Persistent exercise intolerance after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension

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Despite normalisation of haemodynamics, exercise capacity remains abnormal in two-thirds of chronic thromboembolic pulmonary hypertension patients after pulmonary endarterectomy. Not all exercise intolerance is explained by the presence of residual PH. http://bit.ly/2Wie64s

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ABSTRACT

Aim: Haemodynamic normalisation is the ultimate goal of pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH). However, whether normalisation of haemodynamics translates into normalisation of exercise capacity is unknown. The incidence, determinants and clinical implications of exercise intolerance after PEA are unknown. We performed a prospective analysis to determine the incidence of exercise intolerance after PEA, assess the relationship between exercise capacity and (resting) haemodynamics and search for preoperative predictors of exercise intolerance after PEA.

Methods: According to clinical protocol all patients underwent cardiopulmonary exercise testing (CPET), right heart catheterisation and cardiac magnetic resonance (CMR) imaging before and 6 months after PEA. Exercise intolerance was defined as a peak oxygen consumption (V'_{O_2}) <80% predicted. CPET parameters were judged to determine the cause of exercise limitation. Relationships were analysed between exercise intolerance and resting haemodynamics and CMR-derived right ventricular function. Potential preoperative predictors of exercise intolerance were analysed using logistic regression analysis.

Results: 68 patients were included in the final analysis. 45 (66%) patients had exercise intolerance 6 months after PEA; in 20 patients this was primarily caused by a cardiovascular limitation. The incidence of residual pulmonary hypertension was significantly higher in patients with persistent exercise intolerance (p=0.001). However, 27 out of 45 patients with persistent exercise intolerance had no residual pulmonary hypertension. In the multivariate analysis, preoperative transfer factor of the lung for carbon monoxide (T_{LCO}) was the only predictor of exercise intolerance after PEA.

Conclusions: The majority of CTEPH patients have exercise intolerance after PEA, often despite normalisation of resting haemodynamics. Not all exercise intolerance after PEA is explained by the presence of residual pulmonary hypertension, and lower preoperative T_{LCO} was a strong predictor of exercise intolerance 6 months after PEA.

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Introduction

Pulmonary endarterectomy (PEA) is a highly effective treatment for chronic thromboembolic pulmonary hypertension (CTEPH), resulting in excellent survival [1, 2]. However, in ∼40–50% of patients, pulmonary artery pressures remain elevated after PEA [2, 3]. Residual pulmonary hypertension with a pulmonary vascular resistance (PVR) >425 dyn·s·cm^{-5} is associated with increased long-term mortality [2, 3], justifying treatment with pulmonary hypertension specific medication [1, 4] or, in selected cases, balloon pulmonary angioplasty.

While mortality and residual pulmonary hypertension at rest are the most commonly reported outcome measures after PEA, few studies have focused on exercise capacity. Peak oxygen consumption (V'_{O_2}) determined during cardiopulmonary exercise testing (CPET) [5] predicts survival in pulmonary arterial hypertension (PAH) and CTEPH [6–8], and exercise capacity in general has an important impact on quality of life both in health [9] and disease [10, 11]. It has been suggested that the recovery of exercise capacity lags behind haemodynamic recovery after PEA [12]. Overall, it is unknown how often exercise intolerance persists after PEA and it has not been determined whether persistent exercise intolerance always coincides with residual pulmonary hypertension at rest. Because the correlation between PVR and peak V'_{O_2} disappears after PEA [13], it is possible that determinants other than resting haemodynamics explain persistent exercise intolerance. In addition to residual pulmonary hypertension, deconditioning or persistent right ventricular dysfunction and ventilatory inefficiency could be responsible for persistent exercise intolerance after PEA. To determine the incidence of persistent exercise intolerance after PEA, to evaluate its determinants and relation with resting haemodynamics (*i.e.* residual pulmonary hypertension) and to analyse potential preoperative predictors of exercise intolerance after PEA, we performed a prospective cohort study using haemodynamic assessments, CPET, lung function testing and cardiac magnetic resonance imaging (CMR) in 68 CTEPH patients after PEA.

Material and methods

Study subjects

All patients undergoing PEA in our centre were included in a prospective cohort study. According to our local clinical protocol, patients underwent CPET, 6-min walk test (6MWT), right heart catheterisation (RHC) and CMR imaging before and 6 months after PEA. All patients undergoing PEA between July 2012 and January 2018 who performed CPET 6 months (±2 weeks) after PEA were enrolled in this analysis.

The study did not fall within the scope of the Medical Research Involving Human Subjects Act, since an analysis was performed based on available clinical data obtained for clinical purposes. This was confirmed by the medical ethics review committee of the VU University Medical Centre (2017.313).

Procedures

RHC (resting pulmonary haemodynamics) was performed as described previously [14]. The following variables were recorded: (mean) pulmonary artery pressure ((m)PAP), right atrial pressure, pulmonary artery wedge pressure (PAWP), heart rate and central venous oxygen saturation. Cardiac output was determined by thermodilution or the direct Fick method (indexed for body surface area: cardiac index). PVR was calculated from (80×(mPAP–PAWP)/cardiac output). Pulmonary arterial compliance was calculated as stroke volume divided by pulse pressure. (Residual) pulmonary hypertension was defined as mPAP >20 mmHg and PVR ⩾240 dyn·s·cm^{-5}, in accordance with the new proposed definition of precapillary pulmonary hypertension by the 6th World Symposium on Pulmonary Hypertension Task Force [15].

