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RESEARCH ARTICLE

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Patients with CTEPH and mild hemodynamic severity of disease improve to a similar level of exercise capacity after pulmonary endarterectomy compared to patients with severe hemodynamic disease

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Abstract

The correlation between hemodynamics and degree of pulmonary vascular obstruction (PVO) is known to be poor in chronic thromboembolic pulmonary hypertension (CTEPH), which makes the selection of patients eligible for pulmonary endarterectomy (PEA) challenging. It can be postulated that patients with similar PVO but different hemodynamic severity have different postoperative hemodynamics and exercise capacity. Therefore, we aimed to assess the effects of PEA on hemodynamics and exercise physiology in mild and severe CTEPH patients. We retrospectively studied 18 CTEPH patients with a mild hemodynamic profile (mean pulmonary arterial pressure [mPAP] between 25 and 30 mmHg at rest) and CTEPH patients with a more severe hemodynamic profile (mPAP > 30 mmHg), matched by age, gender, and PVO. Cardiopulmonary exercise testing parameters were evaluated at baseline and 18 months following PEA. At baseline, exercise capacity, defined as oxygen uptake, was less severely impaired in the mild CTEPH group compared to the severe CTEPH group. After PEA, in the mild CTEPH group, ventilatory

Abbreviations: 6-MWT, 6-min walk test; AT, anaerobic threshold; BMI, body mass index; CI, cardiac index; CO, cardiac output; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusion capacity of the lung for carbon monoxide; DLCO/VA, DLCO dived by alveolar volume; ERA, endothelin receptor antagonist; FEV1, forced expiratory volume in 1 s; HbO_2 sat, peripheral oxygen saturation; HRR, heart rate reserve; IQR, interquartile range; kPa, kilopascal; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-Terminal pro-B-type natriuretic peptide; O_2-pulse, oxygen pulse; PAWP, pulmonary artery wedge pressure; PDE-5, phosphodiesterase-5; PEA, pulmonary endarterectomy; $P_{ET}CO_2$, end-tidal CO_2 pressure; PH, pulmonary hypertension; PVO, percentage vascular obstruction; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SD, standard deviation; sGC, soluble guanylate cyclase; SHIP, Study of Health in Pomerania; SvO_2, mixed venous oxygen saturation; VA, alveolar volume; $V'CO_2$, carbon dioxide output; V′E, minute ventilation; $V'O_2$, peak oxygen uptake; V/Q scans, ventilation-perfusion scans; WHO-FC, World Health Organization classification functional class; WU, Wood Units.

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efficiency and oxygen pulse improved significantly ($p < 0.05$), however, the change in ventilatory efficiency and oxygen pulse was smaller compared to the severe CTEPH group. Only in the severe CTEPH group exercise capacity improved significantly ($p < 0.001$). Hence, in the present study, postoperative hemodynamic outcome and the CPET-determined recovery of exercise capacity in mild CTEPH patients did not differ from a matched group of severe CTEPH patients.

KEYWORDS
cardiopulmonary exercise test, chronic thromboembolic pulmonary hypertension, long-term follow-up, pulmonary endarterectomy, pulmonary vascular obstruction

INTRODUCTION

The hemodynamic severity of disease in chronic thromboembolic pulmonary disorders ranges from chronic thromboembolic pulmonary disease (CTEPD) without pulmonary hypertension (PH) at rest, to severe chronic thromboembolic pulmonary hypertension (CTEPH) with right ventricular failure.[1,2] Regardless of the hemodynamic severity, virtually all CTEPD patients experience exertional symptoms and have a reduction in peak oxygen uptake ($V'O_2$). Moreover, abnormal cardiocirculatory responses and decreased ventilatory efficiency during a cardiopulmonary exercise test were demonstrated in CTEPD without PH.[3–7]

Pulmonary endarterectomy (PEA), the treatment of choice in CTEPH patients, lowers and in most cases even normalizes resting pulmonary artery pressures, and improves functional status, exercise capacity, and long-term survival.[8] The hemodynamic and functional outcome after a successful surgical procedure is in part determined by the extent of the small vessel arteriopathy[1] and consequent restoration of the right ventricular stroke volume response upon exercise.[9]

A recent study from our center showed that preoperative hemodynamics in CTEPH were only modestly associated with postoperative hemodynamics and postoperative exercise capacity.[10] In this study, patients with various degrees of hemodynamic severity were included, however, the degree of obstruction of the pulmonary vessels, often expressed as a percentage of (pulmonary) vascular obstruction (PVO),[11,12] was not taken into account. Therefore, the observed relatively small improvements in exercise capacity and hemodynamics might be related to a milder hemodynamic severity of disease and a relatively lower degree of PVO, explaining the limited improvement from surgery.

