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Long-term effects of pulmonary endarterectomy on pulmonary hemodynamics, cardiac function, and exercise capacity in chronic thromboembolic pulmonary hypertension

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BACKGROUND: Long-term changes in exercise capacity and cardiopulmonary hemodynamics after pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) have been poorly described.

METHODS: We analyzed the data from 2 prospective surgical CTEPH cohorts in Hammersmith Hospital, London, and Amsterdam UMC. A structured multimodal follow-up was adopted, consisting of right heart catheterization, cardiac magnetic resonance imaging, and cardiopulmonary exercise testing before and after PEA. Preoperative predictors of residual pulmonary hypertension (PH; mean pulmonary artery pressure > 20 mm Hg and pulmonary vascular resistance ≥2 WU) and long-term exercise intolerance (VO_{2max} < 80%) at 18 months were analyzed.

RESULTS: A total of 118 patients (61 from London and 57 from Amsterdam) were included in the analysis. Both cohorts displayed a significant improvement of pulmonary hemodynamics, right ventricular (RV) function, and exercise capacity 6 months after PEA. Between 6 and 18 months after PEA, there were no further improvements in hemodynamics and RV function, but the proportion of patients with impaired exercise capacity was high and slightly increased over time (52%-59% from 6 to 18 months). Long-term exercise intolerance was common and associated with preoperative diffusion capacity for carbon monoxide (DLCO), preoperative mixed venous oxygen saturation, and postoperative PH and right ventricular ejection fraction (RVEF). Clinically significant RV deterioration (RVEF decline > 3%; 5 [9%] of 57 patients) and recurrent PH (5 [14%] of 36 patients) rarely occurred beyond 6 months after PEA. Age and preoperative DLCO were predictors of residual PH post-PEA.

CONCLUSIONS: Restoration in exercise tolerance, cardiopulmonary hemodynamics, and RV function occurs within 6 months. No substantial changes occurred between 6 and 18 months after PEA in the Amsterdam cohort. Nevertheless, long-term exercise intolerance is common and associated with postoperative RV function.

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Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by persistent occlusion of the pulmonary arteries by organized thromboembolic material and subsequent remodeling of the pulmonary vasculature, leading to increased vascular resistance (PVR) and pressure overload. If left untreated, this results in right ventricular (RV) dilatation, failure, and death.[1] Pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH, resulting in hemodynamic improvement and restoration of RV dimensions within months.[2-12] Although PEA is potentially curative, postoperative residual pulmonary hypertension (PH) is common.[2,4,10,13-15] Residual PH early after PEA has been described in up to 50% of patients[16] and is thought to be the result of a number of factors, including incomplete removal of thrombi and co-existent microvascular disease.[17]

However, clinically relevant residual PH is more complex than rather an elevated pressure after surgery, as prior studies report conflicting data on short-term postoperative hemodynamics and long-term survival.[4,13,16,18-21] In addition, whether there is any long-term postoperative hemodynamic or functional evolution has not been thoroughly investigated yet.[11,22] In the past, different definitions were used for residual PH, few data were systemically acquired, and center-to-center variation was left unstudied.[2,16,21,23] As such, the definition of residual PH after treatment remains unanswered.

To address these questions, we conducted a binational cohort study and analyzed long-term follow-up measurements of invasive pulmonary hemodynamics, cardiac magnetic resonance (CMR) imaging, and cardiopulmonary exercise testing (CPET) in London (Hammersmith Hospital) and Amsterdam (Amsterdam UMC). The objective of this study was to provide more insight into the evolution of long-term cardiopulmonary and functional effects after PEA.