CMR was performed and analysed as described previously [14].

CPET consisted of a symptom-limited maximal incremental exercise test using a cycle ergometer [16]. Measurements consisted of continuous recording of ECG, V'_{O_2}, carbon dioxide production (V'_{CO_2}), heart rate, tidal volume, breathing frequency, expiratory oxygen and carbon dioxide pressures, peripheral oxygen saturation and intermittent recording of blood pressure. The anaerobic threshold was determined using the V-slope method [17]. Predicted maximum ventilation was based on 40×forced expiratory volume in 1 s (with minute ventilation calculated as breathing frequency times tidal volume). Reference values from the Study of Health in Pomerania (SHIP) were used [18]. The majority of CPET was performed without arterial blood sampling, therefore calculations of dead space to tidal volume ratio were not included in the analysis. Exercise intolerance was defined as a peak V'_{O_2} <80% predicted [19]. The cause of exercise limitation was determined using the flowcharts proposed by Wasserman *et al.* [20]. Five different categories were used: normal peak V'_{O_2}, cardiovascular limitation (including left ventricular failure, myocardial ischaemia, heart disease, pulmonary vascular disease), ventilatory limitation (including obstructive lung disease, restrictive lung disease, lung disease with impaired peripheral oxygenation), other (including musculoskeletal disorders, peripheral arterial disease and anaemia) and submaximal CPET.

6MWT was performed according to the 2002 American Thoracic Society (ATS) statement [21].

Single-breath carbon monoxide uptake, *i.e.* transfer factor of the lung for carbon monoxide (T_{LCO}) was determined before surgery according to the 2005 joint European Respiratory Society/ATS statement [22].

Baseline tests (RHC, CMR, CPET, 6MWT and T_{LCO}) were defined as the most recent test performed before PEA; a minority of patients performed the test while using pulmonary hypertension specific medication.

Study design and statistical analysis

The primary outcome of this study was (decreased) peak V'_{O_2} (*i.e.* persistent exercise intolerance). Secondary outcomes consisted of a variety of exercise parameters, haemodynamic parameters and CMR imaging-based right ventricular function parameters.

Data are presented as mean±SD, median (interquartile range (IQR)) or n (%). Missing data were not imputed. Normal distribution was tested by using the D'Agostino–Pearson omnibus normality test; log transformation was performed when distribution was not normal. Differences regarding continuous data were tested using unpaired t-test or paired t-test where appropriate; Wilcoxon matched-pairs signed rank test or Mann–Whitney test were used where appropriate when distribution remained not normal despite log transformation. Differences regarding categorical data were tested using Chi-squared test or Fisher's exact test. Correlation analysis was performed using Pearson correlation. Univariate and multivariate logistic regression analysis was performed to analyse preoperative parameters predicting persistent exercise intolerance.

Values of $p<0.05$ were considered to reflect statistical significance. Statistical analysis was performed using GraphPad Prism (version 8; GraphPad Software Inc, La Jolla, CA, USA) and SPSS Statistics (version 24; IBM, Armonk, NY, USA).

Results

68 patients were enrolled in the cohort analysis, including two patients with chronic thromboembolic disease without pulmonary hypertension (figure 1). Median (range) age at the time of PEA was 63 (17–79) years, and there was a slight predominance of males (57%). Median (IQR) time between CTEPH diagnosis and PEA was 153 (92–251) days. Median (IQR) body mass index (BMI) at time of diagnosis was 26.5 (24.3–29.3) $kg \cdot m^{-2}$. At the time of CTEPH diagnosis, 6% of patients were in New York Heart Association (NYHA) class I, 37% were in NYHA class II, 51% were in NYHA class III and 6% in NYHA class IV. The proportions and changes in NYHA class after PEA are shown in supplementary figure A. In addition, 23 (34%) patients were pretreated with pulmonary hypertension specific medication. The overall incidence of comorbidities was low (data not shown); eight (12%) patients had obstructive lung disease.

From baseline to 6 months after PEA all haemodynamic and CMR right ventricular indices improved significantly (table 1). Baseline RHC, CMR and CPET were defined as the last test performed before PEA. 14, nine and seven patients were using pulmonary hypertension specific medication at the time of the last RHC, CMR and CPET, respectively. Median (IQR) time between last CPET before PEA and PEA was 155 (92–232) days. The majority of CPET parameters (including circulatory and gas exchange parameters) improved, while heart rate and breathing reserve remained unchanged 6 months after PEA (figure 2 and supplementary table A).

