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Determinants and Prognostic Significance of Exercise Pulmonary Hypertension in Asymptomatic Severe Aortic Stenosis

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Abstract:

Background **-** Recent studies emphasized the usefulness of exercise stress echocardiography (ESE) in asymptomatic patients with aortic stenosis (AS). Nevertheless, the additive value of exercise pulmonary hypertension (Ex-PHT) in such patients remains unexplored. We, therefore, aimed to identify the determinants and to test the impact on outcome of Ex-PHT in asymptomatic patients with severe AS.

Method and Results **-** Asymptomatic patients with severe AS (n=105, aortic valve area<0.6cm²/m^2, 71±9 years, 59% of male) and preserved left ventricular (LV) systolic function (ejection fraction≥55%) were prospectively submitted to ESE. Resting and ExPHT were defined as a systolic pulmonary arterial pressure (SPAP) >50mmHg and >60mmHg, respectively. Ex PHT was more frequent than resting PHT (55% vs. 6%, p<0.0001). On multivariable logistic regression, the independent predictors of ExPHT were male gender (odds-ratio [OR]=4.3, p=0.002), resting SPAP (OR=1.16, p=0.002), exercise indexed LV end-diastolic volume (OR=1.04, p=0.026), exercise e'-wave velocity (OR=1.35, p=0.047) and exercise-induced changes in indexed LA area (OR=1.36, p=0.006). Ex-PHT was associated with reduced cardiac event-free survival (3-year: 22±7 vs. 55±9%, p=0.014). In multivariable Cox proportional hazard model, Ex-PHT was identified as an independent predictor of cardiac events (hazard ratio [HR]=1.8, 95% confidence interval [CI]: 1.0-3.3, p=0.047). When adding exercise-induced changes in mean aortic pressure gradient to the multivariable model, Ex-PHT remained independently associated with reduced cardiac event-free survival (HR=2.0, 95%CI: 1.1-3.6, p=0.025).

Conclusions **-** In asymptomatic patients with severe AS, the main determinants of Ex-PHT are male gender, resting SPAP and exercise parameters of diastolic burden. Moreover, Ex-PHT is associated with 2-fold increased risk of cardiac events. These results strongly support the use of ESE in asymptomatic AS.

Key words: aortic valve stenosis; exercise echocardiography; pulmonary hypertension; valves

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Introduction

The management and the timing of surgery in asymptomatic patients with severe aortic stenosis (AS) remains a matter of concern. In this setting, valve replacement is recommended when the left ventricular ejection fraction (LVEF) is reduced (<50%). However, LVEF is often preserved in severe AS due to adapted LV remodeling to the increased afterload, often leading to late surgical referral. Furthermore, recent studies have showed that irreversible LV myocardial fibrosis may be present even when LVEF[1;2] is preserved.

A recent registry reported that compared to the conventional treatment strategy (i.e. "wait for symptoms"), early surgery in patients with very severe AS was associated with an improved long-term survival by decreasing cardiac mortality[3]. However, surgeons may be reluctant to operate on asymptomatic patients. The risks of aortic valve surgery and late complications of prosthesis need to be balanced against the possible prevention of sudden death and lowering of cardiac mortality. Hence, early elective surgery could be proposed to selected patients with a high risk of rapid LV function deterioration or symptomatic status impairment (i.e. high risk of poor outcome)[4;5]. This strategy requires the identification of accurate markers of poor outcome. In this regard, the presence of pulmonary hypertension (PHT) in patients with severe AS seems to be associated with a poorer prognosis[6;7], a higher mortality rate after valve replacement[8] and represents an independent predictor of hospital mortality and postoperative major adverse cardiovascular and cerebrovascular events[9]. In patients receiving transcatheter aortic valve implantation, PHT was a strong independent predictor of poor outcome, augmenting by 2 the risk of late mortality[10].

We have recently identified that exercise PHT in asymptomatic patients with primary mitral regurgitation was a good marker of high risk of reduced symptom-free survival. To the

best of our knowledge, the prognostic value of exercise PHT in AS is still unknown. The aims of this study were to identify the determinants and the potential prognostic importance of exercise PHT in asymptomatic patients with severe AS.

