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ORIGINAL PAPER

Prognostic values of exercise echocardiography and cardiopulmonary exercise testing in patients with primary mitral regurgitation

Augustin Coisne [1]*, Samy Aghezzaf[1], Elena Galli[2], Stéphanie Mouton[1], Marjorie Richardson[1], Denis Dubois[1], Pascal Delsart[1], Olivia Domanski[1], Christophe Bauters[3], Marion Charton[2], Guillaume L'Official[2], Thomas Modine[1], André Vincentelli[1], Francis Juthier[1], Patrizio Lancellotti [4,5], Erwan Donal [2], and David Montaigne [1]

[1]University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011 - EGID, F-59000 Lille, France; [2]University of Rennes, CHU Rennes, Inserm, LTSI – UMR 1099, F-35000 Rennes, France; [3]University of Lille, Inserm, CHU Lille, Institut Pasteur, U1167, F-59000 Lille, France; [4]Departments of Cardiology, University of Liège Hospital, GIGA Cardiovascular Sciences, Heart Valve Clinic, CHU Sart Tilman, 4000 Liège, Belgium; and [5]Gruppo Villa Maria Care and Research, Maria Cecilia Hospital, Cotignola, and Anthea Hospital, 70100 Bari, Italy

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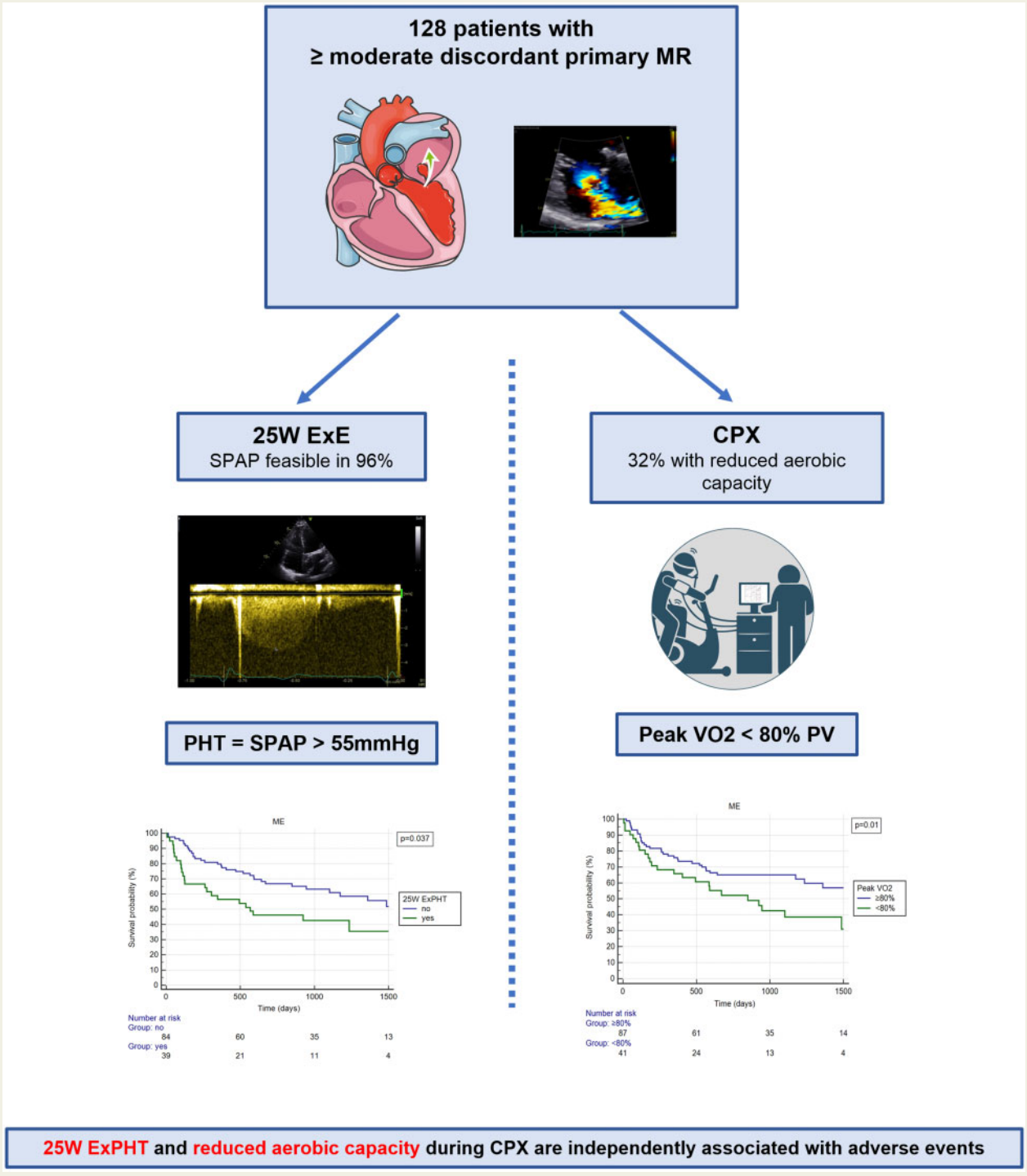
Aims To compare the clinical significance of exercise echocardiography (ExE) and cardiopulmonary exercise testing (CPX) in patients with ≥moderate primary mitral regurgitation (MR) and discrepancy between symptoms and MR severity.