The hemodynamic severity of the disease cannot be predicted by PVO.[11] As mild and severe CTEPH may have similar PVO, we reasoned that mild CTEPH patients would reveal different, and presumably better hemodynamics and exercise capacity after PEA than patients with severe CTEPH with similar PVO. Therefore, we evaluated the effects of PEA on exercise physiology by studying mild CTEPH (mean pulmonary arterial pressure [mPAP] ≤ 30 mmHg) and severe CTEPH patients (mPAP > 30 mmHg), matched by PVO.

METHODS

Study subjects and design

All consecutive CTEPH patients ($n = 18$) who had a mild hemodynamic profile, defined as mPAP between 25 and 30 mmHg, and who had performed a noninvasive cardiopulmonary exercise test prior to and 18 months after PEA in the Amsterdam UMC (a tertiary PH referral center) between 2005 and 2021 were retrospectively selected from our ongoing CTEPH registry. Diagnosis of CTEPH and operability of all patients were discussed in a multidisciplinary team. As part of clinical protocol, pulmonary angiography, right heart catheterization (RHC), and pulmonary function testing were performed. PEAs were performed by two surgeons: J. W. and P. S.

The same retrospective cohort was used to select patients with a mPAP > 30 mmHg to compare with the mild CTEPH group. For this comparison, a random sample of 80 patients with a mPAP > 30 mmHg was taken. A total 37 of these patients had performed cardiopulmonary exercise test at baseline and after 18 months of follow-up. Of these, 18 patients were selected who matched to the mild CTEPH patients with respect to age (with a range of ± 5 years), gender and the extent of the PVO as assessed by ventilation-perfusion scans (V/Q scans). Our Institutional Review Board reviewed the study and concluded that the Medical Research Involving

Human Subjects Act did not apply to this study. Therefore, the study was exempt from further review (W22_203/22.252).

Assessment of PVO

V/Q scans were obtained after inhalation of Kr81m gas and after the intravenous injection of 84–105 MBq Tc99m labeled macroaggregated (MAA) albumin. Images were acquired using a Symbia T2 or Symbia Intevo T16 (Siemens Medical Solutions USA Inc.). A total of 5 scans were performed before 2010 according to the following protocol: images were obtained immediately after the administration of 148–155 MBq of technetium-99 m MAA particles. The images were acquired using ECAM dual-head γ-camera or Orbiter (Siemens Medical Solutions USA Inc.). The degree of PVO was quantified on standard V/Q scan according to an established method in acute PE.[13] In short, each lobe was assigned a weight based upon the regional distribution of pulmonary blood flow in the supine position: right lower lobe 25%, right middle lobe 12%, right upper lobe 18%, left lower lobe 20%, lingula 12%, and left upper lobe 13%. For each lobe, a semiquantitative perfusion score (0, 0.25, 0.5, 0.75, or 1) was estimated from the film density in the anterior, posterior, and oblique views by comparison with the photo density of an apparently normally perfused area. Each lobar perfusion score was calculated by multiplying the weight with the perfusion score. The overall perfusion score was determined by summing the six separate lobar perfusion scores and the PVO was calculated as (1 − overall perfusion score) times 100. All images on V/Q scan were analyzed by two independent readers. The extent of PVO in all cases was discussed in a consensus meeting J. v. E, C. v. K., and J. T.

Functional assessment

Symptom-limited cardiopulmonary exercise test was performed and assessed according to the American Thoracic Society guidelines.[14] Briefly, patients were placed on a cycle ergometer in the upright position and continuous measurements were made of minute ventilation ($V'E$), $V'O_2$, carbon dioxide output ($V'CO_2$), heart rate, blood pressure, and electrocardiography. The workload was increased by steps of 5–15 W, depending on the predicted maximum exercise capacity, and in such a way that maximal effort was attained within 10–15 min. Oxygen consumption at maximal exercise ($V'O_2$-peak) was defined by the highest achieved value averaged over eight breaths. Oxygen pulse (O_2-pulse) was calculated as $V'O_2$ divided by heart rate. The anaerobic threshold was determined using the V-slope method. The predicted maximum $V'E$ was based on 40 × forced expiratory volume in 1 s (FEV1). All other predicted values were used from the Study of Health in Pomerania (SHIP).[15] Exercise limitation was defined by $V'O_2$ at peak exercise below 80% of the predicted value.[16]

