ORIGINAL ARTICLE

Systolic Pulmonary Artery Pressure Thresholds Predictive of Dyspnea on Stress Doppler Echocardiography in Mitral Stenosis

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Abstract

Background: **On Stress Doppler Echocardiography (SDE) in mitral stenosis, the systolic pulmonary artery pressure (SPAP) threshold at peak exercise recommended by the guidelines as an indication for percutaneous mitral commissurotomy (PMC) used to be 60 mmHg. However, because of the paucity of studies, that threshold has been controversial. The Europeans stopped using the value in 2007, followed by the Americans in 2014.**

Objective: **Determine SPAP thresholds on SDE at peak exercise and post-exercise predictive of dyspnea as an indication for PMC in mitral stenosis.**

Method and results: **Three hundred mitral stenosis patients with a mitral valve area (MVA) ≤ 2 cm^2 and NYHA I-II-III were included. A treadmill stress test (Bruce protocol) was used in all cases to distinguish dyspneic patients (n = 182) from non dyspneic patients (n = 118). SDE was performed on a stress echocardiography bed, starting at 30 W and increasing by 30 W every 3 min. At peak exercise, the best SPAP threshold obtained was 75 mmHg: specificity (Sp) = 0.98 (0.94−1), positive likelihood ratio (LR+) = 47 (41−50), positive predictive value (PPV) = 0.99 (0.95−1), and positive predictive error (PPE) = 0.01 (0.002−0.05). This compared with, respectively, 0.34, 1, 0.69 and 0.31 at 60 mmHg. Post-exercise, the best SPAP threshold found was 60 mmHg: Sp = .94 (0.88−0.97), LR = 9 (4−10), PPV = 0.94 (0.87−0.97), and PPE = 0.06 (0.03−0.13).**

Conclusion: **Regarding the prediction of dyspnea as an indication for PMC, our study shows that a SPAP value at peak exercise of 60 mmHg lacks predictive power (LR+ = 1). The optimal threshold observed was 75 mmHg at peak exercise (LR+ = 47 [41−50]) and 60 mmHg post-exercise (LR+ = 9 [4−10]).**

Keywords: Mitral stenosis, Exercise testing, Stress echocardiography, Mean systolic pulmonary pressure

1. Introduction

Following a clinical examination and Doppler Echocardiography at rest, a mitral intervention, particularly percutaneous mitral commiss urotomy (PMC), is indicated in tight mitral stenosis (MS)with a mitral valve area (MVA) of less than 1.5 cm^2 in symptomatic patients or in asymptomatic patients whose resting systolic pulmonary artery pressure (SPAP) is more than 50 mmHg [1−3]. Beginning in 1998, the American guidelines, followed by the European guidelines, recommended Stress Doppler Echocardiography (SDE) in mitral stenosis when there are discrepancies between anatomic and functional findings − in other words, in patients who have tight MS but no symptoms − as well as in symptomatic patients with moderate MS [4−6]. A SPAP at peak exercise of 60 mmHg was taken to

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justify PMC [4–6]. However, given the dearth of studies, some authors think that this value lacks specificity and that the true threshold may be more than 60 mmHg [7,8]. Because of the paucity of research confirming the value, the European guidelines stopped using this threshold in 2007, followed by the American guidelines in 2014 [2,6]. Our study aimed to determine SPAP thresholds on SDE at peak exercise and post-exercise predictive of the occurrence of dyspnea as an indication for PMC in MS.

2. Methods

2.1. Patients

We prospectively included MS patients who had a MVA of 2 cm^2 or less and a resting SPAP of less than 60 mmHg and who were class I, II or III according to the New York Heart Association (NYHA) classification. We excluded patients who were incapable of pedaling on DSE; those whose tricuspid insufficiency (TI) flow was difficult to assess; those who had mitral insufficiency (MI) and/or aortic insufficiency (AI) if regurgitant orifice area was, respectively, more than or equal to 0.18 cm^2; those with aortic stenosis (AS) with a mean gradient of 30 mmHg or more; and all conditions besides MS that cause elevated SPAP, such as pleuro-pulmonary pathologies, anemia with a hemoglobin level below 10 g/dL, and pregnancy. All patients included consented to participate in the study.