Methods and results Patients consulting for ≥moderate discordant primary MR prospectively underwent low (25 W) ExE, peak ExE, and CPX within 2 months in Lille and Rennes University Hospital. Patients with Class I recommendation for surgical MR correction were excluded. Changes in MR severity, systolic pulmonary artery pressure (SPAP), left ventricular ejection fraction (LVEF), and tricuspid annular plane systolic excursion were evaluated during ExE. Patients were followed for major events (ME): cardiovascular death, acute heart failure, or mitral valve surgery. Among 128 patients included, 22 presented mild-to-moderate, 61 moderate-to-severe, and 45 severe MR. Unlike MR variation, SPAP and LVEF were successfully assessed during ExE in most patients. Forty-one patients (32%) displayed reduced aerobic capacity (peak VO2 < 80% of predicted value) with cardiac limitation in 28 (68%) and muscular or respiratory limitation in the 13 others (32%). ME occurred in 61 patients (47.7%) during a mean follow-up of 27 ± 21 months. Twenty-five Watts SPAP [hazard ratio (HR) (95% confidence interval, CI) = 1.03 (1.01–1.06), $P = 0.003$] and reduced aerobic capacity [HR (95% CI) = 1.74 (1.03–2.95), $P = 0.04$] were independently predictive of ME, even after adjustment for MR severity. The cut-off of 55 mmHg for 25 W SPAP showed the best accuracy to predict ME (area under the curve = 0.60, $P = 0.05$).

Conclusion In patients with ≥moderate primary MR and discordant symptoms, 25 W exercise pulmonary hypertension, defined as an SPAP ≥55 mmHg, and poor aerobic capacity during CPX are independently associated with adverse events.

*Corresponding author. Tel: +33 320445962; Fax: +33 20444414. E-mail: augustin.coisne@chru-lille.fr

Graphical Abstract



Keywords Mitral regurgitation • Exercise pulmonary hypertension • Aerobic capacity • Cardiac surgery

Introduction

Symptom onset and functional limitation play a crucial role in the management of patients with severe primary mitral regurgitation (MR).[1,2] Because dyspnoea is particularly subjective, possibly multifactorial, and mostly underestimated by sedentary patients, supine exercise echocardiography (ExE), and cardiopulmonary exercise testing (CPX) have been proposed for an objective assessment of exercise capacity and therefore risk stratification in valvular heart disease (VHD). Exercise-induced worsening of MR severity,[3] abnormal increase in systolic pulmonary arterial pressure (SPAP),[4] and poor left (LV) and right (RV) ventricular contractile reserve[5,6] have been demonstrated to be useful in medical decision-making for MR patients. However, performing ExE in VHD is time-consuming, tedious and its use has been restricted the past 10 years to European tertiary expert centres. CPX provides quantitative and objective evaluation of functional capacity. Interestingly, Messika-Zeitoun *et al.*[7] showed that functional limitations in patients with MR were associated with clinical events. Exploring a limited number of asymptomatic patients with moderate to severe degenerative MR, Suzuki *et al.* showed that elevated SPAP in ExE and reduced aerobic capacity were associated with the occurrence of symptoms. However, these authors did not indicate whether a low level of exercise capacity was associated with an accurate hard end-point prediction.[8]

In the present study, we aimed at determining whether low (25 W), peak ExE, and CPX were associated with poor clinical outcome in patients with primary MR and with a discrepancy between MR severity and symptoms. We hypothesize that both ExE and CPX could provide useful information to tailor medical decision-making in this population.

Methods

Study population

The study population consisted of patients with ≥moderate primary MR, referred to Lille and Rennes University Hospital for risk stratification. Patients were prospectively enrolled and underwent ExE and CPX in case of discrepancy between symptoms and MR severity. ExE and CPX were performed within 2 months. Patients were excluded in case of severe mitral annulus calcification, significant mitral stenosis (mean gradient > 5 mmHg), other VHD ≥moderate at rest, prior cardiac surgery, Class I recommendation for surgical MR correction, poor echogenicity, or inability to perform exercise exploration. The local ethics committee approved the protocol and all patients gave informed consent.

Resting and supine ExE

A comprehensive transthoracic echocardiogram (TTE) was performed by an experienced graduated medical doctor specialized in VHD according to current guidelines[9–11] using state-of-the-art echocardiographic ultrasound systems (Vivid 9 or Vivid 95, GE Healthcare, Horten, Norway). All Doppler echocardiographic data were stored on a dedicated workstation (Echo-PAC software v203 GE Healthcare) for subsequent offline analysis. A symptom-limited maximal bicycle exercise test was performed the same day in semi-supine position (eBike EL, GE Healthcare) and all exercise 2D and Doppler data were obtained at low (25 W) and at peak exercise as previously described.[12,13] No medication was stopped before ExE. Peak exercise pulmonary hypertension (ExPHT) was defined as an exercise increase in SPAP >60 mmHg at peak exercise,[4] and abnormal LV contractile reserve (CR) as an increase LV ejection fraction (EF) lower than 4%[5] as previously described. Changes in MR severity [effective regurgitant orifice area (EROA)][3] and RV function assessed by tricuspid annular plane systolic excursion[6] were also evaluated.

Patients were categorized using quantitative (EROA and regurgitant volume) and semi-quantitative parameters (time velocity integral mitral/aortic ratio and systolic flow reversal in the pulmonary vein) as previously described.[14]

Cardiopulmonary exercise testing

All patients underwent a treadmill CPX on an Ergoline 800® bicycle (Sensormedics, Yorba Linda, CA, USA) with respiratory gas-exchange analysis, using a modified Bruce protocol (progressive increase in workload of 10–15 W/min) as already described.[15] Patients' medications were not stopped before CPX. Blood pressure was measured every 2 min, continuous 12-lead electrocardiogram and saturation monitoring (SpO2) were recorded. Room temperature, barometric, and hygrometric pressure were noted. A calibration of the pneumotach (Oxycon Pro, Viasys, France) was realized before every exam using a dosing syringe of 2 L, first slowly then quickly. Peak VO2 was expressed as absolute peak or normalized peak [percent of predicted value (PV) derived from Wasserman formula].[16] The O2-pulse, an estimate of stroke volume, was calculated as VO2/heart rate. Altered O2-pulse was defined as <80% of PV or <100% when patients were under beta-blocker therapy (due to induced bradycardia under treatment). Functional capacity was considered reduced when peak VO2 was <80% of PV. Cardiac limitation was defined in case of peak VO2 <80% associated with low O2-pulse as previously described.[7] Pulmonary limitation was defined as peak VO2 <80% associated with ventilatory reserve <20% or occurrence of oxygen blood desaturation (SpO2 < 92%) during exercise. Muscular limitation was diagnosed when functional capacity was reduced without cardiac or pulmonary limitation.

