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ORIGINAL ARTICLE
Atrio-ventricular valvular heart disease

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

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Abstract

Background 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.

Aims The aim of this study is to investigate the value of the mPAP/CO slope in patients with at least moderate primary MR with preserved ejection fraction and no or discordant symptoms.

Methods A total of 184 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.

Results Mean age was 63 years, 59% male, and mean LVEF 67 ± 6%. The mPAP/CO slope correlated with peak VO_2 ($r = -0.37$, $P < .001$), while peak sPAP did not ($r = -0.05$, $P = .517$). Thirty-nine per cent ($n = 73$) had peak exercise sPAP ≥60 mmHg, and 32% ($n = 58$) had mPAP/CO slope >3 mmHg/L/min. Event-free survival was 71% at 1 year and 59% at 2 years, with more clinical events in patients with mPAP/CO slope >3 mmHg/L/min (HR of 4.1 (95% CI 2.6–6.5). In 61 patients, mPAP/CO slope and peak sPAP were discordant. Patients with slope >3 mmHg/L/mmHg and sPAP <60 mmHg ($n = 23$) had worse outcome versus peak sPAP ≥60 mmHg and normal slope ($n = 38$, log rank $P = .037$). The mPAP/CO slope improved predictive models for outcome, incremental to resting and exercise sPAP, and peak VO_2.

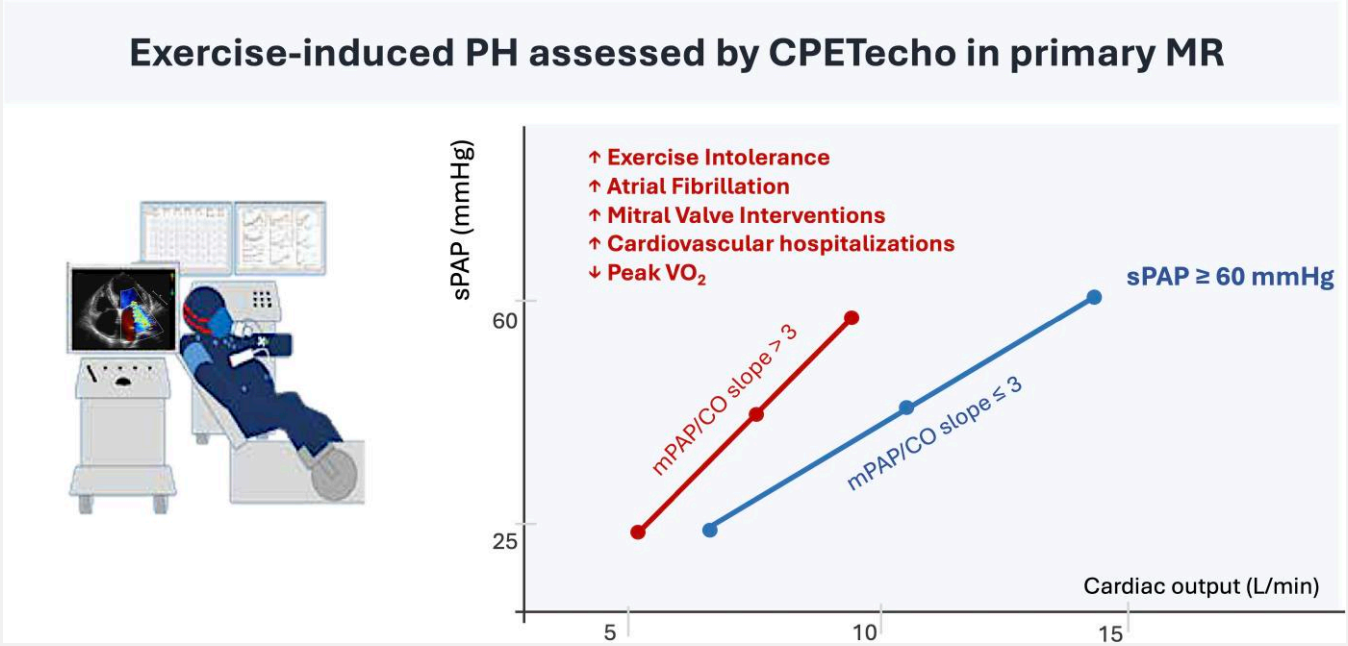
Conclusions Exercise PH defined by the mPAP/CO slope >3 mmHg/L/min is associated with decreased exercise capacity and higher risk of adverse events in significant primary MR and no or discordant symptoms. The slope provides a greater prognostic value than single sPAP measures and peak VO_2.