Methods

Study subjects

In this study, patients were selected from 2 prospective observational cohort studies of adult patients diagnosed with CTEPH who underwent PEA between 2012 and 2020 in the tertiary referral centers for CTEPH in Hammersmith Hospital, United Kingdom, and Amsterdam UMC, the Netherlands. Patients managed at Hammersmith Hospital underwent surgery in the National PEA Centre at Royal Papworth Hospital, Cambridge, UK. Patients unable to perform a baseline CPET or CMR imaging were excluded. Patients were followed according to a local standardized guideline-based protocol. In the London cohort, right heart catheterization (RHC) and CMR were performed before PEA and 6 months after PEA, and follow-up measurements of CPET were made at baseline and at 6 and 18 months after PEA. In the Amsterdam cohort, patients with baseline RHC and long-term follow-up were selected. Patients underwent follow-up measurements consisting of RHC, CMR imaging, and maximal CPET before PEA and at 6 and 18 months after treatment. Some of the patients participated in a previous study published.[24]

Long-term follow-up period consisted of measurements at 18 months after surgery. In both centers, CTEPH was diagnosed according to the most recent guidelines available at the time of inclusion.[25] Residual PH at 6 and 18 months after PEA was

defined as a mean pulmonary artery pressure (mPAP) > 20 mm Hg and PVR ≥2 WU.[1] Renal disease was defined as an glomerular filtration rate < 60 ml/min or the presence of known chronic renal disease. Chronic obstructive pulmonary disease (COPD) was noted in patients with a known history of COPD or with a forced expiratory volume in 1 second (FEV_1) decline consistent with the diagnosis of COPD. The study at Hammersmith Hospital was approved under the research ethics committee number 17/LO0563. In Amsterdam, the study did not fall within the scope of the Medical Research Involving Human Subjects Act since the diagnostic procedures were performed for clinical purposes (confirmed by the Medical Ethics Review Committee of the VU University Medical Center 2012.288).

Surgery

The PEA procedure has been described previously.[2,23] In the London cohort, patients were referred and discussed at the multidisciplinary PEA team at Royal Papworth Hospital (national single center for CTEPH treatment), Cambridge, UK. In the Amsterdam cohort, patients were discussed in the Amsterdam UMC expert multidisciplinary PH team. Operability was based on the accessibility of pulmonary artery obstructions, imbalance between increased PVR, and amount of accessible occlusions, suggesting microvascular disease and comorbidities.

Right heart catheterization

Hemodynamic assessment was performed using an air-filled balloon-tipped 7 F Swan-Ganz TD catheter (131F7; Edwards Lifesciences, Irvine, CA) in London and a fluid-filled balloon-tipped 7 F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp., Irvine, CA) in Amsterdam. During continuous electrocardiographic monitoring, mean right atrial pressure (mRAP), mean pulmonary artery pressure (mPAP), and pulmonary artery wedge pressure (PAWP) were recorded, and mixed venous oxygen saturation (SvO_2) was measured. All pressure measurements were performed at end-expiration. In case of large intrathoracic pressure changes of the PAWP curve during the respiratory cycle, an average over at least 3 to 4 respiratory cycles was obtained. Cardiac output was determined by thermodilution or the direct Fick method. PVR [WU] was calculated as (mPAP − PAWP)/cardiac output.[26]

Cardiac MRI

Cardiac MRI was performed on a 1.5 T Aera scanner (Siemens Healthcare, Erlangen, Germany) in London and a 1.5 T Avanto or Sonata scanner (Siemens Healthcare, Erlangen, Germany) in Amsterdam. A short-axis stack was performed at breath-hold per slice, with a slice thickness and interslice gap of 5 mm. RV and left ventricular volumes and masses were determined by manually drawing endocardial and epicardial contours at end diastole and end systole using commercially available software (Circle CVI42).[26] Ejection fraction was calculated for both ventricles as ejection fraction = (EDV − ESV)/EDV * 100%. Ventricular volumes were indexed for body surface area. RV deterioration was defined as a change of −3% in RVEF.[27,28]

Exercise

A maximal CPET in upright position using an electromagnetically braked cycle-ergometer (Ergoline GmbH, Bitz, Germany) according to the American Thoracic Society guidelines was performed.[29] Oxygen consumption ($V'O_2$), carbon dioxide production ($V'CO_2$), heart rate, breathing frequency, expiratory O_2 and CO_2 pressures, peripheral oxygen saturation, and work load were recorded continuously. O_2 pulse at peak was computed from the formula $VO_{2\ peak}/HR_{\ peak}$. The anaerobic threshold was determined using the V-slope method.[30] Reference values from the Study of Health in Pomerania were used.[31] Exercise intolerance was defined as a peak VO_2 < 80% predicted.[32]