In order to objectively distinguish between dyspneic and non dyspneic patients, we conducted a treadmill stress test in all patients based on the Bruce protocol (30 W/3 min). Dyspneic subjects were those who stopped the exercise at a workload of 90 W (<9 METs) or less because of significant dyspnea [9]. In these, dyspnea was considered moderate if they stopped on the second or third increment and significant if they stopped on the first increment. All patients included underwent a treadmill stress test and Doppler Echocardiography at rest and during exercise.

2.2. Doppler echocardiography at rest

The Vivid 7 Pro machine was used (General Electrics, USA) with a 3-MHz transducer probe. The variables assessed were MVA as measured by planimetry calculated in the left lateral sternal short-axis view (with the commissures open); left atrial (LA) area in apical four-chamber view; and Wilkinsscore [10]. Functional MVA was calculated by measuring the pressure half-time of diastolic mitral flow obtained in the apical four-chamber view [11,12].

Abbreviations List

AF	Atrial fibrillation
AI	Aortic insufficiency
AS	Aortic stenosis
AUC	Area under the curve
ECG	Electrocardiogram
HR	Heart rate
LA	Left atrial
LR	Likelihood ratio
MHz	Mega Hertz
MI	Mitral insufficiency
MS	Mitral stenosis
MVA	Mitral valve area
NYHA	New York Heart Association
PMC	Percutaneous mitral commissurotomy
PPE	Positive predictive error
PPV	Positive predictive value
ROC	Receiver operating characteristic
SDE	Stress Doppler Echocardiography
Se	Sensitivity
Sp	Specificity
SPAP	Systolic pulmonary artery pressure
TMHR	Theoretical maximum heart rate
TI	Tricuspid insufficiency
USA	Unites State American
W	Watts

SPAP was measured from the right atrium and right ventricular (RA-RV) pressure gradient obtained by calculating the peak velocity of the IT flow in the apical four-chamber or parasternal short-axis views. To this gradient, we added the value of right atrial pressure (5 or 10 mmHg) which can be estimated based on several variables. Our choice was the diameter of the inferior vena cava (IVC) and its respiratory variations in M-mode in the subcostal four-chamber view. The respiratory variation of IVC diameter was quantified by calculating the diameter collapsibility index using the formula: expiratory diameter - inspiratory diameter/expiratory diameter. For this calculation, we considered the smallest inspiratory diameter and the largest expiratory diameter, avoiding any Valsalva maneuver [13].

Mean values for MVA and SPAP were obtained from three consecutive cardiac cycles in patients in sinus rhythm (SR) and from five consecutive cardiac cycles in those in atrial fibrillation (AF). Any associated valvulopathies were checked for and assessed on transthoracic Doppler echocardiography supplemented, on occasion, by transesophageal Doppler echocardiography.

2.3. Stress doppler echocardiography

The assessment was performed on a tilting echocardiography exercise bed set at 45°. Patients were in a semi-supine position. The assessment started at 30 W and increased by 30 W every 3 min. The exercise was continued until theoretical maximum heart rate was reached (TMHR = 220 − age) or until severe dyspnea or intense pain in the legs appeared requiring the exercise to be stopped. The assessment was judged to be maximal if the maximum heart rate (HR) reached was 80 % or more of the TMHR. HR and SPAP were recorded at rest, then every 90 s up to the peak of the exercise, and lastly around the second minute of post-exercise recovery. ECG, HR and blood pressure were continuously monitored throughout the examination. Antiarrhythmics, including beta blockers, were not discontinued before the assessment.

2.4. Statistical analysis

Quantitative variables are expressed as mean ± standard deviation, and qualitative variables as frequency n (%). Receiver operating characteristic (ROC) curves were constructed to determine the diagnostic performance of peak-exercise and post-exercise SPAP, taking dyspnea on the treadmill stress test as the reference test. The thresholds predictive of dyspnea as an indication for PMC were determined using the ROC curve inflection point that gave the best sensitivity to specificity ratio (Se/Sp). Next, based on 10 values above these thresholds, we looked for the value that best improved the positive likelihood ratio (LR+). The diagnostic performances of the two tests studied were evaluated at the value obtained in our study and at 60 mmHg. After that, we investigated the peak-exercise SPAP threshold when patients who had had significant dyspnea during the stress test were excluded.