Persistent exercise intolerance (defined as peak V'_{O_2} <80% pred) was present in 45 (66%) out of 68 patients at 6 months after PEA. According to the flowcharts by Wasserman *et al.* [20], 20 (29%) patients had exercise limitation due to cardiovascular pathology (including the only patient receiving pulmonary hypertension specific medication at the time of this re-evaluation), five (7%) patients had a primarily

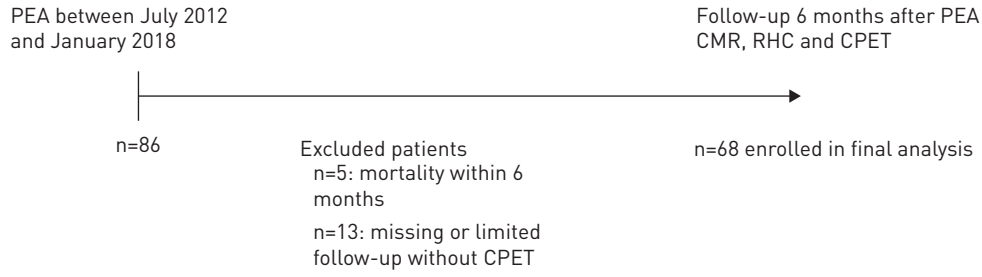

FIGURE 1 Timeline and flow chart of patient selection. PEA: pulmonary endarterectomy; CPET: cardiopulmonary exercise testing; CMR: cardiac magnetic resonance; RHC: right heart catheterisation.

TABLE 1 Comparison of haemodynamic and cardiac magnetic resonance (CMR) parameters pre-pulmonary endarterectomy (PEA) *versus* 6 months post-PEA

	Pre-PEA	Post-PEA	p-value
RHC			
mPAP mmHg	43 (33–50)	23 (18–27)	<0.001#
PVR dyn·s·cm^{-5}	551 (330–726)	176 (131–243)	<0.001#
PAWP mmHg	10.0±2.7	9.7±3.3	0.567
Cardiac index L·min^{-1}·m^{-2}	2.4 (2.1–2.8)	2.9 (2.6–3.4)	<0.001#
RAP mmHg	7 (6–10)	5 (3–6)	<0.001#
S_{vO_2} %	65 (61–70)	70 (68–74)	<0.001#
CMR imaging			
RVEF %	46 (30–55)	58 (48–63)	<0.001#
RVESVI mL·m^{-2}	43 (29–67)	24 (17–34)	<0.001#
RVEDVI mL·m^{-2}	78 (68–96)	58 (46–69)	<0.001#
LVEF %	64±8	64±7	0.663
Other			
6MWD m	418±108	482±89	<0.001
NT-proBNP ng·L^{-1}	474 (144–1372)	204 (106–365)	<0.001#

Data presented as median (interquartile range) or mean±SD, unless otherwise stated. RHC: right heart catheterisation; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; RAP: right atrial pressure; S_{vO_2}: central venous oxygen saturation; RVEF: right ventricular ejection fraction; RVESVI: right ventricular end-systolic volume index; RVEDVI: right ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide. Statistical test: paired t-test. #: parametric test performed after log-transforming data.

ventilatory limitation (including two patients with a known diagnosis of obstructive lung disease), and in nine (13%) patients the primary cause of exercise limitation was musculoskeletal or peripheral arterial disease. 11 (16%) patients had decreased peak V'_{O_2} in the context of a presumed submaximal test.

Before PEA, peak V'_{O_2} was decreased in 89% of patients, and in 62% this was primarily due to cardiovascular pathology, while in 7% this was primarily ventilatory and in 8% due to musculoskeletal or peripheral arterial disease; five (11%) patients had a decreased peak V'_{O_2} in the context of a presumed submaximal test (figure 3).

In comparison to patients with a normalised peak V'_{O_2}, mPAP and PVR were slightly, but significantly, higher in those with persistent exercise intolerance post-PEA (figure 4). However, CMR-derived right ventricular functional parameters were not different between groups (figure 4). While N-terminal pro-brain natriuretic peptide was not different between those with or without persistent exercise intolerance (166 (96–390) ng·L^{-1} *versus* 233 (115–365) ng·L^{-1}, p=0.319), 6-min walk distance (6MWD) was significantly higher in patients with normalised peak V'_{O_2} post-PEA (539±72 m *versus* 454±84 m, p<0.001).

Residual pulmonary hypertension (mPAP >20 mmHg and PVR ⩾240 dyn·s·cm^{-5}) was present in 16 (36%) out of 45 patients with persistent exercise intolerance post-PEA (RHC data were unavailable in two patients), and 75% of these patients had a primarily cardiovascular limitation during exercise. None of the patients with normalised peak V'_{O_2} after PEA had residual pulmonary hypertension (RHC data unavailable in three patients). Two patients had an increased PAWP at follow-up. PVR and diastolic pressure gradients indicated isolated post-capillary pulmonary hypertension in one patient and combined pre- and post-capillary pulmonary hypertension in the other patient. The incidence of residual pulmonary hypertension was significantly higher in patients with persistent exercise intolerance (Fisher's exact test p=0.001). Supplementary figure B illustrates that exercise intolerance can persist after PEA despite normalisation of resting haemodynamics.

In a large UK cohort, the start of pulmonary hypertension specific medication was associated with a mPAP ⩾30 mmHg after PEA [2]. Seven patients in our cohort fulfilled the criterion of mPAP ⩾30 mmHg; none of these patients had a normalised peak V'_{O_2} after PEA.

