Prognostic relevance of exercise pulmonary hypertension: results of the multicentre PEX-NET Clinical Research Collaboration

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The mPAP/CO slope is a robust and independent predictor of prognosis in patients with normal or mildly elevated resting pulmonary arterial pressure that provides prognostic information beyond resting haemodynamics and appears suitable to define exercise PH. https://bit.ly/4gc8GyM

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Abstract

Background Exercise pulmonary hypertension (PH) was defined by a mean pulmonary arterial pressure (mPAP)/cardiac output (CO) slope >3 mmHg·min·L^{-1} between rest and exercise in the 2022 European Society of Cardiology/European Respiratory Society PH guidelines. However, large, multicentre studies on the prognostic relevance of exercise haemodynamics and its added value to resting haemodynamics are missing.

Patients and methods The PEX-NET (Pulmonary Haemodynamics during Exercise Network) registry enrolled patients who underwent clinically indicated right heart catheterisations both at rest and ergometer exercise from 23 PH centres worldwide. In this retrospective analysis we included subjects with resting mPAP <25 mmHg and complete haemodynamic data at rest and exercise in the same body position. Mixed

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effects Cox proportional hazard models with random effect centre were applied to identify independent markers of prognosis among the haemodynamic parameters.

Results We included 764 patients (64% females; median (interquartile range) age 59 (46–69) years and mPAP 17 (14–20) mmHg). Median (range) observation time was 6.8 (0.1–15.9) years and 87 patients (11%) died during follow-up. After adjustment for age, sex, haemoglobin level and resting haemodynamics, CO (hazard ratio (HR) 0.85, 95% CI 0.77–0.93; p=0.001) and transpulmonary gradient (HR 1.04, 95% CI 1.00–1.08; p=0.044) at peak exercise and the mPAP/CO slope (HR 1.12, 95% CI 1.06–1.18; p<0.001) were the only independent predictors of prognosis. Patients with a mPAP/CO slope >3 mmHg·min·L^{-1} had significantly worse survival compared to those with a mPAP/CO slope ⩽3 mmHg·min·L^{-1} (HR 2.04, 95% CI 1.16–3.58; p=0.013).

Conclusion The mPAP/CO slope is a robust and independent predictor of prognosis in patients with normal or mildly elevated resting PAP that provides prognostic information beyond resting haemodynamics and appears suitable to define exercise PH.

Introduction

Exercise pulmonary hypertension (PH) is a pathological haemodynamic condition that is characterised by an abnormal increase of pulmonary arterial pressure (PAP) over flow during exercise [1]. According to the most recent 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines, exercise PH is defined by a mean PAP (mPAP)/cardiac output (CO) slope >3 mmHg·min·L^{-1} between rest and exercise [2, 3]. This current haemodynamic definition is largely based on the upper limit of normal [4] and retrospective single-centre data that show an association between mPAP/CO slope >3 mmHg·min·L^{-1} and cardiovascular end-points [5, 6]. However, prognostic variables during exercise haemodynamic assessment have not been evaluated in large, multicentre studies. Furthermore, there remains equipoise on whether exercise haemodynamics provides additional prognostic data beyond resting haemodynamics.

The Pulmonary Haemodynamics during Exercise Network Clinical Research Collaboration (PEX-NET CRC) has been established with the support of the ERS in order to address these important questions and to provide a platform for further scientific studies on exercise haemodynamics [7]. Currently, 23 PH expert centres from Europe, North America and South America are contributing to the PEX-NET CRC. This study represents the primary analysis of the PEX-NET database. We aimed to identify haemodynamic variables during exercise that independently predict survival of patients undergoing clinically indicated right heart catheterisation (RHC) and provide additional prognostic information beyond resting haemodynamics.

Patients and methods

The PEX-NET CRC registry contains a retrospective arm with 1311 patients and a prospective arm that is still enrolling patients to include a total number of at least 500 subjects. All patients underwent at least one clinically indicated RHC both at rest and exercise in an expert centre for PH. The indications for the individual RHCs were made by every participating centre based on clinical reasoning and current clinical guidelines (*e.g.* exercise dyspnoea and/or risk condition for PH and increased probability of PH based on non-invasive investigations). Patients with severe left heart or lung disease as well as patients with comorbidities leading to severely compromised survival were excluded. For the main inclusion and exclusion criteria, see supplementary table S1. In all patients, detailed clinical and haemodynamic data were captured in the databank. For the complete list of parameters, see supplementary table S2.