Follow-up

Follow-up was obtained by direct patient interview and clinical examination, phone calls with physicians, patients, or next of kin, or review of autopsy records and death certificates. The clinical management was determined independently by patient's personal physician. Major events (ME) were defined as occurrence of cardiovascular death, acute heart failure, or mitral valve intervention motivated by onset of symptoms or LV systolic dysfunction (i.e. LVEF < 60% and/or LV end-systolic diameter ≥ 40 mm). Events were adjudicated by two independent investigators blinded to clinical and echocardiographic data.

Statistical analysis

Continuous variables with a Gaussian distribution are given as mean ± standard deviation. Continuous variables with no Gaussian distribution are given as median (25th to 75th) percentiles. Categorical variables are given as the number (percentage) of patients with the respective attribute. Bivariate comparisons were performed using the *t*-test for normally distributed continuous variables or the Mann–Whitney *U* test for variables not normally distributed. Bivariate comparisons of categorical variables were performed with the χ^2 test. Linear regression with Person's correlation was used to explore the correlation between ExE and CPX peak workload. Cox-proportional hazards regression model was used to determine whether 25 W ExE, Peak ExE, or CPX were associated with ME onset. Exercise variables with a *P*-value <0.10 on bivariate analysis were entered into the multivariable models. We tested each model for log-linearity and proportionality assumptions. To assess the incremental advantage of ExE and CPX on top of current Class II recommendation

criteria for the risk of ME, the change in χ^2 was assessed. Comparison tests between models were performed with the STATA 14.2 software (STATA Corporation, College Station, TX, USA). Receiver operating characteristics (ROC) curve analysis was used to predict the 25 W SPAP cut-off with the higher discriminating power to predict ME. Time-related clinical events were plotted with Kaplan–Meier curves and compared with log-rank tests. A value of *P*-value <0.05 was considered statistically significant. Statistics were performed using MedCalc v16.4 (Olstead, Belgium).

Results

Patients' characteristics and supine ExE

From 2013 to 2019, 164 patients were referred and 36 were excluded (13 for concomitant VHD, 10 for too poor echogenicity, 8 for inability to perform exercise exploration, and 5 for prior cardiac surgery (*Figure 1*). A total of 128 patients successfully underwent ExE and CPX (81 in Lille and 47 in Rennes). Characteristics of these patients are summarized in *Table 1*. Mean age was 58 ± 16 years. The population was composed of 65% of male with few comorbidities. Although the vast majority (95%) of patients presented no or mild symptoms (New York Heart Association I or II), 22 (17.2%) patients displayed mild-to-moderate MR, 61 (47.7%) moderate-to-severe MR, and 45 (35.1%) severe MR. No patient with mild-to-moderate MR was asymptomatic. MR mechanism was a prolapse in 116 patients (91%) with or without flail leaflet, and a restriction in the 12 others (9%). No patient displayed leaflet perforation. Among the 36 patients with a bileaflet prolapse, 31 (86%) had a Barlow disease. No patient displayed >moderate tricuspid regurgitation. Although 23 (18%) patients had a significant increase in SPAP (SPAP > 40 mmHg) at rest, no patient displayed a severe SPAP (SPAP > 60 mmHg).

Feasibility of ExE parameters

The feasibility of ExE parameters (SPAP, EF, and EROA) at rest and at different stages of exercise (25 W and peak exercise) is detailed in Supplementary data online, *Table S1*. EROA calculation was feasible in 74 patients (57.8%) at 25 W ExE and 60 patients (46.9%) at peak exercise. Among these 60 patients, 22 (36.7%) displayed an increased EROA. SPAP recording was feasible in 123 patients (96.1%) at 25 W ExE and in 117 patients (91.4%) at peak ExE. Peak ExPHT was observed in 52 patients (44.4%). Contractile reserve was successfully studied in all patients (100%) at 25 W and peak ExE, with half of the patients displaying abnormal contractile reserve at peak exercise.

Comparison between ExE and CPX

Although the correlation between ExE and CPX peak workload was good ($r = 0.86$, $P < 0.0001$) (*Figure 2*), patients displayed lower peak heart rate (respectively, 132.1 ± 251 vs. 146.8 ± 25.4 bpm, $P < 0.0001$), systolic blood pressure (168.5 ± 27.4 vs. 186.4 ± 25.7 mmHg, $P < 0.0001$), and workload (112.4 ± 44.6 vs. 132.6 ± 48.6 W, $P < 0.0001$) during ExE than during CPX.