Se, Sp, LR+, positive predictive value (PPV), and positive predictive error (PPE) of the two tests are expressed with 95 % confidence intervals. Comparisons were performed using the Mann–Whitney test for means and the chi^2 and Fisher tests for percentages. Paired tests were used to compare HR and SPAP between peak exercise and post-exercise. A p value < 0.05 was considered statistically significant. The programs used were EPIDATA version 302 for data entry, EPI INFO version 6.04 dfr (CDC, Atlanta, USA) for analysis and SPSS version 19.0 for the ROC curves.

3. Results

3.1. Patient characteristics

Three hundred consecutive patients were included (244 women, mean age 43 ± 11 yrs). The main characteristics of these patients are shown in Table 1. From history-taking, 126 subjects were asymptomatic (NYHA I), 81 were taking diuretics, and 159 were taking antiarrhythmics (124 on beta blockers). Prior mitral intervention had been

Table 1. Patient characteristics.

Characteristics	Total	Dyspnea on stress test	No dyspnea on stress test	p
Number of patients	N = 300	N = 182	N = 118	
Age (yrs)	43 ± 11	41 ± 12	45 ± 10	<0.001
Women	244 (81)	142 (78)	102 (86)	0.07
Mitral intervention	49 (16)	21 (11)	28 (24)	<0.001
NYHA I/II/III	126 (42)/163 (54)/11 (4)	18(10)/154 (85)/10 (5)	108 (91)/9 (8)/1 (1)	<0.001
Sinus rhythm	239 (80)	138 (76)	101 (86)	0.04
Beta blocker	124	84	20	<0.001
Diuretic	81	63	18	<0.001
Doppler echo at rest				
MVA planimetry (cm^2)	1.34 ± 0.35	1.15 ± 0.27	1.63 ± 0.23	<0.001
MVA planimetry <1.5 cm^2	200 (67)	166 (91)	34 (29)	<0.001
MVA planimetry ≥1.5 cm^2	100 (33)	16 (9)	84 (71)	<0.001
MVA PHT (cm^2)	1.30 ± 0.35	1.12 ± 0.28	1.59 ± 0.24	<0.001
Wilkins score	8.4 ± 1.6	8.8 ± 1.6	7.7 ± 1.3	<0.001
LA area (cm^2)	27 ± 7	29 ± 7	25 ± 6	<0.001
MR/AR/AS/TR	300 (100)/260 (87)/12 (4)/300 (100)	AI: 159 (87); AS: 6 (3)	AI: 102 (86); AS: 6 (5)	0.82 0.54
HR (/min)	74 ± 11	75 ± 11	74 ± 11	0.45
MMG (mmHg)	8 ± 4	10 ± 4	6 ± 2	<0.001
SPAP (mmHg)	34 ± 8	38 ± 8	29 ± 4	<0.001

p: compares patients with and without dyspnea on the stress test, NYHA: New York Heart Association, MVA: Mitral valve area, PHT: pressure half-time, LA: left atrium, MR: mitral Regurgitation, AR: aortic Regurgitation, AS: aortic stenosis, TR: tricuspid Regurgitation, HR: heart rate, MMG: mean mitral gradient, SPAP: systolic pulmonary artery pressure. Qualitative variables expressed as n (%) and quantitative variables as mean ± standard deviation.

performed in 49 patients: 28 had had PMC, 16 closed commissurotomy, and 5 open commiss urotomy. On ECG, 61 (20 %) patients were in AF.

On Doppler Echocardiography at rest, anatomic MVA was 1.34 ± 0.35 cm^2 (range: 0.63–2.00 cm^2). MS was tight in 200 patients (Table 1). The mean area of the LA was 27 ± 7 cm^2 and the Wilkins score was 8.4 ± 1.6 cm^2. Mean HR was 74 ± 11/min, MMG was 8 ± 4 mmHg, and SPAP was 34 ± 8 mmHg (range: 22–58 mmHg).