In this study, we analysed the retrospective arm of the PEX-NET database. For the list of participating centres who contributed to this dataset (19 out of the 23 centres), see supplementary table S3. In this analysis, we only included patients with resting mPAP <25 mmHg who provided haemodynamic data from the same body position at rest and exercise, in order to avoid bias from heterogeneity and severe pulmonary haemodynamic impairment [8]. Methodological details regarding the performance of RHC by the different centres are provided in supplementary table S4. The number of haemodynamic measurements during exercise varied among centres and individuals in a range between 1 and 13 (median (interquartile range (IQR)) 4 (3–7)). Cycle ergometry was used for exercise in all patients.

The mPAP/CO relationship between rest and peak exercise was determined as (mPAP at peak exercise−mPAP at rest)/(CO at peak exercise−CO at rest). Similarly, the pulmonary arterial wedge pressure (PAWP)/CO and the transpulmonary gradient (TPG)/CO relationships were determined based on values at rest and at peak exercise. These relationships will be referred to as the mPAP/CO, PAWP/CO and TPG/CO slopes throughout this article.

Statistical analysis

Patient characteristics are presented as median (IQR) or number (percentage). Analyses were performed to identify haemodynamic variables that independently predict survival and provide additional prognostic information on top of resting haemodynamics. Survival time was defined as the time from RHC to death. Since lung transplantation was performed in only six patients, these patients were censored and no competing risk analysis was performed. In these patients, time of lung transplantation was used for censoring. In Step 1, resting haemodynamics adjusted for age, sex and haemoglobin (Hb) were separately analysed using mixed effects Cox proportional hazards models with random effect centre. Assumptions for this model were checked and in case of non-proportional hazards, time-dependent covariates were included in the model. Significant variables were considered for further analysis. Within the set of significant predictors, the number of missing values and multicollinearity were analysed, and parameters were excluded if 1) >20% of the data were missing or 2) multicollinearity was evident. The resulting variables were analysed using a backwards strategy to obtain a parsimonious model. In Step 2, haemodynamic variables measured at peak exercise and in Step 3, changes of haemodynamic parameters between rest and peak exercise were analysed following the same approach, except that significant predictors from Step 1 were also included in these models. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

After excluding patients with missing mPAP, PAWP or CO values at rest or exercise, patients with severe obstructive or restrictive lung diseases or resting mPAP ⩾25 mmHg and those without available haemodynamic data in the same body position at rest and exercise, 764 patients were included in the final analysis (figure 1).

The main clinical characteristics and resting pulmonary haemodynamics of patients are presented in tables 1 and 2; relevant comorbidities are presented in supplementary table S5. Median (range) observation time was 6.8 (0.1–15.9) years and 87 (11%) patients died during follow-up.

Prognostic relevance of resting haemodynamics

Out of the resting haemodynamic values, after adjustment for age, sex and Hb (Model A), pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), mPAP, TPG, stroke volume (SV), diastolic

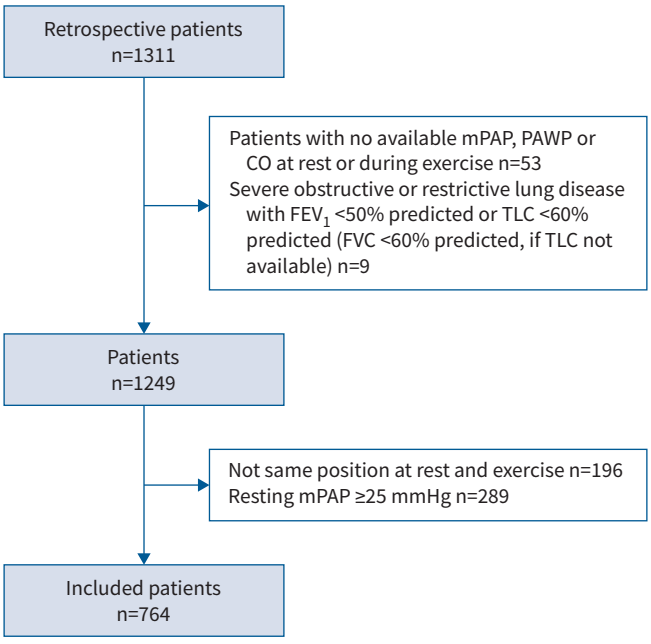


FIGURE 1 Flowchart for inclusion of patients from the PEX-NET (Pulmonary Haemodynamics during Exercise Network) database into the primary analysis. mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; FVC: forced vital capacity.