Each patient was classified by an independent physician according to the World Health Organization classification of functional class (WHO-FC) before enrollment in the study and at 18 months after PEA.[17] N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was assessed at baseline. The 6-min walk test (6-MWD) was performed according to the guidelines of the American Thoracic Society.[18] Diffusion capacity of the lung for carbon monoxide (DLCO) and alveolar volume (VA) was determined by the single breath method and corrected for hemoglobin concentration. DLCO/VA was determined by dividing DLCO by VA.[19]

RHC

RHC at rest was performed as previously described.[20] The following variables were recorded: mPAP, right atrial pressure, pulmonary artery wedge pressure (PAWP), heart rate, and central venous oxygen saturation (SvO_2). Cardiac output (CO) was determined by thermodilution or the direct Fick method (indexed for body surface area: cardiac index [CI]). PVR was calculated from ([mPAP − PAWP]/CO). Residual PH post-PEA was defined as mPAP > 20 mmHg and PVR > 2 Wood Units (WU) according to the updated hemodynamic definition.[21]

Statistical analysis

Baseline and follow-up results are expressed as mean ± standard deviation (SD), median interquartile range [IQR] for skewed data or number of patients (% of total). For normally distributed variables, an unpaired Student *t* test was used to compare differences between mild versus severe CTEPH at baseline and follow-up and mean differences with 95% confidence intervals (CIs) were calculated. The Student paired *t* test was used to analyze the effect of PEA. Mann–Whitney *U* and Wilcoxon matched pairs signed ranks test were used to compare skewed data where appropriate. Differences regarding categorical data were tested using χ^2 test or Fisher's exact test. Correlations were assessed by Pearson's or Spearman's correlation test where appropriate, and was tested for two-sided significance. A *p* value of less than 0.05 was

considered significant. All analyses were conducted using statistical software SPSS, version 27.0; (SPSS Inc.) and GraphPad Prism version 7.0b (GraphPad Software).

RESULTS

Patients' characteristics

Baseline characteristics, pulmonary function tests, and data from cardiopulmonary exercise tests and RHC are shown in Table 1. In mild and severe CTEPH the PVO was 44.7 ± 12.2 and 44.6 ± 10.3, respectively (mean difference: 0.02%; 95% CI: [−7.6 to 7.6]). Compared to the severe CTEPH group, DLCO/VA was higher (mean difference: 8%; 95% CI: [−0.7 to 16.8]) and NT-proBNP (mean difference: 892 µmol; 95% CI: [−615 to −99]) was lower in the mild CTEPH group. The majority of all patients were in WHO-FC class II or III. In the mild CTEPH group, 6-MWD was 501 ± 89 m compared to 423 ± 119 m in the severe CTEPH group ($p = 0.063$, mean difference: 57 m; 95% CI: [−24 to 139]).

Cardiopulmonary exercise test before PEA

Cardiopulmonary exercise test variables are shown in Table 2. As expected at baseline, all cardiopulmonary exercise test variables were better in the mild CTEPH group compared to the severe CTEPH group. Exercise capacity, expressed as mean $V'O_2$-peak in relation to the predicted value, was on the lower limit of normal in the mild group ($85.3 \pm 23.1\%$) and was decreased in the severe CTEPH group ($61.5 \pm 13.0\%$, $p < 0.001$, mean difference: 31.4%; 95% CI: [11 to 36]). Second, the mean peak O_2-pulse was normal ($82 \pm 12\%$ of predicted) in the mild CTEPH group, and significantly higher compared to the severe CTEPH group ($63 \pm 14\%$, $p < 0.001$, mean difference: 19.4%; 95% CI: [10 to 28]). Parameters reflecting V/Q matching were also less affected in the mild CTEPH group. As compared to the reference value, the $V'E/V'CO_2$ ratio at AT was increased in mild CTEPH (34.8 ± 5.6), but even higher in severe CTEPH (49.6 ± 14.2; $p = 0.001$, mean difference: −53.9; 95% CI: [−85 to −23]). Similarly, the $P_{ET}CO_2$ at peak exercise was decreased in mild CTEPH (3.5 ± 0.61), and was more

TABLE 1 Demographics.

