Prognostic Value of Peak Exercise Systolic Pulmonary Arterial Pressure in Asymptomatic Primary Mitral Valve Regurgitation

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ABSTRACT (250 words)

Background: The contribution of exercise echocardiography in primary asymptomatic mitral regurgitation (MR) remains debated. We aimed to gain evidence regarding its usefulness in this setting, and investigate the prognostic value of peak exercise systolic pulmonary artery pressure (SPAP).

Methods: We identified 177 patients (56±13 years, 69% males) with moderate-to-severe (3+)/severe (4+) degenerative MR and preserved left ventricular ejection fraction (LVEF), in sinus rhythm, referred for a clinically indicated exercise echocardiography. Our end-point, MR-related events, was a composite of all-cause death or occurrence of symptoms, heart failure, atrial fibrillation, LVEF<60%, LV end-systolic diameter≥45mm or resting SPAP>50mmHg.

Results: At rest, effective regurgitant orifice area was 48±16mm^2, regurgitant volume 74±26ml, SPAP 32±7mmHg, and MR severe in 138 patients (78%). The peak exercise SPAP was 55±10mmHg. Exercise test positivity motivated surgery in 26 patients, 11 underwent prophylactic surgery, 10 were lost to follow-up and 130 included for the outcome analysis. During a follow-up of 19±7 months, 31 MR-related events (24%) were reported. Peak exercise SPAP was predictive of outcome in univariate analysis (p=0.01) and after adjustment for age, gender, MR severity, and resting SPAP (p<0.05). A peak exercise SPAP≥50mmHg was associated with worse event-free survival (HR=5.24; 95%CI:1.77-15.53; p=0.003), but not the threshold of ≥60mmHg proposed in previous guidelines (HR=1.70; 95%CI:0.71-4.03; p=0.24).

Conclusions: Our findings support the use of exercise echocardiography for risk stratification in asymptomatic primary MR and suggest a lower peak exercise SPAP threshold (50 mmHg) than previously recommended to define the timing of intervention. Prospective studies are needed to confirm these findings.

Key words. Mitral valve regurgitation, valvular heart disease, exercise echocardiography, systolic pulmonary artery pressure

ABBREVIATIONS

AF: Atrial fibrillation

AUC: Area under the curve

CI: Confidence interval

EROA: Effective regurgitant orifice area

HR: Hazard ratio

LA: Left atrium

LV: Left ventricle

LVEF: Left ventricular ejection fraction

MR: Mitral regurgitation

ROC: receiver-operating characteristic

RVol: regurgitant volume

SPAP: Systolic pulmonary arterial pressure

INTRODUCTION

Primary mitral valve regurgitation (MR) is the second most frequent indication for valvular heart surgery in Western countries [1,2]. MR evaluation mainly relies on echocardiography, which provides key parameters to guide treatment decision including MR severity grade and mechanism, left ventricular (LV) dimensions and function [3], left atrial (LA) volume [4,5] and systolic pulmonary arterial pressure (SPAP). In patients with MR-related symptoms [6], atrial fibrillation (AF) [7], LV systolic dysfunction or dilatation, or elevated SPAP at rest, the guidelines endorse intervention due to the adverse prognostic implications of these findings [8–10]. In contrast, the management of patients with asymptomatic severe MR in sinus rhythm and preserved LV ejection fraction (LVEF) remains debated [11,12], emphasizing the crucial need to further identify prognostic factors in this subgroup of patients. In this setting, an incremental prognostic value of exercise echocardiography has been suggested with a SPAP ≥60 mmHg at peak exercise reported to be predictive of symptoms occurrence during follow-up [13,14]. Nonetheless, the publication of discordant results on the potential usefulness of exercise echocardiography, including peak SPAP in patients with aortic valve stenosis [15–18], and the limited supporting evidence [19–22], has resulted into the removal of this parameter in the latest version of the European guidelines [8]. In the latest North American guidelines, the use of exercise echocardiography is presented as a class IIa of recommendation, B-NR level of evidence, in patients with primary MR (Stages B and C) with the aim of establishing true exercise tolerance like other exercise tests or in case of discrepancies between symptoms and MR evaluation at rest. The use of peak exercise SPAP to orientate patients toward intervention is not mentioned [10].

To further gain evidence in favor of the clinical usefulness of exercise echocardiography, we investigated the prognostic value of peak exercise SPAP in a cohort of patients with asymptomatic primary MR who underwent a clinically indicated exercise echocardiography at our institution.

