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ORIGINAL PAPER

Exercise pulmonary hypertension by the mPAP/CO slope in primary mitral regurgitation

Sebastiaan Dhont [1,2], Jan Stassen[3], Lieven Herbots[2,3], Sarah Hoedemakers[2,3], Youri Bekhuis[2,3], Ruta Jasaityte[3], Sarah Stroobants[3], Thibault Petit[1], Elise Bakelants[4], Maarten Falter[2,3], Sara Moura Ferreira[2,3], Guido Claessen[3], Petra Nijst[1], Pieter M. Vandervoort[1,2], Philippe B. Bertrand [1,2]*†, and Jan Verwerft[2,3]†

[1]Department of Cardiology, Ziekenhuis Oost-Limburg, Synaps Park 1, 3600 Genk, Belgium; [2]Faculty of Medicine and Life Sciences, Hasselt University, Agoralaan, 3590 Diepenbeek, Belgium; [3]Department of Cardiology, Jessa Hospital, 3500 Hasselt, Belgium; and [4]Department of Cardiology, Imeldaziekenhuis, 2820 Bonheiden, Belgium

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Aims

Exercise-induced pulmonary hypertension (PH), defined by a mean pulmonary arterial pressure over cardiac output (mPAP/CO) slope >3 mmHg/L/min, has important diagnostic and prognostic implications. The aim of this study is to investigate the value of the mPAP/CO slope in patients with more than moderate primary mitral regurgitation (MR) with preserved ejection fraction and no or discordant symptoms.

Methods and results

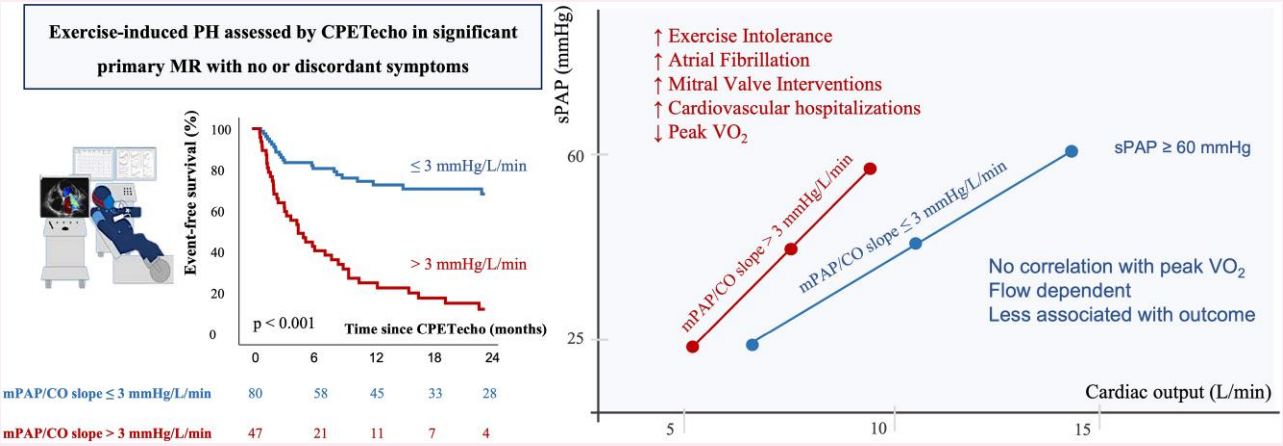
A total of 128 consecutive patients were evaluated with exercise echocardiography and cardiopulmonary testing. Clinical outcome was defined as the composite of mitral valve intervention, new-onset atrial fibrillation, cardiovascular hospitalization, and all-cause mortality. The mean age was 63 years, 61% were male, and the mean LVEF was 66 ± 6%. The mPAP/CO slope correlated with peak VO_2 ($r = -0.52$, $P < 0.001$), while the peak systolic pulmonary artery pressure (sPAP) did not ($r = -0.06$, $P = 0.584$). Forty-six per cent ($n = 59$) had peak exercise sPAP ≥60 mmHg, and 37% ($n = 47$) had mPAP/CO slope >3 mmHg/L/min. Event-free survival was 55% at 1 year and 46% at 2 years, with reduced survival in patients with mPAP/CO slope >3 mmHg/L/min (hazard ratio, 4.9; 95% confidence interval, 2.9–8.2; $P < 0.001$). In 53 cases (41%), mPAP/CO slope and peak sPAP were discordant: patients with slope >3 mmHg/L/mmHg and sPAP <60 mmHg ($n = 21$) had worse outcome vs. peak sPAP ≥60 mmHg and normal slope ($n = 32$, log-rank $P = 0.003$). The mPAP/CO slope improved predictive models for outcome, incremental to resting and exercise sPAP, and peak VO_2.

Conclusion

Exercise PH defined by the mPAP/CO slope >3 mmHg/L/min is associated with decreased exercise capacity and a higher risk of adverse events in significant primary MR and no or discordant symptoms. The slope provides a greater prognostic value than single sPAP measures and peak VO_2.

* Corresponding author. E-mail: philippe.bertrand@zol.be
† Co-senior authorship.

Graphical Abstract



Enhanced risk stratification in MR: mPAP/CO slope vs. sPAP measures. The left panel illustrates the event-free survival curves with an mPAP/CO slope threshold of 3 mmHg/L/min. The right panel displays the correlation between the slope and solitary sPAP measures, as well as their association with the outcome. CO, cardiac output; CPET, cardiopulmonary exercise testing; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; VO_2, oxygen consumption.