Baseline characteristics	mPAP ≤ 30 ($N = 18$)	mPAP > 30 ($N = 18$)	*p* Value
Age (years, [range])	52 [27–65]	56 [18–69]	0.279
Female (*n*, (%))	12 (67)	13 (72)	0.500
BMI (kg/m^2)	29.7 ± 4.3	27.5 ± 6.2	0.225
Diuretics (*n*, (%))	1 (6)	6 (33)	0.044
Vasodilators (*n*, (%))	0 (0)	3 (17)	0.114
PDE-5 inhibitors (*n*, (%))	0 (0)	1 (6)	
ERA (*n*, (%))	0 (0)	2 (11)	
Prostacyclin analog (*n*, (%))	0 (0)	0 (0)	
sGC stimulator (*n*, (%))	0 (0)	0 (0)	
Creatinine (µmol/L)	83 [23]	86 [27]	0.462
NT-proBNP (pg/mL)	64 [39]	393 [1244]	<0.001
PVO (%)	44.7 ± 12.2	44.6 ± 10.3	0.997
Pulmonary function			
FVC (% predicted)	104 ± 17	103 ± 16	0.928
FEV1 (% predicted)	75 ± 8	70 ± 9	0.143
FEV1/FVC (%)	92 ± 18	89 ± 17	0.633
DLCO (% predicted)	70 ± 13	63 ± 12	0.147
DLCO/VA (% predicted)	81 ± 14	73 ± 11	0.070

Note: Data presented as mean ± SD, median [IQR], or number (%). $p < 0.05$ was considered significant.

Abbreviations: 6-MWD, 6-min walk distance; BMI, body mass index; DLCO, diffusion capacity; DLCO/VA, DLCO dived by alveolar volume; ERA, endothelin receptor antagonist; FEV1, forced expiratory volume 1st second; FVC, forced vital capacity; IQR, interquartile range; PDE-5, phosphodiesterase-5; PVO, pulmonary vascular obstruction; sGC, soluble guanylate cyclase; VA, alveolar volume.

TABLE 2 Cardiopulmonary exercise test variables before and 18 months after PEA in patients with mild versus severe CTEPH.

	Baseline mPAP ≤ 30 ($N = 18$)	Post-PEA mPAP ≤ 30 ($N = 18$)	p Value	Baseline mPAP > 30 ($N = 18$)	Post-PEA mPAP > 30 ($N = 18$)	p Value
6-MWD (m)	501 ± 90	517 ± 60	0.017	444 ± 116	533 ± 79	0.009
WHO-FC (n, (%))			<0.001			<0.001
I	0 (0)	14 (78)		0 (0)	15 (83)	
II	11 (61)	3 (17)		11 (61)	3 (17)	
III	7 (39)	0 (0)		6 (33)	0 (0)	
IV	0 (0)	0 (0)		1 (6)	0 (0)	
DLCO (% predicted)	70 ± 13	70 ± 17	0.978	63 ± 12	69 ± 14	0.081
DLCO/VA (% predicted)	81 ± 14	87 ± 16	0.022	73 ± 11	74 ± 11	0.679
Hemodynamics						
RAP mean (mmHg)	5 [3]	6 [2]	0.496	8 [7][a]	6 [5]	0.071
PAP mean (mmHg)	27 [2]	19 [4]	0.003	49 [14][a]	20 [9]	<0.001
PCWP (mmHg)	9.5 ± 2.9	11.2 ± 3.3	0.412	10.8 ± 2.9	11.5 ± 3.2	0.443
CI (L/min/m^2)	2.9 [0.8]	2.7 [1.1]	0.514	2.5 [0.7]	3.0 [1.2]	0.347
PVR (WU)	3.0 [0.9]	1.5 [0.9]	0.003	7.7 [5.0][a]	1.5 [1.3]	<0.001
SvO_2 (%)	69 [7]	72 [7]	0.201	66 [7][a]	71 [4]	0.009
Cardiopulmonary exercise test						
Peak workload (W)	120.1 ± 48.0	129.7 ± 50.7	0.182	80.7 ± 19.9[a]	125.1 ± 46.5	<0.001
$V'O_2$ peak (mL/min)	1651.2 ± 525.0	1755.8 ± 625.3	0.161	1115.4 ± 260.4[a]	1625.9 ± 513.5	<0.001
$V'O_2$ peak (% predicted)	85 ± 23	91 ± 28	0.175	62 ± 13[a]	88 ± 23	<0.001
$V'O_2$@AT (% $V'O_2$ peak predicted)	50 ± 10	57 ± 14	0.014	46 ± 12	57 ± 16	0.012
V′E peak (L/min)	72.4 ± 29.1	71.1 ± 26.8	0.811	63.3 ± 12.2	67.3 ± 22.0	0.388
Ventilatory reserve (%)	28 ± 22	26 ± 17	0.638	29 ± 17	29 ± 17	0.972
$V'E/V'CO_2$ at AT	34.8 ± 5.6	31.7 ± 4.4	0.037	49.6 ± 14.2[a]	31.7 ± 5.5	<0.001
$V'E/V'CO_2$ at AT (% predicted)	129 ± 24	118 ± 19	0.035	183 ± 54[a]	116 ± 21	<0.001
$P_{ET}CO_2$ peak (kPa)	3.5 ± 0.6	4.1 ± 0.5	0.001	2.9 ± 0.8[a]	4.2 ± 0.5	<0.001
Heart rate reserve (bpm)	26 ± 20	30 ± 23	0.398	25 ± 18	17 ± 17	0.172
Peak O_2-pulse (mL/beat)	11.1 ± 2.9	12.5 ± 3.5	0.003	7.7 ± 2.3[a]	11.2 ± 3.3	<0.001
Peak O_2-pulse (% predicted)	82 ± 12	92 ± 18	0.011	63 ± 14[a]	90 ± 16	<0.001
$V'O_2$/workload (L/min/W)	9.3 ± 1.5	9.5 ± 1.8	0.859	8.5 ± 1.9	9.5 ± 1.6	0.056
RER	1.01 ± 0.13	1.06 ± 0.09	0.017	1.08 ± 0.12	1.11 ± 0.11	0.256
HbO_2 sat. max (%)	91 ± 5	95 ± 3	<0.001	90 ± 6	93 ± 5	0.001