METHODS

Study design

We retrospectively included 177 patients with moderate-to-severe (grade 3+) / severe (grade 4+) asymptomatic degenerative MR and preserved systolic function (LVEF ≥60%), in sinus rhythm, who underwent a clinically indicated exercise echocardiogram at our institution (Bichat Hospital, Paris, France) between May 2005 and December 2018 [23]. Mean age was 56±13 years and 123 patients (69%) were males. Exercise echocardiogram is part of the routine evaluation of asymptomatic patients with MR and echocardiographic parameters are not used to determine indication for surgery at our institution. Exclusion criteria were rheumatic valve disease, congenital heart valve disease, endocarditis, associated mitral stenosis or other valvular disease of grade ≥2/4 and SPAP at rest >50 mmHg. All baseline data were collected from a review of the patients' charts. The outcome was determined by direct contact with the patients and/or referring practitioners or collected from their medical records. The study complies with the Declaration of Helsinki and was approved by our local ethics committee.

Echocardiographic evaluation at rest

All patients underwent a comprehensive Doppler transthoracic echocardiography using EPIQ 7 (Philips Healthcare, Andover, Massachusetts), iE33 (Philips Healthcare, Andover, Massachusetts) or Vivid 7 (General Electrics, Chalfont, St. Giles, United Kingdom) ultrasound machines [18]. Mitral valve anatomy and MR characteristics were assessed using multiple views with color Doppler imaging [23]. MR severity was quantified using the proximal isovelocity surface area (PISA) method with calculation of the mitral regurgitant volume (RVol) and effective regurgitant orifice area (EROA) [23]. An EROA ≥40 mm^2 or a RVol ≥60 ml defined severe MR (4+), and an EROA=30-39 mm^2 or a RVol=45-59 ml defined moderate to severe MR (3+) [23,24]. LVEF was determined using the biplane Simpson's method or visual assessment.

LA volume was calculated using the biplane Simpson's method in end-systole. Continuous wave Doppler measurement of the tricuspid regurgitation velocity was used to calculate SPAP using the simplified Bernoulli equation in the apical 4-chamber and right ventricular inflow views [25]. As no intra-venous line was inserted, we did not use saline injection to increase detection rate of the TR signal. Right atrial pressure was estimated at 10 mmHg at rest as well as at peak exercise.

Exercise-stress echocardiography

Following the resting echocardiogram, patients underwent a symptom-limited exercise-stress echocardiography on a bicycle ergometer in a semi-supine position [18,23]. Blood pressure and a continuous 12-lead electrocardiogram were monitored throughout the test. Workload was increased every 2 or 3 minutes by 20/30 W depending on the physical ability of the patient [18]. At each stage, LV systolic function, occurrence of LV wall motion abnormalities, and SPAP were evaluated. MR quantification during exercise was not part of our standard protocol. The maximum predicted heart rate was 220 - age. The exercise test was defined as positive if it was stopped because of the occurrence of dyspnea, angina, syncope, ST-segment depression of ≥2 mm or sustained ventricular arrhythmia. Criteria for a positive echocardiographic test were independently analysed and defined by a SPAP ≥60 mmHg at peak exercise [13,14], the occurrence of LV dysfunction (LVEF <60%) or absence of contractile reserve, or the development of LV wall motion abnormalities. Contractile reserve was defined as the difference between LVEF at peak exercise and at rest. In the case of a non-measurable peak exercise SPAP, the exercise echocardiogram was considered negative in the absence of other criteria for positivity.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and median (25%; 75%), and categorical variables as numbers (percent). Distribution of variables was assessed using the Shapiro-