25 W ExPHT and altered aerobic capacity are independently associated with outcomes

A total of 41 patients (32%) displayed reduced aerobic capacity defined as a peak VO2 <80% of PV with cardiac limitation in most patients (68%). Three patients (7%) displayed respiratory limitation and 10 (25%) muscular limitation. The mean follow-up was 27 ± 21 months. ME occurred in 61 patients (47.7%) with mitral surgical intervention in 59 patients (because of Class I indication, i.e. new

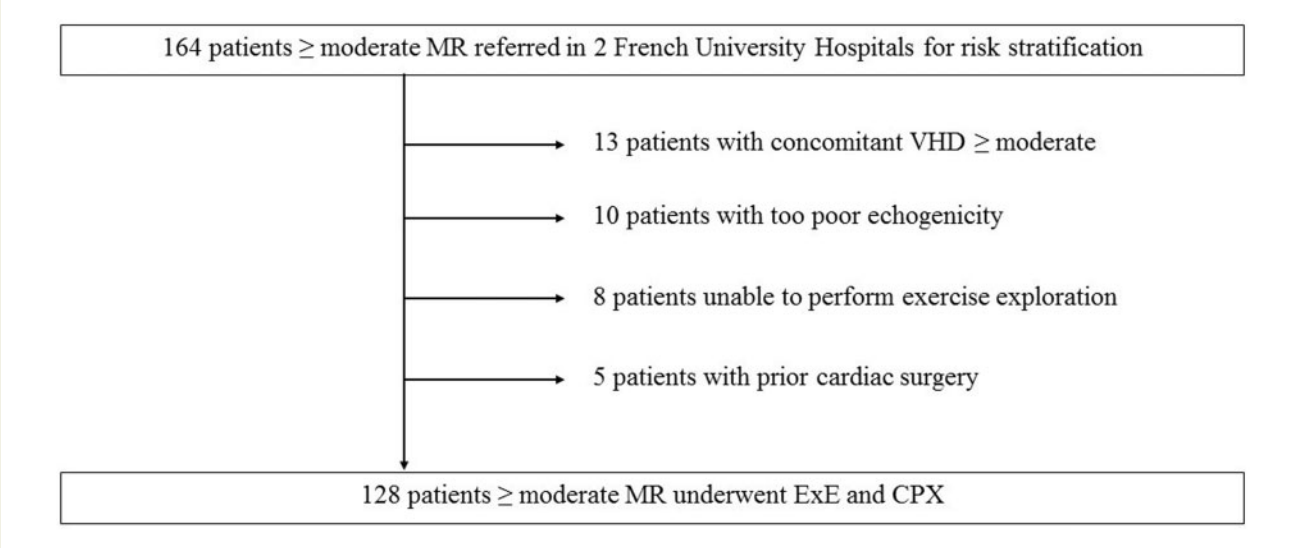


Figure 1 Flow diagram of the study. A total of 164 patients with ≥moderate mitral regurgitation were assessed in two French University Hospitals for risk stratification. Thirteen patients were excluded for concomitant valvular heart disease ≥moderate, 10 for too poor echogenicity, 8 patients for inability to perform exercise exploration, and 5 for prior cardiac surgery. Finally, 128 patients were analysed. CPX, cardiopulmonary exercise testing; ExE, exercise echocardiography; MR, mitral regurgitation; VHD, valvular heart disease.

Table 1 Clinical and rest TTE data on patients presenting major clinical event or not

	All population ($n = 128$)	No ME ($n = 67$)	ME ($n = 61$)	*P*-value
Clinical data				
Age (years)	58.0 ± 15.9	56.7 ± 18.3	59.4 ± 12.7	0.35
Gender male, *n* (%)	83 (64.8)	42 (62.7)	41 (67.2)	0.59
BMI (kg/m^2)	24.9 ± 3.8	24.9 ± 3.8	24.9 ± 3.8	0.94
BSA (m^2)	1.82 ± 0.19	1.81 ± 0.18	1.84 ± 0.20	0.34
NYHA, *n* (%)				0.77
1	70 (54.7)	36 (53.7)	34 (55.7)	
2	52 (40.6)	27 (40.3)	25 (41.0)	
3	6 (4.7)	4 (6.0)	2 (3.3)	
AF, *n* (%)	13 (10.2)	4 (6.0)	9 (14.8)	0.12
Stroke, *n* (%)	6 (4.7)	3 (4.5)	3 (4.9)	0.95
Hypertension, *n* (%)	33 (25.8)	15 (22.4)	18 (29.5)	0.44
Smoker, *n* (%)	16 (12.5)	4 (6.0)	12 (19.7)	**0.03**
Diabetes mellitus, *n* (%)	8 (6.25)	5 (7.5)	2 (3.3)	0.17
Beta-blockers, *n* (%)	31 (24.2)	16 (23.9)	15 (24.6)	0.96
ACE inhibitor, *n* (%)	37 (28.9)	20 (29.9)	17 (27.9)	0.68
Statins, *n* (%)	16 (12.5)	64 (95.5)	61 (100)	0.67
Diuretics, *n* (%)	20 (15.6)	7 (10.4)	13 (21.3)	0.12
Haemoglobin (g/dL)	14.6 ± 1.46	14.7 ± 1.56	14.5 ± 1.37	0.57
NT-proBNP (ng/mL)	130 (64–247)	129 (62.5–244.5)	132.0 (70.8–247.3)	0.51
TTE data				
HR (bpm)	73.7 ± 13.1	73.6 ± 13.6	71.7 ± 12.5	0.41
SBP (mmHg)	136.4 ± 18.2	139.5 ± 19.4	132.7 ± 16.0	**0.04**
Prolapse, *n* (%)	116 (90.6)	58 (86.6)	58 (95.1)	0.10
Restriction, *n* (%)	12 (9.4)	9 (13.4)	3 (4.9)	0.10
Posterior leaflet, *n* (%)	78 (60.9)	40 (59.7)	38 (62.3)	0.76
Anterior leaflet, *n* (%)	11 (8.6)	6 (9.0)	5 (8.2)	0.88
Both leaflet, *n* (%)	39 (30.5)	19 (28.4)	20 (32.8)	0.59
MR grade, *n* (%)				**0.002**
Mild to moderate	22 (17.2)	18 (26.9)	4 (6.6)	
Moderate to severe	61 (47.7)	31 (46.3)	30 (49.2)	
Severe	45 (35.2)	18 (26.9)	27 (44.3)	
EROA (mm^2)	37.4 ± 16.7	33.3 ± 13.8	41.4 ± 18.3	**0.01**
RVol (mL)	53.2 ± 26.7	47.5 ± 24.5	59.1 ± 27.8	**0.02**
TVI mitral/aortic ratio >1.4, *n* (%)	**54 (42.2)**	**21 (31.3)**	**33 (54.1)**	**0.01**
Systolic flow reversal, *n* (%)	**86 (67.2)**	**38 (56.7)**	**48 (78.7)**	**0.009**
LVEF (%)	66.6 ± 7.1	66.0 ± 8.0	67.2 ± 6.0	0.37
LVESD (mm)	35.1 ± 6.2	34.4 ± 5.6	35.9 ± 6.7	0.16
LVEDV (mL)	139.3 ± 37.4	134.4 ± 34.2	144.8 ± 40.3	0.15
GLS (%)	21.2 ± 2.9	21.1 ± 2.7	21.3 ± 3.1	0.69
LAVi (mL/m^2)	53.8 ± 18.2	47.8 ± 15.5	60.5 ± 18.8	**0.0002**
SPAP (mmHg)	33.8 ± 8.9	33.4 ± 9.0	34.3 ± 8.9	0.58
TAPSE (mm)	25.0 ± 5.2	25.3 ± 5.4	24.7 ± 5.1	0.51
TAPSE/SPAP (mm/mmHg)	0.81 ± 0.26	0.82 ± 0.26	0.80 ± 0.26	0.58