Statistical analysis

Data were presented as mean (standard deviation) for normally distributed data, median (25th-75th percentiles) for not normally distributed data, or number of patients (%). All continuous variables were tested for normal distribution by carefully assessing the mean, median, and standard deviation. Data that failed the normal distribution were log- (mRAP, PVR, brain natriuretic peptide, N-terminal pro-brain natriuretic peptide) or square root (pulmonary arterial compliance) transformed for analysis. Comparisons of characteristics before and 6 months after PEA and between 6 and 18 months after PEA were performed using paired *t*-test with Bonferroni correction, where 0.05 was divided by the number of comparisons being made to determine statistical significance. Categorical variables are presented as frequencies and percentages. For comparison of categorical variables between the groups, Pearson's chi-square test or Fisher's exact test was used, if the number of cases was less than 5 in any group. Previously reported risk factors for residual PH and exercise limitation after surgery in CTEPH and all potential relevant predictors were identified from the univariate analyses with a p value of < 0.10 and were included in a multivariable backward stepwise logistic regression model. Univariate significant variables were assessed for collinearity using the variance inflation factor.

Missing data were not imputed. A p value of < 0.05 was considered statistically significant. Statistical analyses were performed using R software version 3.6.3.

Results

Baseline characteristics

As indicated in the flowchart (Figure 1), CTEPH patients who underwent PEA between 2012 and 2020 with available long-term follow-up were included at both centers. Included in the analysis were 61 patients in London and 57 patients in Amsterdam. Baseline characteristics are presented in Table 1. The overall cohort of operated CTEPH patients in the same time frame did not significantly differ from the included cohort of patients in terms of baseline characteristics and postoperative hemodynamics (Table S1a and b). The mean age at CTEPH diagnosis was 53 (16) years in the London cohort and 59 (12) in Amsterdam (p < 0.013), with a slight predominance of males in both groups. The median time from the onset of symptoms to diagnosis was 16 months in both cohorts.

Most frequently observed comorbidities were systemic hypertension, history of cancer, and thrombophilic disorders. At baseline, London patients showed more compromised cardiopulmonary hemodynamics and functional impairments as indicated by a higher PVR, mRAP, RV dimensions and a lower CI, DLCO, 6-minute walking distance (6MWD), and peak