Methods

We prospectively included consecutive patients with asymptomatic severe AS (n=195), defined as an aortic valve area (AVA) indexed for body size area <0.6cm²/m², and preserved LVEF (≥ 55%) referred to our laboratory for exercise stress echocardiography. Only patients with a normal exercise stress test (i.e. "truly" asymptomatic patients) were considered for the final analysis of the study, resulting in the exclusion of 45 patients with abnormal exercise response. The other exclusion criteria were (1) more than mild concomitant valvular heart disease (n=3), (2) atrial fibrillation (n=2), (3) known pulmonary disease (n=1), (4) inability to perform an exercise test (n=4) and (5) absence of measurable systolic pulmonary arterial pressure (SPAP) at exercise (n=35). The final population was composed of 105 patients (71±9 years, 59% of male). The collection of baseline demographic and clinical data was standardized and performed at the time of exercise stress echocardiography.

Echocardiographic study

Before exercise stress test, resting comprehensive transthoracic echocardiography was performed using VIVID 7 ultrasound system (General Electric Healthcare, Little Chalfont, UK). All Doppler-echocardiographic recordings were stored on a dedicated workstation for off-line subsequent analysis. For each measurement, at least two cardiac cycles were averaged. Continuous wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated using the simplified Bernoulli equation ($\Delta P=4v^2$, where v is

maximal aortic velocity in m/s). The LV stroke volume was calculated by multiplying the LV outflow tract area by the LV outflow tract velocity–time integral measured by pulsed-wave Doppler. AVA was calculated using the continuity equation. The bi-apical Simpson disk method was applied to quantify LV end-diastolic and end-systolic volumes and EF. In addition to this conventional evaluation of LV systolic function, 2D speckle tracking analysis (2D strain) was performed to quantify global longitudinal myocardial deformation as previously described[5;11]. Briefly, 2D strain is a non-Doppler-based method using standard 2D images with a frame rate acquisition >60Hz. By tracing the endocardial borders on an end-systolic frame, the software automatically tracked the contour on the subsequent frames. Adequate tracking was verified in real-time and was manually corrected, when necessary. The global longitudinal deformation strain (GLS) represents the average of the segment strains from the conventional apical 4-, 3- and 2-chamber views. Left atrial area was obtained by planimetry of an end-systolic frame from the apical 4-chamber view. Peak E- and A-wave velocities of the mitral inflow were measured using pulsed wave Doppler. Tissue Doppler imaging was applied for the measurement of e'-wave. The average of septal and lateral mitral annulus Ea-wave velocities was used for the calculation of the E/e' ratio.

SPAP was derived from the regurgitant jet of tricuspid regurgitation using systolic transtricuspid pressure gradient and the addition of 10 mm Hg for right atrial pressure as previously performed[12;13]. Resting PHT and exercise PHT were defined as SPAP >50 and >60 mm Hg, respectively. Right atrial pressure was assumed to be constant from rest to exercise.

Exercise protocol

A symptom-limited graded maximum bicycle exercise test was performed in the semi-supine position on a tilt-table. After an initial workload of 25W maintained for 2 min, the workload was

increased every 2 min by 25W. A 12-lead ECG was monitored continuously and blood pressure was measured at rest and every 2 min during exercise. If patients were on beta-blocker, they were asked to stop their medication 24 h before the test. The other medications, if any, were left unchanged. Patients with an abnormal exercise test were excluded from the present study. Abnormal exercise test was defined as: (1) occurrence of limiting breathlessness or fatigue at low workload (<75watts), (2) occurrence of angina, dizziness, syncope, or near-syncope; (3) fall in systolic blood pressure below baseline or rise in systolic blood during exercise <20 mm Hg; (4) ≥2 mm ST segment depression in comparison to baseline levels; (5) complex ventricular arrhythmia.

Event-free survival

Follow-up information was obtained every 6 to 12 months from standardized interviews with the patients, their physicians or, if necessary, with next of kin, according to guidelines[14;15]. The primary outcome variable was the time to occurrence of the first composite endpoint defined as cardiovascular death or need for AVR motivated by the development of symptoms or LV systolic dysfunction. Their personal physicians determined the clinical management of the patients independently.

Statistical analysis

Results are expressed as mean±SD or percentage unless otherwise specified. Data comparisons were performed according to the presence or absence of exercise PHT using Student unpaired t test, Chi^2 test or Fisher exact test, as appropriate. The prevalence of PHT at rest and during exercise was compared using McNemar test. The significant changes from rest to exercise in continuous variables were assessed using paired t test. The relationship between exercise SPAP and other continuous variables (i.e. demographic data, exercise data, and resting and exercise

echocardiographic data) were evaluated using simple linear regression. Independent predictors of exercise SPAP was obtained with the use of stepwise multiple linear regression. Predictors of exercise PHT were determined with stepwise logistic regression. In both multiple linear regression and logistic regression, variables with a univariable value of $p<0.10$ were incorporated into the multiple regression, then variables with a p-value>0.20 were removed. Sensitivity, specificity, positive predictive value, and negative predictive value for the prediction of the occurrence of cardiac event were determined for various cutoff values of exercise SPAP with receiver-operating characteristic curves.