TABLE 1 Patient characteristics

	All patients	Male[#]	Female	p-value
Patients	764 (100)	272 (36)	491 (64)	
Age (years)	59 (46–69)	60 (50–69)	58 (43–69)	0.035
BMI (kg·m^{-2})	27.5 (24.1–30.9)	28.7 (25.6–31.6)	26.6 (23.4–30.5)	<0.001
Hb (g·dL^{-1})	13.1 (12.1–14.2)	14.3 (12.9–15.5)	13.0 (12.1–14.0)	<0.001
WHO FC				
I	93 (20.3)	26 (18)	67 (21)	0.562
II	245 (53.5)	77 (53)	168 (54)	
III	118 (25.8)	42 (29)	76 (24)	
IV	2 (0.4)	0 (0)	2 (1)	
FVC (% pred)	95 (84–105)			
FEV_1 (% pred)	91 (80–102)			
D_{LCOcSB} (% pred)	73 (59–90)			
D_{LCOcVA} (% pred)	82 (68–94)			
6MWD (m)	450 (393–516)			
NT-proBNP (pg·mL^{-1})	126 (63–310)			
Ongoing PH therapy				
Yes	26 (3.4)			
No	729 (96.6)			
Death				
Yes	87 (11.4)			
No	677 (88.6)			
Lung transplantation				
Yes	6 (0.8)			
No	758 (99.2)			

Data are presented as n (%) or median (interquartile range). BMI: body mass index; Hb: blood haemoglobin concentration; WHO FC: World Health Organization Functional Class; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCOcSB}: single-breath diffusing capacity of the lung for carbon monoxide corrected for Hb; D_{LCOcVA}: diffusing capacity of the lung for carbon monoxide corrected for Hb and alveolar volume; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; PH: pulmonary hypertension. [#]: in one patient sex was unknown.

systemic blood pressure and systemic arterial oxygen tension were significant predictors of survival (table 3 and supplementary figure S1). In multivariate analysis (Model B), out of the resting haemodynamic parameters, only mPAP, PVR and diastolic systemic blood pressure remained independent predictors of survival. Of note, increased mPAP and PVR but decreased diastolic blood pressure were associated with impaired survival.

Prognostic relevance of haemodynamics at peak exercise

At peak exercise, after adjustment for age, sex and Hb (Model A), several haemodynamic variables remained significant predictors of survival, including PVR, TPR, TPG, mPAP and CO (table 4 and supplementary figure S2). In multivariate analysis (Model B), lower CO (hazard ratio (HR) 0.80, 95% CI 0.73–0.87; p<0.001), lower diastolic blood pressure (HR 0.98, 95% CI 0.97–1.00; p=0.018) and higher TPG (HR 1.07, 95% CI 1.04–1.10; p<0.001) remained significant predictors of impaired survival. After additional adjustment for resting values (Model C), lower CO (HR 0.85, 95% CI 0.77–0.93; p=0.001) and higher TPG (HR 1.04, 95% CI 1.00–1.08; p=0.044) at peak exercise remained significant predictors of death. Of note, the inclusion of indexed haemodynamic values into the model led to very similar results (supplementary table S6).

Prognostic relevance of haemodynamic response to exercise

Among the responses of the haemodynamic variables to exercise, after adjustment for age, sex and Hb (Model A), the mPAP/CO, PAWP/CO and TPG/CO slopes as well as the responses of mPAP, CO, SV, heart rate and TPR to exercise were identified as significant predictors of prognosis (table 5 and supplementary figure S3). In the multivariate analysis (Model B), CO (HR 0.77, 95% CI 0.70–0.86; p<0.001) and mPAP (HR 1.01, 95% CI 1.00–1.01; p<0.001) responses to exercise remained significant predictors of prognosis. After additional adjustment for resting haemodynamic values (Model C), the mPAP/CO slope was the only time-independent predictor of survival (HR 1.12, 95% CI 1.06–1.18; p<0.001). Of note, the inclusion of indexed haemodynamic values into the model led to very similar results, with the difference that the mPAP/cardiac index slope was an independent predictor of survival

TABLE 2 Main haemodynamic data

	At rest[#]	At peak exercise	Response to exercise (rest to peak exercise)
Heart rate (beats·min^{-1})	72 (64–81)	122 (104–141)	49 (33–65)
BP_{syst} (mmHg)	133 (122–145)	169 (153–189)	36 (21–52)
BP_{diast} (mmHg)	72 (65–80)	85 (75–95)	11 (3–22)
sPAP (mmHg)	28 (24–33)	51 (42–61)	23 (15–31)
dPAP (mmHg)	12 (9–14)	23 (17–28)	11 (7–16)
mPAP (mmHg)	17 (14–20)	33 (27–40)	16 (11–22)
PAWP (mmHg)	7 (5–10)	17 (13–23)	10 (6–15)
RAP (mmHg)	4 (2–5)	8 (6–12)	5 (3–8)
CO (L·min^{-1})	5.0 (4.1–6.0)	10.9 (8.8–13.6)	5.8 (3.9–8.1)
TPG (mmHg)	9 (7–12)	15 (11–20)	6 (2 −10)
SV (mL)	70 (58–85)	91 (74–109)	21 (8–33)
PVR (WU)	1.80 (1.33–2.45)	1.36 (0.90–2.00)	−0.38 (−0.82– −0.01)
TPR (WU)	3.40 (2.62–4.33)	2.95 (2.21–4.19)	−0.28 (−0.81–0.34)
P_{aO_2} (mmHg)	84 (73–97)	88 (75–101)	3.2 (−6.4–11.0)
P_{aCO_2} (mmHg)	37 (34–39.2)	35 (31–38)	−2.0 (−4.1–1.0)
S_{aO_2} (%)	97 (95.7–98.0)	96 (94–98)	0.3 (−2.2–0.80)
mPAP/CO slope (mmHg·min·L^{-1})			2.69 (1.78–4.42)
PAWP/CO slope (mmHg·min·L^{-1})			1.61 (0.88–2.98)
TPG/CO slope (mmHg·min·L^{-1})			0.95 (0.40–1.86)