Note: Data presented as mean ± SD, median [IQR], or number (%).

Abbreviations: AT, anaerobic threshold; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO/VA, DLCO dived by alveolar volume; HbO_2 sat., peripheral oxygen saturation; IQR, interquartile range; kPa, kilopascal; O_2-pulse, oxygen pulse; PAP, pulmonary arterial pressure; PEA, pulmonary endarterectomy; PCWP, pulmonary capillary wedge pressure; $P_{ET}CO_2$, end-tidal CO_2 pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; SvO_2, mixed-venous O_2 saturation; $V'CO_2$, carbon dioxide output; V′E, minute ventilation; $V'O_2$, oxygen uptake; WHO-FC, World Health Organization functional class.

[a]$p < 0.05$; comparison of variables at baseline between mPAP ≤ 30 mmHg versus mPAP > 30. Postoperative comparison between mPAP ≤ 30 mmHg versus mPAP > 30 did not show differences in any of the variables at the level of a $p < 0.05$.

profoundly decreased in severe CTEPH (2.9 ± 0.75; $p = 0.020$; 0.55 kPa; 95% CI: [0.09 to 1.0]).

Effects of PEA

The distribution of PEAs was unequally distributed over the study period. The mild CTEPH group included five patients who were operated in 2005–2009. In this time interval, none of the selected severe CTEPH patients were operated. From 2010 to 2014, two mild CTEPH and eight severe CTEPH patients were operated. From 2015, the patients were equally distributed. Directly after PEA, the mean mPAP decreased from 27.0 [2.0]–19.0 [10.5] mmHg ($p < 0.001$) in the mild CTEPH group, and from 49.0 [28.0]–21.0 [5.0] mmHg ($p < 0.001$) in the severe CTEPH group (median difference: 2.0 mmHg; 95% CI: [−5.0 to 3.0]). The effects of PEA after 18 months are shown in Table 2 and Figure 1. In both groups, resting mPAP and PVR had improved significantly to a similar level and even had normalized in the majority of patients (Table 2). Residual PH was present in one of the 18 (6%) patients in the mild CTEPH group and in five out of 18 patients (28%) in the severe CTEPH group. WHO-FC and 6-MWD also improved significantly (Table 2) and to comparable values at follow-up between mild and severe CTEPH (WHO-FC; $p = 0.939$; odds ratio [OR]: 0.933; 95% CI: [0.16 to 5.4] and 6-MWD; $p = 0.620$ mean difference: 15.4 m; 95% CI: [−79 to 49]). In the severe CTEPH group, mean $V'O_2$-peak in relation to the predicted value improved significantly (from 62 ± 13 to $88 \pm 23\%$; $p < 0.001$). The peak O_2-pulse, the mean $V'E/V'CO_2$ ratio at the anaerobic threshold, and the mean end-tidal CO_2 pressure ($P_{ET}CO_2$) at peak exercise and peripheral oxygen saturation (HbO_2 sat.) improved significantly in both groups (Table 2).