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Graphical Abstract



Enhanced Risk Stratification in MR: mPAP/CO Slope vs sPAP Measures. CO, cardiac output; CPET, cardiopulmonary exercise testing; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; VO2, oxygen consumption.

Keywords Primary mitral regurgitation • CPETecho • Pulmonary hypertension mPAP/CO slope

Introduction

Optimal timing of intervention in patients with significant primary mitral regurgitation (MR) remains a contentious topic and becomes increasingly critical as accumulating evidence suggests a survival advantage with early intervention in appropriately selected patients.[1–4] The presence of any of the following—symptoms, a reduced left ventricular ejection fraction (LVEF ≤60%) or LV dilatation (LV end-systolic diameter ≥40 mm)—constitutes a compelling indication for intervention.[5–7] However, emerging evidence indicates that exercise testing may offer enhanced sensitivity for identifying patients at increased risk of adverse outcomes.[4,8–10]

Treatment decisions hinge on the precise characterization of the mechanism and severity of MR.[11] Despite its status as the clinical cornerstone and gold standard for MR quantification, echocardiography possesses intrinsic constraints that may affect diagnostic precision and reproducibility. Current guidelines recommend a multiparametric approach with multimodality imaging to resolve incongruous data.[5] Beyond delineating MR mechanism and severity, substantial attention is directed to its consequences, including the emergence of pulmonary hypertension (PH). Echocardiographic systolic pulmonary arterial pressure (sPAP) thresholds of ≥50 mmHg at rest or ≥60 mmHg during exercise are frequently considered potential indications for surgery.[9,12–14]

Historically, PH was defined as a mean pulmonary arterial pressure (mPAP) >25 mmHg at rest or >30 mmHg during exercise.[15] The fourth World Symposium on PH (in 2008) removed the exercise criterion, recognizing that exercise-induced elevations in mPAP during exercise may be physiological, particularly in elderly and athletes.[16] More recently, multipoint assessment of mPAP across graded cardiac outputs (mPAP/CO) has gained traction as a more robust characterization of pulmonary haemodynamics; the derived pulmonary pressure-flow relationship is increasingly recognized as a valuable tool in pulmonary arterial hypertension and heart failure.[17–19] The most recent ESC guidelines on PH (2022) have therefore reintroduced the concept of exercise PH, defined by an mPAP/CO slope >3 mmHg/L/min rather than a single peak exercise sPAP value.[19,20] 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.[18,21,22] Yet, available data for its use in primary MR is scarce. The primary aim of our study was to evaluate the prognostic value of exercise PH in patients with moderate or more chronic primary MR and absent 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 2024. The study enrolled patients who presented with at least 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 (AF). Prior to CPETecho, patients underwent detailed assessment: clinical examination, 12-lead ECG, blood tests, spirometry, and resting echocardiography. The study population primarily comprised asymptomatic patients with severe MR and symptomatic patients with at least moderate MR in whom the clinical presentation was discordant with resting echocardiographic findings. The severity of MR was based on a multiparametric echocardiographic approach including both qualitative (valve morphology, colour Doppler, the flow pattern in pulmonary veins) and quantitative

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(effective regurgitant orifice area (EROA), and regurgitant volume (RV) when appropriate) markers. The study obtained approval from the local ethics committees, and due to its retrospective design, the requirement for written informed consent was waived. This article was written in accordance with the STROBE guidelines for observational research.

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). A predefined ramp and stress echocardiography protocol was used as previously described.[18] 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. Tissue Doppler was used for measuring velocities at mitral annulus and the lateral side of the tricuspid annulus. All measurements were averaged over at least three cardiac cycles. Stroke volume was calculated by multiplying the LV outflow tract 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.[23] 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.[9,24] *Figure 1* illustrates an example. The mPAP was calculated based on sPAP using the Chemla equation ($mPAP = 0.61 \times sPAP + 2$).