Weak correlations were observed between post-PEA peak V'_{O_2} and mPAP (Pearson R^2=0.216, p<0.001), PVR (R^2=0.090, p=0.017) and pulmonary arterial compliance (R^2=0.155, p=0.002) (figure 5). Post-PEA compliance was lower in patients with persistent exercise intolerance compared to those with normal peak V'_{O_2} post-PEA (3.5 (3.3–6.1) *versus* 3.0 (2.0–3.9) mL·mmHg^{-1}, p=0.003). A weak correlation was found

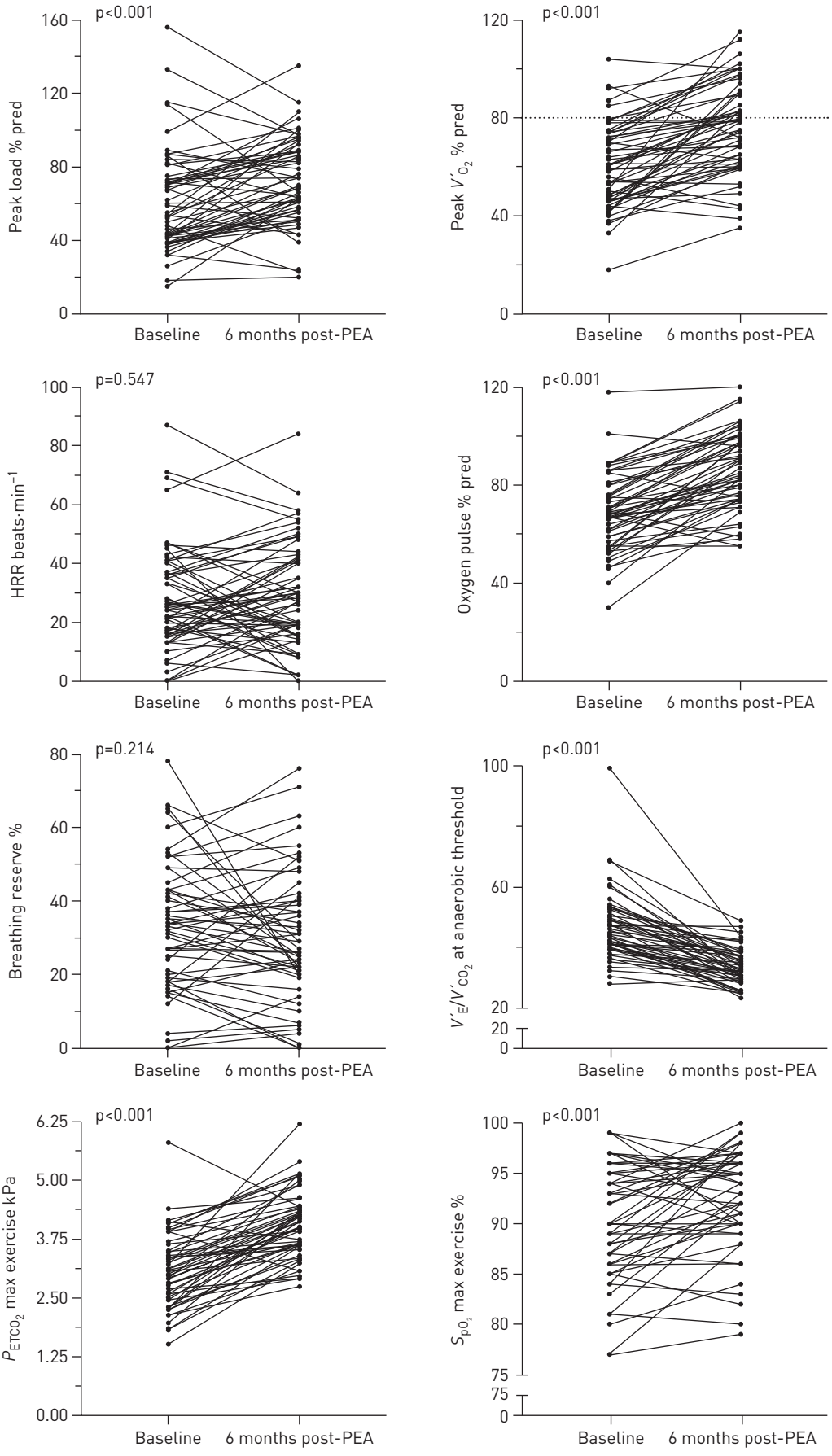
p<0.001
Peak load % pred
160
120
80
40
0
Baseline
6 months post-PEA
p<0.001
Peak V'_{O_2} % pred
120
80
40
0
Baseline
6 months post-PEA
p=0.547
HRR beats·min^{-1}
100
80
60
40
20
0
Baseline
6 months post-PEA
p<0.001
Oxygen pulse % pred
120
80
40
0
Baseline
6 months post-PEA
p=0.214
Breathing reserve %
80
60
40
20
0
Baseline
6 months post-PEA
p<0.001
V'_E/V'_{CO_2} at anaerobic threshold
100
60
20
20
0
Baseline
6 months post-PEA
p<0.001
P_{ETCO_2} max exercise kPa
6.25
5.00
3.75
2.50
1.25
0.00
Baseline
6 months post-PEA
p<0.001
S_{pO_2} max exercise %
100
95
90
85
80
75
75
0
Baseline
6 months post-PEA

FIGURE 2 Cardiopulmonary exercise testing parameters pre-pulmonary endarterectomy (PEA) compared to 6 months post-PEA. V'_{O_2}: oxygen consumption; HRR: heart rate reserve; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide; P_{ETCO_2}: end-tidal carbon dioxide tension; S_{pO_2}: peripheral oxygen saturation.

between post-PEA peak V'_{O_2} and right ventricular ejection fraction (RVEF) (Pearson R^2=0.080, p=0.043), but not with any other CMR parameter.