In contrast to the baseline variables, a comparison of the CPET variables at 18 months follow-up did not show statistical differences between the mild and severe CTEPH group ($V'O_2$-peak: $p = 0.782$, mean difference 2.4%; 95% CI: [−15.0 to 19.8]. Peak O_2-pulse: $p = 0.714$,

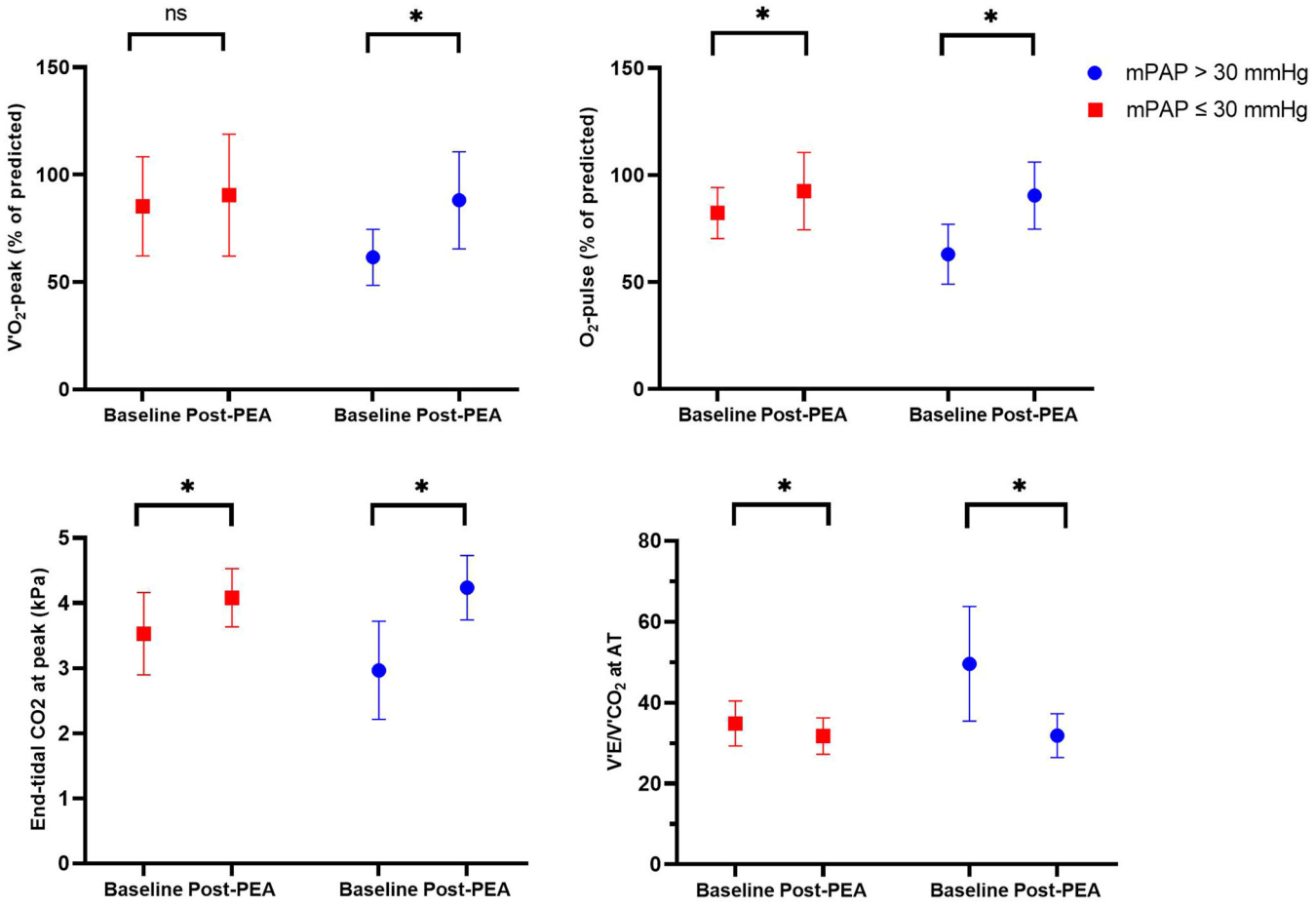

FIGURE 1 Oxygen uptake ($V'O_2$) peak (% predicted), oxygen pulse (O_2)-pulse (% predicted), minute ventilation ($V'E$)/carbon dioxide output ($V'CO_2$) at anaerobic threshold (AT), end-tidal CO_2 pressure (kilopascal) at baseline in mild CTEPH (red) versus severe CTEPH (blue) and 18 months after pulmonary endarterectomy (PEA). *$p < 0.05$; mPAP, mean pulmonary arterial pressure; NS, nonsignificant.

mean difference: 2.1%; 95% CI: [−9.4 to 13.5]. $P_{ET}CO_2$ at peak exercise: $p = 0.330$, mean difference −0.16 kPa; 95% CI: [−0.48 to 0.16]. $V'E/V'CO_2$ ratio at the anaerobic threshold: $p = 0.935$, mean difference −0.14; 95% CI: [−3.6 to 3.3]. Interestingly, the heart rate reserve (HRR) appeared somewhat higher after PEA in the mild CTEPH group compared to the severe CTEPH group ($p = 0.056$; mean difference 14 bpm; 95% CI: [−0.4 to 27]).

Exercise intolerance, defined as $V'O_2 \leq 80\%$ of predicted, after PEA was present in seven out of 18 patients (39%) in both groups. After PEA, in the mild CTEPH group with persistent exercise limitation, the HRR was 48 ± 25 versus 25 ± 19 bpm in the severe group ($p = 0.080$, mean difference: 23 bpm; 95% CI: [−3.2 to 49.2]). Moreover, in the patients with persistent exercise limitation after PEA, O_2-pulse was higher in the mild CTEPH group compared to the severe CTEPH group ($83 \pm 21\%$ vs. $77 \pm 12\%$, $p = 0.577$, mean difference; 5.2% 95% CI: [−14.8 to 25.4])

DISCUSSION

In this retrospective study, we demonstrated that before PEA mild CTEPH patients, matched for PVO, have a significantly better exercise capacity, higher ventilatory efficiency, and O_2-pulse compared to severe CTEPH patients. Contrary to our hypothesis, after 18 months of follow-up, PVO-matched mild and severe CTEPH patients did not differ with respect to postoperative pulmonary hemodynamics and exercise capacity.