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. Peak VO_2 was expressed as an absolute value or as a percentage of the predictive value (derived from the Wasserman formula).[25] Maximal voluntary ventilation (MVV) was defined as $40 \times FEV_1$. 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 July 2025). Data were collected on mitral valve intervention (including both surgery and percutaneous interventions), new-onset AF, cardiovascular hospitalizations, and all-cause mortality. 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 endpoint was event-free survival, including new-onset AF, 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 multidisciplinary Heart Team discussion following the indications for intervention by the actuarial ACC/AHA and ESC valvular heart disease guidelines.[5–7] 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 chi-squared 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 CPETecho. Subsequently, peak VO_2 max was categorized into two groups (above or below 70% of the predictive value) to enable the Receiver Operating Characteristic (ROC) analysis. The sensitivity and specificity in predicting peak VO_2 for both sPAP ≥60 mmHg and mPAP/CO slope >3 mmHg/L/min was 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 (HR) 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. Variables included in the multivariable models were selected based on clinical relevance and previously established prognostic determinants in primary MR, including demographic characteristics, comorbidities, and echocardiographic markers of MR severity and cardiac remodelling. 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 Chi-square value between each multivariate model. Statistical significance was a 2-tailed probability level of <.05. All statistical analyses were performed using SPSS version 22 (IBM, Chicago, IL).

Data integrity and study evolution

This study represents a substantially revised and expanded analysis of work that was previously accepted for publication but subsequently retracted after the authors identified inconsistencies in the original dataset related to patient inclusion and outcome event tracking (originally DOI: 10.1093/ehjci/jead313). To ensure full transparency and data integrity, a comprehensive institutional audit of the database was performed across participating centres. All patients were re-verified against source records, and all clinical endpoints were independently re-adjudicated. In addition, the cohort was expanded by including consecutive patients recruited after the initial study period, and the follow-up duration was extended. The current dataset therefore represents a corrected and substantially strengthened version of the original cohort with updated outcome ascertainment and additional patients.

Results

Patient population

A total of 184 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 59% being male. The mean EROA was 38 mm^2, corresponding to a RV of 52 mL. At the time of inclusion, all patients had a non-dilated LV with preserved ejection fraction and no right ventricular failure. 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 1*. The mean RER at peak exercise was 1.11 ± 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 53%. The CO increased significantly from 5 ± 1 at rest to 12 ± 3 L/min at peak exercise. Corresponding sPAP measurements were respectively 39 ± 6 mmHg and 49 ± 10 mmHg. The mean mPAP/CO slope was 2.7 mmHg/L/min. Of the total cohort, 73 (40%) patients had peak sPAP ≥60 mmHg and 58 (32%) had mPAP/CO slope >3 mmHg/L/min. The overall indexed peak VO_2 was 20 ± 7 L/min/kg (85 ± 24% of predictive value). The mPAP/CO

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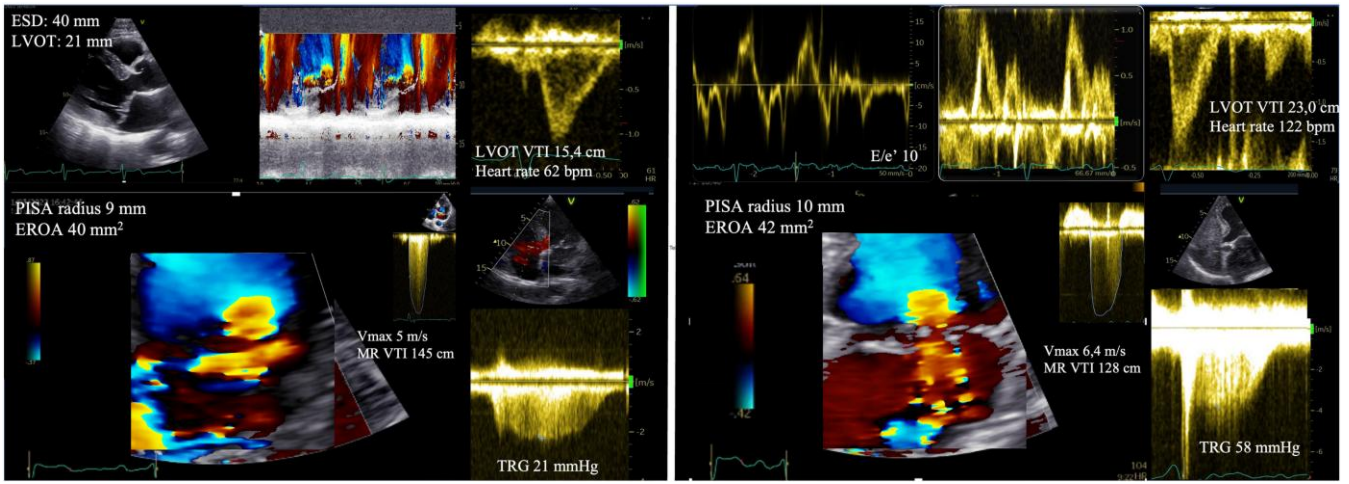