Data in bold: $P < 0.05$.
ACE, angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; EROA, effective regurgitant orifice area; GLS, global longitudinal strain; HR, heart rate; LAVi, left atrial volume index; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; ME, major event; MR, mitral regurgitation; NYHA, New York Heart Association; RVol, regurgitant volume; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane excursion; TTE, transthoracic echocardiogram; TVI, time velocity integral.

symptom onset in 33 and LV dilation or dysfunction in 26 patients) and acute heart failure before cardiac surgery in 2 patients (1.6%). No patient died during the follow-up.

Patients presenting ME displayed a higher MR severity as assessed by EROA (41.4 ± 18.3 vs. 33.3 ± 13.8 mm^2, $P = 0.01$) or RV (59.1 ± 27.8 vs. 47.5 ± 24.5 mL, $P = 0.02$) with larger left atrial volume

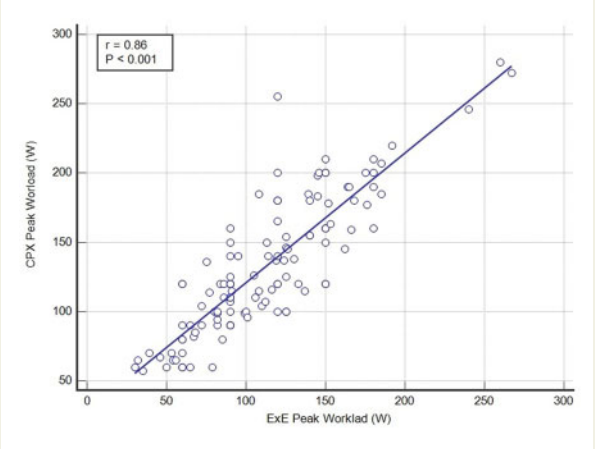


Figure 2 Correlation between exercise echocardiography and cardiopulmonary exercise testing peak workload. Linear regression with Pearson's correlation was used to explore the correlation between exercise echocardiography and cardiopulmonary exercise testing peak workload. *P*-value by linear regression. CPX, cardiopulmonary exercise testing; ExE, exercise echocardiography.

index (LAVi) (60.5 ± 18.8 vs. 47.8 ± 15.6 mL/m^2, $P = 0.0002$). No other clinical or rest TTE parameter was different between the two groups (*Table 1*). Regarding exercise data, patients presenting ME displayed higher 25 W SPAP (52.9 ± 13.7 vs. 48.4 ± 9.6 mmHg, $P = 0.03$), peak exercise EROA (40.1 ± 15.2 vs. 29.8 ± 11.3 mm^2, $P = 0.02$), and higher prevalence of altered exercise capacity during CPX (42.6 vs. 22.4%, $P = 0.01$) (*Table 2*). After multivariable adjustment using Cox regression analysis with selection of exercise variables (Model 1, *Table 3*), 25 W SPAP [hazard ratio (HR) (95% confidence interval, CI): 1.05 (1.01–1.10), $P = 0.03$] and altered aerobic capacity [(HR (95% CI): 4.13 (1.29–13.25), $P = 0.02$] were the only two parameters independently associated with long-term occurrence of ME (C index = 0.82). Conversely, neither, peak EROA nor altered O2-pulse were significantly associated with increased occurrence of ME (respectively, $P = 0.11$ and $P = 0.35$). Interestingly, both 25 W SPAP [HR (95% CI): 1.05 (1.00–1.10), $P = 0.04$] and altered aerobic capacity [HR (95% CI): 3.78 (1.18–12.16), $P = 0.03$] remained significantly associated with occurrence of ME after adjustment for MR severity (rest EROA) (Model 2, *Table 3*).

ROC curve analysis showed that a cut-off of 55 mmHg for 25 W SPAP had the higher discriminating power to predict ME onset [Youden index = 0.22, sensitivity = 45%, specificity = 77%, area under the curve (AUC) = 0.60, $P = 0.05$].

As displayed on Kaplan–Meier survival curves, patients with a Peak VO2 <80% ($P = 0.01$) or 25 W ExPHT defined as an SPAP ≥55 mmHg ($P = 0.037$) had lower event-free survivals (*Figure 3*). Furthermore, an incremental and significant increase of the χ^2 value of the predicting model was observed by successively adding Peak VO2 <80% and 25 W SPAP to LAVi as predictors (*Figure 4*).

