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RESEARCH ARTICLE

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Exercise pulmonary hypertension in chronic thromboembolic pulmonary disease: A right heart catheterization study

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Abstract

Many patients with chronic thromboembolic pulmonary disease (CTEPD) suffer from exertional dyspnea. It is unclear if CTEPD is associated with exercise pulmonary hypertension (ePH). This cross-sectional study aimed to determine the occurrence of ePH in patients with CTEPD and to identify the haemodynamic changes during exercise. We recruited 36 patients with persistent dyspnoea and residual perfusion defects by ventilation/perfusion scintigraphy from a large cohort of patients with previous pulmonary embolism. All patients underwent exercise right heart catheterization before being classified into the following groups: (1) CTEPD without ePH; comprising patients with normal mean pulmonary artery pressure (mPAP) of ≤20 mmHg, but with mPAP/cardiac output (CO) slope of ≤3 mmHg/L/min, (2) CTEPD with ePH (CTEPD-ePH); those with CTEPD with an mPAP/CO slope of >3 mmHg/L/min, (3) chronic thromboembolic pulmonary hypertension (CTEPH); those with mPAP >20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance >2 WU. The postcapillary contribution during exercise was considered present if the PAWP/CO slope of >2 mmHg/L/min. CTEPD without resting pulmonary hypertension (PH) was present in 29 (81%) of the 36 patients, of whom six (21%) had ePH, while five (14%) had CTEPH. Two patients had unclassified PH. Two (33%) of the six patients with CTEPD-ePH had a PAWP/CO slope of >2 mmHg/L/min, compared with two (40%) of the five of those with CTEPH. In conclusion, about 20% of patients with CTEPD and exertional dyspnoea had ePH. Exercise right heart catheterization revealed a notable proportion of patients with postcapillary contribution.

KEYWORDS
exertional dyspnoea, mPAP/CO slope, pulmonary circulation, pulmonary embolism

Clinical Trial Registration: clinicaltrials.gov No. NCT03405480.

INTRODUCTION

Approximately half of the patients experiencing acute pulmonary embolism (PE) suffer from exertional dyspnoea a long time after the acute event,[1–3] and reportedly 0.4–4.8% will develop chronic thromboembolic pulmonary hypertension (CTEPH), which is the most severe long-term complication after PE.[4] About 25% of patients with acute PE will develop chronic thromboembolic pulmonary disease (CTEPD), which is characterized by pulmonary perfusion defects, but without elevated pulmonary arterial pressure at rest.[5]

Exercise pulmonary hypertension (ePH) is an important clinical finding with diagnostic and prognostic consequences, and is associated with mortality.[6,7] The definition of pulmonary hypertension (PH) was recently revised, and ePH was defined as an increase in the ratio of the mean pulmonary artery pressure (mPAP) to the cardiac output (CO) of more than 3 mmHg/L/min from rest to peak exercise.[8,9] Exercise right heart catheterization (RHC) data in patients with CTEPD are scarce and inconclusive, and little is known about the significance of ePH.[10] There is no evidence of temporal associations between CTEPD without ePH, CTEPD with ePH (CTEPD-ePH) and CTEPH.[11–13]

This study aimed to determine the occurrence of ePH in patients with CTEPD and to characterize the haemodynamics at rest and during exercise in these patients.

METHODS

Study design and sample

This cross-sectional study involved patients with persistent dyspnoea and residual perfusion defects after PE. The study formed part of the PE-REHAB project (clinicaltrials.gov No. NCT03405480).

Between January 1, 2018 and June 1, 2022, patients aged 18–75 years who had been diagnosed with acute PE 6–72 months previously and had no other cardiopulmonary comorbidity were invited to participate in the PE-REHAB project. As part of the project, the patients underwent ventilation/perfusion (V/Q) single-photon-emission computed tomography (CT).[14,15]

All patients with persisting perfusion defects in V/Q scintigraphy were invited to participate in this study. If the initial V/Q scintigraphy had been performed more than 3 months previously, the examination was repeated. All included patients had used oral anticoagulation therapy for at least 3 months following acute PE.

We initially enrolled 72 patients between October 1, 2020 and October 1, 2022. Twenty-five of these patients withdrew or did not complete the diagnostic medical examinations, and a further 11 were excluded because they had no persisting perfusion defects in repeated V/Q scintigraphy. Thus, 36 patients with persistent perfusion defects completed the RHC study (Figure 1).

Study procedures and variables

All participants underwent clinical evaluations, a modified incremental shuttle walk test (mISWT),[16,17] pulmonary function tests (Jaeger MasterScreen PFT, Program Sentry Suite version 2.11, Carefusion) using Global Lung Initiative reference values,[18,19] laboratory tests, echocardiography, and RHC, all within 24–36 h of presentation. We performed interviews and reviews of computerized medical records to collect relevant variables at the time of inclusion in this study. The severity of PH symptoms was assessed by one of the authors (A. D.) using the WHO Functional Assessment for PH.[9]

V/Q scintigraphy was performed using 99mTechnetium-labeled macroaggregated albumin for perfusion scintigraphy and 99mTechnetium-labeled diethylene triamine pentaacetic acid aerosol for ventilation scintigraphy. Images were acquired using the GE Discovery NM/CT 670 SPECT/CT platform (General Electric HealthCare). The images were analyzed by a specialist in nuclear medicine and scored according to the European Association of Nuclear Medicine criteria.[20] Positive V/Q scintigraphy findings corresponded to a V/Q mismatch in at least one segment or in two subsegments conforming to the pulmonary vasculature.