Data are presented as median (interquartile range). BP_{syst}: systolic systemic blood pressure; BP_{diast}: diastolic systemic blood pressure; sPAP: systolic pulmonary arterial pressure; dPAP: diastolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; RAP: right atrial pressure; CO: cardiac output; TPG: transpulmonary gradient; SV: stroke volume; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation. [#]: resting haemodynamic values were assessed in the same position in which exercise was performed (n=357 supine, n=92 semi-supine, n=315 upright).

TABLE 3 Prognostic relevance of resting pulmonary haemodynamic parameters

	Model A		Model B	
	p-value	HR (95% CI)	p-value	HR (95% CI)
Heart rate	0.492	1.01 (0.99–1.02)		
BP_{syst}	0.177	0.99 (0.98–1.00)		
BP_{diast}	0.019	0.98 (0.96–1.00)	0.006	0.97 (0.95–0.99)
mPAP	<0.001	1.15 (1.08–1.22)	0.009	1.09 (1.02–1.17)
PAWP	0.158	1.05 (0.98–1.12)		
RAP	0.285	1.05 (0.96–1.13)		
CO	0.068	0.83 (0.69–1.01)		
TPG	<0.001	1.13 (1.06–1.20)		
SV	0.045	0.99 (0.97–1.00)		
PVR	<0.001	1.82 (1.50–2.22)	<0.001	1.62 (1.30–2.01)
TPR	<0.001	1.61 (1.39–1.87)		
P_{aO_2}	0.006	0.98 (0.96–0.99)		
P_{aCO_2}	0.115	0.96 (0.91–1.01)		
S_{aO_2}	0.133	0.93 (0.84–1.02)		

Model A: each variable analysed separately (adjusted for age, sex and Hb); Model B: multivariate analysis adjusted for age, sex and Hb. BP_{syst}: systolic systemic blood pressure; BP_{diast}: diastolic systemic blood pressure; mPAP: mean pulmonary arterial pressure. PAWP: pulmonary arterial wedge pressure; RAP: right atrial pressure; CO: cardiac output; TPG: transpulmonary gradient; SV: stroke volume; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation; Hb: haemoglobin.

TABLE 4 Prognostic relevance of pulmonary haemodynamic parameters at peak exercise

	Model A		Model B		Model C	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Heart rate	0.034	0.99 (0.98–1.00)				
BP_{syst}	0.032	0.99 (0.98–1.00)				
BP_{diast}	0.012	0.98 (0.97–1.00)	0.018	0.98 (0.97–1.00)		
mPAP	0.007	1.03 (1.01–1.06)				
PAWP	0.706	1.01 (0.98–1.04)				
RAP	0.615	1.01 (0.97–1.05)				
CO	<0.001	0.83 (0.77–0.90)	<0.001	0.80 (0.73–0.87)	0.001	0.85 (0.77–0.93)
TPG	0.002	1.05 (1.02–1.08)	<0.001	1.07 (1.04–1.10)	0.044	1.04 (1.00–1.08)
SV	0.001	0.98 (0.97–0.98)				
PVR	<0.001	2.16 (1.78–2.61)				
TPR	<0.001	1.60 (1.41–1.82)				
P_{aO_2}	<0.001	0.97 (0.99–0.98)				
P_{aCO_2}	0.056	0.95 (0.91–1.00)				
S_{aO_2}	0.001	0.91 (0.86–0.86)				

Model A: each variable analysed separately (adjusted for age, sex and Hb); Model B: multivariate analysis adjusted for age, sex and Hb; Model C: multivariate analysis adjusted for age, sex, Hb and significant resting haemodynamic predictors (mPAP, PVR, BP_{diast}). BP_{syst}: systolic systemic blood pressure; BP_{diast}: diastolic systemic blood pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; RAP: right atrial pressure; CO: cardiac output; TPG: transpulmonary gradient; SV: stroke volume; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation; Hb: haemoglobin.

both in Models B and C (HR 1.04, 95% CI 1.01–1.08; p=0.018 in Model B; and HR 1.06, 95% CI 1.03–1.09; p<0.001 in Model C) (supplementary table S7).