Analysis of other circulatory and ventilatory/gas exchange parameters measurements during CPET showed that peak oxygen pulse was lower in those with exercise intolerance compared to those with normal exercise tolerance (77.4±13.3 *versus* 99.7±10.3% pred, p<0.001). The correlation between peak V'_{O_2} and oxygen pulse was strong (Pearson R^2=0.617, p<0.001), while the correlations with minute ventilation $(V'_E)/V'_{CO_2}$ ratio at the anaerobic threshold and end-tidal carbon dioxide tension (P_{ETCO_2}) at maximal exercise were moderate to weak (Pearson R^2=0.217, p<0.001 and Pearson R^2=0.076, p=0.023, respectively).

Patients with persistent exercise intolerance after PEA were characterised before surgery with more frequent treatment with pulmonary hypertension specific medication, a higher NYHA class, a lower 6MWD and a lower T_{LCO} (supplementary table B). Preoperative pulmonary haemodynamics, CMR-based right ventricular functional parameters, and imaging characteristics (proximal *versus* distal disease) were not related to exercise intolerance after PEA (see comparison of groups and the univariate analysis). Preoperative CPET was more impaired in patients with persistent exercise intolerance after PEA (supplementary table C). Pre-surgical T_{LCO} was the only predictor of exercise intolerance after PEA in the multivariate analysis (table 2). The presence of obstructive lung disease in eight patients was not predisposing to persistent exercise intolerance after PEA nor was it predisposing to a lower T_{LCO} at baseline compared to the patients without obstructive lung disease.

Discussion

In this prospective cohort of operated CTEPH patients, 66% of patients had exercise intolerance 6 months post-PEA, despite good haemodynamic results. Exercise capacity was limited mainly by cardiovascular constraints. Although exercise intolerance was associated with the presence of residual pulmonary hypertension, the correlation between peak V'_{O_2} and mPAP or PVR 6 months post-PEA was moderate at most, and not all exercise intolerance was explained by the presence of residual pulmonary hypertension. Lower preoperative T_{LCO} was a strong predictor of persistent exercise intolerance 6 months after PEA, while presurgical haemodynamics, CMR and imaging were not predictive.

This is the first study to describe the incidence and determinants of decreased peak V'_{O_2} after PEA. Most studies on functional outcomes after PEA were based on a determination of the 6MWD [23–26]. It was shown that the presence of residual pulmonary hypertension was associated with a lower 6MWD [23–25], but conflicting results were presented regarding correlations between (changes in) 6MWD and (changes in) mPAP and/or total PVR [24–26]. More consistent correlations were reported between exercise

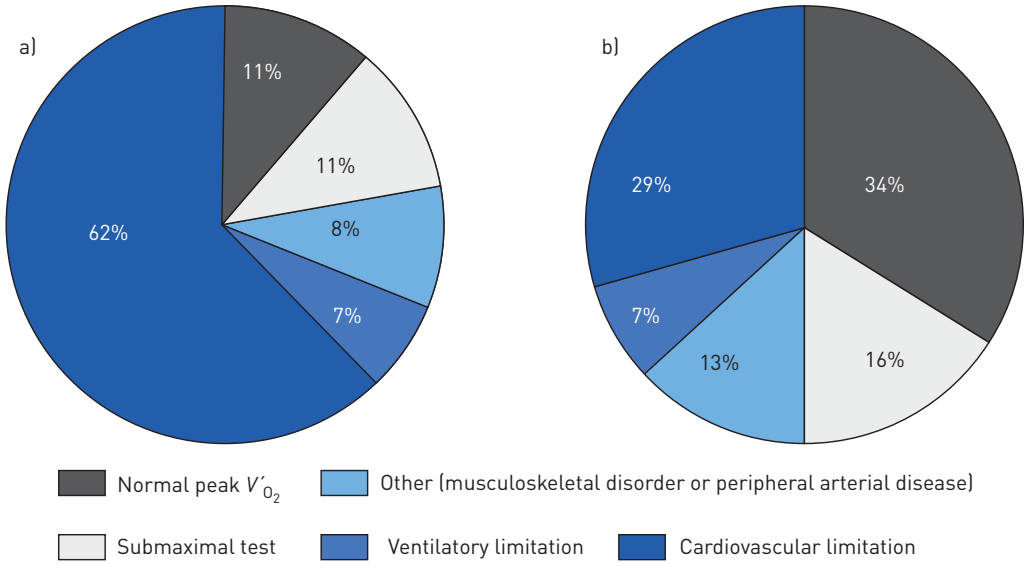

FIGURE 3 Pie charts indicating main determinants of exercise limitation a) before pulmonary endarterectomy (PEA) and b) 6 months post-PEA. V'_{O_2}: oxygen consumption.