Figure 1 Case example: echocardiography variables at rest and peak exercise. 70-year-old man with bileaflet mitral valve prolapse and holosystolic severe MR [ERO 40 mm^2; RVol 55 mL; ESD 40 mm; LVEF 68%; LV strain 23%; sPAP = TRG + RAP (10 mmHg); mPAP/CO slope 2,4 mmHg/L/min]. Rest imaging (left panel) 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

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Table 1 Baseline characteristics of the total population ($n = 184$)

Clinical characteristics	
Age (years)	63 ± 12
Female sex	75 (41%)
BMI (kg/m^2)	24 ± 4
Beta-blocker use	64 (35%)
Lab results	
Hb (mg/dL)	14 ± 1
NTproBNP (ng/L)	140 (67–310)
Comorbidities	
DM type 2	9 (5%)
Arterial hypertension	74 (40%)
Resting echocardiogram	
LVEDV (mL)	135 ± 42
LVESV (mL)	47 ± 20
LVED diameter (mm)	50 ± 7
LVEF (%)	67 ± 6
PLAX LA (mm)	35 ± 7
LAVi (mL/m^2)	37 ± 17
EROA (mm^2)	38 ± 19
RV (mL)	52 ± 26
MR severity	
Moderate	85 (46%)
Severe	99 (54%)
Medial E/e'' ratio	12 ± 5
TR gradient (mmHg)	23 ± 6
S' RV (cm/s)	11 ± 3
TAPSE (mm)	22 ± 5
CPETecho-derived variables	
mPAP/CO slope (mmHg/L/min)	2.7 ± 1.9
V_E/V_{CO2} slope	29 ± 6
CO/VO_2 slope	6 ± 3
V_E/MVV (%)	53 ± 16
O_2 pulse peak (mL/beat)	9 ± 5

Body surface area was measured using the Mosteller formula.
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; CO, cardiac output; CO/VO_2, cardiac output/oxygen consumption; mPAP, mean pulmonary artery pressure; MVV, maximum voluntary ventilation; VE/VCO_2, minute ventilation/carbon dioxide production

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

Echocardiography	Rest	Low exercise	Peak exercise
LVEDV (mL)	135 ± 42*	136 ± 41*	129 ± 40
LVESV (mL)	47 ± 20*	43 ± 17*	40 ± 16
LVEF (%)	67 ± 6*	68 ± 6*	70 ± 7
SV (mL)	69 ± 16*	87 ± 20*	91 ± 22
E-wave velocity (cm/s)	87 ± 28*	110 ± 28*	132 ± 27
e' septal (cm/s)	7 ± 2*	10 ± 3*	15 ± 6
TR gradient (mmHg)	23 ± 6*	39 ± 8*	49 ± 9
TAPSE (mm)	22 ± 5*	26 ± 6*	28 ± 7
S' RV (cm/s)	11 ± 3*	14 ± 3*	16 ± 4
LVOT VTI (cm)	17 ± 3*	21 ± 3*	22 ± 4
CO (L/min)	5 ± 1*	9 ± 2*	12 ± 3
Cardiopulmonary exercise testing			
SpO_2 (%)	99 ± 1	98 ± 2	98 ± 2
Heart rate (bpm)	71 ± 13*	99 ± 13*	132 ± 21
VO_{2i} (L/min/kg)	4 ± 2*	12 ± 4*	20 ± 7
% pred (%)			85 ± 24
RER	0.82 ± 0.1*	0.94 ± 0.1*	1.11 ± 0.1
Watt (W)	0 ± 0*	48 ± 24*	110 ± 45
SBP (mmHg)	143 ± 21*	166 ± 26*	190 ± 33
DBP (mmHg)	82 ± 12*	83 ± 14*	86 ± 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; SpO2, oxygen saturation; SV, stroke volume; SVi, stroke volume indexed; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VO2, oxygen consumption.
*Difference $P < .05$