Probabilities of event-free survival were obtained by Kaplan-Meier estimates for the 2 groups and then compared by a 2-sided log-rank test.

The impact of exercise PHT on event-free survival was assessed with Cox proportional-hazards models in univariable and multivariable analyses. Variables with a univariable value of $p<0.10$ were incorporated into the multivariable models. The selection of variables included in the multivariate model was performed with a special care. To avoid colinearity among a subset of several variables measuring the same phenomenon (e.g., AVA, peak gradient, mean gradient), we entered in the multivariate models the variable that had the strongest association with event-free survival on univariable analysis. In addition, to assess the accuracy of prediction of cardiac event by each model, we generated the Harrell correspondence index (C-statistic).

Values of $p<0.05$ were considered significant. All statistical analyses were performed with STATISTICA version 7 (StatSoft Inc, Tulsa, Okla). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Population characteristics

PHT, as previously defined, was significantly more frequent during exercise (55% vs. 6%, p<0.0001), than at rest. Patients with exercise PHT were more frequently male and had significant lower resting heart rate than those with no exercise PHT (**Table 1**). In addition, all patients with resting PHT (n=6, **Table 2**) also developed exercise PHT (resting PHT prevalence in exercise PHT compared to no exercise PHT group: p=0.027). There was no other significant difference between the 2 groups regarding demographic, clinical or exercise data, as well as risk factors and medications. The maximal exercise capacity reached was 4.8±1.2METs (64±14% of the predicted METs), ranging from 2.3 to 8.6 METs without significant difference between the 2 groups (p=0.12 and p=0.74 for the percentage of predicted METs).

Resting and exercise echocardiography

SPAP significantly increased from rest to exercise (from 38±8 mmHg to 62±16 mmHg, p<0.0001). Patients with exercise PHT had significant higher resting SPAP (p<0.0001, **Table 2**) and exercise-induced changes in SPAP **(Figure 1, Panel A and** B: +14.9±7 mmHg vs. +33.6±10 mmHg, p<0.0001). In patients with exercise PHT, the mean relative change in SPAP was 121±61%. During exercise, SPAP was doubled in 10 patients (21%) without exercise PHT and in 32 patients (56%, p<0.0001) with exercise PHT.

Compared to patients with no exercise PHT, those with exercise PHT (**Table 2**) had higher resting and exercise indexed LV end-diastolic volume (p=0.045 and p=0.04), and more severe resting and exercise AS severity (peak transaortic gradient: p=0.046 and p=0.008; mean transaortic gradient: p=0.04 and p=0.04), higher exercise e'-wave velocity (p=0.004) and larger exercise indexed LA area (p=0.001). There were also trends for significant higher resting and

exercise E-wave velocity (p=0.10 and p=0.07) and exercise indexed LV end-systolic volume (p=0.07).

Determinants of exercise SPAP and PHT

In simple linear regression, exercise SPAP was significantly correlated with resting SPAP (r=0.57, p<0.0001), heart rate (r=-0.20, p=0.045), E-wave velocity (r=0.19, p=0.05), exercise e'-wave velocity (r=0.19, p=0.009) and indexed LV end-diastolic volume (r=0.17, p=0.044). Both resting and exercise peak (r=0.23, p=0.02 and r=0.29, p=0.003) and mean (r=0.23, p=0.016 and r=0.24, p=0.013) transaortic pressure gradient were significantly correlated with exercise SPAP. In addition, the best correlation was found between exercise SPAP and exercise-induced changes in indexed LA area (r=0.40, p<0.0001). Multiple linear regression revealed that the independent predictors of exercise SPAP were exercise e'-wave velocity (β=11±5, p=0.046), exercise indexed LV end-diastolic volume (β=0.14±0.07, p=0.038), resting SPAP (β=0.9±0.2, p<0.0001) and exercise-induced changes in indexed LA area (β=1.3±0.4, p=0.001).