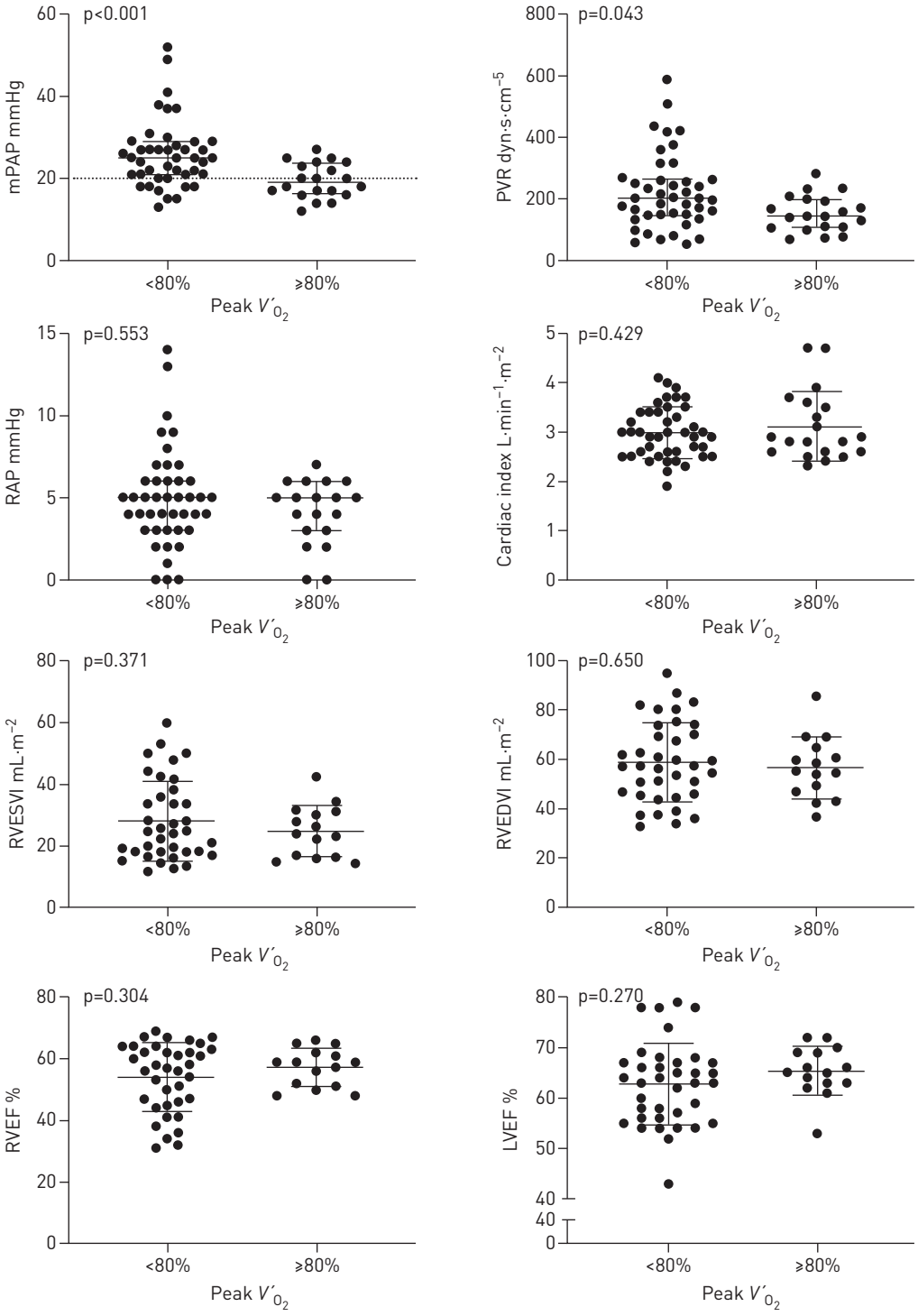

FIGURE 4 Comparison of right heart catheterisation and cardiac magnetic resonance parameters 6 months post-pulmonary endarterectomy (PEA) between those with or without persistent exercise intolerance 6 months post-PEA. Horizontal bars indicate median and interquartile range (mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), right atrial pressure (RAP)) or mean±SD (cardiac index, right ventricular end-systolic volume index (RVESVI), right ventricular end-diastolic volume index (RVEDVI), right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF)). Statistical test: unpaired t-test (after log transformation of non-normally distributed data). V'_{O_2}: oxygen consumption.

parameters and pulmonary arterial compliance [26, 27]. In a recent study, 41% of patients were reported to have persistent exercise limitation 12 months after PEA, as defined by a distance walked <400 m in a modified Bruce protocol [28]. However, the cut-off of 400 m was somewhat arbitrary, and based on the