Wilk normality test. Comparison between groups was performed using the t test, the Wilcoxon test or the χ^2 test as appropriate. Event-free survival was analyzed using the Kaplan-Meier method and defined as the time from the exercise echocardiogram to the occurrence of all-cause death or indication for intervention out to a follow-up period of 2 years, in order to assess the short-term prognostic value of SPAP at peak exercise. Indication for intervention referred to class I or IIa recommendation for intervention according to the 2017 ESC guidelines (occurrence of symptoms, heart failure, AF, LVEF <60%, LV end-systolic diameter ≥45 mm or resting SPAP >50mmHg) [8]. Patients who underwent prophylactic surgery (absence of class I or IIa recommendation for intervention) were censored at the time of intervention. Surgery performed while patients remained asymptomatic with a LV end-systolic diameter between 40 and 44 mm, a reparable valve and LA enlargement or flail leaflet, was considered as prophylactic. The two-sided log-rank test was used to determine survival differences. The Cox proportional hazards model was used to evaluate the predictive value of echocardiographic parameters for event-free survival in univariate analysis and after adjustment. The optimal cut-off value of SPAP at peak exercise to predict outcome was determined from the receiver-operating characteristic (ROC) curve after calculation of the area under the curve (AUC). A p value <0.05 was considered statistically significant. Statistical analyses were performed using the JMP 14 software (SAS institute, Cary, NC, USA).

RESULTS

Baseline characteristics of the study population

At rest, EROA was 48±16 mm^2, RVol was 74±26 ml, SPAP was 32±7 mmHg, LA volume index was 67±29 ml/m^2. LVEF was 67±4% and was assessed visually in 43 patients (24%). Severe MR was present in 138 patients (78%). A flail leaflet was observed in 61 cases (35%). Baseline clinical and echocardiographic characteristics are presented in Table 1.

Exercise echocardiography

All patients completed the exercise test without complications. The most frequent reasons for stopping the test were fatigue (62%) and dyspnea (21%). The mean percentage of maximum predicted heart rate was 87±10% and was ≥85% in 102 patients (63%). The peak exercise SPAP was 55±10 mmHg. Peak exercise SPAP was ≥60 mmHg in 49 patients (28%) and ≥50 mmHg in 116 patients (66%) (Table 1).

Twenty-six patients (15%) had a positive exercise test (Figure 1). The main reason for test positivity was dyspnea in 24 patients (92%) and ventricular arrhythmias in 2 patients (8%). Both patients had normal baseline LVEF measured at 65% and presented with several episodes of non-sustained polymorphic ventricular arrhythmia at peak exercise (5 to 7 complexes). Compared to those with a negative exercise test, patients with a positive exercise test were older (62±10 vs 55±14 years, p=0.006), presented with more severe MR (RVol 81±19 vs. 72±27 ml, p=0.02) and more often had a flail leaflet (62 vs. 30%, p=0.002). SPAP at rest (36±6 vs 32±7 mmHg, p=0.006) and at peak exercise (61±9 vs 54±10 mmHg, p<0.0001) were significantly higher in patients with a positive exercise test as was the rate of patients with a SPAP at peak exercise >60 mmHg (73 vs. 20%, p<0.0001). No difference was observed for LVEF (p=0.75) or LA volume index (p=0.28) (Table 1).

Among the 151 patients (85%) with a negative exercise test (mean percentage of maximum predicted heart rate 87±9%), exercise echocardiography was positive in 30 patients (20%). All positive exercise echocardiograms were due to a SPAP ≥60 mmHg. No patients developed a wall motion abnormality or LVEF impairment. Compared to patients with a negative exercise echocardiogram, those with a positive exercise echocardiogram were older (62±11 vs. 53±13 years, p=0.0005), but presented with a similar degree of MR based on the EROA and RVol (44±13 vs. 47±17 mm², p=0.54 and 72±24 vs. 72±28 ml, p=0.95 respectively). SPAP at rest was slightly higher (37±8 vs 30±6 mmHg, p<0.0001) (Table 1).

Management and outcome of patients

The 26 patients with a positive exercise test were referred for mitral valve surgery. Among the 151 remaining patients, 11 (7%) underwent a prophylactic mitral valve surgery within 3 months and 10 (7%) were lost to follow-up. The outcome analysis was performed on the 130 remaining patients (86%). In these 130 patients, mean age was 55±14 years, 95 patients (73%) were males, 93 (72%) presented with severe MR and 35 (27%) with a flail leaflet. SPAP at rest was 31±7 mmHg and SPAP at peak exercise was 53±10 mmHg. SPAP at peak exercise was ≥60 mmHg in 23 patients (18%) and ≥50 mmHg in 79 (61%).

During a mean follow-up of 19±7 months, no deaths were observed and 31 patients (24%) developed a class I/IIa indication subsequently leading to mitral valve surgery. The main reason for surgery was the new onset of dyspnea in 22 patients (71%). AF occurred in six patients (19%) and was associated with dyspnea in five cases. In the remaining eight asymptomatic patients (26%), surgery was indicated during follow-up due to the development of LV dilation, an LVEF <60% and/or SPAP >50 mmHg at rest [8]. The flow chart of the population is presented in Figure 1.