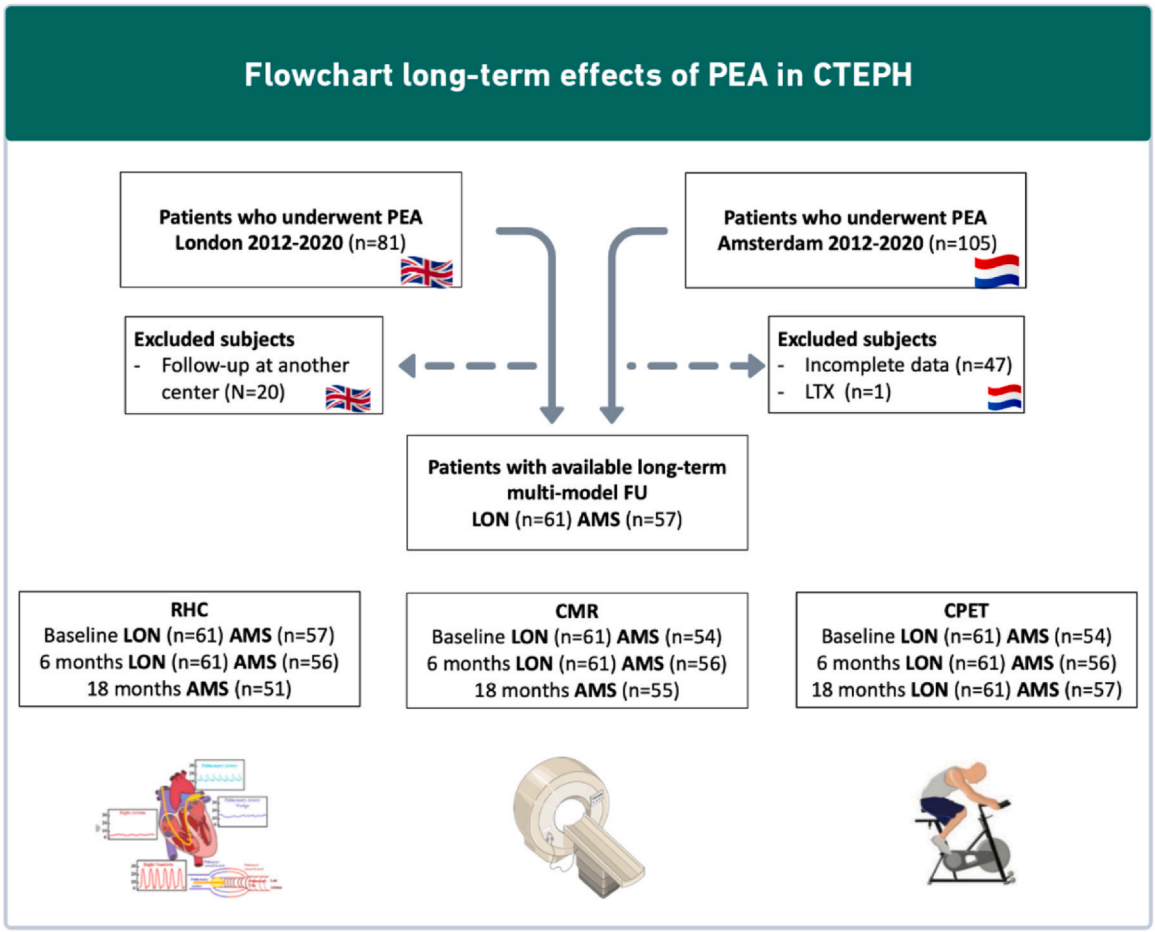

Figure 1 Flowchart.

oxygen uptake (VO_{2max}). Accordingly, after baseline cardiopulmonary and functional measurements, PH-specific therapy was more often prescribed in the London cohort.

Change in invasive pulmonary hemodynamics after PEA

PEA resulted in early hemodynamic improvements in both groups (Figure 2, Figure S1) as reflected by significant improvements in measures of RV afterload (i.e., mPAP, PVR) and a subsequent increase in cardiac index (Figure S1**,** from 2.2 [0.6] to 2.7 [0.7] in London and from 2.5 [0.7] to 3.1 [0.6] liter/min/m^2 in Amsterdam, both $p < 0.0001$) and SvO_2 (from 65 [8] to 70 [7]%, $p < 0.0001$ in London and from 66 [8] to 69 [5]%, $p = 0.007$ in Amsterdam) at 6 months. In addition, mRAP decreased (from 9 [6-13] to 6 [3-8] mm Hg in London and from 7 [5-10] to 5 [3-6] mm Hg in Amsterdam, both $p < 0.0001$), whereas no change in PAWP was observed before and after surgery (Figure S1). No further hemodynamic improvement was observed between 6 and 18 months after PEA in the Amsterdam cohort.

Cardiopulmonary effects of PEA

In line with the hemodynamic improvements, we also observed improved RV function and dimensions 6 months after PEA (Figure 3) as indicated by an improved RV function (RVEF increased from 39 [14] to 54 [9]% in London and from 43 [14] to 54 [9]% in Amsterdam both $p < 0.0001$) and RV dilation (indexed right ventricular end-diastolic volume decreased from 101 [28] to 72 [21] ml/m^2 in London and from 88 [27] to 64 [16] ml/m^2 in Amsterdam, both $p < 0.0001$). LV dimensions and function did not change during follow-up (Figure S2). Improvements in RV function and dilation were retained between 6 and 18 months after PEA. In addition, RV deterioration (RVEF decline >3%) occurred in only 5 (9%) of 57 patients at 18 months.