slope correlated well with peak VO_2 ($r = -0.37$, $P < .001$), while the peak exercise sPAP value did not ($r = -0.05$, $P = .517$) (*Figure 2*). Moreover, *Figure 3* displays the ROC analysis; the mPAP/CO slope was significantly associated with reduced peak VO_2 (AUC = 0.61, $P = .025$), while sPAP was not (AUC = 0.51, $P = .533$). The sensitivity and specificity of a mPAP/CO slope >3 mmHg/L/min in predicting reduced exercise capacity was 49% and 80%, respectively.

Event-free survival

All patients were subject to follow-up for a median duration of 23 (8–47) months. Event-free survival was 71% at 1 year and 59% at 2 years. During the follow-up period, 66 (36%) patients underwent mitral valve intervention. Out of these, 4 patients underwent percutaneous treatment with transcatheter edge-to-edge repair (Mitraclip, Abbott Vascular, Menlo Park, CA), while the remaining patients underwent cardiac surgery. Until the intervention date or the end of follow-up, 17 (9%) developed AF, and 31 (17%) were hospitalized for cardiovascular events. Eight 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 $P < .001$), thereby yielding a non-adjusted HR of 4.1

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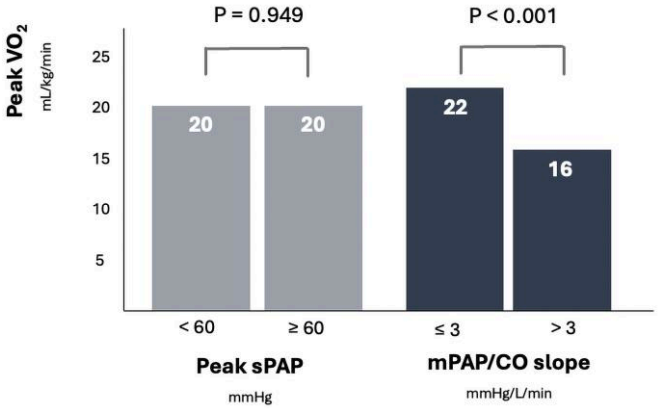


Figure 2 Bar charts depicting peak VO_2 by categories of peak sPAP and mPAP/CO slope. CO, cardiac output; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; VO2, oxygen consumption

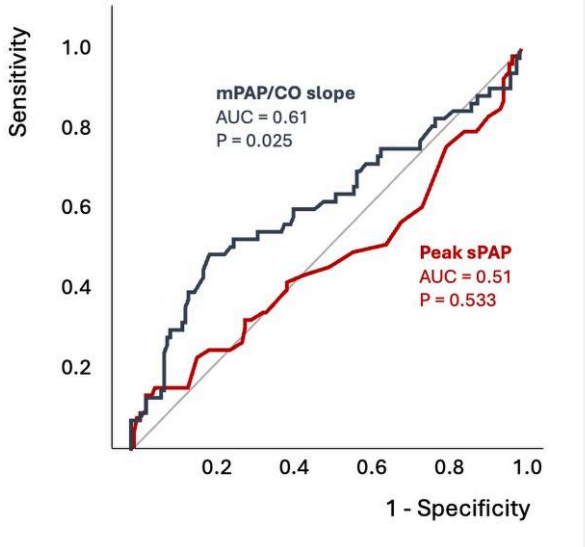


Figure 3 ROC curve and analysis—comparing the association of mPAP/CO slope vs peak sPAP with reduced peak VO_2 (<70% of the predictive value). AUC, area under curve; CO, cardiac output; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure

(95% CI 2.6–6.5) for clinical events. The adjusted HR are presented in *Table 3*, sensitivity analysis restricted to patients with moderate MR is presented in Supplementary Table S1. The unadjusted HR for mitral valve intervention, AF occurrence and cardiovascular hospitalizations were respectively 3.5 (95% CI 2.2–5.8, $P < .001$), 11.8 (95% CI 3.4–41.1, $P < .001$), and 6.6 (95% CI 3.0–14.3, $P < .001$). Furthermore, discordant patients with a mPAP/CO slope >3 mmHg/L/min and peak sPAP <60 mmHg ($n = 23$) had worse outcome compared to patients with peak exercise sPAP ≥60 mmHg but at normal slope ($n = 38$, log rank $P = .037$, *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 $\chi 2 = 39$, $P < .001$) and subsequently significantly improved by peak sPAP (likelihood $\chi^2 = 47$, $P < .001$) and mPAP/CO slope (likelihood $\chi^2 = 71$, $P < .001$).

Discussion

This study provides emerging insights on the additive value of CPETecho in assessing the impact of MR on cardiopulmonary performance: (1) exercise PH, defined by the mPAP/CO slope >3 mmHg/L/min, is frequently observed in patients with primary MR and discordant symptoms, (2) increase in mPAP disproportionate to the rise in CO exhibits a stronger correlation with peak VO_2 when compared to peak sPAP, (3) a mPAP/CO slope >3 mmHg/L/min yields prognostic data, even when the peak sPAP is <60 mmHg and vice versa and (4) increased mPAP/CO slope is, incremental to sPAP and peak VO_2, linked with adverse outcome.

Symptom onset, functional limitation, and pulmonary hypertension are crucial in evaluating patients with significant primary MR.[5,6,8] 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.[8,13,26] Coisne *et al.* demonstrated that impaired aerobic capacity is associated with adverse outcomes in patients with at least moderate primary MR.[8] 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 (32%) 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, a 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.[17,19,27] This study is the first to address its incremental prognostic value in primary MR. The elegant work of Lancellotti and colleagues established that patients with MR and exercise-induced pulmonary hypertension, defined at that time by sPAP ≥60 mmHg was associated with a greater incidence of postoperative complications and a reduced event-free survival

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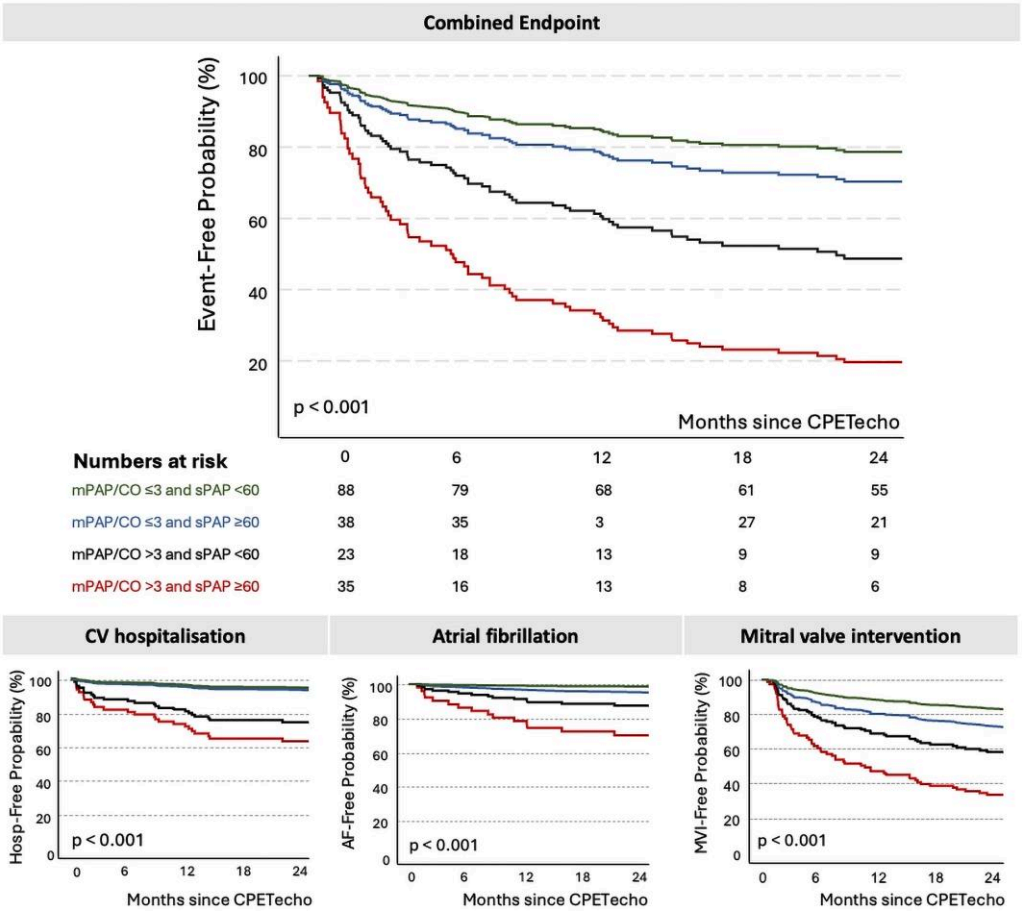