Applying the current haemodynamic definition of exercise PH, a mPAP/CO slope >3 mmHg·min·L^{-1} was significantly associated with worse survival compared to a mPAP/CO slope ⩽3 mmHg·min·L^{-1} (adjusted for age, sex, Hb, significant resting haemodynamic predictors and mPAP response to exercise; HR 2.04, 95% CI 1.16–3.58; p=0.013) (figure 2). Main clinical characteristics and pulmonary haemodynamics of patients with

TABLE 5 Prognostic relevance of pulmonary haemodynamic responses to exercise (rest to peak difference)

	Model A		Model B		Model C	
	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Heart rate	<0.0001	0.97 (0.95–0.98)				
BP_{syst}	0.232	1.00 (0.99–1.00)				
BP_{diast}	0.340	0.99 (0.98–1.01)				
mPAP	0.029	0.94 (0.89–0.99)	<0.001	1.01 (1.00–1.01)	0.004	0.92 (0.87–0.97)
mPAP×time					0.002	1.01 (1.01–1.02)
PAWP	0.808	1.00 (0.96–1.03)				
RAP	0.625	1.01 (0.97–1.06)				
CO	<0.0001	0.81 (0.73–0.89)	<0.001	0.77 (0.70–0.86)		
TPG	0.142	1.03 (0.99–1.06)				
SV	0.009	0.98 (0.97–1.00)				
PVR	0.275	1.17 (0.89–1.54)				
TPR	0.047	1.24 (1.00–1.53)				
mPAP/CO slope	<0.0001	1.12 (1.08–1.16)			<0.001	1.12 (1.06–1.18)
PAWP/CO slope	0.0003	1.12 (1.06–1.20)				
TPG/CO slope	<0.0001	1.15 (1.09–1.20)				

Model A: each variable analysed separately (adjusted for age, sex and Hb); Model B: multivariate analysis adjusted for age, sex and Hb; Model C: multivariate analysis adjusted for age, sex, Hb and significant resting haemodynamic predictors (mPAP, PVR, BP_{diast}). BP_{syst}: systolic systemic blood pressure; BP_{diast}: diastolic systemic blood pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; RAP: right atrial pressure; CO: cardiac output; TPG: transpulmonary gradient; SV: stroke volume; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; Hb: haemoglobin.

