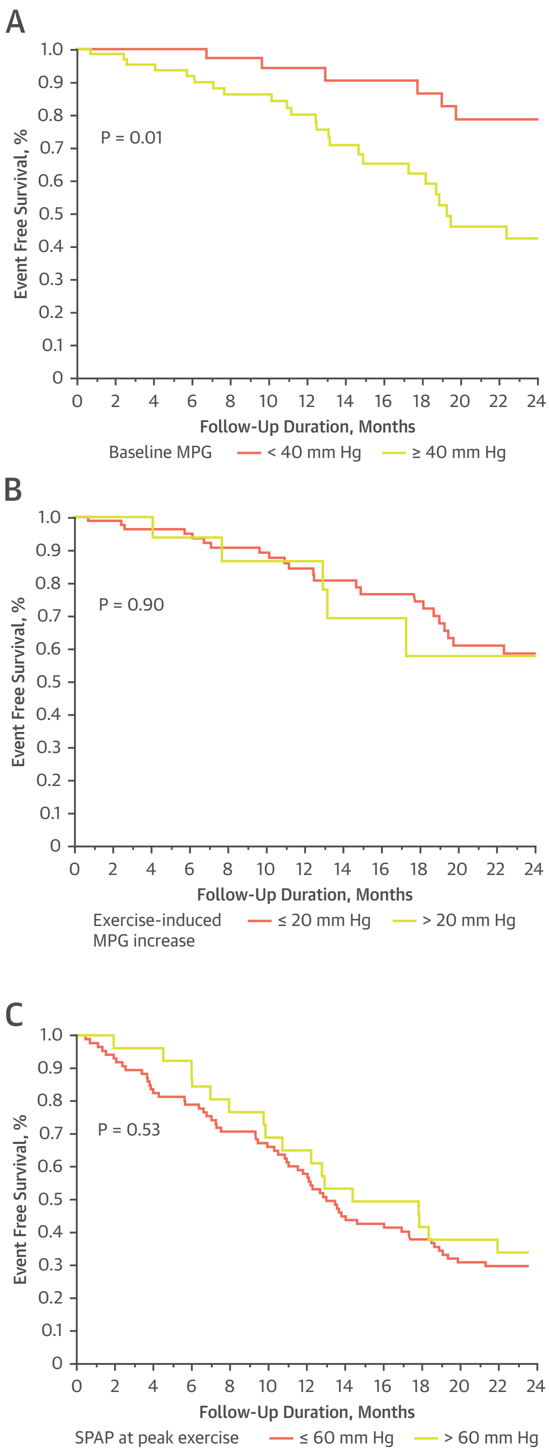
15 patients and SPAP at peak exercise of >60 mm Hg in 25 patients (2 patients had both an increase in MPG, >20 mm Hg, and in SPAP, >60 mm Hg, at peak exercise). No LWMA was observed during exercise in our population. Comparisons between patients with positive and those with negative exercise echocardiography (but normal exercise testing) results are presented in Table 1, right side. Patients with a positive exercise echocardiography results tended to present with higher AS severity (48 ± 15 mm Hg vs. 43 ± 11 mm Hg, respectively; $p = 0.07$), but other clinical and echocardiographic characteristics were similar. There was a significant correlation between MPG at peak exercise and MPG at rest ($r = 0.84$; $p < 0.0001$) (Figure 2A), but there was a modest correlation between exercise-induced MPG increase and MPG at rest ($r = 0.17$; $p = 0.05$) (Figure 2B).

IMMEDIATE MANAGEMENT AND MID-TERM OUTCOME. The 36 patients with positive exercise test results were referred for AVR, whereas the remaining 112 patients with a negative exercise test results were managed conservatively. Among these 112 patients, 4 were lost to follow-up, and outcome was thus evaluated in 108 patients (67 ± 12 years of age; 78% men). Mean MPG was 45 ± 13 mm Hg, and mean AVA was 1.00 ± 0.23 cm^2, and 82 patients (76%) had a severe AS. Compared to rest examination, MPG increased by +12 ± 9 mm Hg. None of the 4 patients lost to follow-up had an MPG increase >20 mm Hg or peak SPAP of >60 mm Hg, and thus, an MPG increase >20 mm Hg was observed in 15 patients (14%) and a SPAP of >60 mm Hg in 25 patients (21%).