On multivariable analysis, using logistic regression (**Table 3**), the independent predictors of exercise PHT were male gender (odds-ratio [OR]=4.3, p=0.002), resting SPAP (OR=1.16, p=0.002), exercise indexed LV end-diastolic volume (OR=1.04, p=0.026), exercise e'-wave velocity (OR=1.35, p=0.047) and exercise-induced changes in indexed LA area (OR=1.36, p=0.006).

Cardiac event-free survival

The follow-up was complete in all patients (100%). The mean follow-up time was 19±11 months (median: 16 months, range: 2 to 48 months). During follow-up, 56 patients (53%) fulfilled the predefined end-point resulting in event-free survival of 72±4%, 50±5% and 34±6% at 1-, 2- and 3-year follow-up, respectively. There were 7 cardiovascular deaths during the follow-up (3

sudden deaths and 4 deaths following heart failure hospitalization). Of note, the 7 patients who died had developed exercise PHT (12%) but only 1 had resting PHT (p=0.014). The remaining cardiac events were aortic valve replacement dictated by the onset of symptoms (n=49). The main indication for surgery was the occurrence of syncope (n=4), angina (n=6), dyspnea (n=38) and significant arrhythmia (n=1).

During the follow-up, among the 6 patients with resting PHT, 1 died, 2 underwent an AVR and 3 remained free of event.

The raw rate of cardiac event (number of patients with an event divided by total number of patients in each group) was significantly higher in patients with exercise PHT (n=39 vs. n=17, 67% vs. 36%, p=0.0015).

Patients with exercise PHT had lower cardiac event-free survival (1-year: 65±6 vs. 81±6%, 2-year: 43±7 vs. 59±8%, 3-year: 22±7 vs. 55±9%, p=0.014; **Figure 2**). In univariable analysis, exercise PHT was associated with 2-fold increase in cardiac events compared to patients without exercise PHT (p=0.017, **Table 4**). Other univariable predictors of cardiac event were: peak aortic jet velocity ([HR]=2, 95% confidence interval [CI]: 1.35-2.97, p=0.001), mean aortic transvalvular gradient (HR=1.03, 95%CI: 1.01-1.04, p=0.02), LV filling time (HR=1.01, 95%CI: 1.00-1.01, p=0.014), indexed LV end-systolic volume (HR=1.03, 95%CI: 1.01-1.05, p=0.018), indexed LV end-diastolic volume (HR=1.02, 95%CI: 1.01-1.04, p=0.002) and indexed LA area (HR=1.06, 95%CI: 1.00-1.13, p=0.049). Of note, exercise capacity, as assessed by the maximal reached METs, was not associated with reduced cardiac-event free survival (HR=1.83, 95% CI: 0.7-4.8, p=0.21) and none of the other exercise parameters was associated with outcome.

Resting PHT (n=6) was not associated with reduced cardiac event-free survival (p=0.37).

However, there was a significant relationship between resting SPAP and outcome (Hazard ratio HR=1.03, 95%CI: 1.00-1.06, p=0.03). This relationship remained significant after adjustment for age and sex (HR=1.04, 95%CI: 1.00-1.07, p=0.03), but no longer after adjustment for peak or mean aortic transvalvular gradient (HR=1.03, 95% CI: 0.99-1.06, p=0.135 and HR=1.03, 95% CI: 0.99-1.06, p=0.08, respectively). Further adjustment with other resting echocardiographic data leads to a definite non-significant association between resting SPAP and cardiac event-free survival (HR=1.03, 95%CI: 0.99-1.07, p=0.15).

After adjustment for age and sex, exercise PHT was independently associated with reduced cardiac event-free survival (**Table 4**: HR=1.9, 95%CI: 1.1-3.4, p=0.025). With further adjustment including resting echocardiographic data, exercise PHT remained independently associated with cardiac events (HR=1.8, 95%CI: 1.0-3.3, p=0.047). As previously reported, exercise-induced changes in mean transaortic pressure gradient was associated with reduced event-free survival (HR=1.02, 95%CI: 1.01-1.03, p=0.003). In multivariable model (**Table 4**), after adjustment for age, sex, resting echocardiographic data and exercise-induced changes in mean transvalvular pressure gradient, exercise PHT remained an independent predictor of high risk of cardiac events (HR=2.0, 95%CI: 1.1-3.6, p=0.025). Of note, in this multivariable model, exercise-induced change in mean transaortic pressure gradient was also an independent predictor of events (p=0.043).