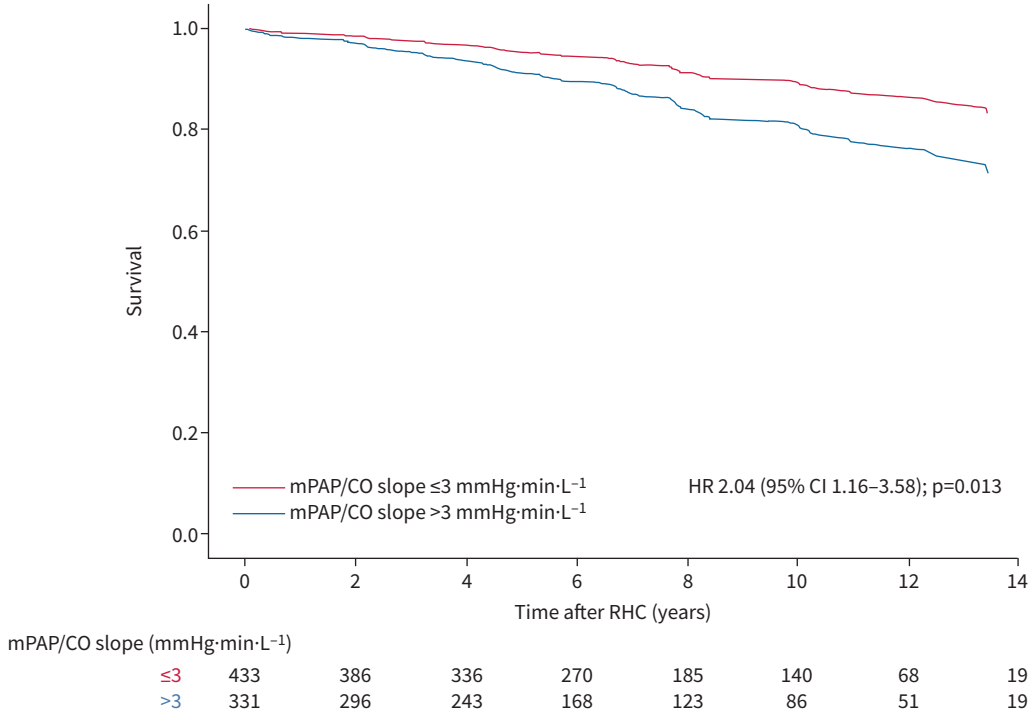


FIGURE 2 Survival of patients with mean pulmonary arterial pressure (mPAP)/cardiac output (CO) slope ⩽3 *versus* >3 mmHg·min·L^{-1}, according to Cox regression analysis adjusted for sex, age, haemoglobin, resting mPAP, resting pulmonary vascular resistance, resting diastolic systemic blood pressure and mPAP response to exercise. HR: hazard ratio; RHC: right heart catheterisation.

a mPAP/CO slope >3 *versus* ⩽3 mmHg·min·L^{-1} are presented in supplementary table S8. Comorbidities of patients with a mPAP/CO slope >3 *versus* ⩽3 mmHg·min·L^{-1} are shown in supplementary tables S9 and S10. Notably, patients with a mPAP/CO slope >3 mmHg·min·L^{-1} had significantly worse survival than patients with a mPAP/CO slope ⩽3 mmHg·min·L^{-1} even after adjustment for age, sex and modified Charlson Comorbidity Index (HR 1.899, 95% CI 1.168–3.088; p=0.01).

When analysing only patients with resting mPAP ⩽20 mmHg (588 patients and 52 events), those with a mPAP/CO slope >3 mmHg·min·L^{-1} had significantly worse survival than patients with a mPAP/CO slope ⩽3 mmHg·min·L^{-1} after adjustment for significant resting haemodynamic predictors (HR 2.5, 95% CI 1.4–4.7; p=0.003) or for age, sex and modified Charlson Comorbidity Index (HR 1.905, 95% CI 1.003–3.620; p=0.049). Demographic, clinical and haemodynamic characteristics of patients with resting mPAP ⩽20 mmHg (n=588) and those with mPAP 21–24 mmHg (n=176) are presented in supplementary table S11.

In addition to the mPAP/CO slope, a smaller increase in mPAP between rest and peak exercise was associated with poor survival in the initial observation period (HR 0.92, 95% CI 0.87–0.97; p=0.004). However, this effect was significantly time dependent: a larger mPAP increment to exercise was associated with poor survival during the later periods of observation (HR 1.01, 95% CI 1.01–1.02; p=0.002) over time (supplementary figure S4).

Causes of death

Out of the 764 included patients, 87 (11%) died during follow-up. Based on the data provided by the centres, there was a relatively equal distribution of pulmonary and cardiac causes, as well as malignancy and other causes of death from the field of internal medicine (*e.g.* kidney disease) (supplementary table S12). Whether pulmonary vascular diseases contributed to the death of the patients is not retrievable from the provided data. We performed a competing risk analysis with causes of death most probably unrelated to PH (*i.e.* due to malignancy and "other internal causes") serving as competing risk. Based on the remaining 49 events, after adjustment for age, sex and Hb, patients with a mPAP/CO slope >3 mmHg·min·L^{-1} still had significantly worse survival compared to patients with a mPAP/CO slope ⩽3 mmHg·min·L^{-1} (HR 2.75, 95% CI 1.37–5.52; p=0.004).

Discussion

In this study, we provide results from the currently largest international multicentre database on the prognostic relevance of pulmonary haemodynamics during exercise in patients presenting with resting mPAP <25 mmHg. Out of a large panel of haemodynamic variables, after adjusting for all relevant demographic and resting haemodynamic parameters, we identified the mPAP/CO slope as a robust, independent predictor of survival. Our results support the clinical relevance of exercise haemodynamics and the recently introduced definition of exercise PH.

The mPAP/CO slope and the definition of exercise PH

Pulmonary haemodynamics during exercise was already addressed at the first World Health Organization meeting on primary PH in 1973 [9] and a haemodynamic definition for exercise PH was introduced in the 2004 ESC PH guidelines [10]. At that time, exercise PH was defined as mPAP >30 mmHg during exercise. However, this definition was challenged during the 4th World Symposium on PH in Dana Point in 2008 [11], because a systematic literature review revealed that exercise haemodynamics depend on the level of exercise and the age of the subject [12]. Consequently, exercise PH was removed from the haemodynamic definition of PH and further studies in the field were recommended. It was in 2022, when, based on the accumulated data, the definition of exercise PH was re-introduced in the ESC/ERS PH guidelines as a mPAP/CO slope >3 mmHg·min·L^{-1} between rest and exercise [2, 3]. Three main arguments supported the new definition of exercise PH. First, recent single-centre retrospective data showed that a mPAP/CO slope >3 mmHg·min·L^{-1} was associated with increased mortality and cardiovascular morbidity [5]. Second, by including CO into this composite parameter and assuming a near-linear correlation between the increase in mPAP and CO during physiological exercise, no correction for exercise level is needed for diagnosing exercise PH [12, 13]. Third, although the value of the mPAP/CO slope is dependent on age (healthy older subjects having higher values than healthy younger subjects), a recent systematic review and meta-analysis revealed that a mPAP/CO slope >3 mmHg·min·L^{-1} is not physiological, even in the elderly [4].