Keywords primary mitral regurgitation • CPETecho • mPAP/CO slope • exercise pulmonary hypertension

Introduction

The optimal timing for intervention in patients with significant primary mitral regurgitation (MR) remains a contentious topic and becomes increasingly critical, given the mounting evidence suggesting the survival benefits of early intervention in carefully selected patients.[1–6] The presence of symptoms, reduced left ventricular ejection fraction (LVEF ≤60%), or LV dilatation (LV end-systolic diameter ≥40 mm) already constitute compelling indications.[7–11] However, recent research indicates that exercise testing may offer enhanced sensitivity in identifying patients at increased risk of adverse outcomes.[5,12–15]

Treatment decisions hinge on the accurate diagnosis of the mechanisms and severity of MR.[16] Despite its widespread use as a diagnostic tool, echocardiography has limitations affecting the accuracy and reproducibility of both qualitative and quantitative parameters. Guidelines recommend a multiparametric approach and multimodality imaging to resolve incongruous data. Beyond elucidating the mechanisms and severity of MR, substantial attention is devoted to its consequences, including the emergence of pulmonary hypertension (PH). Elevated systolic pulmonary arterial pressure (sPAP) assessed by echocardiography exceeding 50 mmHg at rest or above 60 mmHg during exercise are often used as potential surgical indications.[9,13,17–19]

PH has historically been defined by mPAP exceeding 25 mmHg at rest or 30 mmHg during exercise.[20] The fourth PH Symposium (2008) eliminated the exercise criterion, as elevated mPAP during exercise might not necessarily indicate pathology, such as in elderly or athletes.[21] A more recent development has been the adoption of multipoint measurement of mPAP over CO as a more reliable indicator of pulmonary haemodynamics, where the pulmonary pressure-flow relationship has been identified as a valuable tool in pulmonary arterial hypertension and heart failure.[22–24] The most recent ESC guidelines on PH (2022) have therefore reintroduced the concept of exercise PH, which is defined as the mPAP/CO slope >3 mmHg/L/min rather than a single sPAP value at peak exercise.[24,25] Cardiopulmonary exercise testing with echocardiography (CPETecho) is gaining momentum in assessing valvular heart disease, given its non-invasive nature and ability to evaluate exercise capacity, PH, CO, and—dynamic—MR.[19,23,26,27] Yet, available data for its use in primary MR are scarce.

The primary aim of our study was to evaluate the prognostic value of exercise PH, defined by the mPAP/CO slope > 3 mmHg/L/min, in patients with more than moderate chronic primary MR and no or discordant symptoms.

Methods

Study population

This observational cohort study examined consecutive patients with chronic primary MR at Jessa Hospital and Ziekenhuis Oost-Limburg in Belgium who underwent a CPETecho between 2016 and 2022. The study enrolled patients who presented with more than moderate primary MR and no or discordant symptoms, in the setting of preserved LV function (LVEF >60%; LV end-systolic diameter <40 mm) and in the absence of significant (moderate or more) concomitant valvular disease, or history of atrial fibrillation. Before the CPETecho, the patients underwent a detailed evaluation involving clinical examination, 12-lead electrocardiogram, blood testing, spirometry, and a resting echocardiogram according to current guidelines.[28] The severity of MR was based on a multiparametric echocardiographic approach including both qualitative (valve morphology, colour Doppler, and the flow pattern in pulmonary veins) and quantitative [effective regurgitant orifice area (EROA), and regurgitant volume (RV) when appropriate] markers. In addition, clinical variables (e.g. diabetes mellitus, hypertension, and body mass index) were collected before the CPETecho. The study obtained approval from the local ethics committees, and due to its retrospective design, the requirement for written informed consent was waived.

Exercise echocardiography

All patients underwent a maximal, symptom-limited bicycle ergometry test in a semi-supine position on a tiltable ergometer with simultaneous

acquisition of echocardiographic data by experienced sonographers using a GE ViVid Scanner (General Electric Healthcare, Horten, Norway) or a Philips EPIQ7 (Philips Healthcare, Andover, MA, USA). Secondary data analysis was done offline with the EchoPac (General Electric Healthcare, Horten, Norway) or TomTec (TomTec Imaging Systems GmbH) software at the time of testing. A predefined ramp and stress echocardiography protocol was used as previously described.[19,23] Briefly, a ramp protocol was initiated with a first hold stage at low-intensity exercise, identified mainly by a heart rate of 85–100 bpm to avoid E/A fusion. After acquiring a complete set of images, patients were encouraged to reach maximal exertion at which the second hold stage was performed. Chamber volumes and LVEF were calculated with the modified Simpson method using apical two- and four-chamber views. Tissue Doppler was used for measuring velocities at the septal and lateral sites of the mitral annular and the lateral side of the tricuspid annulus to quantify longitudinal RV function. Stroke volume was calculated by multiplying the LV outflow tract (LVOT) area, which was determined based on the resting mid-systolic LVOT diameter, by the LV outflow tract velocity-time integral. The LVOT area was considered constant throughout the exercise test. CO was obtained by stroke volume × heart rate. Agitated colloid (Gelofusine 4%, Braun, Melsungen, Germany) was injected in the left antecubital vein to enhance the tricuspid regurgitation (TR) velocity signal during all TR measurements.[29] The sPAP was estimated from the CW Doppler velocity of the TR jet and the addition of 10 mmHg for right atrial pressure as previously performed.[13,30–32] *Figure 1* illustrates an example. The mPAP was calculated based on sPAP using the Chemla equation ($mPAP = 0.61 \times sPAP + 2$).[33] All measurements were averaged over three cardiac cycles.

Ventilation and gas analysis

Breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2), tidal volume (V_T), respiratory rate, and minute ventilation (V_E) were measured during rest and exercise (Schiller, CS-200, Ergo-Spiro, Baar, Switzerland). Exercise effort was estimated by the respiratory exchange ratio (RER, ratio between VCO_2 and VO_2) and aerobic capacity by peak VO_2. Maximal effort was defined as RER ≥ 1.05. The peak VO_2 was expressed as an absolute value or as a percentage of the predictive value (derived from the Wasserman formula).[34] Maximal voluntary ventilation (MVV) was defined as 40 × FEV_1. Functional limitation was defined as peak VO_2 < 70%. Additionally, all patients were monitored with a 12-lead electrocardiogram, oxygen saturation, and blood pressure registration (non-invasively, sphygmomanometer) throughout the entire exercise and recovery phase.