In univariate analysis, SPAP at peak exercise was a determinant of the occurrence of an MR-related event (Hazard Ratio [HR] = 1.05; 95% confidence interval [CI]: 1.01-1.09; p=0.01). MR severity based on EROA (HR=1.01; 95% CI: 0.99-1.04; p=0.34), RVol (HR=1.01; 95% CI: 0.99-1.03; p=0.29), or MR grade (HR=1.34; 95% CI: 0.64-2.80; p=0.43) were not associated with outcome. In multivariate analysis after adjustment for age, gender, MR severity grade and SPAP at rest, SPAP at peak exercise remained significantly associated with outcome (p<0.05). Adjusting for age, gender, MR severity grade, LA volume index and LV end-systolic diameter, did not change the result (p=0.01).

The threshold of 60 mmHg for SPAP at peak exercise as proposed in the previous version of the ESC guidelines [14] for valve intervention was not discriminative in terms of event free survival as shown in the Kaplan-Meier analysis (p=0.14) (Figure 2). However, the ROC analysis revealed that a peak exercise

SPAP of 50 mmHg (AUC=0.63, sensitivity=0.90, specificity=0.37) provided the best cut-off value for predicting MR-related events. In univariate analysis, a peak exercise SPAP ≥50 mmHg was significantly associated with the occurrence of MR-related events (HR=4.90; 95% CI: 1.71-14.02; p=0.0004). Event-free survival analysis confirmed that patients with a peak exercise SPAP ≥50 mmHg had a significantly worse event-free survival than those with a peak exercise SPAP <50 mmHg (27 vs. 4 events at 2 years respectively, p=0.001) (Figure 2). After adjustment for age, gender and MR severity grade, peak exercise SPAP ≥50 mmHg remained significantly predictive of outcome (HR=5.24; 95% CI: 1.77-15.53; p=0.003). Adding LA volume index and LV end-systolic diameter into the multivariate model did not affect the results (HR=5.03; 95% CI: 1.66-15.30; p=0.004). Adjusting for SPAP at rest (HR=3.40; 95% CI: 1.10-10.57; p=0.03) or excluding the 21 patients (12%) in whom SPAP was not measurable at peak exercise (HR=4.27; 95% CI: 1.29-14.09; p=0.02) did not change the results.

The results were similar when restricting the analysis to the subgroup of 93 patients (72%) with severe MR, in whom 22 MR-related events (71%) occurred and a significantly worse event-free survival was observed in patients with a peak exercise SPAP ≥50 mmHg (p=0.01). Similarly, in the subgroup of 35 patients (30%) with a flail leaflet, 14 patients (40%) had an MR-related event, and event-free survival was significantly worse in patients with a peak exercise SPAP ≥50 mmHg (p=0.03). In both subgroups, a threshold of peak exercise SPAP ≥60 mmHg was not discriminative in terms of event-free survival (p=0.22 and p=0.18 respectively) (Figure 3).

DISCUSSION

In this observational study, we confirmed and extended the incremental value of peak exercise SPAP as an important determinant of outcome in patients with asymptomatic degenerative MR. One main finding was that a peak exercise SPAP ≥50 mmHg was a strong independent predictor of the occurrence of indication for intervention, suggesting that a lower SPAP cut-off value than the 60 mmHg mentioned in previous guidelines should be used to define indication for intervention [14,26].

Determining the symptomatic status of patients with primary MR can be an arduous task as symptoms may develop indolently in chronic MR. Some patients may progressively reduce their everyday activity to avoid MR-related symptoms, leading to them potentially overestimating their exercise tolerance. Others may minimize their functional limitation because of the fear of intervention or cultural factors. Exercise testing to uncover functional limitations in patients with an unclear symptomatic status may facilitate the identification of class I recommendation [27,28]. However, a striking observation of both the Euro Heart Survey [2] and of the more recent Valvular Heart Disease II survey [1], is the underuse of exercise testing in asymptomatic patients with valvular heart disease. In the latter study, less than 5% of patients with primary MR underwent an exercise test despite a clear class I recommendation [8,9]. Similar to previous publications [29], we observed that 15% of patients who claimed to be asymptomatic in the present study displayed functional limitations, emphasizing the importance of exercise testing in patients with asymptomatic MR who are able to exercise.