The current study supports that the mPAP/CO slope is a robust, independent predictor of prognosis in patients who have mPAP <25 mmHg at rest and reveals prognostic information that significantly exceeds the prognostic information of resting haemodynamics. Notably, despite heterogenous exercise methodology applied by sites in our multicentre study and confinement of our population to resting mPAP <25 mmHg, our finding that a mPAP/CO slope >3 mmHg·min·L^{-1} conferred a mortality HR of 2.04 is highly consistent with single-centre findings from a large retrospective study that demonstrated a HR of 2.03 associated with a PAP/CO slope >3 mmHg·min·L^{-1} [5]. This supports that the mPAP/CO slope is a robust marker of prognosis and appears suitable to define exercise PH.

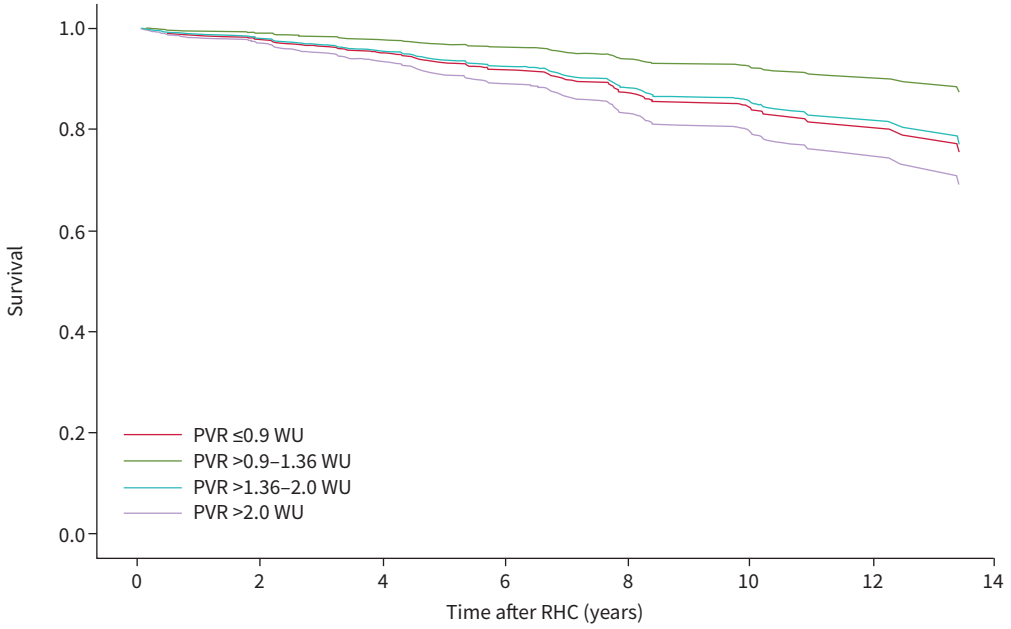
Further independent predictors of prognosis

Besides the mPAP/CO slope, the response of mPAP to exercise as well as CO and TPG at peak exercise were also independent predictors of prognosis after adjusting for resting haemodynamics. This further highlights the clinical relevance of exercise haemodynamics. The peak CO and the CO response to peak exercise have been previously acknowledged as prognostic factors in patients with manifest PH [14] but not in patients with normal or only mildly elevated PAP.

The mPAP response to exercise was significantly associated with prognosis, but in a time-dependent manner. In the initial period of observation, an increased mPAP response indicated an improved prognosis, but during the later periods of observation it was associated with a poor prognosis (supplementary figure S4). This is difficult to interpret but could be explained by the fact that patients with limited increases in mPAP during exercise have a poor right ventricular contractile reserve and decreased short-term survival, as also suggested by a previous echocardiographic study [15]. On the other hand, increased mPAP responses may arise from patients with pulmonary vascular or left heart diseases, which are associated with increased long-term mortality [16]. These complexities render the mPAP response in isolation challenging to use in clinical decision making.