Using receiver-operating characteristic curve analysis, exercise SPAP had a good accuracy to predict cardiac events (area under the curve: 0.69). Of interest, the best cut-off value to predict cardiac events was exercise SPAP>60mmHg: sensitivity= 70%, specificity= 62%, positive predictive value= 67% and negative predictive value=64%.

In addition, to assess whether exercise SPAP was more accurate than resting SPAP to

predict cardiac event, we generated the C-statistic for each model. The C-statistics were systematically higher with exercise SPAP than resting SPAP in univariate, age- and sex-adjusted or age-, sex- and resting echocardiographic data-adjusted models (0.610 vs. 0.515, 0.613 vs. 0.557, and 0.664 vs. 0.611, respectively).

Incremental prognostic value of exercise PHT over resting AS severity

In the whole multivariate model, peak aortic jet velocity was the strongest resting echocardiographic predictor of outcome (HR=1.02, 95%CI: 1.01-1.03, p<0.0001). **Figure 3** shows the incremental value of exercise PHT over markedly elevated peak aortic jet velocity (>4.0m/s) in the prediction of cardiac events. The combination of both high peak aortic jet velocity and exercise PHT resulted in the worse outcome (p=0.008). As compared to the whole cohort, patients with high peak aortic jet velocity and exercise PHT had a 2.4-fold increase in risk of reduced event-free survival (95%CI: 1.4-4.03, p=0.002). Reducing the analysis only to the subset of patients with markedly elevated peak aortic jet velocity resulted in a significant impact of exercise PHT on outcome (HR=2.4, 95%CI: 1.1-5.2, p=0.014). Of note, patients with exercise PHT but without markedly elevated peak aortic jet velocity had similar 2-year event-free survival (54±10% vs. 56±11%, p=0.77) than those with markedly elevated peak aortic jet velocity but without exercise PHT.

Furthermore, the 7 deaths occurring during the follow-up were patients with both markedly elevated peak aortic jet velocity and exercise PHT (p=0.001).

Discussion

The main findings of the present study show that (1) exercise PHT (i.e. exercise SPAP>60mmHg) is a frequent condition (55% of the cohort) in patients with asymptomatic

severe AS and preserved LVEF, (2) the independent determinants of exercise PHT are male gender, resting SPAP and exercise parameters of diastolic burden (exercise indexed LV end-diastolic volume, exercise e'-wave velocity and exercise induced changes in indexed LA area), (3) exercise PHT is associated with alarming rate of cardiac death (12%) and with significant reduced cardiac event-free survival, (4) independent of age, sex, resting echocardiographic data and exercise-induced changes in mean transaortic pressure gradient, exercise PHT doubles the risk of cardiac events and (5) exercise PHT had an incremental prognostic value as compared to resting AS severity parameter. Conversely, although resting elevated SPAP may affect the clinical outcome, its prognostic value was weak in our study.

Pulmonary arterial hypertension in aortic stenosis

The prevalence of PHT varies considerably over studies according to patient selection criteria and the threshold used to define PHT. Overall, a SPAP >50mmHg is found in 15-30% of patients with severe AS [16-18] and recently, severe SPAP (>60mmHg) was reported in 19% of a large cohort of 626 AS patients [19].

However, no study, to the best of our knowledge, reported the prevalence of PHT in "truly" asymptomatic patients. In our cohort, a SPAP >50mmHg was rare and only identified in 6 patients (6%) suggesting that the impact of severe AS on LV diastolic function[20] and LA geometry and function [21;22] may be generally well counterbalanced by LA compliance and/or pulmonary vascular resistance. Of interest, these patients with resting PHT were particularly old, had a very severe AS, and half of them experienced cardiac events (including 1 death and 2 AVR), suggesting the poor outcome of this subset.

In contrast, a recent study has shown that PHT is frequent in surgery-referred patients with LV dysfunction and is independently associated with LA function impairment[23].

The potential impact on outcome of PHT in patients with AS is also a source of debate. In 1979, McHenry et al.[7] showed that PHT could be considered as a harbinger for sudden death and clinical deterioration. More recently, PHT in severe AS was also associated with a dismal prognosis under conservative management[24;25]. Nevertheless, PHT may frequently and rapidly be abolished following aortic valve replacement[24-26] leading to a more favorable long-term outcome[27].

Exercise pulmonary hypertension in aortic stenosis.