Clinical outcome

All patients were followed according to the current guidelines with regular follow-up assessments, and the date of their last visit to the cardiology department served as the basis for evaluating the clinical endpoints (last inquiry in March 2023).[7,8,10,11] Data were collected on mitral valve intervention (including both surgery and percutaneous interventions), new-onset atrial fibrillation (AF), cardiovascular hospitalizations, and all-cause mortality. Notably, the occurrences of AF and hospitalizations were recorded only until the day of mitral valve intervention or the end of follow-up if no intervention occurred. The primary combined clinical endpoint was event-free survival, including new-onset atrial fibrillation, mitral valve intervention, cardiovascular hospitalizations, and all-cause mortality. The decision towards mitral valve intervention was taken by the treating physician based on the available clinical data, and only after a multidisciplinary Heart Team discussion following the indications for intervention by the actuarial ACC/AHA (2014) and ESC (2017) valvular heart disease guidelines.[7,8,10,11] Exercise PH by either peak sPAP or elevated mPAP/CO slope by itself was not considered an indication for intervention within the study timeframe.

Statistical analysis

Continuous variables are expressed as mean (±standard deviation) if normally distributed or median (interquartile range) if otherwise. Categorical data are expressed as numbers and percentages and compared with Pearson's χ^2 test or Fisher's exact test when appropriate. Linear regression evaluated the association between sPAP and mPAP/CO slope with the highest oxygen uptake (peak VO_2) during the index CPETecho. Subsequently, peak VO_2 max was categorized into two groups (above or below 70% of the predictive value) to enable the receiver operating

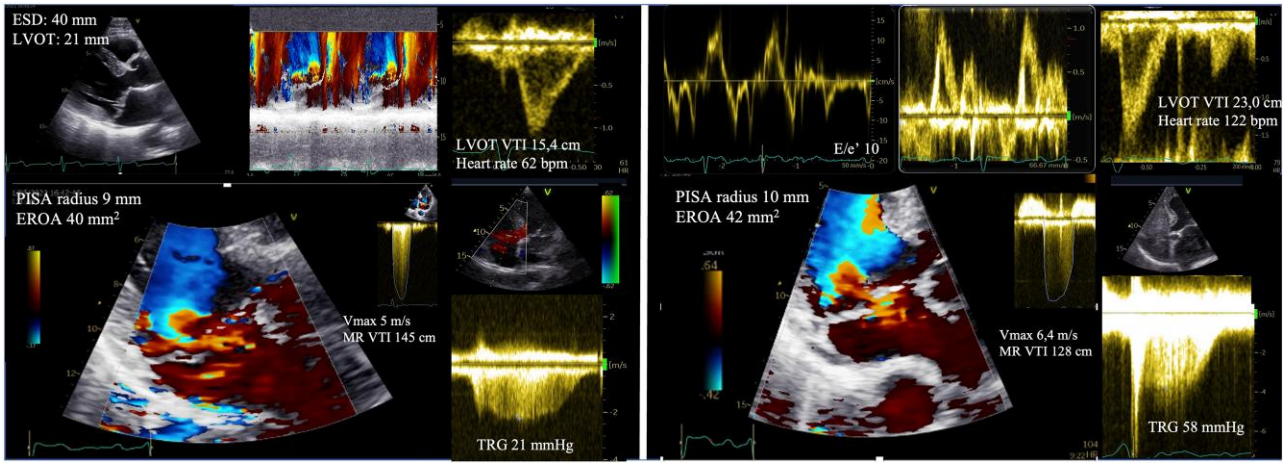


Figure 1 Case example: echocardiography variables at rest and peak exercise. A 70-year-old man with bileaflet mitral valve prolapse and holosystolic severe MR (ERO, 40 mm^2; RVol, 55 mL; ESD, 40 mm; LVEF, 68%; LV strain, 23%; sPAP = TRG + RAP (10 mmHg); mPAP/CO slope 2.4 mmHg/L/min). Rest imaging (left panel) vs. peak exercise (right panel). CO, cardiac output; EF, ejection fraction; ESD, end-systolic diameter; HR, heart rate; LV, left ventricle; LVOT, left ventricular outflow tract; MR, mitral regurgitation; mPAP, mean pulmonary artery pressure; PISA, proximal isovelocity surface area; RAP, right atrial pressure; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TRG, tricuspid regurgitation gradient; TVI, time–velocity integral.

characteristic (ROC) analysis. The sensitivity and specificity in predicting the peak VO_2 for both sPAP ≥ 60 mmHg and mPAP/CO slope > 3 mmHg/L/min were evaluated. These cut-off values were then used to categorize the data into four distinct groups based on dichotomized mPAP/CO slope and sPAP (3 mmHg/L/min and 60 mmHg, respectively), allowing for the identification of concordant and discordant groups. Subsequently, a time-to-event Cox analysis and Life Tables were carried out to generate Kaplan–Meier curves, log-rank tests (Mantel–Cox), and hazard ratios (HRs) for the clinical endpoints, which were subsequently stratified by the four distinct groups. Additionally, univariable and multivariable Cox proportional hazard models were employed to examine the correlation between mPAP/CO slope > 3 mmHg/L/min and the likelihood of event-free survival. Finally, the incremental value of the mPAP/CO slope over sPAP measures to predict the composite endpoint was evaluated by the likelihood ratio test and the change in global χ^2 value between each multivariate model. Statistical significance was a two-tailed probability level of <0.05. All statistical analyses were performed using SPSS version 22 (IBM, Chicago, IL, USA).