Currently, the timing of intervention in "truly" asymptomatic severe MR patients with sinus rhythm, preserved LV function and dimensions, and a SPAP at rest <50 mmHg remains a topic of debate [11,12]. On the one hand, early intervention exposes patients to the potential risks of surgery and, in case of mitral valve replacement, to prosthesis-related complications. In this latter regard, it is worth noting that mitral valve repair rates remain suboptimal in the USA [30] and in France [31], and that "prophylactic" surgery should only be performed in experienced hands in patients at low surgical risk with a high likelihood of successful mitral valve repair. On the other hand, late intervention ("rescue surgery") in patients with severe symptoms or LV consequences considerably increases the operative risk, exposes the patient to potential irreversible myocardial damage that may persist after surgery and impede long term-survival [32].

Identifying prognostic parameters that may identify asymptomatic patients who may potentially benefit from an early intervention is thus critical.

In addition to evaluating functional capacity and unmasking falsely asymptomatic patients, exercise echocardiography also allows the measurement of echocardiographic parameters of potential prognostic value in MR patients [23,33–36]. However, strong evidence from large scale cohorts is lacking and has contributed to the low rate of integration of exercise echocardiography into the management algorithm of these patients. In a study published a decade ago, Magne et al demonstrated that exercise-induced pulmonary hypertension was associated with a significantly lower 2-year event-free survival in 78 asymptomatic patients with at least moderate degenerative MR. A peak exercise SPAP >56 mmHg best predicted the occurrence of symptoms in this study [13]. These results supported a level IIb / evidence C recommendation in both the 2006 ACC/AHA and 2012 ESC/EACTS guidelines, advocating the use of a peak exercise SPAP ≥60 mmHg to guide patients toward surgery [14,26]. However, the latest North American and European guidelines no longer integrate this parameter, advocating for the search of further evidence [22,36,37] and emphasizing the importance of the present study. In the current study, we confirmed these previous observations, in a larger cohort of patients and propose a lower peak exercise SPAP threshold of 50 mmHg to identify patients potentially benefitting from early intervention. In our study, a peak exercise SPAP ≥50 mmHg (which provided the best sum of sensitivity and specificity in the ROC analysis) was a strong and independent predictor of outcome and associated with a 5-fold increase in the risk of developing MR-related events during follow-up. The prognostic value of a peak exercise SPAP ≥50 mmHg was observed in the overall population as well as in the subsets of patients with severe MR or flail leaflet (which also provided prognostic information). These data support a greater integration of exercise echocardiography in the evaluation and management of all subsets of patients with degenerative MR, irrespective of the phenotype.

Our study has several limitations that need to be acknowledged. First, this is a retrospective, single center, observational study, with a relatively small number of patients. Although this is the largest cohort to date of patients with asymptomatic primary MR who underwent exercise echocardiography, there is an important need for prospective and multicenter studies to confirm our results. However, it is worth mentioning that a single center design provides a more homogenous assessment and management of patients. Second, only patients with degenerative MR were included in the present study. Consequently, our results may not be generalizable to other causes of primary MR such as rheumatic valve disease. Third, SPAP at peak exercise could not be measured in 21 patients (12%) due to poor Doppler signals. These patients were considered as having normal SPAP during exercise. This was an uncommon situation occurring in only 12% of our patients, and the outcome analyses remained unchanged after excluding the patients in whom SPAP was not measurable. We used a 10 mmHg right atrial pressure value at rest and at peak exercise in all patients. Although it may have led to some overestimation of the SPAP at rest, measurement of the right atrial pressure during exercise is challenging, and our choice increased both the feasibility and reproducibility of SPAP measurement during exercise. Fourth, a threshold of peak exercise SPAP ≥60 mmHg was not discriminative in terms of event-free survival in our study. However, the number of cases with SPAP ≥60 mmHg was relatively small (23 patients) and a lack of discriminatory power cannot be excluded. Nevertheless, even if a threshold of 60 mmHg would have been associated with a higher MR-related event rate, it would not have changed the fact that a lower threshold was predictive of the outcome and could guide the decision-making process. The younger age observed in our population compared to other publications, with less LV and LA remodeling, better chamber compliance and lower SPAP at baseline, might have contributed to the lower peak exercise SPAP threshold we identified. Fifth, only baseline and peak exercise SPAP were recorded. In a prospective cohort of 111 asymptomatic patients with primary MR, Toubal et al showed that an early rise in SPAP >15 mmHg at a low level of exercise during stress echocardiography (workload 25 Watts) was associated with a 2-fold increase in the risk of cardiac events defined by a composite of mitral valve surgery, new onset of AF, heart failure, cardiac-related hospitalization, or death of cardiac origin [37]. Although, the kinetics of SPAP changes was not available in the present study, it may represent an interesting parameter to take into consideration in addition to the absolute rise in SPAP. Sixth, the additional value of other parameters such as the global longitudinal strain or the TAPSE and tissue Doppler imaging for the assessment of the left and right ventricular systolic functions respectively deserve further evaluation. Finally, peak exercise SPAP above 50 mmHg has also been reported in healthy individuals [38]. Although the outcome of these patients remains unclear, we acknowledge that specificity of such SPAP elevation in our study was relatively low but on the other hand, sensitivity was high and the absence of elevation was reassuring. Therefore, we do not recommend using SPAP elevation during exercise in isolation but integrated with other parameters such as comorbidities, LA size, and likelihood of valve repair for the decision-making process of patients with asymptomatic degenerative MR.