The volume of the perfusion defects at study inclusion was assessed by manually tracing the defects on V/Q scintigraphy images, and the total lung volume was assessed by manually tracing on low-dose CT images. The size of perfusion defects was quantified as a percentage of the total lung volume.[21]

We retrospectively assessed the thrombotic burden at the time of PE diagnosis using the mean bilateral proximal extension of the clot (MBPEC) score. The MBPEC score was obtained by identifying the proximal extension of the embolus in each lung as follows: subsegmental = 1; segmental = 2; lobar = 3; and interlobar arteries, main pulmonary arteries or pulmonary trunk = 4. The final MBPEC score was reported as the mean bilateral score rounded up to the next integer.[22]

Right-heart catheterization

RHC at rest (Mac-Lab, GE HealthCare) was performed using a balloon-tipped 7-F Swan-Ganz catheter that was

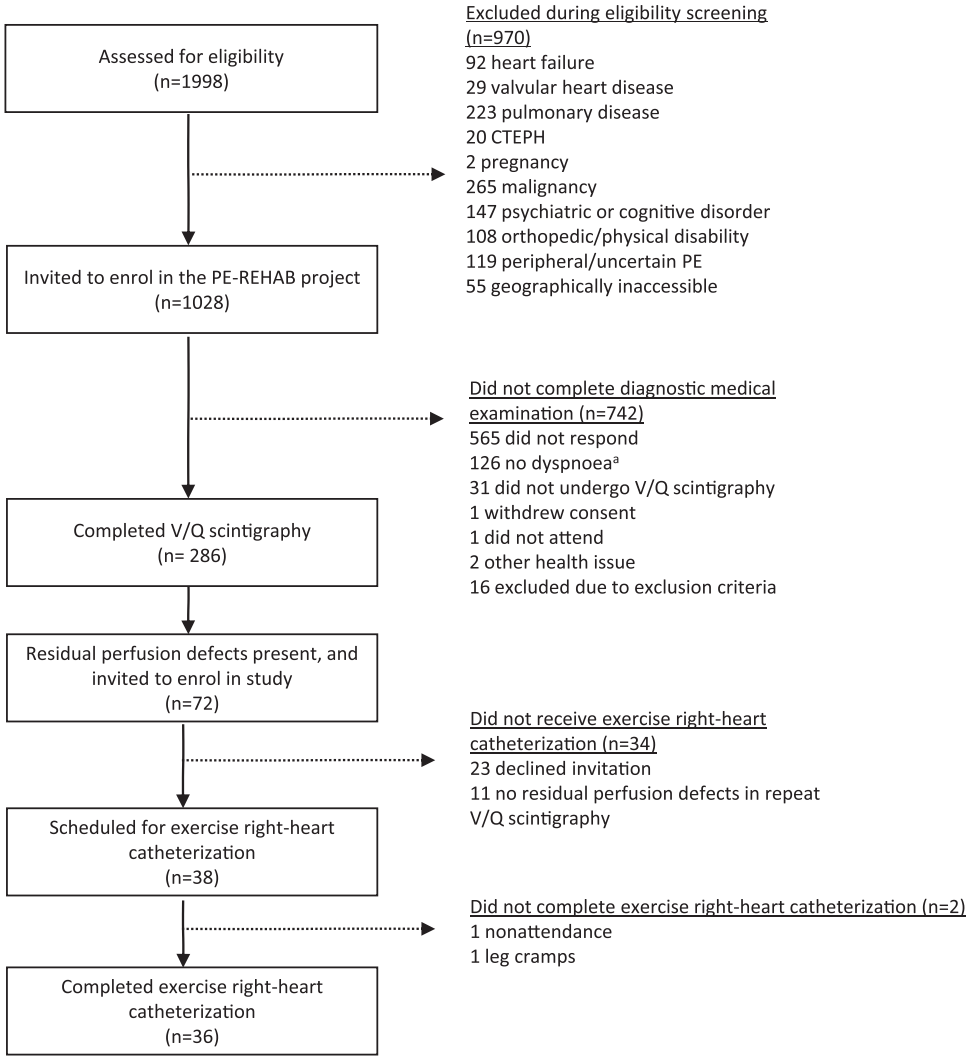

FIGURE 1 Flow chart of patient selection in both the main project and this study. CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism; V/Q, ventilation/perfusion. [a]These participants were not included due to lack of dyspnoea. Further details about the selection process in the PE-REHAB project are available in Jervan et al.[14]

inserted with ultrasound guidance via the right jugular vein into the right pulmonary artery with the patient in the supine position. The zero reference level was at the midaxillary line at the right atrial level, which was used as an approximation for the mid-thoracic plane. As we did not measure the patient's oxygen consumption simultaneously during RHC, CO was estimated by averaging 3–5 measurements using a thermodilution technique. Resting pressures were measured during temporary breath holding at the end of expiration and verified by a flat respiration curve to minimize the effect of the respiratory cycle on the measured intrathoracic pressure.[23,24] Pressure measurements at rest and during exercise were averaged over five to seven respiratory cycles. Postprocessing was applied to the pressure curves at the end of expiration at rest and during exercise by manually correcting the region of interest if necessary.