Table 1 Baseline characteristics of the total population ($n = 128$)

Demographics	
Age (years)	63 ± 11
Female sex	50 (39%)
BMI (kg/m^2)	25 ± 4
Lab results	
Hb (mg/dL)	14 ± 1
Creatinine (mg/dL)	1.3 (0.25)
NTproBNP (ng/L)	160 (267)
Comorbidities	
DM Type 2	7 (6%)
Arterial hypertension	51 (40%)
Beta-blocker use	40 (31%)
Resting echocardiogram	
LVEDV (mL)	130 ± 45
LVESV (mL)	50 ± 24
LVEDVi (mL/m^2)	68 ± 22
LVESVi (mL/m^2)	24 ± 13
LVED diameter	48 ± 7
LVEF (%)	66 ± 6
PLAX LA (mm)	35 ± 8
LAVi (mL/m^2)	28 ± 23
EROA (mm^2)	37 ± 11
RV (mL)	50 ± 31
Medial *E*/e′ ratio	13 ± 6
TR gradient (mmHg)	23 ± 6
S′ RV (cm/s)	11 ± 3
TAPSE (mm)	21 ± 6

AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; EDV, end-diastolic volume; EF, ejection fraction; EROA, effective regurgitant orifice area; ESV, end-systolic volume; Hb, haemoglobin; I, indexed; LA, left atrium; LV, left ventricle; NTproBNP, *n*-terminal prohormone of brain natriuretic peptide; PLAX, parasternal long axis; RV, regurgitant volume; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation. Body surface area was measured using the Mosteller formula.[35]

Results

Patient population

A total of 128 patients were included in the study. *Table 1* summarizes the baseline characteristics at the time of study inclusion. The clinical features of the study group were typical of a degenerative MR population, with a mean age of 63 years and 61% being male. The mean EROA was 37 mm^2, corresponding to an RV of 50 mL. At the time of inclusion, all patients had a non-dilated LV with preserved ejection fraction and no right ventricular failure. Among the patients included, 4 patients (3%) had mild or less concomitant mitral stenosis, 21 patients (16%) had mild or less aortic insufficiency, 5 patients (4%) had mild or less aortic stenosis, and 53 patients (41%) had mild or less tricuspid insufficiency.

Table 2 CPETecho measurements at rest, low-intensity exercise, and peak exercise

	Rest	Low exercise	Peak exercise
Echocardiography			
LVEDV (mL)	130 ± 45*	131 ± 49*	127 ± 44
LVESV (mL)	50 ± 24*	46 ± 26*	41 ± 20
LVEF (%)	66 ± 6*	68 ± 7*	71 ± 9
SV (mL)	69 ± 17*	85 ± 21*	87 ± 23
SVi (mL/m^2)	37 ± 8*	45 ± 10*	47 ± 10
E-wave velocity (cm/s)	85 ± 28*	112 ± 30*	133 ± 29
e′ septal (cm/s)	7 ± 2*	10 ± 3*	14 ± 6
Medial *E*/e′ ratio	13 ± 6	13 ± 5*	11 ± 5
TR gradient (mmHg)	23 ± 6*	41 ± 9*	49 ± 9
TAPSE (mm)	21 ± 6*	24 ± 7*	26 ± 7
S′ RV (cm/s)	11 ± 3*	14 ± 4*	16 ± 5
LVOT VTI (cm)	18 ± 4*	22 ± 4*	23 ± 4
CO (L/min)	5 ± 1*	8 ± 2*	11 ± 3
CI (L/min/m^2)	2.5 ± 0.6*	4.3 ± 1.2*	5.9 ± 1.6
RV FAC (%)	47 ± 11*	51 ± 10*	54 ± 12
Cardiopulmonary exercise testing			
SpO_2 (%)	98 ± 2	98 ± 2	97 ± 2
Heart rate (bpm)	68 ± 13*	97 ± 14*	128 ± 21
VO_2 (L/min)	0.3 ± 0.1*	0.9 ± 0.3*	1.5 ± 0.5
VO_{2i} (L/min/kg)	4 ± 2*	12 ± 4*	20 ± 8
% pred (%)			81 ± 23
RER	0.85 ± 0.1*	0.95 ± 0.1*	1.13 ± 0.1
Watt (W)	0 ± 0*	50 ± 25*	112 ± 49
SBP (mmHg)	143 ± 23*	165 ± 27*	184 ± 36
DBP (mmHg)	82 ± 12*	83 ± 14*	85 ± 14

CI, cardiac index; CO, cardiac output; DPB, diastolic blood pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FAC, fractional area change; LAVI, left atrial volume index; LV, left ventricle; LVOT, left ventricle outflow tract; RER, respiratory exchange ratio; RV, right ventricle; SBP, systolic blood pressure; SpO_2, oxygen saturation; SV, stroke volume; SVi, stroke volume indexed; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VO_2, oxygen consumption.
*Difference $P < 0.05$.

Furthermore, no individuals had established significant pulmonary pathology.

Exercise testing

Table 2 displays the CPETecho data at rest, low exercise, and peak exercise; derived variables are shown in *Table 3*. The mean RER at peak exercise was 1.13 ± 0.1, indicating that a vast majority of patients were able to perform a maximal test. No pulmonary restrictions were observed among the cohort, as evidenced by the absence of significant reductions in oxygen saturation levels and an adequate ventilatory reserve, with an average of 55%. The CO increased significantly from 5 ± 1 at rest to 11 ± 3 L/min at peak exercise. Corresponding sPAP measurements were, respectively, 33 ± 6 and 59 ± 9 mmHg. The mean mPAP/CO slope was 2.7 mmHg/L/min. Of the total cohort, 59 (46%) patients had peak sPAP ≥60 mmHg, and 47 (37%) had mPAP/CO slope >3 mmHg/L/min. The overall indexed peak VO_2 was 20 ± 8 L/min/kg (81 ± 23% of predictive value). The mPAP/CO slope correlated well with peak VO_2 ($r = -0.52$, $P < 0.001$), while the peak exercise sPAP value did not ($r = -0.06$, $P = 0.584$; *Figure 2*). Moreover, *Figure 3* displays the ROC analysis; the mPAP/CO slope was significantly associated with reduced peak VO_2 (AUC = 0.66, $P = 0.002$), while sPAP was not (AUC = 0.48, $P = 0.667$). The sensitivity and specificity of a mPAP/CO slope > 3 mmHg/L/min in predicting reduced exercise capacity were 56 and 76%, respectively.