CONCLUSION

In a cohort of patients with asymptomatic degenerative MR who underwent a clinically indicated exercise echocardiography, SPAP was an independent predictor of outcome and a threshold of peak exercise SPAP ≥50 mmHg was associated with a 5-fold increase in the risk of developing an indication for intervention during follow-up. Our findings support the use of exercise echocardiography for risk stratification and the management of asymptomatic patients with degenerative MR and suggest that a lower peak exercise SPAP threshold value than the previously recommended 60 mmHg should be used to define the timing of intervention. Future prospective studies are needed to confirm these findings.

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DATA AVAILABILITY STATEMENT:

The data underlying this article will be shared on reasonable request to the corresponding author.

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FIGURE LEGENDS

Figure 1. Flow chart describing the management of the study population according to the outcome of the exercise test and of the exercise echocardiography.

Figure 2. A peak exercise SPAP ≥50mmHg is a strong prognostic factor in asymptomatic degenerative mitral regurgitation.

Kaplan-Meier curves display event-free survival (occurrence of MR-related events) according to (A) a SPAP at peak exercise ≥60 mmHg or <60 mmHg, and (B) ≥50 mmHg or <50 mmHg.

Figure 3. Event-free survival curves presenting the prognostic value of systolic pulmonary arterial pressure (SPAP) at peak exercise in the subgroups of patients with severe MR and a flail leaflet.

Kaplan-Meier curves display event-free survival (occurrence of MR-related events) according to a SPAP at peak exercise ≥60 mmHg or <60 mmHg, and ≥50 mmHg or <50 mmHg in the subgroups of patients with severe MR (A and B respectively) and a flail leaflet (C and D respectively).

Table 1. Baseline clinical and echocardiographic characteristics of the study population