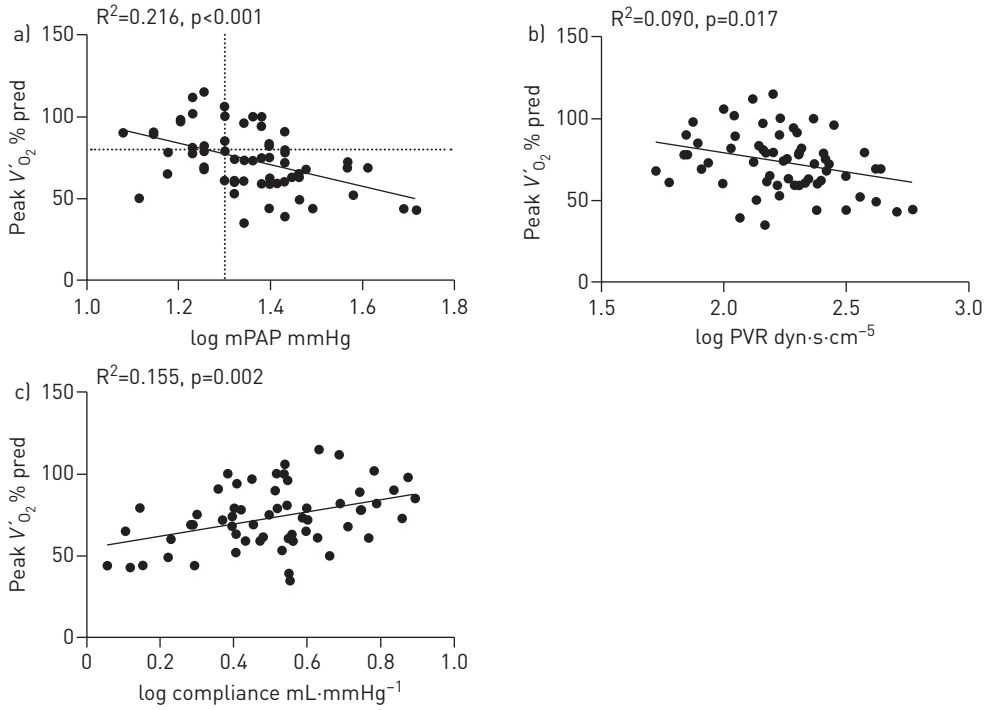

FIGURE 5 Correlation between mean pulmonary artery pressure (mPAP)/pulmonary vascular resistance (PVR)/pulmonary arterial compliance post-pulmonary endarterectomy (PEA) and peak oxygen consumption (V'_{O_2}) post-PEA. a) Correlation between log-transformed mPAP and peak V'_{O_2}. The vertical dotted line indicates mPAP 20 mmHg; the horizontal dotted line indicates peak V'_{O_2} 80% predicted. b) Correlation between log-transformed PVR and peak V'_{O_2}. c) Correlation between log-transformed pulmonary arterial compliance and peak V'_{O_2}. Pearson correlation coefficients shown, after log transformation of mPAP, PVR and compliance.

median distance walked in their previous analysis [29]. Such a fixed cut-off is probably affected by factors such as age, sex and height (*i.e.* stride length) and is therefore quite arbitrary as an indicator of exercise limitation. In addition, there is increasing discussion regarding the use of 6MWD as a biomarker and end-point in clinical trials [30], while peak V'_{O_2} determined by CPET has been shown to be a strong predictor of survival in PAH and CTEPH patients [6, 7].

The high frequency of exercise intolerance after PEA (66% in this study) contrasts with the considerably lower incidence of residual pulmonary hypertension. The question is whether in this regard exercise intolerance (decreased peak V'_{O_2}) would constitute a more optimal outcome measure of PEA than presence or absence of residual pulmonary hypertension. Moreover, it is important to consider the possible causes of exercise intolerance after PEA. We propose three possible explanations, as follows.

A likely explanation for persistent exercise intolerance is that even when resting haemodynamics normalise, exercise haemodynamics may remain abnormal post-PEA. Although we did not perform

TABLE 2 Univariate and multivariate analysis of baseline predictors for persistent exercise intolerance after pulmonary endarterectomy (PEA)

	Univariate analysis		Multivariate analysis (backward, conditional)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Time CTEPH diagnosis to PEA days	1.006 (1.000–1.013)	0.048	1.009 (1.000–1.019)	0.062
Baseline RAP mmHg	1.147 (0.982–1.338)	0.083		
Baseline 6MWD m	0.992 (0.985–0.999)	0.017		
Baseline T_{LCO} % predicted	0.915 (0.866–0.967)	0.002	0.935 (0.883–0.991)	0.023

CTEPH: chronic thromboembolic pulmonary hypertension; RAP: right atrial pressure; 6MWD: 6-min walk distance; T_{LCO}: transfer factor of the lung for carbon monoxide.

invasive haemodynamic measurements during exercise, our finding of a low exercise oxygen pulse (an index of stroke volume) is consistent with this hypothesis. Indeed, it was previously reported that the mPAP/cardiac output slope during exercise remains elevated after PEA, indicating an abnormal pulmonary vascular response and increase in right ventricular afterload during exercise [31–33]. The finding that preoperative T_{LCO} predicts persistent exercise intolerance after PEA is interesting in this context. T_{LCO} could be considered a marker of distal vasculopathy not accessible to PEA; distal vasculopathy and/or vascular remodelling could increase right ventricular afterload, especially during exercise, and thereby explain persistent exercise intolerance. In contrast, in patients with chronic thromboembolic disease, significant improvements in exercise RHC and normalised mPAP/cardiac output slope have been shown [34]. Exercise RHC was not performed in our analysis, but would certainly have been useful in determining whether abnormal exercise haemodynamics are a major factor. Correlations between peak V'_{O_2} and resting PVR and mPAP were only weak to moderate in strength, but exercise mPAP and PVR are probably not predicted by resting values. In a previous cohort study of PAH and inoperable CTEPH patients, exercise cardiac index was the only good predictor of peak V'_{O_2}, whereas resting mPAP and PVR were not strongly related to peak V'_{O_2} [7]. However, our observation of a low exercise oxygen pulse is not exclusively explained by an abnormal increase in afterload during exercise. An alternative explanation would be a low exercise stroke volume due to afterload independent right ventricular dysfunction, for example related to changes of intrinsic right ventricular contractility (*e.g.* due to irreversible right ventricular damage or deconditioning) or diastolic dysfunction, for example caused by right ventricular fibrosis. While CMR-based right ventricular function significantly improved after PEA, RVEF was only weakly correlated with peak V'_{O_2} (comparable to previous research in PAH [35]). Right ventricular end-diastolic volume index or right ventricular end-systolic volume index did not correlate with peak V'_{O_2}, not even in the subgroup of patients with primarily cardiovascular limitation (data not shown). This discrepancy might again be explained by a poor correlation between resting and exercise measurements of right ventricular dimensions.