Table 3 CPET echo-derived variables

Derived variables during CPET echo	
mPAP/CO slope (mmHg/L/min)	2.7 ± 2.0
V_E/V_{CO2} slope	30 ± 6
CO/VO_2 slope	6 ± 2
V_E/MVV (%)	55 ± 17
O_2 pulse peak (mL/beat)	9 ± 5

CO, cardiac output; CO/VO_2, cardiac output/oxygen consumption; CPET, cardiopulmonary exercise testing; mPAP, mean pulmonary artery pressure; MVV, maximum voluntary ventilation; VE/VCO_2, minute ventilation/carbon dioxide production.

Event-free survival

All patients were subject to follow-up for a median duration of 24 (10–46) months. Event-free survival was 55% at 1 year and 46% at 2 years. During the follow-up period, 49 (38%) patients underwent mitral valve intervention. Out of these, four patients underwent percutaneous treatment with transcatheter edge-to-edge repair (Mitraclip, Abbott Vascular, Menlo Park, CA, USA), while the remaining patients

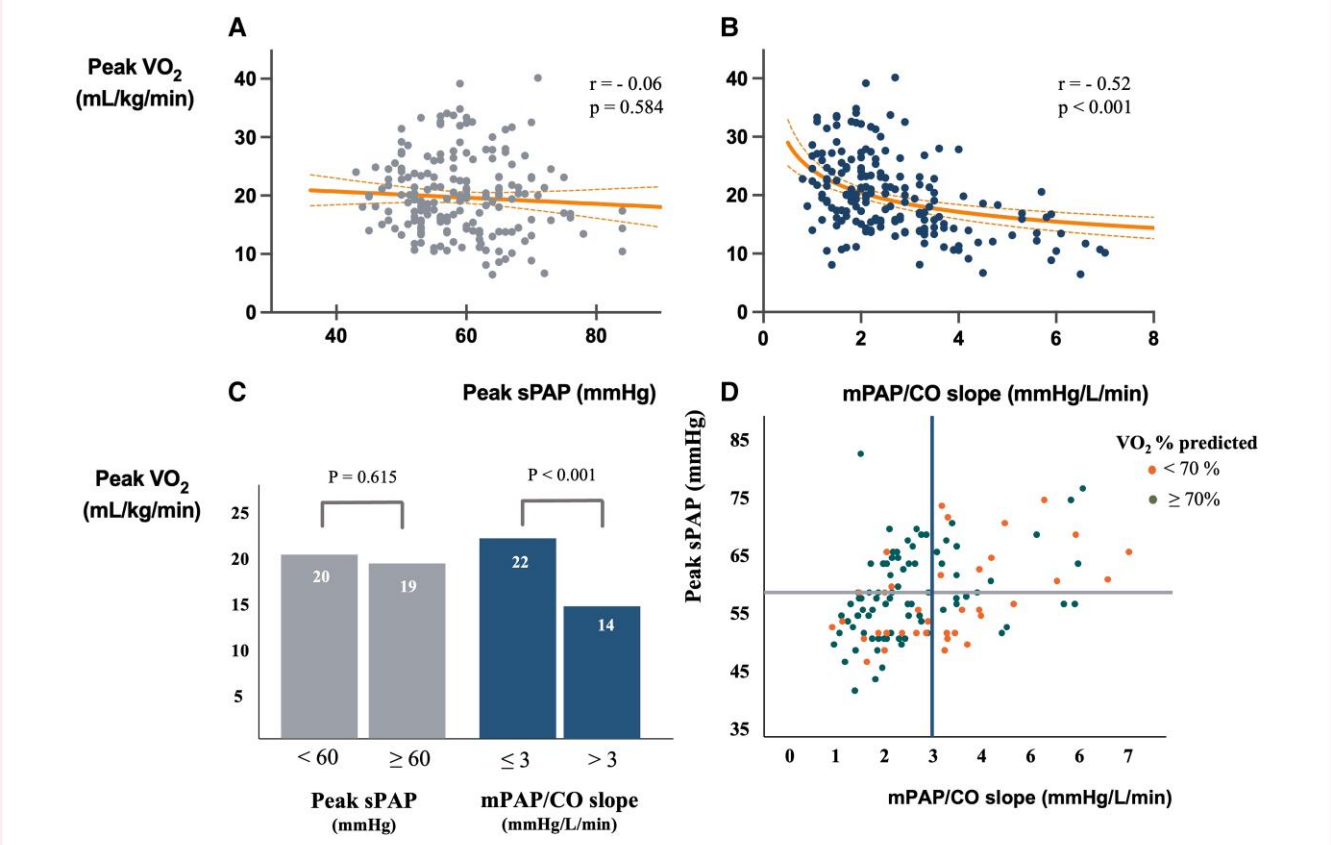


Figure 2 Correlations between peak VO_2, peak sPAP, and mPAP/CO slope. Peak VO_2 vs., respectively, sPAP (*A*) and mPAP/CO slope (*B*) along with bar charts (*C*) depicting peak VO_2 by categories of sPAP and mPAP/CO slope and scatterplot analysis (*D*) of peak sPAP vs. mPAP/CO slope in relation to VO_2% predicted. Goodness-of-fit plots + 95% confidence bands; CO, cardiac output; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; VO_2, oxygen consumption.