Previous studies reporting on CTEPD patients without PH at rest (mPAP < 25 mmHg) also showed mild decreases in peak work rate, peak $V'O_2$, O_2-pulse, and ventilatory efficiency expressed as $V'E/V'CO_2$ at anaerobic threshold,[4,22] which are in line with the observations in the mild CTEPH group studied here. The observed baseline exercise profile in severe CTEPH patients are also in line with well-recognized characteristics found in previous studies in patients with CTEPH and other forms of PH.[16,23–25] Compared to severe CTEPH patients at baseline, the mild CTEPH patients had a significantly better exercise capacity although the patients were matched for a similar degree of PVO. Therefore, the degree of central vascular obstruction did not seem to the determine exercise capacity. In the mild CTEPH group, the observation of a normal exercise capacity and normal circulatory responses are likely explained by a lower afterload on, and preserved function of the right ventricle. This may be associated with the absence of a clinically relevant small vessel arteriopathy in these patients,[12] which is supported by the higher diffusion capacity and only mildly decreased ventilatory efficiency.[26]

The results of a previous study from our group by Ruigrok et al. showed only a modest relation of exercise capacity with preoperative hemodynamics and postoperative hemodynamic recovery. However, in this study, patients with various degree of hemodynamic severity were included and the degree of PVO was not taken into account. Therefore, for this analysis, we selected a group of patients with mild hemodynamic severity of disease with similar PVO and assumed that in the mild group the postoperative exercise capacity would be different and probably even better.[10] However, we found a similar level of exercise capacity in mild and severe CTEPH after PEA. On the one hand, the similar exercise capacity could simply be explained by the fact that both groups reached their normal exercise capacity. On the other hand, our observation of similar exercise capacity after PEA could be related to a better than expected recovery of the severe CTEPH patients. This could be related to unloading of the right ventricle and improvement its function, which has previously shown to take more time.[27,28]