A third explanation for exercise intolerance and a low exercise oxygen pulse is impaired peripheral oxygen extraction due to peripheral muscle dysfunction or deconditioning. The importance of deconditioning to explain exercise intolerance after PEA cannot be deduced from our data. However, as peak V'_{O_2} has been shown to improve after exercise training in severe PAH and inoperable CTEPH patients [36], it is likely that this also holds true for operated patients and underlines the importance of a structured rehabilitation and exercise training programme after PEA. Since a structured rehabilitation/exercise training programme was not part of standard care after PEA, no conclusions regarding the role of deconditioning can be drawn.

Whether persistent dead space ventilation and ventilatory (in)efficiency are determining factors of exercise capacity after PEA is questionable. We made no direct measurements of dead space, but V'_E/V'_{CO_2} at the anaerobic threshold (a marker of ventilatory efficiency) was only weakly correlated with peak V'_{O_2}. Surprisingly, P_{ETCO_2} was similar between patients with a normal exercise tolerance and patients with exercise intolerance. Moreover, a ventilatory limitation as the primary cause of exercise intolerance was only present in 7% of patients; while eight patients had a known diagnosis of obstructive lung disease, this led to a ventilatory limitation as the primary cause of exercise intolerance in only two patients.

Comorbidities did not seem to be a major explanation of exercise capacity in our cohort of patients. Median BMI was slightly increased, but not different between patients with normal or low exercise capacity. Overall prevalence of comorbidities was low and similar in patients with or without exercise intolerance. The one exception is left ventricular function. Although median left ventricular ejection fraction (LVEF) was normal and comparable between groups, a larger number of patients with exercise intolerance had a slightly decreased LVEF (figure 4). However, because PAWP was normal in both patient groups, it seems unlikely that left ventricular dysfunction (systolic or diastolic) was a relevant factor explaining exercise intolerance.

Preoperative prediction of postoperative exercise intolerance may help to select patients suitable for surgery and may also help to manage patients' expectations from the procedure. Lower preoperative T_{LCO} was a strong predictor of persistent exercise intolerance 6 months after PEA, while presurgical haemodynamics, CMR and imaging were not predictive. This adds to the existing data on T_{LCO} and outcomes after PEA in CTEPH. In a French cohort, pre-PEA T_{LCO} predicted haemodynamic improvement (PVR decline) after PEA; an association with post-PEA mortality could not be found, perhaps because of the low mortality rates after PEA [37]. Another cohort analysis found a lower T_{LCO}/alveolar ventilation ratio to be a predictor for poor long-term survival and a smaller decline in PVR after PEA [38]. While these previous publications provide evidence regarding pre-PEA T_{LCO} and haemodynamic response, we add evidence of an association between pre-PEA T_{LCO} and the functional response after PEA. T_{LCO} probably reflects distal vasculopathy and (post-)capillary remodelling, as previously shown to be present in CTEPH [39].

Since in our cohort 13 out of 86 patients did not undergo follow-up investigations due to logistical and/or medical reasons, there is a potential selection bias in our study. In our centre, approximately two-thirds of CTEPH patients receive surgery. This is in agreement with rates of operability in a large international CTEPH registry [1]. In addition, outcomes after PEA (survival and haemodynamic outcomes) were comparable to other intermediate-size CTEPH centres [1].

16% of patients had a presumed submaximal test as the explanation for the decreased peak V'_{O_2}. This constitutes a minority and did not skew the results of our analysis. Since chronotropic incompetence is often present in pulmonary hypertension [7, 35], applying the criteria for a maximal test may result in labelling a test as submaximal, while in reality a cardiovascular limitation is present.

We did not analyse the consequences of exercise intolerance for quality of life. This would have provided more insight into the clinical importance of exercise intolerance post-PEA and could have indicated whether exercise capacity would be a more useful outcome measure after PEA instead of resting haemodynamics. Previous studies showed clinically significant improvements in all domains after PEA, but in the physical domain scores remained behind in comparison with reported normal scores [40, 41].

In conclusion, although PEA is the treatment of choice in eligible CTEPH patients and leads to excellent haemodynamic improvements and survival, exercise intolerance was present in two-thirds of patients after PEA. While persistent exercise intolerance was mainly determined by a cardiovascular limitation, not all exercise intolerance could be explained by the presence of residual pulmonary hypertension. While pre-PEA haemodynamics, right ventricular function and imaging do not predict persistent exercise intolerance after PEA, a lower preoperative T_{LCO} serves as a strong predictor of persistent exercise intolerance after PEA. T_{LCO} thereby provides an easily accessible marker to predict the functional response to PEA in CTEPH.

Although additional research is needed regarding its impact on survival and need for additional treatment after PEA, CPET provides clinically meaningful outcome parameters in CTEPH after PEA.

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