Residual PH

Residual PH 6 months after PEA was present in 50 (42%) of 118 patients; 29 (48%) in London compared with 21 (37%) patients in Amsterdam. Patients with residual PH were older, had more often a history of systemic hypertension, a low DLCO, and worse 6MWD (Table 2). At 18-month follow-up, patients with persistent PH had a worse hemodynamic profile (Figure 2). Similar results were seen in long-term exercise function in patients with residual PH compared to no PH at 18 months after PEA (Figures 4 and S3). After 18 months of follow-up, additional spontaneous hemodynamic improvement (mPAP < or >20 mm

Table 1 Baseline characteristics

	London	Amsterdam	*p* value
General	*n* = 61	*n* = 57	
Age (years)	53 (16)	59 (12)	0.013
Male gender, *n* (%)	36 (59)	32 (56)	0.90
BMI (kg/m^2)	28 (6)	27 (5)	0.59
Current or previous smoker, *n* (%)	23 (38)	27 (47)	0.29
Time from onset symptoms to diagnosis (months)	16.2 [9.7-26.8]	16.3 [10.5-31.8]	0.62
Comorbidities, *n* (%)			
DM	4 (7)	4 (7)	1.0
Hypertension	12 (20)	15 (26)	0.52
Ischemic heart disease	3 (5)	3 (5)	1.0
Renal disease	2 (3)	1 (2)	1.0
COPD	2 (3)	4 (7)	0.61
History of cancer	6 (10)	3 (5)	0.58
Thrombophilic disorder	4 (7)	5 (9)	1.0
Residual PH 6 months post-PEA, *n* (%)	29 (48)	21 (37)	< 0.001
PH medication (*n*)	25	5	< 0.001
NYHA Fc, (*n*)			
I/II/III/IV	0/9/49/3	1/27/25/4	< 0.001
NT-proBNP (ng/ml)	-	308 [103-1,276]	-
BNP (ng/ml)	123 [47-511]	-	-
6MWD (m)	284 (138)	434 (103)	0.023
Angiographic obstruction, *n* (%)[a]			0.60
Main PA	10 (16)	6 (11)	
Lobar	24 (40)	26 (46)	
Segmental	27 (44)	25 (43)	
RHC			
mPAP (mm Hg)	43 (13)	42 (11)	0.54
PVR (WU)	8.2 [4.9-12.6]	6.5 [4.2-9.8]	0.04
Cardiac index (liter/min/m^2)	2.2 (0.6)	2.5 (0.7)	0.005
PAWP (mm Hg)	10 (3)	10 (3)	0.72
mRAP (mm Hg)	9 [6-13]	7 [5-10]	0.026
SvO_2 (%)	64 (8)	65 (8)	0.50
PAC (ml/mm Hg)	1.21 [0.84-1.76]	1.58 [0.86-2.16]	0.16
CMR			
RVEDVi (ml/m^2)	101 (28)	88 (26)	0.008
RVESVi (ml/m^2)	64 (29)	53 (27)	0.047
RVEF (%)	39 (14)	43 (14)	0.17
SVi (ml/m^2)	36 (10)	37 (9)	0.83
CPET			
VO_{2max} (% pred)	51 (17)	60 (19)	0.008
VO_2 (ml/kg/min)	13 (5)	14 (4)	0.18
RER	1.1 (0.1)	1.0 (0.1)	0.03
Peak O_2 pulse (% pred)	60 (18)	66 (16)	0.069
VE/VCO_2 at AT	52 (11)	47 (11)	0.006
Peak work load max (% pred)	40 (18)	46 (22)	0.10
Peak heart rate (% pred)	84 (14)	88 (12)	0.12
SpO_{2max} (%)	93 (4)	91 (5)	0.002