Discussion

Exploring patients with at least moderate MR and discrepancy between symptoms and MR severity, we demonstrated that: (i) about one-third of them had reduced exercise capacity; (ii) EROA calculation was feasible in only one half of patients during ExE while SPAP recording was obtained in the majority of the cases (96% at 25 W ExE, 91% at peak ExE); (iii) patients performed more intense exercise with CPX than with ExE, (iv) 25 W ExPHT, as defined by an SPAP ≥55 mmHg, and altered aerobic capacity, as defined by a peak VO2 <80%, were independently associated with long-term occurrence of ME (Graphical Abstract).

Feasibility and prognostic significance of ExE

Although ExE has been reported to provide additional information on changes in MR severity, optimal visualization of the flow convergence region at peak ExE is challenging. In line with previous studies,[12] EROA quantification in primary MR was only feasible in one out of two patients at 25 W and peak ExE in our study. These results suggest that EROA quantification is challenging when heart rate increases in primary MR, as emphasized by latest recommendations,[17] which clearly limits its interest in this population in daily practice. EROA quantification seems more interesting in ischaemic MR, with higher feasibility, and allowing to identify patients at high risk of morbidity and of death.[3]

Moreover, the usefulness of information provided at peak ExE is controversial. Lancellotti *et al.* reported that ExPHT defined as a per-exercise SPAP >60 mmHg was independently associated with the occurrence of symptoms in asymptomatic MR.[4] However, Mahjoub *et al.*[18] showed that SPAP could reach values >60 mmHg in healthy individuals. Recently, Toubal *et al.*[19] showed that early increase in SPAP >15 mmHg at low level of exercise (25 W) was associated with a two-fold increase in the risk of cardiac events in asymptomatic patients with primary MR. We showed that SPAP at 25 W per se rather than its variation was recordable in most of cases, and importantly was independently associated with ME occurrence. Particular attention should thus be paid at low level of exercise instead of only at peak exercise.

Prognostic significance of CPX

Unlike previous studies, we chose to explore patients with a discrepancy between MR severity and symptoms, i.e. not just asymptomatic patients, to answer a question often problematic in our daily practice. We observed an alteration of functional capacity in barely one-third of our population, which is a noticeably larger proportion of patients than in previous studies. Indeed, Suzuki *et al.* and Messika-Zeitoun *et al.* showed an alteration in 24% and 19% of cases, respectively.[7,8]

In addition to detecting patients with impaired functional capacity, CPX allows to define the origin of the exercise limitation and therefore to avoid offering an invasive treatment to patients with symptoms unrelated to MR. In our study, the origin of the limitation of exercise capacity was cardiac in two-third of cases despite a relatively young age, few comorbidities, no LV consequences of the MR detected at rest TTE, and no or mild symptoms. CPX seems therefore interesting to unmask symptoms and, as already highlighted previously, to predict events in no or paucisymptomatic patients with primary MR.

While global χ^2 showed statistical incremental value of 25 W SPAP and aerobic capacity to LAVi, C index did not change between the

Table 2 Exercise data on patients presenting major clinical event or not

	All population ($n = 128$)	No ME ($n = 67$)	ME ($n = 61$)	*P*-value
25 W				
HR (bpm)	95.1 ± 16.4	95.8 ± 16.6	94.2 ± 16.2	0.66
SBP (mmHg)	148.0 ± 22.3	148.0 ± 21.9	148.1 ± 22.9	0.98
DBP (mmHg)	80.0 ± 13.7	81.5 ± 12.2	78.5 ± 15.1	0.25
LVEF (%)	66.4 ± 8.1	65.7 ± 8.9	67.2 ± 6.9	0.32
Increased LVEF	39 (30.5)	19 (28.4)	20 (32.9)	0.42
Contractile reserve, *n* (%)	27 (21.1)	13 (19.4)	14 (23.0)	0.49
EROA (mm^2) ($n = 74$)	34.7 ± 14.2	31.4 ± 13.0	37.8 ± 14.8	0.15
SPAP (mmHg) ($n = 123$)	50.6 ± 11.9	48.4 ± 9.6	52.9 ± 13.7	**0.03**
TAPSE	27.4 ± 5.9	27.8 ± 5.4	26.9 ± 6.5	0.48
Peak exercise				
HR (bpm)	132.7 ± 24.7	134.5 ± 27.1	130.6 ± 21.8	0.38
SBP (mmHg)	169.5 ± 27.6	167.1 ± 28.1	171.1 ± 27.0	0.32
DBP (mmHg)	87.8 ± 16.9	89.8 ± 17.9	85.5 ± 15.5	0.17
Workload (W)	112.7 ± 44.5	116.3 ± 49.8	108.7 ± 37.7	0.34
LVEF (%)	68.9 ± 8.9	68.4 ± 9.9	69.4 ± 7.8	0.51
Contractile reserve, *n* (%)	63 (49.2)	35 (52.2)	28 (45.9)	0.54
EROA (mm^2) ($n = 60$)	35.6 ± 14.5	29.8 ± 11.3	40.1 ± 15.2	**0.02**
SPAP (mmHg) ($n = 117$)	60.4 ± 13.7	58.9 ± 13.2	61.8 ± 14.1	0.26
ExPHT ($n = 117$)	52 (44.4)	23 (39.7)	29 (49.2)	0.30
TAPSE	27.3 ± 6.1	27.9 ± 6.2	26.8 ± 5.8	0.36
CPX				
Peak workload (W)	131.8 ± 48.7	134.7 ± 53.8	128.8 ± 42.7	0.50
Peak VO2 (mL/kg/min)	24.0 ± 7.1	24.9 ± 8.0	23.0 ± 6.1	0.13
Peak VO2 (% PV)	89.9 ± 19.8	92.0 ± 19.3	87.5 ± 20.2	0.20
Peak VO2 <80%, *n* (%)	41 (32)	15 (22.4)	26 (42.6)	**0.01**
O2 pulse (mL/beat/min)	11.9 ± 3.7	12.3 ± 4.0	11.5 ± 3.3	0.23
O2 pulse (% PV)	101.6 ± 27.2	105.7 ± 31.0	97.1 ± 21.9	0.08
Altered O2 pulse, *n* (%)	31 (24.2)	14 (20.9)	17 (27.9)	0.32