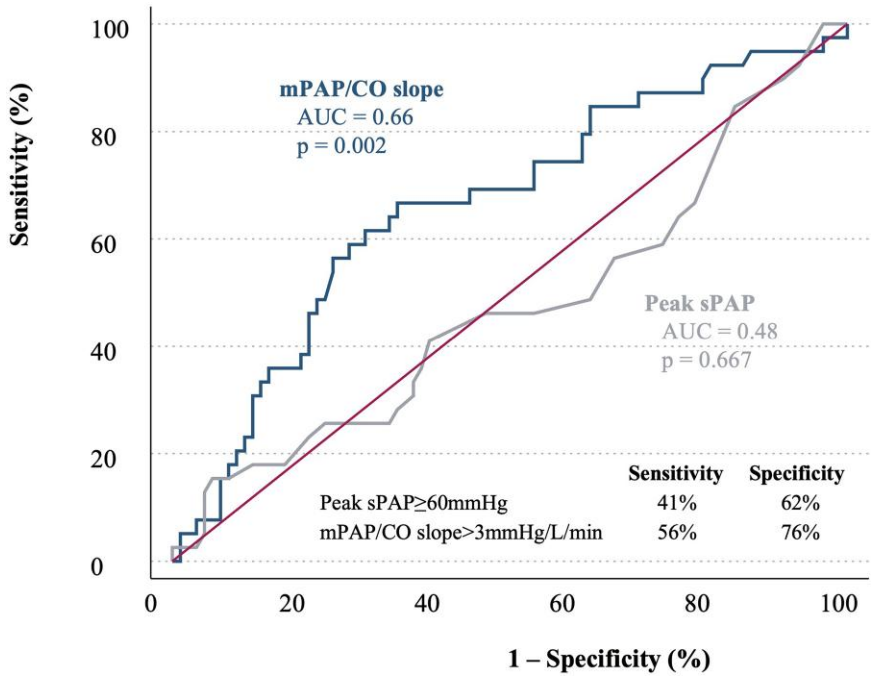


Figure 3 ROC curve and analysis: comparing the association of mPAP/CO slope vs. peak sPAP with reduced peak VO_2 (70% of the predictive value). AUC, area under the curve; CO, cardiac output; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure.

underwent cardiac surgery. Until the intervention date or the end of follow-up, 30 (23%) developed AF, and 28 (22%) were hospitalized for heart failure. No deaths occurred during the study period. The Kaplan–Meier survival curves, stratified by concordance and discordance between mPAP/CO slope > 3 mmHg/L/min and peak exercise sPAP ≥60 mmHg, are presented in *Figure 4*. Patients with mPAP/CO slope > 3 mmHg/L/min had a lower likelihood of event-free survival (log-rank $P < 0.001$), thereby yielding a non-adjusted HR of 4.9 [95% confidence interval (CI), 2.9–8.2] for clinical events. The adjusted HRs are presented in *Table 4*. The unadjusted HRs for mitral valve intervention, AF occurrence, and cardiovascular hospitalizations were, respectively, 4.8 (95% CI, 2.7–8.8, $P < 0.001$), 4.0 (95% CI, 1.9–8.7, $P < 0.001$), and 3.3 (99% CI, 1.6–7.1, $P = 0.002$). Furthermore, discordant patients with an mPAP/CO slope > 3 mmHg/L/min and peak sPAP <60 mmHg ($n = 21$) had worse outcome compared with patients with peak exercise sPAP ≥60 mmHg but at normal slope ($n = 32$, log-rank $P = 0.003$, *Figure 4*). The incremental value of the mPAP/CO slope in predicting the composite outcome is illustrated in *Figure 5*. A predictive model based on age and rest sPAP was significantly refined by adding VO_2% predictive (likelihood $\chi^2 = 23$, $P < 0.001$) and subsequently significantly improved by peak sPAP (likelihood $\chi^2 = 27$, $P < 0.001$) and mPAP/CO slope (likelihood $\chi^2 = 51$, $P < 0.001$).

Discussion

This study provides novel insights on the additive value of CPETecho in assessing the impact of MR on cardiopulmonary performance: (i) exercise PH, defined by the mPAP/CO slope >3 mmHg/L/min, is frequently observed in patients with primary MR, (ii) increase in mPAP disproportionate to the rise in CO exhibits a stronger correlation with peak VO_2 when compared to peak sPAP, (iii) an mPAP/CO slope > 3 mmHg/L/min yields pivotal prognostic data, even when the peak sPAP is <60 mmHg and vice versa, and (iv) increased mPAP/CO slope is, incremental to sPAP and peak VO_2, linked with adverse outcome.

Symptom onset, functional limitation, and PH are crucial in evaluating patients with significant primary MR.[7,8,12] Nonetheless, given the subjective nature of symptom expression, implementing CPET has been suggested as an objective measure to evaluate exercise capacity, particularly the peak VO_2 as a biomarker for general fitness and cardiovascular health.[6,12,18] Coisne *et al.*[12] demonstrated that impaired aerobic capacity is associated with adverse outcomes in patients with at least moderate MR. The incorporation of simultaneous stress echocardiography facilitates the comprehensive appraisal of not only the dynamic nature of MR but also its consequences, such as PH and reduced CO. Our investigation revealed that exercise PH, as indicated by an elevated mPAP/CO slope, is a common finding (37%) in patients with significant MR and no or discordant symptoms and demonstrates a robust correlation with peak VO_2, unlike solitary peak sPAP measurements. While determining a cut-off value is an arbitrary construct given the continuous nature, an mPAP/CO slope exceeding 3 mmHg/L/min is an effective discriminator of patients at an elevated risk of reduced aerobic capacity.