During a mean follow-up of 14 ± 8 months, an AS-related event (occurrence of symptoms or congestive heart failure but no deaths) occurred in 30 patients. In univariate analysis, MPG at rest (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 1.03 to 1.09; $p < 0.0001$) and MPG at peak exercise (HR: 1.04; 95% CI: 1.01 to 1.06; $p = 0.004$) but not exercise-induced MPG increase (HR: 0.99; 95% CI: 0.94 to 1.01; $p = 0.54$) were associated with the occurrence of AS-related events. As illustrated in Figure 3, event-free survival was significantly different between patients with MPG above or below 40 mm Hg ($p = 0.01$) but very similar between patients with MPG increases above or below <20 mm Hg ($p = 0.90$). SPAP at rest (HR: 1.06; 95% CI: 0.98 to 1.12; $p = 0.15$) or at peak exercise (HR: 0.99; 95% CI: 0.95 to 1.01; $p = 0.75$) were not predictive of outcome, and rates of event-free survival were not different between patients with SPAP at peak exercise above or below 60 mm Hg ($p = 0.53$) (Figure 3). In multivariate analysis, after adjustment for age, sex, and LVEF, MPG at rest but not at peak exercise was predictive of outcome (HR: 1.07; 95% CI: 1.04 to 1.10; $p < 0.0001$). Using AVA or PV instead of MPG at rest did not change the results. Furthermore, similar results were observed after exclusion of the 26 patients with moderate AS.

Twenty-five patients underwent an AVR within 24 months of exercise echocardiography (mean: 14 ± 8

FIGURE 3 **Event-Free Survival Curves Presenting the Prognostic Value of Rest and Exercise-Stress Echocardiographic Parameters**



Kaplan-Meier curves display event-free survival (occurrence of AS-related events) according to **(A)** mean pressure gradient at rest, **(B)** mean pressure gradient increase of >20 mm Hg or ≤20 mm Hg during exercise, or **(C)** presence or absence of exercise-induced systolic pulmonary hypertension (>60 mm Hg).

months); and 11 patients had a positive exercise echocardiography result (29%) and 14 had a negative exercise echocardiography result (20%; p = 0.29%). Similar to the occurrence of AS-related events, neither MPG changes >20 mm Hg (p = 0.51) nor SPAP at peak of >60 mm Hg (p = 0.45) were predictive of occurrence of AVR, whereas resting MPG remained a powerful predictor (p = 0.003).

DISCUSSION

In this observational study, we enrolled 148 patients with moderate to severe asymptomatic AS, and the main findings were: 1) 24% of patients considered asymptomatic based on patients' interview had a positive exercise; 2) among the 112 patients with negative symptom-limited exercise test results, 28% developed symptoms (dyspnea, angina, syncope, or heart failure) within 2 years of follow-up; and 3) AS severity at rest but not MPG changes, peak SPAP, or SPAP changes during exercise were predictive of outcome. These findings may have important implications for the clinical management of asymptomatic AS patients.

EXERCISE TESTING IN ASYMPTOMATIC AS PATIENTS. Development of symptoms is a turning point in the natural history of AS disease, and these patients should be promptly referred for aortic valve replacement (3,4). However, assessment of symptoms may have important limitations. In some patients, clinical presentation may be unclear, whereas others either may have masked functional impairment due their sedentary life styles or may underestimate their functional limitations. To unveil or unmask functional limitations, exercise testing has been proposed. Although conventionally not recommended in AS patients 2 decades ago, since the seminal publication by Amato et al. (5), all studies are concordant, showing that exercise testing is safe and provides important prognostic information (5-7,10-15). In AS, as in other valvular heart diseases, exercise testing is now a Class I/IIa indication, especially in physically active patients. In addition to the assessment of exercise tolerance, a fall or limited rise of BP is also a well-validated criterion that should lead to valve replacement. The rate of "falsely asymptomatic patients" may vary across studies depending on the characteristics of the population considered but is usually between one-quarter and one-third. In the present study, no adverse events occurred during the test, and 24% of patients considered asymptomatic had a positive exercise test outcome (6,7,13,14). As recommended, these patients were considered for valve replacement even if, finally, 3 patients decided not to undergo surgery and, thus, remained under conservative management. It is worth noting that in our series, as in others, mean age of the patients referred for exercise testing is significantly lower than the average age observed in regular AS population. Such bias is expected as only physically active patients are able to exercise.