RHC during exercise was performed with dynamic supine leg exercise (Ergometer pedal exerciser, Lode), starting with 4 min of unloaded pedaling at 60 revolutions per min, followed by 25-W increases every 4 min until exhaustion or until the workload reached 150 W. The right atrial pressure (RAP), pulmonary arterial wedge pressure (PAWP), and mPAP were measured and averaged over five to seven respiratory cycles during unrestricted respiration with the leg raised and in the steady state after 30 s at every workload level. The CO and arterial and mixed venous blood samples were obtained when the workload was 25 and 75 W, and at peak exercise, reflecting low and moderate workloads, respectively. This was chosen to ensure data collection at standardized intensities, particularly in case the patient reached a maximum workload of 150 W. Arterial blood samples were obtained from a radial artery cannula. Continuous electrocardiography monitoring was performed.

The following haemodynamic variables were calculated: total pulmonary vascular resistance (TPR) = mPAP/CO (Wood units), pulmonary vascular resistance (PVR) = (mPAP – PAWP)/CO (Wood units), pulmonary arterial compliance = stroke volume/pulse pressure (mL/mmHg), mPAP/CO slope and PAWP/CO slope. Slopes were defined either as multipoint changes from rest to peak exercise, or as two-point measurements for individually paired slopes, when multipoint measurements were not possible. Based on the RHC results, we categorized the patients into the following groups[1]: CTEPD without ePH, comprising patients with a normal mPAP of ≤20 mmHg and an mPAP/CO slope of ≤3 mmHg/L/min,[2] CTEPD-ePH, comprising CTEPD patients with an mPAP/CO slope of >3 mmHg/L/min, and[3] CTEPH, comprising patients with mPAP >20 mmHg, PAWP ≤ 15 mmHg and PVR > 2 WU).

Patients with a resting mPAP >20 mmHg who could not be classified into the pre- or postcapillary definitions of PH were classified as CTEPD with unclassified PH. The postcapillary contribution during exercise was defined as a PAWP/CO slope of >2 mmHg/L/min.[9]

Statistical analyses

Data are reported as median [25th to 75th percentile] or *n* (%) values since most of the data did not conform to a normal distribution. Continuous data were compared between groups using the Wilcoxon rank-sum test. Categorical data were compared between groups using Fisher's exact test. We used the Wilcoxon signed-rank test to compare continuous variables between resting and peak exercise within groups. The mPAP/CO slope was calculated from multipoint plots of mPAP and CO for each patient using least-squares linear regression. For patients where this was not possible, we used two-point measurements.

Since the slope of the pressure–flow relationship becomes steeper with age, we also compared exercise haemodynamics between groups after adjusting for age. Because the residuals in the linear regression analysis were not normally distributed, we used multivariable median regression analysis[25] and present the median group differences with 95% confidence intervals. We chose a 5% significance threshold, and applied two-sided tests. All statistical analyses were performed using Stata software (version SE 17, StataCorp).

RESULTS

Thirty-six patients were examined using RHC both at rest and during exercise. CTEPD without resting PH was present in 29 (81%) of these patients, of whom 6/29 (21%) had ePH. Of the remaining patients, seven (19%) had resting PH (Figure 2), five (14%) had CTEPH and two (6%) had unclassified PH.

Patients with CTEPD-ePH were older than those with CTEPD without ePH, but there was no intergroup difference in the proportion of females or body mass index (Table 1). None of the patients had undergone thrombolysis. Risk factors for CTEPH such as inherited thrombophilia, thrombotic burden at the diagnosis as assessed by the MBPEC score and the size of the perfusion defects showed no difference between the groups. N-terminal probrain natriuretic peptide and functional capacity measured by both maximal workload on exercise RHC and mISWT did not differ between the groups (Table 1).

Haemodynamics

At rest, TPR was higher in those with CTEPD-ePH than in those with CTEPD without ePH, whereas mPAP, PAWP, PVR, and pulmonary arterial compliance were similar in the two groups (Table 2). However, patients with CTEPD-ePH showed mPAP and PVR values at the upper limits of the normal ranges. The cardiac index (CI) and right ventricular end-diastolic pressure at rest were similar across the groups. None of the patients had PAWP ≥ 15 mmHg at rest.