On the Treadmill stress test, 182 patients developed dyspnea that was moderate in 141 cases and significant in 41 cases (Table 2). We noted that a not insignificant proportion of truly dyspneic patients had minimized the degree of functional difficulty during history-taking. Hence 78 % (n = 32) of severely dyspneic patients and 13 % (n = 18) of moderately dyspneic patients were classed, respectively, NYHA II and I instead of III and II. What is more, 14 % of NYHA class I patients displayed moderate dyspnea on the treadmill test (n = 18/126).

The rate of cases of discrepancy between NYHA and MVA was 22 %: 46 NYHA I patients had tightMS, and 20 NYHA II–III patients had moderate MS (MVA ≥1.5 cm^2). In the 182 patients who were dyspneic on the treadmill test, resting SPAP was more than 50 mmHg in 14 of them (Se = 8 %). This low sensitivity may be due to pharmacological treatment, as 60 % (n = 109)of dyspneic patients were on vasodilators and/or diuretics. In the 14 patients who had a resting SPAP of more than 50 mmHg, mitral stenosis was tight or very tight (MVA of 0.74–1.17 cm^2), they were all dyspneic on history-taking, and dyspnea was severe on the treadmill test and forced 10 of them to stop the exercise at 30 W. Thus, SPAP of more than 50 mmHg yielded a positive predictive value of100 % for both MS tightness and dyspnea. In all patients non dyspneic on the treadmill test, SPAP was less than 50 mmHg (Sp = 100 %).

Table 2. Evaluation of dyspnea on exertion by the NYHA classification versus treadmill stress test.

NYHA		Treadmill stress test		
		No dyspnea N = 118	Moderate dyspnea N = 141	Significant dyspnea N = 41
I	N = 126	108	18	–
II	N = 163	9	122	32
III	N = 11	1	1	9

NYHA: New York Heart Association.

3.2. Results of SDE

On SDE, 2, 97, 184 and 17 patients reached workloads of, respectively, 30, 60, 90 and 120 W (Table 3). In 58 patients, SDE was prematurely halted (maximum HR < 80 % of TMHR) owing to intense muscle pain in the legs in 25 patients and severe dyspnea in 33 patients. One case of acute pulmonary edema occurred, which responded well to medical treatment; the patient's MVA was 1.65 cm^2. Milder symptoms like fatigue, muscle pain in the lower limbs or moderate dyspnea were more frequent but did not lead to the exercise being stopped.

At the peak of the exercise, HR was 150 ± 13/min and SPAP was 78 ± 18 mmHg (range 45–146 mmHg) (Table 3). In 84 % of cases (n = 252), SPAP at peak exercise exceeded 60 mmHg. Of the 118 patients who were not dyspneic on the stress test, SPAP at peak exercise was less than 60 mmHg in 40 (Sp = 34 %). Even in the 84 patients with moderate MS and no dyspnea on the stress test, SPAP at peak exercise was less than 60 mmHg in only 36 (Sp = 43 %), despite their having moderate MS and no dyspnea (Table 1).

Compared with peak exercise, Table 3 shows a post-exercise drop in HR to 116/min ($p < 10^{-6}$) and

Table 3. Results of Stress Doppler Echo in entire study population.

Characteristics	Total	Dyspnea on stress test	No dyspnea on stress test	p
Peak exercise				
Workload (W) 30/60/90/120 (n) (%)	2/97/184/17 (1/32/61/6)	1/69/109/3 (0.5/38/60/2)	1/28/75/14 (1/24/64/12)	<0.001
Max. HR ≥ 80 % TMHR	242 (81)	145 (80)	97 (82)	0.59
HR (/min)	150 ± 13	151 ± 13	149 ± 13	0.12
SPAP (mmHg)	78 ± 18	88 ± 16	63 ± 8	<0.001
SPAP ≥60 mmHg	252 (84)	174 (96)	78 (66)	<0.001
Post-exercise				
HR (/min)	116 ± 12	116 ± 13	115 ± 12	0.32
SPAP (mmHg)	57 ± 1	63 ± 14	48 ± 8	<0.001
SPAP ≥60 mmHg	115 (38)	106 (58)	9 (8)	<0.001

p: compares patients with and without dyspnea on the stress test, W: watts, HR: heart rate, TMHR: theoretical maximum heart rate, SPAP: systolic pulmonary artery pressure. Qualitative variables expressed as n (%) and quantitative variables as mean ± standard deviation.