Exercise PHT was significantly more frequent (55%) than resting PHT (6%) in our cohort. This entity is characterized by lower resting heart rate and higher both rest and peak exercise indexed LV end-diastolic volume. During exercise, whereas some patients with no exercise PHT may only have mild increase in SPAP (**Figure 1, Panel A**), the vast majority of those with exercise PHT (**Figure 1, Panel B**) experienced a marked rise in SPAP. This phenomenon is essentially determined by the level of exercise e'-wave velocity, the exercise indexed LV end-diastolic volume and the exercise-induced changes in indexed LA area.

In AS, the chronically increased afterload results in progressive LV remodelling and myocardial hypertrophy. Although the increase in LV wall thickness is a compensatory mechanism that reduces systolic wall stress, it can result in impaired LV relaxation, reduced LV compliance and increased metabolic demands. The ability of the LV to adequately fill under normal pressures is thus altered and the LV diastolic pressure increases. As a result, LA slowly expands and becomes dysfunctional and less compliant, making it impossible to limit the transmission to the pulmonary vascular bed of any further increase, even minimal, in LV end-diastolic pressure observed during exercise. Furthermore, any degree of LV diastolic dysfunction (relaxation abnormality) and increased LV filling pressure at rest and/or at exercise can be

sufficient to trigger exercise PHT. In these patients, exercise echocardiography enables to unmask a more advanced impairment in LV diastolic properties, namely latent LV diastolic dysfunction. This is line with our observations since exercise PHT was mainly related to exercise parameters of diastolic burden. Of note, a limitation in LA compliance was confirmed by the significant correlation observed between exercise-induced changes in indexed LA area and exercise SPAP. For a given increase in LV filling pressure, patients with limited changes in LA dimensions (i.e. exhausted LA compliance reserve) during exercise displayed a higher increase in SPAP; this is even truer if LA emptying is not facilitated any more from recruitable LA function.

Clinical implication

Our results are the first to demonstrate that the measurement of SPAP during exercise echocardiography may improve risk stratification of asymptomatic severe AS. Indeed, patients who experienced exercise PHT (SPAP>60mmHg) multiplied by 2 the risk of cardiac events, even after adjustment for demographic and resting and exercise echocardiographic data. Among the 7 cardiovascular-related deaths occurring during follow-up, only 1 patient had resting PHT, but all of them had developed exercise PHT. Of interest, our data show that resting elevated SPAP is not independently associated with reduced cardiac event-free survival in “truly” asymptomatic patients with severe AS.

Hence, these results strongly emphasize the usefulness of exercise stress echocardiography in this clinical situation. Exercise PHT also had incremental prognostic value as compared to AS severity parameters (i.e. aortic jet velocity). Indeed, in patients with markedly elevated aortic jet velocity, those with exercise PHT exhibited a significant lower cardiac event-free survival (**Figure 3**) as compared to the others, resulting in poorer outcome. Furthermore,

patients with exercise PHT but without markedly elevated aortic jet velocity had similar prognosis than those without exercise PHT but with high aortic jet velocity. Thus, in patients with asymptomatic AS and <4m/s aortic jet velocity, the presence of exercise PHT is still able to identify a subset of patients at dismal prognosis (**Figure 3**), who may require a closer follow-up in order to look out for any changes in LV diastolic function and symptoms.

During test, an exercise-induced increase in mean transaortic pressure gradient by >18-20 mmHg has been recently identified as a marker of poor prognosis in asymptomatic AS[28;29]. Our results confirm that this parameter is associated with reduced cardiac event-free survival but we further show that independently to the changes in LV afterload, exercise PHT is an independent predictor of impaired prognosis. Interestingly, only one third of patients with exercise PHT also had marked increase in mean transaortic pressure gradient. This suggests that the presence of elevated exercise SPAP may unmask a subset of asymptomatic patients with latent LV diastolic dysfunction, reduced atrio-ventricular compliance and impaired pulmonary vascular resistance. These patients are probably more subject to rapidly develop symptoms and seem to be at higher risk of cardiac-related death. Consequently, the use of exercise stress echocardiography in asymptomatic patients with severe AS could be recommended. At peak exercise, the measurement of both mean transaortic pressure gradient and SPAP, which are technically easy, rapid and with good reproducibility[13;29-32], may improve the management of such patients. Indeed, the high rate of cardiac-related death observed in patients with exercise PHT (12%), despite normal exercise test, should encourage prompt surgery, which is, in asymptomatic patients, associated with very low operative mortality[3] and low prosthesis-related complication rate. Conversely, patients with no exercise PHT and no marked increase in mean transaortic gradient can be followed-up safely.