At peak exercise, several of the haemodynamic variables differed between the groups (Table 2). After adjusting for age, patients with CTEPD-ePH had a higher PVR (adjusted median difference = 0.5 WU, $p = 0.021$), higher TPR (1.0 WU, $p = 0.009$), lower CI (–0.7 L/min/m^2, $p < 0.001$) and steeper mPAP/CO slope (1.5 mmHg/L/min, $p = 0.030$) relative to those with CTEPD without ePH. The PAWP/CO slope did not differ between the CTEPD-ePH and CTEPD groups after adjusting for age. The latter aspect can be illustrated by three of the four patients with a PAWP/CO slope of >2 mmHg/L/min being >70 years of age, compared with only two of the nine patients with a PAWP/CO slope of ≤2 mmHg/L/min being >70 years of age. Two of the six patients with CTEPD-ePH and two of the five with CTEPH had a PAWP/CO slope of >2 mmHg/L/min (Figure 2).

During exercise, mPAP, PAWP, RAP, and the CI increased from rest to peak exercise in all groups. Similar to patients with mild CTEPH, those with CTEPD-ePH did not show a decrease in TPR or PVR from rest to peak exercise, in contrast to those with CTEPD without ePH (Table 3). The mPAP/CO slope during exercise in CTEPD-ePH patients was also similar to that in CTEPH patients and was steeper than that in CTEPD patients without ePH (Figure 3).

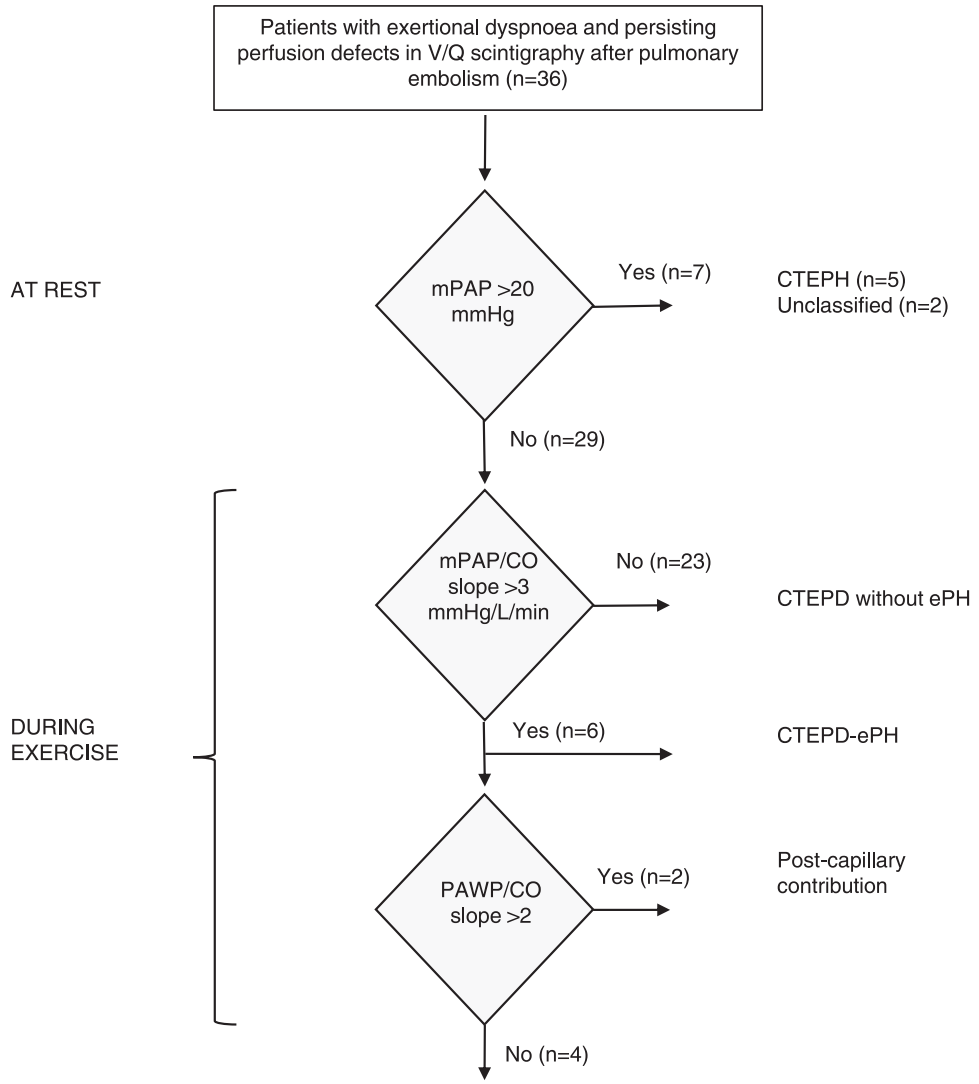

FIGURE 2 Haemodynamic categorization of study patients based on resting and peak exercise right-heart catheterization findings: *CTEPH* (chronic thromboembolic pulmonary hypertension): resting mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 2 WU). *Unclassified pulmonary hypertension* (PH): PH not consistent with the pre- or postcapillary definitions of PH. *CTEPD without ePH* (chronic thromboembolic pulmonary disease): CTEPD without PH at rest and peak exercise. *CTEPD-ePH* (CTEPD with exercise pulmonary hypertension): no PH at rest, but with CTEPD and mPAP/cardiac output (CO) slope >3 mmHg/L/min. ePH was further subclassified using PAWP/CO slope ≤2 mmHg/L/min and >2 mmHg/L/min to reflect pre- and postcapillary contributions, respectively. Slopes are multipoint changes between rest and exercise.