Figure 4 Kaplan–Meier survival curves for the combined endpoint, new-onset AF, mitral valve intervention and cardiovascular hospitalization, stratified by concordance and discordance between mPAP/CO slope >3.0 mmHg/L/min and peak exercise sPAP ≥60 mmHg. CO, cardiac output; CPET, cardiopulmonary exercise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

Table 3 Impact of mPAP/CO slope >3 mmHg/L/min on the combined primary endpoint

Analysis	n	HR for clinical event	*P*-value
Univariate analysis	184	4.1 (95% CI 2.6–6.5)	<.001
Model 1: adjusted for age and sex	184	5.6 (95% CI 3.3–9.3)	<.001
Model 2: Model 1+ hypertension, diabetes and beta-blocker use	142	5.5 (95% CI 2.8–10.6)	<.001
Model 3: Model 2+ LAVI, EROA, rest E/e′, rest LVEDV, and rest S′ RV	107	4.2 (95% CI 1.6–10.9)	.003

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

rate.[3,12,28] However, other groups, such as Mentias *et al*., did not find a significant interaction between exercise sPAP and outcome.[10] 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.[10,12] Indeed, in our study, patients with elevated peak 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.[29] The most recent ESC guidelines on PH (2022) have therefore introduced the concept of exercise PH defined by the mPAP/CO slope above 3 mmHg/L/min.[16,19,30] Our study emphasizes the incremental benefit of this recently introduced parameter for risk stratification of patients with primary MR.

It is important to emphasize that the mPAP/CO slope is an integrative metric. In patients with primary MR, an abnormal slope likely reflects a composite signal of both increased pulmonary vascular tone and, perhaps more significantly, a sharp exercise-induced rise in left

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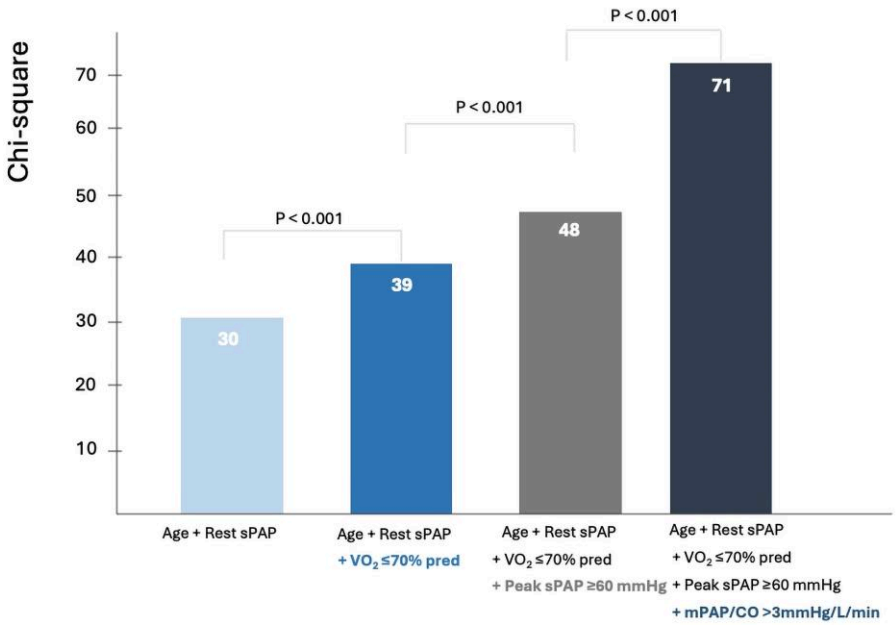