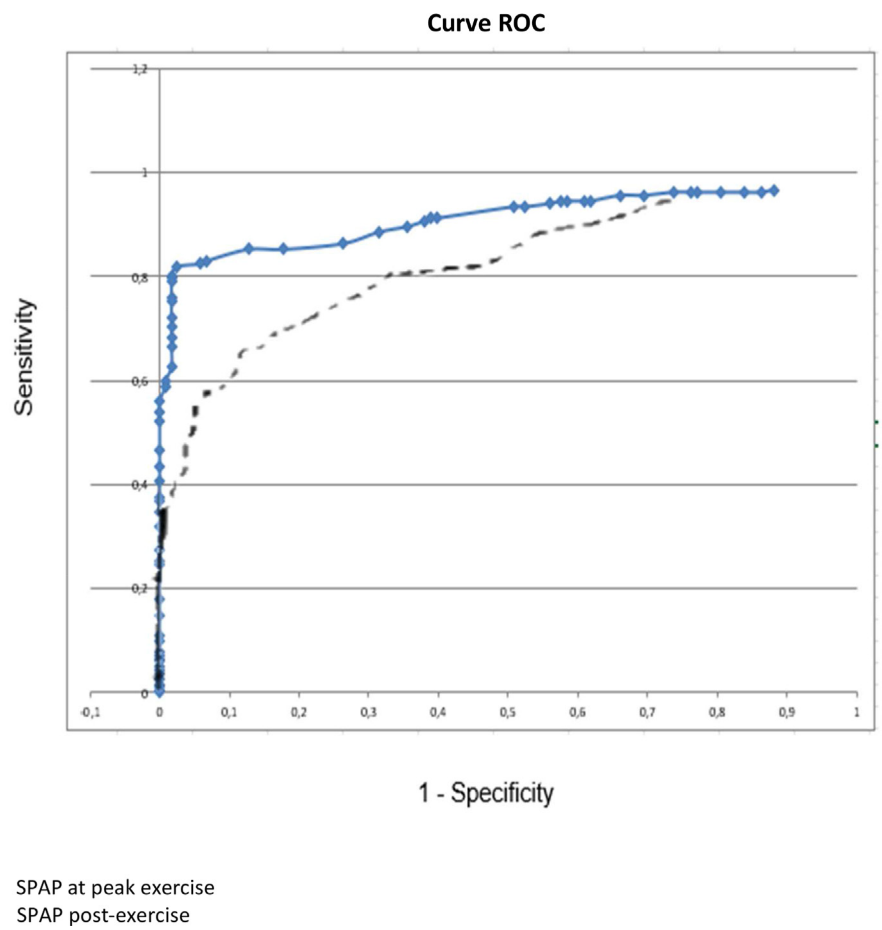

Fig. 1. ROC curves of SPAP at peak exercise and post-exercise.

inSPAP to 57 mmHg ($p < 10^{-6}$). In 38 % of cases (n = 115), post-exercise SPAP exceeded 60 mmHg. In the84 patients with moderate mitral stenosis and no dyspnea on the treadmill stress test, post-exerciseSPAP was less than 60 mmHg in 79 (Sp = 94 %).

3.3. SPAP thresholds predictive of dyspnea

3.3.1. In the entire study population

The area under the curve (AUC) of SPAP at peak exercise was 0.91 ± 0.03, and that of post-exercise SPAP was 0.82 ± 0.04 (Fig. 1). These two curves make it possible to distinguish dyspneic patients from non dyspneic patients (p, respectively, $<10^{-3}$).

At peak exercise, the SPAP value at the curve's inflection point was 74 mmHg (Se = 0.82; Sp = 0.97; LR+ = 33). However, the best threshold obtained was 75 mmHg (Table 4). Compared with 60 mmHg, the 75 mmHg threshold multiplied Sp by nearly 3 (0.34 versus 0.98), multiplied LR + by 47 (1 versus 47), divided PPE by 31 (0.31 versus 0.01), while PPV went from 0.69 to 0.99 (Table 4). Post-exercise, the

Table 4. Diagnostic characteristics of SPAP at study threshold and at 60 mmHg.