DISCUSSION

This study applied the most recent PH and ePH criteria[8] to demonstrate diverse invasive haemodynamic findings in 36 patients with persistent dyspnoea and residual perfusion defects following acute PE. About one in five of those with CTEPD had ePH, which we consider to be an important finding in this patient group. Our approach to categorizing patients with CTEPD into those with and without ePH has revealed several distinctive physiological and clinical characteristics.

Previous RHC studies involving patients with CTEPD that also investigated exercise values[12,26–30] were highly selective when enrolling patients who underwent pulmonary endarterectomy or balloon pulmonary angioplasty. In contrast, our study comprised a population of patients who were identified from hospital registries, rather than being referred due to specific problems or the severity of symptoms.

Most of the previous studies defined CTEPD as a resting mPAP of <25 mmHg, thereby including patients with CTEPD with a resting mPAP of 21–24 mmHg. Only two studies used the new definition of PH.[29,30] Swietlik et al. demonstrated that mPAP and CO increased, while TPR decreased during exercise relative to baseline, which were similar to the findings in our patients with CTEPD

TABLE 1 Patient characteristics.

	All ($n = 36$)	CTEPD without ePH ($n = 23$)	CTEPD-ePH ($n = 6$)
Age, years	62 [55–71]	61 [53–69]	71 [68–74]
Sex, male	20 (56)	13 (57)	3 (50)
Body mass index, kg/m^2	27 [26–30]	26 [25–29]	29 [26–30]
Inherited thrombophilia	7 (19)	6 (26)	1 (17)
Time from PE to V/Q scintigraphy, months	13 [10–21]	16 [10–24]	13 [10–14]
Perfusion defect volume, %	5 [3–8]	4 [2–6]	5 [3–6]
MBPEC score 1/2/3/4	1/11/2/22	1/6/1/15	2/2/0/4
Anticoagulant treatment	31 (86)	18 (78)	6 (100)
COVID-19 before inclusion	5 (14)	2 (9)	1 (17)
Smoking status			
Current	3 (8)	3 (13)	0 (0)
Former	14 (39)	8 (35)	0 (0)
Never	19 (53)	12 (52)	6 (100)
Hypertension	16 (44)	8 (35)	4 (67)
Diabetes	5 (14)	2 (9)	2 (33)
Coronary artery disease	2 (6)	2 (9)	0 (0)
WHO functional class I/II/III/IV	1/27/3/0	2/18/3/0	0/4/2/0
mISWT distance, m	690 [480–950]	865 [620–960]	675 [480–710]
NT-proBNP, ng/L	85 [40–123]	83 [40–108]	101 [79–212]
FEV_1/FVC	0.76 [0.71–0.79]	0.76 [0.74–0.80]	0.76 [0.64–0.78]
FEV_1, % of predicted	91 [82–102]	93 [85–104]	92 [77–104]
FVC, % of predicted	92 [84–103]	92 [85–107]	93 [87–101]
DLCO, % of predicted	89 [78–109]	91 [81–112]	94 [89–109]
DLCO/VA, % of predicted	92 [81–103]	94 [81–103]	91 [82–109]

Note: Baseline data were collected at inclusion except where stated otherwise, and are presented as median [25th–75th percentile], *n* (%) or *n* values. *p* Values are for group differences between CTEPD without ePH and CTEPD-ePH. Categorical data were compared between groups using Fisher's exact test.

Abbreviations: CTEPD, chronic thromboembolic pulmonary disease; DLCO, diffusing capacity of the lungs for carbon monoxide; ePH, exercise pulmonary hypertension; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MBPEC, mean bilateral proximal extension of the clot; mISWT, modified incremental shuttle walk test; NT-proBNP, N-terminal probrain natriuretic peptide; PE, pulmonary embolism; VA, alveolar volume; V/Q, ventilation/perfusion; WHO, World Health Organization.

without ePH.[29] Correspondingly, we observed a decrease in PVR during exercise in line with a previous report on patients with CTEPD.[30] By distinguishing between CTEPD with and without ePH, we also demonstrated that the haemodynamic behavior during both rest and exercise in patients with CTEPD without ePH is similar to those reported historically in healthy controls.[31,32] This indicates that patients with CTEPD without abnormal exercise haemodynamics maintain relatively normal pulmonary vascular function during exertion. The occurrence of ePH of 21% among our patients with CTEPD is lower than previous reports.[12,26,27,29,30,33,34] This is probably because most patients in previous studies had more severe disease, since they were referred to specialized centers for pulmonary endarterectomy and balloon pulmonary angioplasty.

At rest, we found that TPR was higher in patients with CTEPD-ePH than in those with CTEPD without

TABLE 2 Comparison of right-heart-catheterization data at rest and exercise between CTEPD with and without ePH, unadjusted and adjusted for age.