The adoption of multipoint measurements of mPAP over CO as a more reliable indicator of pulmonary haemodynamics has been established in pulmonary arterial hypertension and heart failure.[19,22,24] This study is the first to address its incremental value in valvular heart disease. The elegant work of Lancellotti and colleagues established that patients with MR and exercise-induced PH, defined at that time by sPAP ≥ 60 mmHg, were associated with a greater incidence of postoperative complications and a reduced event-free survival rate.[3,17,26,31] However, other groups, such as Mentias *et al.*,[14] did not find a significant interaction between exercise sPAP and outcome. The exercised-induced increase in sPAP not only varies with age and gender but is highly correlated with CO augmentation, which may in part clarify the inconsistent results.[14,17,36,37] Indeed, in our study, patients with elevated peak

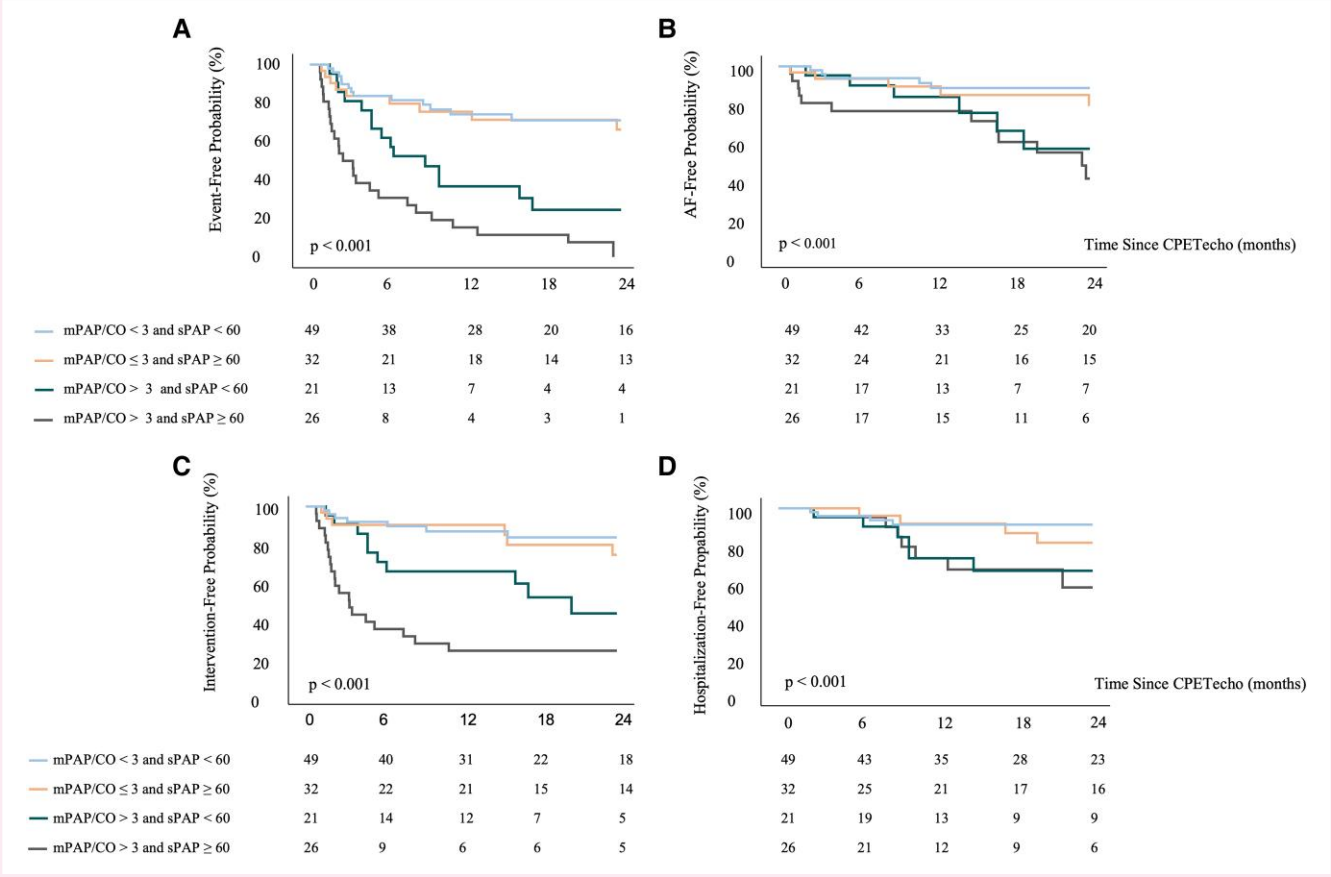


Figure 4 Kaplan–Meier survival curves for the primary endpoint (*A*), new-onset AF (*B*), mitral valve intervention (*C*), and cardiovascular hospitalization (*D*), stratified by concordance and discordance between mPAP/CO slope >3.0 mmHg/L/min and peak exercise sPAP ≥60 mmHg. CO, cardiac output; CPET, cardiopulmonary exercise testing; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure.