Population	Threshold (mmHg)	Se (%)	Sp (%)	LR+	PPV (%)	PPE (%)
	SPAP peak exercise					
	≥75	82 (74–86)	98 (94–100)	47 (41–50)	99 (95–100)	1 (0.2–5)
Entire study population (N = 300)	≥60: AHA/ACC threshold	96	34	1	69	31
	SPAP post-exercise					
	≥60	56 (48–63)	94 (88–97)	9 (4–10)	94 (87–97)	6 (3–13)
	≥60: AHA/ACC threshold	58	92	8	92	8
After excluding patients with significant dyspnea (N = 259)	SPAP peak exercise ≥75	74 (69–79)	98 (96–100)	43 (24–39)	98 (96–100)	2 (0–4)

ACC: American College of Cardiology, AHA: American Heart Association, SPAP: systolic pulmonary artery pressure, Se: sensitivity, Sp: specificity, LR+: positive likelihood ratio, PPV: positive predictive value, PPE: positive predictive error.

SPAP value at the ROC curve's inflection point was 52 mmHg (Se = 0.73; Sp = 0.77; LR+ = 3). However, the best threshold was 60 mmHg (Sp = 0.94; LR+ = 9; PPV = 0.94; and PPE = 0.06) (Table 4).

3.3.2. After excluding patients with significant dyspnea on the stress test

In this group (n = 259), Fig. 2 shows that the AUC of SPAP at peak exercise was 0.89 ± 0.05 ($p < 10^{-3}$). SPAP at the curve's inflection point was 70 mmHg (Se = 0.81; Sp = 0.82; LR+ = 4.5). However, the best threshold was 75 mmHg, because with this value LR+ was multiplied by almost 10, rising to 43 (Table 4).

4. Discussion

Regarding the prediction of dyspnea as taken to be an indication for PMC, our study shows that a SPAP value at peak exercise of 60 mmHg lacks predictive power (LR+ = 1). The best threshold observed was 75 mmHg at peak exercise (LR+ = 47) and 60 mmHg post-exercise (LR+ = 9).

4.1. Functional symptoms

Treatment strategy in MS is mainly based on functional symptoms and resting Doppler echocardiographic findings. For this reason, in asymptomatic subjects with a MVA of 1.50 cm^2 or more and a mean mitral gradient of less than 5 mmHg, the strategy for MS is annual follow-up. The indication for PMC is tight symptomatic mitral stenosis or tight asymptomatic mitral stenosis with a SPAP of more than 50 mmHg [1–3].

There are, nevertheless, situations in which therapeutic decision-making can be difficult, for instance when there is inconsistency between the functional symptoms reported by patients and severity of MS on Doppler Echocardiography at rest. Such inconsistency is estimated to be 30 % [14]. Thus, dyspnea is perceived subjectively, since patients with tight MS may present few or no symptoms because they have gradually adapted their way of living to the disease. Despite the tightness of their mitral stenosis, such patients may describe few or no symptoms during history-taking. Conversely, others may report significant dyspnea as affecting their regular activities, whereas resting Doppler Echocardiographic results show moderate MS. In such cases, causes other than the repercussions of MS may need to be considered, such as lung disease or left ventricular diastolic dysfunction (Our study excluded all such situations.) That said, some are truly affected by their mitral stenosis because of an elevation of mitral gradient by tachycardia, increase in cardiac output and poor LA compliance, which lead to elevated pulmonary blood pressure [7,15].