	Rest, unadjusted			Exercise, unadjusted			Exercise, adjusted for age		
	CTEPD without ePH ($n = 23$)	CTEPD-ePH ($n = 6$)	p Value[a]	CTEPD without ePH ($n = 23$)	CTEPD-ePH ($n = 6$)	p Value[a]	Adjusted median difference[b]	95% CI[b]	p Value[b]
Heart rate/min	69 [61–80]	76 [53–81]	0.94	135 [114–144]	104 [96–122]	0.04	−5.0	(−28.6, 18.6)	0.67
mPAP, mmHg	16 [12–19]	19 [18–20]	0.073	30 [26–34]	41 [38–42]	0.004	3.0	(−3.5, 9.5)	0.36
PAWP, mmHg	8 [6–10]	9 [8–12]	0.26	15 [13–19]	20 [18–22]	0.066	1.3	(−3.9, 6.5)	0.62
RAP, mmHg	4 [2–6]	3 [2–4]	0.38	6 [3–8]	7 [4–9]	0.17	−0.4	(−3.2, 2.4)	0.76
PVR, WU	1.3 [1.0–1.7]	1.7 [1.4–2.4]	0.16	1.0 [0.8–1.2]	2.0 [1.7–2.2]	0.001	0.5	(0.1, 1.0)	0.021
TPR, WU	2.4 [2.1–3.3]	3.6 [3.0–4.0]	0.020	2.2 [1.6–2.6]	3.7 [3.4–4.3]	<0.001	1.0	(0.3, 1.7)	0.009
PAC, mL/mmHg	4.5 [3.7–5.5]	3.6 [2.89–4.1]	0.063	4.3 [3.3–5.4]	2.6 [2.2–4.3]	0.063	−0.5	(−2.4, 1.4)	0.58
CO, L/min	5.9 [5.0–7.1]	5.4 [5.0–5.7]	0.21	14.0 [12.1–16.6]	11.5 [9.0–11.8]	0.009	−1.3	(−3.6, 1.0)	0.26
CI, L/min/m^2	2.9 [2.6–3.3]	2.8 [2.7–3.0]	0.52	6.7 [6.2–8.1]	5.7 [5.4–6.0]	0.002	−0.7	(−1.1, −0.4)	<0.001
RVEDP, mmHg	6.5 [5.0–8.0]	7.0 [3.0–8.0]	0.89	-	-				
Workload, W				100 [75–125]	88 [50–100]	0.13	−10.0	(−54.6, 34.6)	0.65
mPAP/CO slope, mmHg/L/min				1.7 [1.3–2.6]	3.6 [3.3–5.0]	<0.001	1.5	(0.1, 2.8)	0.030
PAWP/CO slope, mmHg/L/min				1.1 [0.4–1.5]	2.0 [1.8–3.1]	0.011	0.5	(−0.6, 1.7)	0.35
sBP, mmHg	159 [145–164]	159 [145–164]	0.57	209 [194–225]	195 [189–220]	0.67	−17.3	(−50.0, 15.4)	0.29
dBP, mmHg	64 [61–72]	68 [64–69]	0.26	71 [66–81]	75 [61–77]	0.98	5.5	(−7.3, 18.3)	0.39
SvO2, %	73 [71–76]	74 [72–75]	0.93	44 [39–48]	36 [34–45]	0.14	−7.0	(−14.6, 0.6)	0.069

Note: Data are median [25th–75th percentile] values. p Values are for group differences. Slopes are multipoint changes from rest to peak exercise.

Abbreviations: CI, confidence interval; CO, cardiac output; CTEPD, chronic thromboembolic pulmonary disease; dBP, diastolic blood pressure; ePH, exercise pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; sBP, systolic blood pressure; SvO2, mixed venous oxygen saturation; TPR, total pulmonary vascular resistance.

[a]Wilcoxon rank-sum test.

[b]Age-adjusted values obtained in multivariable median regression analysis are presented as adjusted median differences, p values and corresponding CIs.

TABLE 3 Right-heart-catheterization data at rest and peak exercise in patients with CTEPD without ePH, CTEPD-ePH, and CTEPH.

	CTEPD without ePH ($n = 23$)			CTEPD-ePH ($n = 6$)			CTEPH ($n = 5$)		
	Rest	Peak exercise	p Value[a]	Rest	Peak exercise	p Value[a]	Rest	Peak exercise	p Value[a]
mPAP, mmHg	16 [12–19]	30 [26–34]	<0.001	19 [18–20]	41 [38–42]	0.027	25 [24–25]	49 [49–52]	0.042
PAWP, mmHg	8 [6–10]	15 [13–19]	<0.001	9 [8–12]	20 [18–22]	0.028	11 [11–12]	25 [21–26]	0.042
RAP, mmHg	4 [2–6]	6 [3–8]	0.049	3 [2–4]	7 [4–9]	0.035	6 [3–8]	12 [10–15]	0.042
PVR, WU	1.3 [1.0–1.7]	1.0 [0.8–1.2]	0.002	1.7 [1.4–2.4]	2.0 [1.7–2.2]	0.92	2.4 [2.2–2.7]	2.1 [1.9–2.3]	0.080
TPR, WU	2.4 [2.1–3.3]	2.2 [1.6–2.6]	<0.001	3.6 [3.0–4.0]	3.7 [3.4–4.3]	0.29	4.0 [4.0–5.5]	4.1 [3.9–4.2]	0.35
PAC, mL/mmHg	4.5 [3.7–5.5]	4.3 [3.3–5.4]	0.63	3.6 [2.89–4.1]	2.6 [2.2–4.3]	0.35	2.7 [2.3–3.2]	1.8 [1.6–2.3]	0.14
CO, L/min	5.9 [5.0–7.1]	14.0 [12.1–16.6]	<0.001	5.4 [5.0–5.7]	11.5 [9.0–11.8]	0.028	6.0 [4.6–6.3]	11.9 [9.7–14.3]	0.043
CI, L/min/m^2	2.9 [2.6–3.3]	6.7 [6.2–8.1]	<0.001	2.8 [2.7–3.0]	5.7 [5.4–6.0]	0.027	2.8 [2.5–3.2]	6.2 [5.2–7.1]	0.043