Limitations

Apparent non-significant results may be related to the relatively small sample size of the study. Specifically, the absence of relationship between maximal exercise capacity parameters and cardiac event-free survival could be mainly due to a type II error. Nevertheless, this limitation does not affect the validity of the main result of the study, which is the demonstration that exercise PHT may have an incremental prognostic value in patients with asymptomatic severe AS.

Despite careful assessment, the evaluation of the occurrence of symptoms at a low workload during exercise remains subjective. Hence, while rare, it is possible that some patients with symptoms during exertion were included in the final population.

As in our previous studies[13;33], the right atrial pressure was estimated at 10 mmHg both at rest and during exercise. Hence, we may have missed the potential influence of exercise-induced changes in right atrial pressure. Nevertheless, the noninvasive evaluation of right atrial pressure during exercise (i.e., when venous compliance is known to decrease) with noninvasive methods such as Doppler echocardiography remains difficult, is probably subject to low accuracy, and is not validated. Moreover, right atrial pressure is frequently assumed to be 5 mmHg in normal subjects[30] and 10 mmHg in patients with valvular disease[12].

The absence of evaluation of the presence and extent of coronary artery disease in patients not referred to surgery is also a limitation of this report. However, these patients have, by definition, no resting symptoms, normal LVEF and exercise test, suggesting that they are "truly" asymptomatic. In this context, coronary angiography is not recommended and the rate of significant coronary artery disease in our population is probably low.

Conclusion

In asymptomatic patients with severe AS, the main determinants of exercise PHT are male gender, resting SPAP and exercise parameters of diastolic burden. Exercise PHT is associated with 2-fold increased risk of cardiac events and provides incremental prognostic value, independently of demographic, resting echocardiographic data and exercise-induced changes in mean transaortic pressure gradient. These results support the use of exercise stress echocardiography in asymptomatic AS.

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Conflict of Interest Disclosures: None

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Table 1. Demographic, clinical and exercise data.

Variables	Whole cohort (n=105)	No Exercise PHT (n=47, 45%)	Exercise PHT (n=58, 55%)	p-value
Demographic and clinical data				
Age, years	71±9	71±7	71±9	0.77
Male gender, n (%)	62 (59)	23 (48)	39 (68)	0.03
Body surface area, m²	1.8±0.2	1.8±0.2	1.8±0.2	0.81
Heart rate, bpm	71±13	73±14	68±12	0.04
Systolic arterial pressure, mmHg	142±20	139±19	144±20	0.13
Diastolic arterial pressure, mmHg	76±11	76±12	77±10	0.64
Risk factor				
Hypertension, n (%)	69 (66)	28 (60)	41 (71)	0.21
Overweight, n (%)	36 (34)	15 (32)	21 (36)	0.68
Dyslipidemia, n (%)	54 (51)	24 (51)	30 (52)	0.94
Diabetes, n (%)	18 (17)	9 (19)	9 (16)	0.68
Smoker, n (%)	35 (33)	14 (30)	21 (36)	0.63
LV hypertrophy, n (%)	51 (49)	27 (57)	25 (43)	0.14
Exercise data				
Maximal exercise capacity, Mets	4.8±1.2	4.6±0.8	4.9±1.3	0.12
Percentage of predicted exercise capacity, %	64±14	64±12	63±15	0.74
Heart rate, bpm	119±17	118±17	119±17	0.62
Systolic arterial pressure, mmHg	177±22	174±20	179±23	0.20
Diastolic arterial pressure, mmHg	86±14	85±15	87±13	0.52

PHT indicates pulmonary arterial hypertension and LV, left ventricular.

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Table 2. Resting and exercise echocardiographic data.