Assessing the functional impact of MS usually makes use of the NYHA classification. Yet our results demonstrate that patients who were truly dyspneic on the treadmill test, particularly those who displayed significant dyspnea, tended to play down their level of

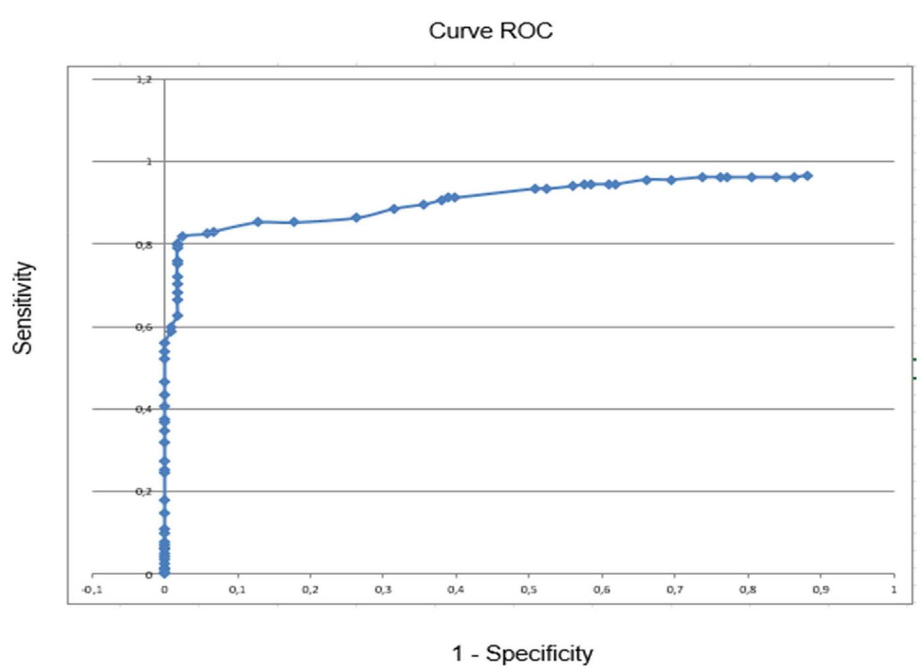

Fig. 2. Curve ROC of SPAP at peak exercise after excluding patients with significant dyspnea on stress test.

dyspnea during history-taking. Thus 13 % of patients who were moderately dyspneic on the treadmill test and 78 % of patients who were severely dyspneic on the treadmill test were classed as, respectively, NYHA I and II. What is more, 14 % of NYHA I patients displayed dyspnea on the treadmill test. Assessing dyspnea using the stress test may therefore reduce discrepancies between anatomic and functional findings. In the study by Brochet, of 48 patients who all had tight MS and who were all NYHA I, 46 % were in fact dyspneic on SDE [7].

Furthermore, the guidelines recommend PMC in asymptomatic tight mitral stenosis when SPAP is more than 50 mmHg [1−3]. In our study, all the patients who had a resting SPAP of more than 50 mmHg were dyspneic on the treadmill test (PPV = 100 %). In these patients, not only was dyspnea constant, but it was severe and usually forced them to stop the exercise on the first increment.

In practice, except in ischemic cardiomyopathy and aortic stenosis, stress tests continue to be rarely employed. In MS, SDE and the treadmill or cycle ergometer stress tests may yield important information on functional capacity during stress. SDE may also be employed to investigate transvalvular gradient and pulmonary blood pressure profile. These results may have an influence on therapeutic decision-making and prognosis [14].

4.2. SDE in mitral stenosis

TVrican guidelines validated SDE in MS for cases of discordant anatomic and functional findings [4]. For assessing the hemodynamic profile of MS on SDE, the protocol used should be taken into account. Physical exertion is preferable to pharmacological stress [4]. The tilting echocardiography exercise bed in the semi-supine position is the best modality for recording hemodynamic variables, both during the assessment up to peak exercise and during the recovery period. It happens that SDE has been performed on treadmill in most studies [16−19]. The consequence is that the results of these studies are not peak exercise but post-exercise, since hemodynamic variables were only recorded one to 2 min after the patient lay down. Our study shows that data obtained post-exercise cannot be extrapolated to peak exercise. Indeed, we observed a post-exercise fall in HR ($p < 10^{-6}$) and SPAP ($p < 10^{-6}$).

4.3. SPAP thresholds predictive of the occurrence of dyspnea as an indication for PMC

Dyspnea on exertion is the key sign of MS severity, so to meet our study's objective we used dyspnea on exertion as the reference test. To better identify dyspneic patients we used the treadmill stress test, which has the advantage of being more objective than the NYHA classification and of reproducing the exertions of everyday life more physiologically than SDE.