ADDITIONAL VALUE OF EXERCISE ECHOCARDIOGRAPHY. If management of symptomatic AS patients is relatively simple, whether asymptomatic patients should be conservatively managed or undergo surgery is debated. The risk of sudden death without preceding symptoms, although low, is not null (16), and there is a risk of irreversible myocardial dysfunction. On the other side, the surgical risk should be taken into account as well as the risk of early prosthetic degeneration and other prosthetic complications, including thrombosis, as recently highlighted (17). In addition, even if patients are under conservative management, they should be seen on a regular basis and informed of the symptoms that should lead to an early visit, timely under-reporting is common, therefore increasing the risk of sudden death and of irreversible myocardial dysfunction. Thus, identification of subsets of asymptomatic AS patients that may benefit from an early valve replacement is of paramount importance.

Exercise echocardiography has emerged as an attractive risk stratification tool that may discriminate among such patients. An MPG increase during exercise >18 or 20 mm Hg and an increase in SPAP >60 mm Hg at peak exercise have been suggested as prognostic markers (12,14,18). However, evidence was still limited, and these parameters were considered only Class IIb indications in European Society of Cardiology recommendations for surgery and not mentioned in the ACC/AHA recommendations. Lancellotti et al. (12) were first to highlight the independent prognostic value of these 2 parameters. However, the authors did not individualize the respective prognostic value of exercise testing and exercise echocardiography, and the prognostic value of both tests combined was analyzed and reported. To further evaluate specifically the incremental prognostic value of exercise echocardiography beyond exercise testing, we excluded patients with a positive exercise test outcome, because in these patients, the added value of exercise echocardiography is limited (these patients should be referred for valve replacement). In this subset of patients, neither MPG changes nor systolic pulmonary hypertension were predictive of outcome in our study. Such a dichotomy, which has not been performed in all studies as mentioned earlier, is crucial because patients with positive exercise test outcomes were those with the highest AS severity at baseline and the highest MPG at peak exercise and MPG changes. This confounding factor may explain the differences between our results and those from the study by the team of Liege (12). Importantly, peak MPG but not MPG increase was correlated with rest MPG, suggesting that MPG changes are on average similar in most patients. The absence of a prognostic value for the MPG we observed, as opposed to the observation by Marechaux et al. (18), is more intriguing as the authors appropriately excluded patients with an abnormal exercise test result. Main differences were the inclusion of less severe AS patients (especially in term of MPG) and a longer follow-up (20 ± 14 months vs. 14 ± 8 months, respectively) compared to the present study. It is worth noting that we decided to restrict our analysis to events that occurred within 2 years of the exercise test as we did not expect that exercise testing would predict AS related-events on a longer term. In addition, AS is a progressive disease; these patients should be regularly followed, and the exercise testing also should also be repeated. From a pathophysiological point of view, both MPG increase and pulmonary hypertension during exercise were appealing. However, MPG increase may on one side reflect valve resistance or compliance and the absence of valvular reserve, but on the other side, MPG increase is also dependent of heart rate and of the myocardial response and contractile reserve (increase in stroke volume). The integration of multiple parameters working in opposite directions may explain the absence of prognostic value of MPG increase observed in the present study. Systolic pulmonary hypertension during exercise should also be carefully interpreted, as previous studies have shown that it is relatively common and can be observed in a normal subject free of any cardiovascular disease (19). It is worth noting that we did not consider specifically patients with discordant grading (with low or normal flow) due to limited sample size. Additional prognostic value of exercise echocardiography in this subset of patients definitely deserves further studies (20).