An increased TPG and a lower CO at peak exercise were independently associated with a poor prognosis, suggesting that PVR (which is calculated as TPG/CO) at peak exercise also has prognostic relevance (figure 3). This was demonstrated when each variable was analysed separately. In the multivariate analysis, PVR was not identified as an independent prognosticator, due to its strong collinearities with TPG and CO. It appears difficult to define generally applicable thresholds for TPG and CO at peak exercise, particularly because CO at “peak exercise”, similar to peak oxygen uptake, strongly depends on age, sex, height and on the applied exercise protocol, which is currently not standardised.

Of note, when survival of patients is presented according to quartiles of PVR at peak exercise (figure 3), it is the quartile with the highest PVR that is associated with the worst prognosis, but interestingly, it is not



PVR (WU)								
≤0.9	190	176	159	132	89	68	37	11
>0.9–1.36	190	170	144	114	84	65	35	11
>1.36–2.0	193	175	151	115	82	57	28	10
>2.0	191	161	125	77	53	36	19	6

FIGURE 3 Survival of patients by quartiles of pulmonary vascular resistance (PVR) at peak exercise according to Cox regression analysis adjusted for age, sex, haemoglobin, resting mean pulmonary arterial pressure, resting PVR and resting diastolic systemic blood pressure. RHC: right heart catheterisation.

the lowest quartile that is associated with the best prognosis. This finding might suggest that a loss of pulmonary vascular tone and systemic tone may be disadvantageous in terms of prognosis and deserves further investigation.

Aetiology of exercise PH

In order to address the aetiology of exercise PH, it is helpful to re-calculate mPAP as a function of its vascular component and its cardiac component as: mPAP=TPG+PAWP. Having done this, the mPAP/CO slope corresponds to: mPAP/CO=TPG/CO+PAWP/CO. This suggests that an increased slope may have a pre-capillary (TPG/CO) and a post-capillary (PAWP/CO) component. In our analysis, all three slopes, *i.e.* mPAP/CO, TPG/CO and PAWP/CO, were significantly associated with survival, suggesting that both pre- and post-capillary dysfunction contribute to a poor survival. Further analysis of our data might reveal deeper insight in the clinical phenotypes that are involved.

Limitations

Our study is limited by its retrospective nature. The prospective arm of PEX-NET is still enrolling patients that will need to be followed for several additional years before analysis with sufficient power is possible.

Further, we decided to include only subjects with mPAP <25 mmHg in this analysis. This decision was made before starting the statistical analysis, because it is well established that resting mPAP ⩾25 mmHg is strongly associated with a poor prognosis and we were interested in the value of exercise haemodynamics in excess of the value of resting haemodynamics. In addition, in patients with more severe pulmonary haemodynamics at rest, other mechanisms may be of clinical and prognostic relevance than in patients without PH or only with mild PH. The detailed analysis of patients with resting mPAP ⩽20 mmHg is planned in the future, but we report on a few results already in this article. A limitation for this cohort is the relatively low number of events that precludes the adjustment for a large number of parameters in the survival analysis.

Although a wide range of clinical parameters have been available in our database, there were, of course, limitations. These included echocardiography measures such as E/e′, which precludes the exact calculation of heart failure with preserved ejection fraction scores.

A further limitation may be the heterogeneity of the exercise protocols among centres, concerning the incremental exercise steps or ramp protocols, pressure reading and the body position. We just excluded patients with different positions at rest and exercise, to rule out the well-known effects of changes in body position on pulmonary haemodynamics. In addition, due to the relatively low number of multipoint haemodynamic measurements during exercise in a large proportion of patients, we decided to calculate the mPAP/CO, PAWP/CO and TPG/CO slopes purely based on the values at rest and peak exercise, instead of calculating a regression line-derived slope for each patient based on matched pressure/CO measurements. For the same reason we did not analyse any curvilinearity of the slopes. We also did not calculate the opening pressure and the incremental resistance in our patients [17]; these physiological aspects potentially contributing to resistance changes during exercise may be addressed in future analyses. However, despite the heterogeneity of the included protocols and simplified calculation of slopes, we identified parameters that were independently associated with survival, including the mPAP/CO slope. This suggests that our main findings may be resilient to methodological differences between different centres. The impact of the differences in methodologies on pulmonary haemodynamics and the determination of the mPAP/CO slope including its potential curvilinearity will be addressed in a future study.

Conclusion

Based on the analysis of the largest currently existing multicentre database on pulmonary haemodynamics during exercise, the mPAP/CO slope appears as a robust and independent predictor of prognosis beyond resting haemodynamics, in patients with normal or mildly elevated PAP. Our data suggest that a mPAP/CO slope >3 mmHg·min·L^{-1} may serve as a simple but sensitive prognosticator in agreement with the current definition of exercise PH.

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