Note: Data are median [25th–75th percentile] values.

Abbreviations: CI, confidence interval; CO, cardiac output; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; ePH, exercise pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TPR, total pulmonary vascular resistance.

[a]Wilcoxon signed-rank test.

ePH, with no difference in PVR, CO, PAWP, or mPAP. We also found that the CI at peak exercise was lower in CTEPD-ePH than in CTEPD without ePH. This difference may reflect an early impairment of right heart function secondary to a short-term overload of the right ventricle during exercise in CTEPD-ePH.[35,36] Exercise RHC may thus be a valuable clinical tool in detecting early right heart dysfunction, which may contribute to reduced exercise capacity and symptoms in these patients. Unlike CTEPD without ePH, we observed no change in PVR and TPR during exercise in CTEPD-ePH patients. Normally we would expect PVR and TPR to decrease in healthy subjects during exercise due to pulmonary vascular recruitment and distension.[37] Our present findings might therefore indicate that despite no difference in thrombotic burden on a CT pulmonary angiogram obtained at the time of a PE diagnosis in CTEPD-ePH patients, and relatively small perfusion defects observed in these patients at inclusion using V/Q scintigraphy, they are more affected by a secondary vasculopathy of the pulmonary vasculature compared with patients with CTEPD without ePH.[38] A similar pattern for TPR and PVR has previously also been demonstrated in patients with CTEPD.[26] This observation highlights the physiological differences between CTEPD patients with and without ePH.

The most recent guidelines recommend long-term anticoagulation based on individualized decision-making for patients with CTEPD without PH at rest.[9] The presence of ePH might be an additional factor in this decision-making process.

Several studies have shown that the resting mPAP is higher in patients with than without ePH, which is related to other underlying diseases such as systemic sclerosis, lung and left-heart diseases.[7,30,39–41] In our study, patients with CTEPD-ePH showed mPAP values in the upper limit of the normal range, but their resting mPAP was not higher than that in patients with CTEPD without ePH. Due to our small sample of only five patients with CTEPH, we avoided a direct comparison with those with CTEPD-ePH. However, it seems that CTEPH and CTEPD-ePH patients respond similarly to exercise, with a smaller increase in CI, an abnormal elevation of pulmonary artery pressure, and an impaired ability of the vascular bed to adapt to the rapid increase in circulating blood volume. Claeys et al. reported similar findings for their CTEPH and CTEPD groups, but they did not discriminate between CTEPD with and without ePH.[34] Since we excluded patients with known CTEPH from our study, our CTEPH group consisted of patients with mild PH with an mPAP of 23–28 mmHg.[8] In addition, the use of the new lower PH definition for CTEPH[8] may have led to the inclusion of more patients

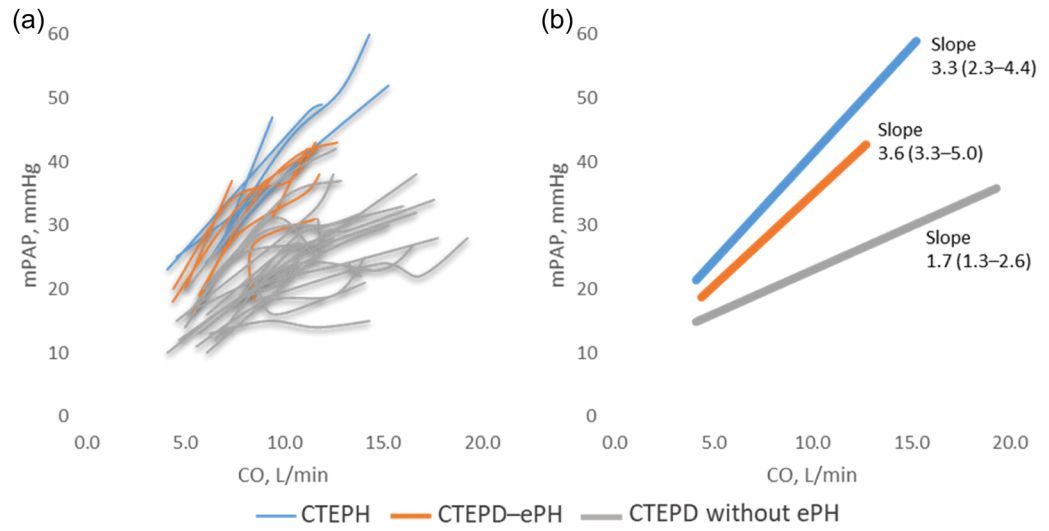

FIGURE 3 Changes in mean pulmonary artery pressure (mPAP)/cardiac output (CO) from resting supine to peak exercise. (a) Individual changes in chronic thromboembolic pulmonary disease (CTEPD) without exercise pulmonary hypertension (ePH) ($n = 23$), CTEPD-ePH ($n = 6$) and CTEPH ($n = 5$). (b) Median changes in the same groups. Slopes are in mmHg/L/min, and are presented as median [25th–75th percentile] values.

with less severe disease, and, therefore, a smaller difference in findings during exercise between CTEPD-ePH and CTEPH.