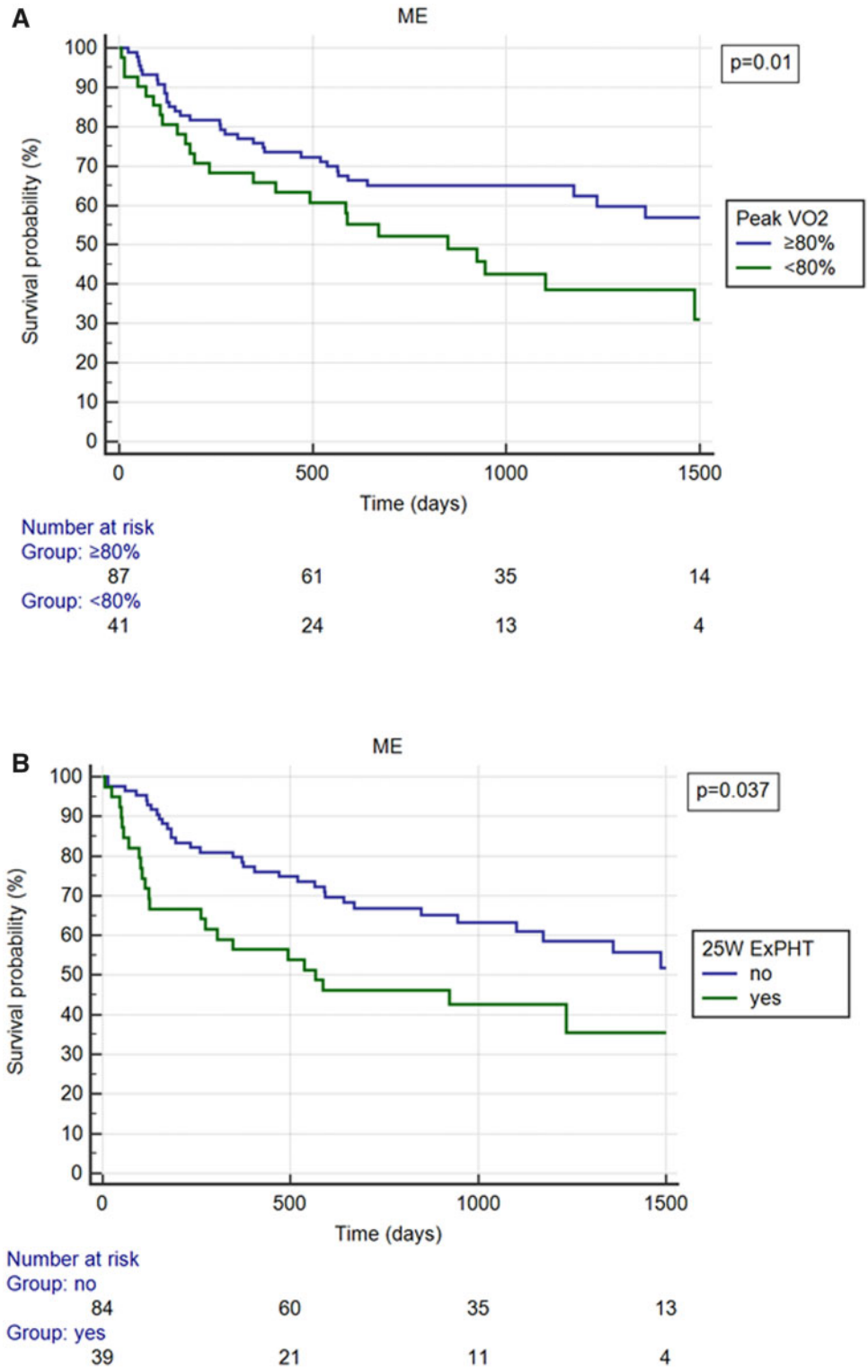
Data in bold: $P < 0.05$.
CPX, cardiopulmonary exercise testing; DBP, diastolic blood pressure; EROA, effective regurgitant orifice area; ExPHT, exercise pulmonary hypertension; HR, heart rate; LVEF, left ventricular ejection fraction; ME, major event; PV, predicted value; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane excursion.

Table 3 Multivariable Cox regression analyses to assess exercise determinants of major events at 1500 days according to exercise modality

	Model 1		Model 2	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
EROA (mm^2)			0.19	1.07 (0.97–1.17)
25 W SPAP (mmHg)	**0.02**	**1.05 (1.01–1.10)**	**0.04**	**1.05 (1.00–1.10)**
Peak EROA (mm^2)	0.11	1.03 (0.99–1.06)	0.60	0.98 (0.90–1.06)
Peak VO2 <80%, *n* (%)	**0.02**	**4.13 (1.29–13.25)**	**0.03**	**3.78 (1.18–12.16)**
O2 pulse (% PV)	0.35	1.01 (0.99–1.02)	0.31	1.01 (0.99–1.02)

Data in bold: $P < 0.05$.
CI, confidence interval; EROA, effective regurgitant orifice area; HR, hazard ratio; PV, predicted value; SPAP, systolic pulmonary artery pressure.

predicting models. Moreover, the AUC of 25 W SPAP was only fair with borderline significance. Although we have demonstrated the interest of the 25 W SPAP and CPX to predict ME, these results underline the need for a multiparametric approach, including rest parameters to stratify the risk in this population. Several parameters have been explored and proposed to go beyond the symptoms in



Figures 3 Long-term prognostic impact of exercise parameters in primary mitral regurgitation. Kaplan–Meier survival curves depicting time to major events. Data are shown according to Peak VO2< or ≥80% in (*A*) and in patients with and without 25 W exercise pulmonary hypertension in (*B*). *P*-value by log-rank test. ExPHT, exercise pulmonary hypertension; ME, major events.