	Overall N=177	Positive exercise test N=26	Negative exercise test N=151	p	Negative exercise test N=151			Negative exercise test and considered for the outcome analysis * N=130		
					Peak exercise SPAP ≥ 60 mm Hg N=30	Peak exercise SPAP < 60 mm Hg N=121	p	Peak exercise SPAP ≥ 50 mm Hg N=79	Peak exercise SPAP < 50 mm Hg N=51	p
Age	56 ± 13	62 ± 10	55 ± 14	0.006	62 ± 11	53 ± 13	0.0005	58±14	49±12	0.0001
Male gender	123 (69)	14 (54)	109 (72)	0.07	21 (70)	88 (73)	0.77	61 (77)	34 (67)	0.19
Body surface area (m2)	1.8 ± 0.2	1.7 ± 0.2	1.9 ± 0.2	0.007	1.8 ± 0.2	1.9 ± 0.3	0.36	1.9±0.2	1.9±0.2	0.85
Body mass index (kg/m2)	24 ± 4	23 ± 3	24 ± 4	0.33	24 ± 3	24 ± 4	0.63	24±4	23±4	0.04
Coronary artery disease	3 (2)	0 (0)	3 (2)	0.37	1 (4)	2 (2)	0.60	3(4)	0 (0)	0.18
History of stroke	5 (3)	0 (0)	5 (4)	0.26	2 (7)	3 (3)	0.28	4 (5)	0 (0)	0.10
Hypertension	35 (23)	8 (40)	27 (21)	0.08	7 (26)	20 (20)	0.48	19 (26)	6 (14)	0.13
Sinus rhythm	177 (100)	26 (100)	151 (100)	N/A	30 (100)	121 (100)	N/A	79 (100)	51 (100)	N/A
Echocardiography at rest										
Flail leaflet	61 (35)	16 (62)	45 (30)	0.002	13 (43)	32 (27)	0.08	23 (29)	12 (24)	0.48
Effective regurgitant orifice (mm2)	48 ± 16	52 ± 15	47 ± 17	0.07	44 ± 13	47 ± 17	0.54	44 ± 15	48 ± 16	0.29
Regurgitant volume (mL)	74 ± 26	81 ± 19	72 ± 27	0.02	72 ± 24	72 ± 28	0.95	70 ± 22	69 ± 27	0.45
Severe MR	138 (78)	25 (96)	113 (75)	0.005	25 (83)	88 (73)	0.22	58 (73)	35 (69)	0.56
End diastolic LV diameter (mm)	58 ± 6	57 ± 6	59 ± 6	0.34	59 ± 6	58 ± 6	0.52	58 ± 6	58 ± 6	0.99
End systolic LV diameter (mm)	33 ± 5	34 ± 4	33 ± 5	0.63	34 ± 5	33 ± 5	0.53	33 ± 5	34 ± 6	0.30
LV ejection fraction (%)	67 ± 4	67 ± 4	67 ± 3	0.75	66 ± 3	67 ± 4	0.56	66 ± 3	67 ± 4	0.41
SPAP (mmHg)	32 ± 7	36 ± 6	32 ± 7	0.006	37 ± 8	30 ± 6	<0.0001	33 ± 7	28 ± 5	0.0001
Left atrial volume index (ml/m2)	67 ± 29	74 ± 34	65 ± 28	0.28	69 ± 27	65 ± 29	0.42	68 ± 35	62 ± 20	0.46
Exercise echocardiography										
Test duration (minutes)	12.1±5	8.5±3	12.6±5	<0.0001	12±4	13±5	0.32	13±4	13±3	0.73
Maximum workload (watt)	123±41	99±29	127±41	0.001	115±39	130±41	0.11	128±42	125±36	0.75
Heart rate at rest (bpm)	74±14	73±13	74±14	0.88	71±12	75±14	0.16	72±13	76±16	0.30
Heart rate at peak exercise (bpm)	142±20	136±22	143±20	0.22	138±25	144±18	0.04	140±21	147±19	0.04
Maximum predicted heart rate (%)	87±11	87±14	87±11	0.49	87±16	87±9	0.80	87±12	86±10	0.96
Systolic blood pressure at rest (mmHg)	141±21	142±23	140±21	0.50	142±20	140±21	0.66	142±17	137±24	0.88
Diastolic blood pressure at rest (mmHg)	84 ±11	86±10	83±11	0.35	83±14	83±10	0.31	83±11	83±12	0.66
Systolic blood pressure at peak exercise (mmHg)	202±28	197±23	204±28	0.38	206±37	203±26	0.54	206±29	200±26	0.33
Diastolic blood pressure at peak exercise (mmHg)	95±18	100±17	94±18	0.14	96±25	93±16	0.86	94±19	93±16	0.97
Peak exercise SPAP (mmHg)	55±10	61±9	54±10	<0.0001	67 ± 7	49 ± 7	<0.0001	58±7	42±5	<0.0001
Peak exercise SPAP ≥ 50 mmHg	116 (66)	23 (89)	93 (62)	0.004	30 (100)	63 (52)	<0.0001	-	-	N/A
Peak exercise SPAP ≥ 60 mmHg	49 (28)	19 (73)	30 (20)	<0.0001	-	-	N/A	23 (29)	0 (0)	<0.0001
SPAP variation (mmHg)	22 ± 9	25 ± 11	22 ± 9	0.09	30 ± 8	19 ± 7	<0.0001	24 ± 8	15 ± 6	<0.0001

Data are presented as numbers (%) or mean±SD. LV=left ventricule, MR=mitral regurgitation, SPAP=systolic pulmonary artery pressure.
* Among the 151 patients with a negative exercise test, 11 underwent a prophylactic surgery and 10 were lost to follow-up.