Variables	Whole cohort (n=105)	No Exercise PHT (n=47, 45%)	Exercise PHT (n=58, 55%)	p-value
Resting LV function				
Indexed LV end-systolic volume, mL/m²	19±10	19±9	20±11	0.64
Indexed LV end-diastolic volume, mL/m²	54±17	51±15	57±18	0.045
LV ejection fraction, %	67±7.6	66±7.5	67.5±7.7	0.40
LV Global longitudinal strain, %	-16.3±2.6	-16.3±2.5	-16.2±2.7	0.82
E-wave velocity, cm/s	0.80±0.2	0.76±0.2	0.84±0.2	0.10
A-wave velocity, cm/s	0.93±0.3	0.89±0.3	0.97±0.3	0.23
e'-wave velocity, cm/s	7.8±2.2	7.6±1.8	8.0±2.5	0.35
E/A ratio	0.92±0.4	0.90±0.3	0.94±0.4	0.64
E/e' ratio	10.9±3.6	10.4±3.1	11.2±4.1	0.28
Exercise LV function				
Indexed LV end-systolic volume, mL/m²	18±8.3	17±7.3	20±8.9	0.07
Indexed LV end-diastolic volume, mL/m²	54±17	50±15	57±19	0.04
LV ejection fraction, %	67±9	67±8	66±10	0.41
E-wave velocity, cm/s	1.27±0.3	1.22±0.3	1.33±0.3	0.07
A-wave velocity, cm/s	1.01±0.3	0.98±0.3	1.05±0.3	0.43
e'-wave velocity, cm/s	10.1±2.7	9.2±2.1	10.8±3.0	0.004
E/A ratio	1.35±0.6	1.25±0.4	1.44±0.8	0.25
E/e' ratio	13.4±5.2	13.3±4.6	13.4±6.0	0.94
Resting Aortic stenosis severity				
Peak transaortic gradient, mmHg	72±23	67±19	76±26	0.046
Mean transaortic gradient, mmHg	45±15	42±12	47±16	0.04
Aortic valve area, cm²	0.89±0.1	0.88±0.1	0.90±0.1	0.59
Indexed aortic valve area, cm/m²	0.50±0.1	0.49±0.1	0.50±0.1	0.63
Exercise Aortic stenosis severity				
Peak transaortic gradient, mmHg	91±28	83±21	97±31	0.008
Mean transaortic gradient, mmHg	57±18	53±14	60±20	0.04
Aortic valve area, cm²	0.97±0.3	0.95±0.2	0.99±0.3	0.41
Indexed aortic valve area, cm/m²	0.54±0.16	0.53±0.1	0.55±0.2	0.46
Resting indexed LA area, cm²/m²	12.5±3.4	12.7±4	12.3±3	0.64
Exercise indexed LA area, cm²/m²	11.2±3.6	9.8±3.6	12.2±3.4	0.001
Resting PHT, n (%)	6 (6)	0 (0)	6 (10)	0.027
Resting SPAP, mmHg	38±8	34±6	41±8	<0.0001
Exercise SPAP, mmHg	62±16	48±9	74±9	<0.0001

LV indicates left ventricular, LA, left atrial and SPAP, systolic pulmonary arterial pressure.

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Table 3. Logistic regression: Independent determinants of exercise PHT.

Variables	Odds Ratio	95%CI	p-value
Male gender	4.3	1.2-15.1	0.002
Resting SPAP, per mmHg	1.16	1.06-1.27	0.002
Exercise indexed LV end-diastolic volume, per mL/m²	1.04	1.00-1.07	0.026
Exercise-induced changes in indexed LA area, per cm²/m^2	1.36	1.1-1.7	0.006
Exercise e'-wave velocity, per cm/s	1.35	1.00-1.8	0.047

Adjustment performed with age, resting heart rate, resting mean transaortic pressure gradient, exercise peak transaortic pressure gradient, exercise e'-wave velocity and exercise indexed LV end-systolic volume. LV indicated left ventricular, SPAP, systolic pulmonary arterial pressure and LA, left atrium area.

Table 4. Cox proportional-Hazards regression analysis for the prediction of cardiac event-free survival.

	Exercise PHT		
Models	Hazard-ratio	95%CI	p-value
Univariable	2.0	1.1-3.5	0.017
Age- and sex-adjustment	1.9	1.1-3.4	0.025
Resting data- adjusted *	1.8	1.1-3.3	0.045
Exercise data-adjusted †	2.0	1.1-3.6	0.025

* adjustment including age, sex, indexed LA area, LV end-systolic volume, LV end-diastolic volume, E/e' ratio, peak aortic jet velocity. † adjustment including age, sex, resting echocardiographic data and exercise-induced changes in mean transaortic pressure gradient. CI indicates confidence interval.

Figure Legends:

Figure 1. Impact of exercise on systolic pulmonary arterial pressure in patients without exercise pulmonary hypertension (Panel A) and with exercise pulmonary hypertension (Panel B).

Figure 2. Cardiac event-free survival according to the presence or absence of exercise pulmonary hypertension (PHT).

Figure 3. Cardiac event-free survival according to the presence or absence of exercise pulmonary hypertension (Ex. PHT) and markedly elevated peak aortic (Ao) jet velocity (>4m/s).