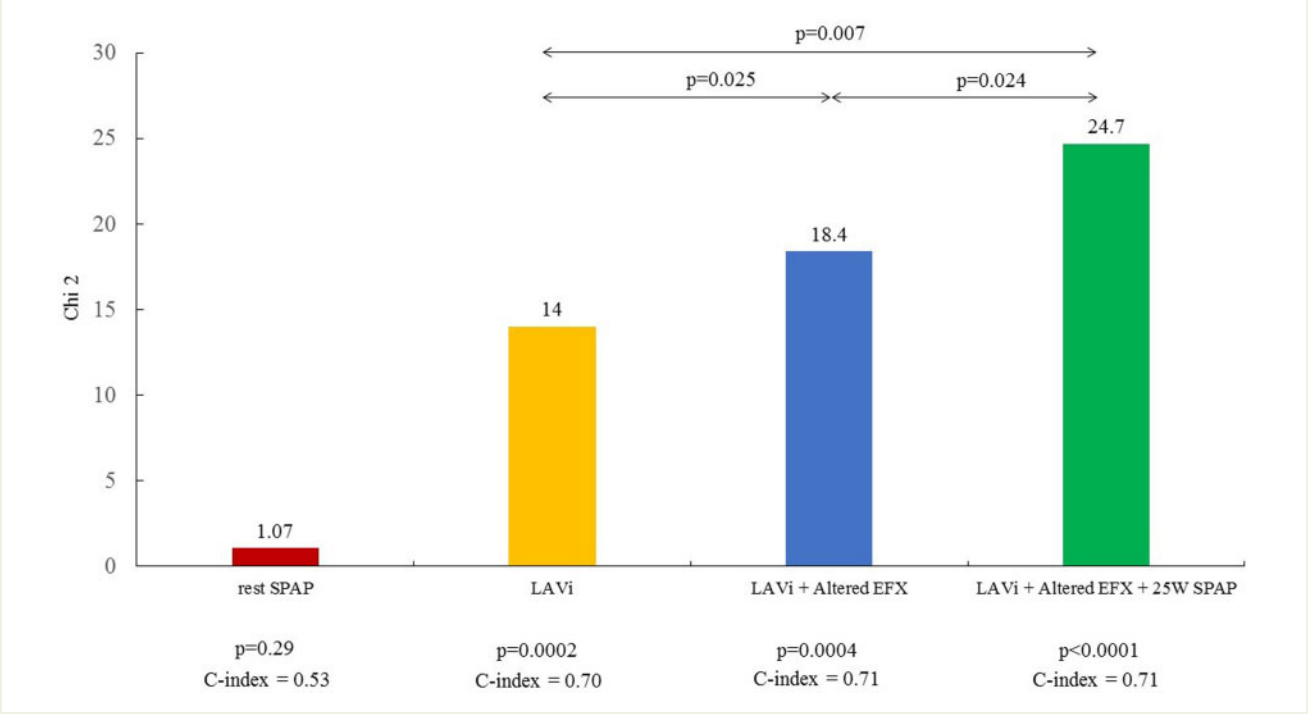


Figure 4 Additive value of exercise testing in primary mitral regurgitation to predict major events. To assess the incremental advantage of exercise echocardiography and cardiopulmonary exercise testing on top of current Class II recommendation criteria for the risk of major events, the changes in χ^2 values of Stepwise Cox regression models were assessed. The bar graphs show the χ^2 value. The addition of Peak VO2 >80% and 25 W systolic pulmonary artery pressure (SPAP) provide incremental prognostic information over rest SPAP and indexed left atrial volume. LAVi, left atrial volume index; SPAP, systolic pulmonary artery pressure.

this population including myocardial deformation in TTE, natriuretic peptides or cardiac fibrosis assessed with cardiac magnetic resonance imaging.[20] Interestingly, in MR with Class I surgery criteria, preoperative global longitudinal strain (GLS) showed a good sensitivity to predict postoperative LVEF and long-term outcomes after the surgery.[21,22] However, LV GLS was not different between patients with and without major clinical events in our study. Further studies will have to determine the incremental value of preoperative GLS and confirm the cut-off of 55 mmHg of 25 W SPAP to consider an earlier intervention.

Limitations

Our study has some limitations. First, we estimated the right atrial pressure from the diameter and breath-induced variability of the inferior vena cava at rest. This method is no validated during exercise, so the right atrial pressure was arbitrary set at an empirical value of 10 mmHg as in all previous studies on the topic. An invasive assessment of pulmonary pressures during exercise was not ethically acceptable. Second, the vast majority of outcome was represented by MVR which unfortunately maybe biased towards patients with severe MR. Third, we chose to include patients with exercise dyspnea but mild-to-moderate MR at rest. These patients might display dynamic MR, the latter becoming moderate to severe while exercising (i.e. dynamic MR).[23,24] Although we presented the largest population of primary MR patients who underwent both ExE and CPX, our findings must be confirmed in a larger multicentre study to confirm its additive value in daily practice.

Conclusion

In patients with ≥moderate primary MR and discrepancy between MR severity and symptoms, evaluation of SPAP at low level of exercise (25 W) during ExE and assessment of aerobic capacity during CPX are associated with adverse outcome. Both 25 W ExE and CPX might help to tailor medical decision-making in this population, while the clinical value of peak ExE remains more uncertain.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Data availability

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

Conflict of interest: none declared.

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