Kovacs et al. used the former definition of PH to show that the mPAP/CO slope during exercise in patients with borderline PH (mPAP=21–24 mmHg) was steeper than that in patients with a resting mPAP of <21 mmHg.[23] Our data showed a similar difference between patients with CTEPH and CTEPD without ePH, but not between those with CTEPH and CTEPD-ePH (Figure 3). This suggests that RHC during exercise can be used to identify patients with CTEPD and haemodynamically significant disease. However, whether patients with CTEPD-ePH represent an intermediate state that will eventually develop from CTEPD without ePH to CTEPH will need to be determined in a future longitudinal study.

In the present study, two of the five patients with CTEPH and two of the six patients with CTEPD-ePH had a postcapillary contribution during exercise, as demonstrated by the PAWP/CO slope of >2 mmHg/L/min representing an additional disease component. However, this finding of increased left ventricular filling pressures in patients with chronic thromboembolic disease supports another recent report on patients with CTEPH.[42] Moreover, the patients with ePH were older than those with CTEPD without ePH, although this relationship was subject to the limitation of the small number of patients. Because the left ventricular filling pressure, PAWP/CO slope, and mPAP/CO slope increase with age,[43] we used median regression to adjust for differences between the groups, despite the smallness of the sample. We, therefore, consider that our findings highlight the importance of exercise testing in potentially revealing occult left heart disease that is not evident at rest. Moreover, we might have identified a contributing cause to exercise intolerance.

The small number of patients and the small group sizes for patients included in this study restricted the statistical power and the methods that could be used, for example multivariable analysis. Because of this, we presented data using medians and 25th to 75th percentiles and used nonparametric statistics. Therefore, the raw numbers may be difficult to compare with mean values in previous studies. It is possible that the symptomatic patients who participated in this study differed from those who declined to participate, thus leading to selection bias. We should, therefore, be careful to generalize our findings to all patients with CTEPD. We did not use the direct Fick method during exercise for CO measurements, as we did not have the specialized equipment required to measure the patient's oxygen consumption (VO_2) simultaneously during RHC.

The exercise RHC applied in this study was performed in the supine position due to this yielding more stable and reliable pressure curves. An upright position during exercise more closely mimics normal physical activity, but this was not possible in our laboratory.[23] Previous studies show that body position plays a role regarding hemodynamics.[44]

However, mPAP/CO slope does not seem to be affected by position.[45] According to the ESC/ERS guidelines, the upper limit of normality for mPAP/CO slope in

the supine position ranges from 1.6 to 3.3 mmHg/L/min with ePH defined as a slope exceeding 3 mmHg/L/min. Although we cannot exclude that the supine position in the present study has had an impact on exercise hemodynamics, we do not consider this to have had a significant impact on our results. Assessing the PAWP during exercise is technically challenging, and the use of fluid-filled catheters could have resulted in measurement errors. We tried to minimize this by ensuring that the catheters were adequately flushed, and by averaging pressures over several cycles. Using thermodilution may also overestimate the occurrence of ePH.[43]

In conclusion, ePH is common in patients with CTEPD and exertional dyspnoea, as shown by more than one in five of the patients in this study having ePH. Exercise RHC revealed that a notable proportion of these patients had postcapillary contributions, which highlights the usefulness of this test for identifying the factors contributing to exercise intolerance.

AUTHOR CONTRIBUTIONS

Øyvind Jervan, Janne Mykland Hilde, Knut Stavem, Kjetil Steine, and Waleed Ghanima were responsible for the design of the study. Adam Dhayyat, Janne Mykland Hilde, and Kjetil Steine had full access to all of the data analyzed in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Diyar Rashid and Jostein Gleditsch interpreted the scintigraphic images. Adam Dhayyat drafted the first version of the manuscript. Adam Dhayyat conducted the analyses with support from Knut Stavem. All authors contributed to the interpretation of the results and revising the manuscript. All authors have read and approved the final version of the manuscript.

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CONFLICTS OF INTEREST STATEMENT

K. Stavem reports consulting fees from MSD and Union Chimique Belge (UCB) unrelated to this study. W. G. reports fees for participation in an advisory board from Amgen, Novartis, Pfizer, Principia Biopharma Inc.—a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire, Alpine, Kedrion and HiBio; lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi and Bayer; and research grants from Bayer, BMS/Pfizer, and UCB. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The project was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK no. 2020/20714) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

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