Figure 5 The incremental prognostic value of mPAP/CO slope. CO, cardiac output; mPAP, mean pulmonary artery pressure; pred, predicted; sPAP, systolic pulmonary artery pressure; VO2, oxygen consumption

atrial pressure due to the regurgitant volume and impaired LV diastolic reserve. Without invasive pressure-flow data to calculate the transpulmonary gradient, the slope should be interpreted as a marker of the overall haemodynamic burden on the pulmonary circulation rather than evidence of intrinsic pulmonary vascular disease alone.

The synergy between CPET and stress echocardiography may establish an advanced framework for risk stratification in significant primary MR. This integrated methodology provides a comprehensive and nuanced assessment of the haemodynamic impact of MR on the global cardiopulmonary axis. Our results indicate that the mPAP/CO slope offers greater prognostic value than single peak exercise sPAP measures, facilitating a more accurate identification of patients who may benefit from timely mitral valve intervention. Ultimately, prospective randomized controlled trials are required to determine whether a clinical strategy utilizing CPETecho-derived metrics can effectively improve long-term outcomes in this population.

Limitations

Firstly, CPETecho findings were available to treating physicians, some degree of referral bias in the decision towards mitral valve intervention cannot be excluded. However, it is important to note that the mPAP/CO slope still holds incremental value for other independent endpoints, such as AF and CV hospitalization. Secondly, the retrospective design carries inherent limitations that may affect the generalizability of the results. Furthermore, the assessment of dynamic changes in MR severity during exercise was not consistently feasible; consequently, the available data were insufficient to permit a robust interpretation. 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.[18,23] Fourthly, we recognize that assuming a constant LVOT area and fixed RAP (10 mmHg) simplifies the dynamic response to exercise. While RAP and LVOT geometry can fluctuate with workload, current non-invasive surrogates lack the precision to track these changes during peak exercise without introducing significant measurement 'noise'. By adopting these standardized fixed values—an approach validated against invasive standards[23] and used in landmark studies[28] —we prioritized the reproducibility of the haemodynamic trend across three stages (rest-mid-peak). Importantly, this likely results in a conservative estimate of the mPAP/CO slope; since RAP typically rises during exercise, our fixed-value approach is more likely to underestimate than overestimate pulmonary vascular impairment, thereby strengthening the clinical robustness of our findings. Furthermore, 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, an increased mPAP/CO slope (>3 mmHg/L/min) is associated with reduced exercise capacity and adverse clinical outcomes. The mPAP/CO slope provides incremental prognostic information beyond peak exercise sPAP and peak VO_2 and may improve risk stratification in patients who do not yet meet guideline criteria for intervention.

Author contributions

Sebastiaan Dhont (Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing [lead]), Sara Moura Ferreira (Data curation, Formal analysis, Writing—review & editing [equal]), Jan Stassen (Writing—review & editing [supporting]), Lieven Herbots (Writing—review & editing [supporting]), Sarah Hoedemakers (Writing—review & editing [supporting]), Youri Bekhuis (Writing—review & editing [supporting]), Ruta Jasaityte (Writing—review & editing [supporting]), Sarah Stroobants (Writing—review & editing [supporting]), Thibault Petit (Writing—review & editing [supporting]), Elise Bakelants (Writing—review & editing [supporting]), Maarten Falter (Writing—review & editing [supporting]), Guido Claessen (Writing—review & editing [supporting]), Petra Nijst (Writing—review & editing [supporting]), Pieter Vandervoort (Writing—review & editing [supporting]),

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Philippe Bertrand (Conceptualization, Data curation, Investigation, Methodology, Writing—review & editing [lead]), and Jan Verwerft (Data curation, Methodology, Visualization, Writing—review & editing [lead])

Supplementary data

Supplementary data are available at *European Heart Journal – Valvular and Structural Heart Disease* online.

Declarations

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.

Disclosure of Interest

The authors have no conflicts of interest to disclose.

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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