Table 4 Impact of mPAP/CO slope >3 mmHg/L/min on event-free survival in Cox models

Analysis	*n*	HR for clinical event	*P*-value
Univariate analysis	128	4.9 (95% CI, 2.9–8.2)	<0.001
Model 1: adjusted for age and sex	128	5.8 (95% CI, 3.2–10.6)	<0.001
Model 2: Model 1 + hypertension, diabetes, and beta-blocker use	128	6.1 (95% CI, 3.3–11.1)	<0.001
Model 3: Model 2 + LAVI, EROA, rest *E*/*e*′, rest LVEDV, and rest *S*′ RV	106	4.2 (95% CI, 1.9–9.5)	<0.001

AF, atrial fibrillation; EROA, effective regurgitant orifice area; HR, hazard ratio; LAVI, left atrial volume index; LVEDV, left ventricle end-diastolic volume; RV, right ventricle.

sPAP ≥ 60 mmHg but at a normal mPAP/CO slope (i.e. good CO augmentation) had better event-free survival than patients with peak sPAP < 60 mmHg but elevated mPAP/CO slope (*Figure 4*). Consequently, there is a physiological rationale for assessing pressure relative to the flow. Moreover, a multipoint evaluation approach significantly enhances the feasibility of assessing exercise-induced PH, considering the challenges of obtaining a single sPAP measurement precisely at the moment of peak exercise.[38] The most recent ESC guidelines on PH (2022) have therefore introduced the concept of exercise PH defined by the mPAP/CO slope > 3 mmHg/L/min.[21,24,25,39] Our study emphasizes the incremental benefit of this relatively novel parameter for risk stratification of patients with primary MR.

In conclusion, integrating CPET and stress echocardiography establishes a valuable approach to symptom evaluation, risk stratification, and decision-making processes in significant primary MR. By employing this combined methodology, a more comprehensive and nuanced view of the impact of MR on global cardiopulmonary function can be obtained. This may facilitate more sensitive and accurate identification of patients who would benefit from timely mitral valve intervention. Randomized controlled trials will need to resolve whether a targeted approach utilizing CPETecho could improve clinical outcomes among patients with primary MR.

Limitations

First, the results of CPETecho may have impacted the decision to proceed with mitral valve intervention. However, it is important to note that the mPAP/CO slope still holds incremental value for other independent endpoints, such as atrial fibrillation and cardiovascular hospitalization irrespective of the decision towards intervention. Secondly, the retrospective design carries inherent limitations that may affect the

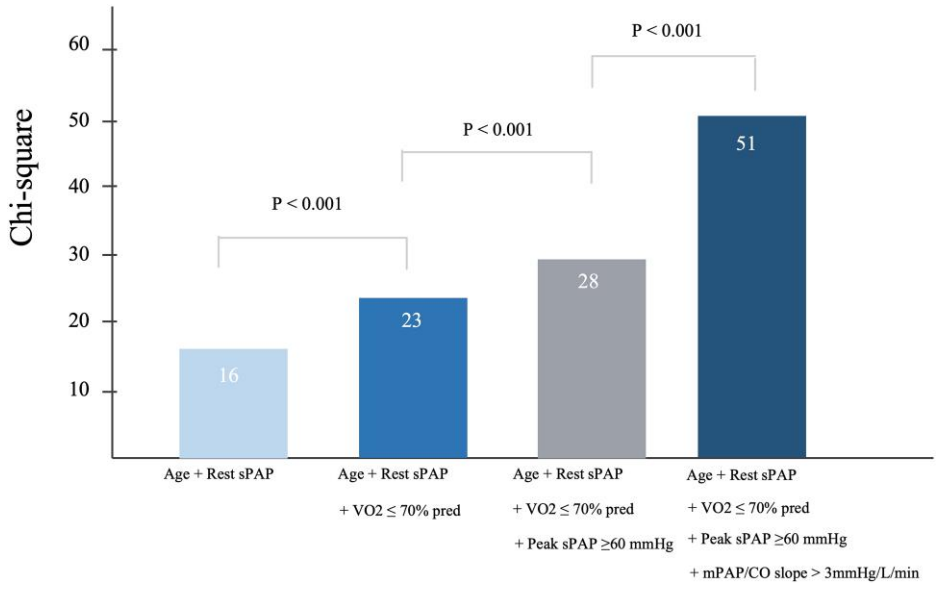


Figure 5 The incremental prognostic value of mPAP/CO slope. The incremental value of the mPAP/CO slope in predicting the composite outcome: the predictive model based on age and rest sPAP was significantly refined by adding VO_2% predictive and subsequently significantly improved by peak sPAP and mPAP/CO slope. CO, cardiac output; mPAP, mean pulmonary artery pressure; pred, predicted; sPAP, systolic pulmonary artery pressure; VO_2, oxygen consumption.

generalizability of the results. In addition, the assessment of the dynamic changes in MR severity during exercise was not feasible in all patients. Thirdly, the accuracy of CPETecho is closely linked to the proficiency of the operator, and in our study, invasive data were not obtained. Nevertheless, prior studies have established the validity of CPETecho.[23,29] Fourthly, we assumed that the LVOT area remained constant for each patient during exercise, and it should be noted that the use of a fixed value of 10 mmHg for estimating RA pressure may have certain limitations. This approach has been employed in previous studies,[13,31,32] and there is currently no conclusive evidence supporting a strong correlation between non-invasive echocardiographic measures and invasive exercise RA pressures. Moreover, accurately measuring invasive RA pressure during peak exercise also poses challenges due to the respiratory fluctuations. Finally, improvement in peak VO_2 or mPAP/CO slope after successful valve intervention remains uncertain.

Conclusion

In patients with significant primary MR and no or discordant symptoms who underwent CPETecho, an increased mPAP/CO slope > 3 mmHg/L/min is associated with reduced peak oxygen uptake and event-free survival, more than a single peak exercise sPAP measure. Adding the mPAP/CO slope significantly enhances the multivariate regression models for the combined endpoint in addition to peak exercise sPAP and peak VO_2. Patients with an increased mPAP/CO slope should at least be closely monitored in a heart valve clinic. Although our findings need prospective validation, the reintroduction of exercise-based criteria in stratifying MR severity merits consideration.

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Conflict of interest: None declared.

Data availability

The data underlying this article are available in the article. Access to the raw patient data cannot be shared publicly due to the privacy of individuals that participated in the study. The anonymized data will be shared on reasonable request to the corresponding author.

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