CLINICAL IMPLICATIONS. One main clinical implication of the present study is to emphasize the important prognostic value of the degree of AS severity at rest and the importance of the performance of exercise testing whatever the modality in physically active patients. Indeed, an important proportion (one-fourth) of AS patients who claim to be asymptomatic exhibit exercise-limiting symptoms during exercise testing. More specifically, our results do not support the use of MPG increase to >20 mm Hg or systolic pulmonary hypertension as measured during exercise

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echocardiography in the risk stratification of asymptomatic AS patients. Recognizing the limitations of the present study and those of published reports and the need for a prospective multicenter evaluation of the incremental value of exercise echocardiography, our results, meanwhile, raise caution regarding use of these parameters for the clinical management of AS patients. Although a simple exercise test offers the simplest and cheapest method compared with exercise echocardiography to evaluate the functional capacity, exercise echocardiography may provide additional information such as occurrence of LWMA. In addition, other parameters, such as subendocardial contractile function assessed using speckle tracking echocardiography (21,22) or LV contractile reserve (assessed based on LVEF or strain) or B-type natriuretic peptide (BNP) analyzed immediately after exercise, may be of interest and need also to be evaluated. Our results thus strongly advocate further research to improve risk-stratification in AS patients.

STUDY LIMITATIONS. First, it is a single-center observational study, and we cannot exclude the bias inherent in this kind of study. In addition, one may argue that, as an observational study, the referring physician was aware of the results of the test. However, the same results were observed when AVR was considered. In contrast to symptom occurrence, decision to perform an AVR might have been influenced by the results of the test but should have favored exercise echocardiography. The absence of prognostic value of MPG increase or systolic pulmonary hypertension using AVR as the endpoint is therefore very reassuring regarding the robustness of our findings. Second, although our sample size compared well to that in previous studies, it was relatively small, with a limited number of events, and larger multicenter prospective studies are strongly required to confirm our results. Third, SPAP at peak exercise could not be measured in a substantial part of the population, and our results should therefore be interpreted with caution. This limitation further emphasizes the importance of a multicenter prospective evaluation which would enable evaluation of the prognostic value of exercise echocardiography in specific subsets such as patients with discordant grading. Fourth, whether symptoms at a given degree of exercise were normal or excessive was at least partially subjective. However, reference values adjusted for age and sex are not available for the semisupine exercise bicycle, and thus, the present study reflects real-life and current practice in most centers. Fifth, other parameters such as valve calcification, BNP, LV systolic strain at rest or during exercise were not measured in the present study (23–29). Finally, we enrolled all consecutive patients with pure isolated asymptomatic AS referred for exercise echocardiography study. Thus, only patients able to exercise were considered. Although some selection bias could not be excluded, exercise testing is mainly recommended for physically active patients. Furthermore, because AS mainly concerns elderly patients, further refinement of risk stratification based on rest parameters and/or biomarkers is crucial.

CONCLUSIONS

In this observational study of 148 patients with asymptomatic moderate to severe AS, we confirmed and extended the importance of exercise testing, whatever the modality, to unveil functional limitations. More importantly, neither the increase of mean pressure gradient or the systolic pulmonary hypertension during exercise were predictive of AS-related events. Further multicenter prospective studies are required to confirm our findings but in the meanwhile, our results do not support the use of these parameters in the risk-stratification and clinical management of asymptomatic AS patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In asymptomatic patients with AS, the performance of an exercise test is crucial as it unveils a functional limitation in one-fourth of the patients who should be referred for surgery. However, measurements of the changes in MPG or SPAP during exercise-stress echocardiography show no additional prognostic value. Thus, for the management of asymptomatic patients with AS, a simple exercise test should be recommended as the first line.

TRANSLATIONAL OUTLOOK: The single-center design of the present study remains an important limitation. Multicenter prospective studies are required to confirm the absence of additional value of changes of MPG of pulmonary artery hypertension assessed using exercise-stress echocardiography and to evaluate whether and to which extent other parameters such as contractile reserve are useful.

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