Remarkably, we still observed in 39% in both the mild and severe CTEPH patients a persistent exercise limitation 18 months after PEA, with a different cardiopulmonary exercise test profile reflected by HRR and O_2-pulse. The mild CTEPH group showed an increased HRR, which might be explained, at least in part, by chronotropic incompetence limiting exercise. This phenomenon has been frequently observed in CTEPH and other forms of PH.[29] Another, more likely explanation for the increased HRR is poor effort or deconditioning of the muscle since these patients showed normal circulatory responses based on a normal O_2-pulse, $V'O_2$ at anaerobic threshold and $V'O_2$ and work-rate relation. Moreover, the ventilatory limits were not reached and ventilatory efficiency was normal.

In the severe CTEPH patients with persistent limitation to exercise, an impaired right ventricular-stroke volume response to exercise was still present after PEA. This phenomenon is described in previous studies.[4,9,30] Although we did not measure stroke volume directly, cardiopulmonary exercise test derived oxygen pulse reflects stroke volume when a constant peripheral oxygen extraction is assumed.[14] We found a decreased O_2-pulse in these severe CTEPH patients, compared to the severe CTEPH patients who fully recovered. This could reflect an impaired right ventricular stroke volume response after PEA. On the other hand, the alternative explanation for a decreased oxygen pulse is a lower peripheral oxygen extraction due to inefficient muscular function. Based on recent data showing a persistently impaired skeletal muscle diffusion capacity after PEA,[31] we consider a relevant change in muscular function

unlikely. Finally, persistent limitation to exercise, in severe CTEPH patients could also be explained by decreased ventilatory efficiency, which is partly attributed to increased dead space ventilation.[32]

This study presents long-term follow-up cardiopulmonary exercise test and RHC data of CTEPH patients, stratified by hemodynamic severity of disease; however, this study has limitations. First, measuring PVO by using perfusion scans, provides an estimation of the perfusion of pulmonary segments on the segmental level and, therefore, could have underestimated the true degree of PVO. However, the PVO was calculated as previously described by Azarian et al. and frequently used in literature for the assessment of vascular obstruction in acute PE.[11] To our knowledge a quantifying method to estimate the percentage of obstruction in chronic PE/CTEPH is lacking. Therefore, we used the PVO, as the best available option, to avoid major differences in vascular obstruction between the two study groups. The method we used to calculate the PVO may be a rough approach and even an underestimation of PVO. However, PVO was not the purpose of the study and this possible underestimating of the amount of obstruction was equal in both groups. Second, the retrospective design of the study prevents firm conclusions on causality. Third, the number of patients studied was relatively low. Furthermore, although all mild CTEPH patients were consecutively evaluated, by matching them to the more severe CTEPH patients, we studied a highly selected severe CTEPH population, which possibly hampers the generalizability. Moreover, from our 80-patient cohort, we selected CTEPH patients who could perform a CPET 18 months after PEA. Hence, in that way, we may have introduced a selection bias, by including CTEPH patients with a favorable functional outcome, that is, mostly WHO-FC 1–2 and, therefore, a relatively high postoperative $V'O_2$-peak. However, CPET at 18 months was also performed in 41 of 44 nonstudied patients. Postoperative outcome, that is, postoperative PVR, $V'O_2$-peak, and 6-MWD distance in these patients did not differ from our study group. Last, since both CTEPH itself and the complications of PEA can have major implications on the quality of life, it would be of interest if we could analyze the quality of life of our study patients next to all physiological data. Unfortunately, the quality of life was not investigated in these study patients. In conclusion, in the present study, postoperative hemodynamic outcome and the CPET-determined restoration of exercise capacity in mild CTEPH patients did not differ from a matched group of severe CTEPH patients; our observations, however, are restricted to the subgroup of severe patients with a favorable postoperative functional outcome.

AUTHOR CONTRIBUTIONS

All authors were involved in the development of the manuscript: Coen van Kan, Jelco Tramper, Anton Vonk Noordegraaf, and Josien van Es were involved in the conception, design, analysis, and interpretation of data, and drafting of the manuscript. Lilian J. Meijboom, Esther J. Nossen, Paul Bresser, Jacobus A. Winkelman, Jurjan Aman, Harm Jan Bogaard, and Petr Symersky were involved in revising the manuscript critically for important intellectual content. Final approval of the manuscript submitted applies to all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Processing of the data was conducted in accordance with the principles of the Declaration of Helsinki.

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