The SPAP threshold at peak exercise recommended by the American guidelines for PMC was60 mmHg [4]. In our study, SPAP at peak exercise at the 60 mmHg value had low specificity (34 %), and it had no predictive power (LR+ = 1) [20]. Moreover, like Brochet, several authors have underlined that SPAP at peak exercise lacks specificity when a 60 mmHg threshold is used. For instance, in the study by Brochet, of the 26 patients who were asymptomatic on SDE, SPAP at peak exercise was more than 60 mmHg in 19 patients (73 %) [7]. In fact, the level of evidence for the guidelines was low (class IIb, grade C), and the recommended thresholds for PMC were based on expert consensus. Inlight of the paucity of studies in this area, the European guidelines stopped using this value in 2007 [2,3]. In their latest guidelines, the Americans have very recently replaced SPAP on SDE by pulmonary wedge pressure during exercise using cardiac catheterization, with the recommended threshold for PMC being 25 mmHg [6].

Our study is the first to have included 300 MS patients to investigate the SPAP thresholds on SDE predictive of the occurrence of dyspnea as an indication for PMC. At peak exercise, the optimal threshold in our study at which SPAP displayed significant predictive power was 75 mmHg (LR+ = 47), whereas the 60 mmHg threshold did not grant this test any predictive power (LR+ = 1). Post-exercise, the best SPAP threshold was 60 mmHg. At this value, the specificity of SPAP post-exercise was good (Sp = 0.94) and the positive predictive power of the test was high (LR+ = 9). Hence this study is the first to show that the 60 mmHg value advanced for PMC does not in fact correspond to peak exercise but to post-exercise. Indeed, in most papers SDE was performed on a treadmill and the hemodynamic variables were recorded during the post-exercise phase [16−19].

After excluding the 41 patients with significant dyspnea on the stress test, the optimal SPAP threshold at peak exercise was 75 mmHg, which coincides with that of the whole population owing to the small number of severely dyspneic patients included.

5. Limitations

In spite of the large number of subjects included, this is a single-center study. Hence multicenter studies will be needed to verify our results.

Although in practice therapeutic strategy is well codified in MS when anatomic and functional findings agree, it is not so when they disagree. SPAP thresholds predictive of dyspnea were defined in our study on the basis of a MS population that comprised cases of both agreement and disagreement. We attempted to determine thresholds in patients whose anatomic and functional findings were discordant. However, because of the small number of such patients, the ROC curves were not able to distinguish between them and the rest of the population (AUC<50 %). Hence it may be worth while conducting studies that only include cases of MS with discordant anatomic and functional findings in order to verify whether the thresholds obtained in our study may be applied to this patient category.

6. Clinical implications and conclusion

In practice, there are times in MS when making a decision can be difficult following clinical examination and Doppler Echocardiography at rest. This may be so in discordant cases or in women who hope to become pregnant. In such situations it is important to assess functional capacity during exercise by a stress test, supplemented, if necessary, by SDE.

This is the first and largest series to have investigated the SPAP thresholds on SDE predictive of dyspnea as an indication for PMC. Based on our results, we may conclude that, when hemodynamic variables are recorded during exercise using an echocardiography bed, PMC is indicated at a peak-exercise SPAP threshold of 75 mmHg.

Moreover, this study is the first to show that the 60 mmHg value does not in fact correspond to peak exercise but to post-exercise. So, when the exercise is performed on a treadmill and SPAP is recorded post-exercise, PMC is indicated at a threshold of 60 mmHg.

Author contributions

Conception and design of Study: SL, FD. Literature review: SL, FD. Acquisition of data: DH, YL. Analysis and interpretation of data: SL, FD, DH, YL. Research investigation and analysis: SL, SK, ZB. Data collection: SL. Drafting of manuscript: SL, FD. Revising and editing the manuscript critically for important intellectual contents: SL, FD, RM, MSI. Data preparation and presentation: SL, Supervision of the research: FD, MSI. Research coordination and management: SL, FD. Funding for the research: SL.

Conflicts of interest

None.

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