6MWD, 6-minute walking distance; BMI, body mass index; CI, cardiac index; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DM, diabetes mellitus; mPAP, mean pulmonary arterial hypertension; mRAP, mean right atrial pressure; *n*, number of patients; NT-proBNP, N-terminal probrainnatriuretic peptide; NYHA Fc, New York Heart Association Functional Classification; O_2 pulse, oxygen pulse; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RER, respiratory exchange ratio; RHC, right heart catheterization; RVEDVi, indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVi, indexed right ventricular end-systolic volume; SpO_2, maximum peripheral saturation; SVi, indexed stroke volume; SvO_2, mixed venous oxygen saturation; VO_{2max}, maximum oxygen uptake; VE/VCO_2 at AT, minute ventilation/carbon dioxide production at anaerobic threshold.

Data are presented as mean (SD), median [interquartile range], or %.

Statistical tests: unpaired *t-test*.

[a]Most proximal vascular lesions.

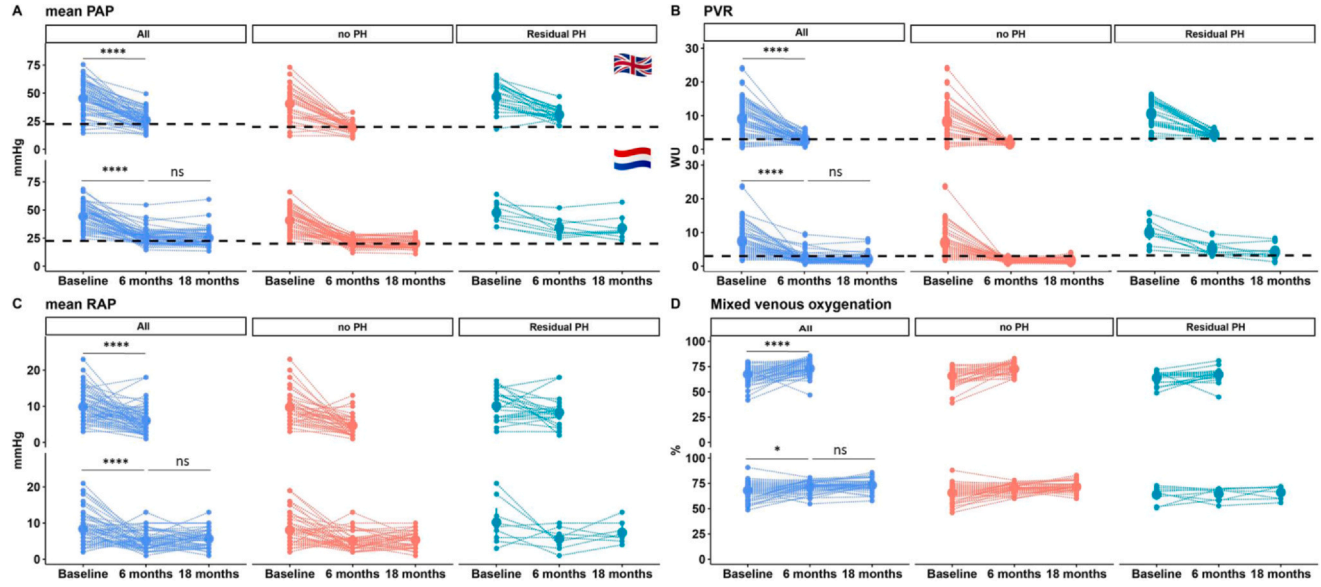

Figure 2 Long-term invasive pulmonary hemodynamics. Long-term changes in (A) mPAP, (B) PVR, (C) mRAP, (D) SvO_2. Data presented as individual data points. No PH: patients without residual pulmonary hypertension 6 months after PEA; residual PH: patients with residual pulmonary hypertension 6 months after PEA; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; PEA, pulmonary endarterectomy. Statistical tests are shown for the whole group: paired *t*-test with Bonferroni correction. The dashed line represents the upper limit of normal for precapillary pulmonary hypertension. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$.

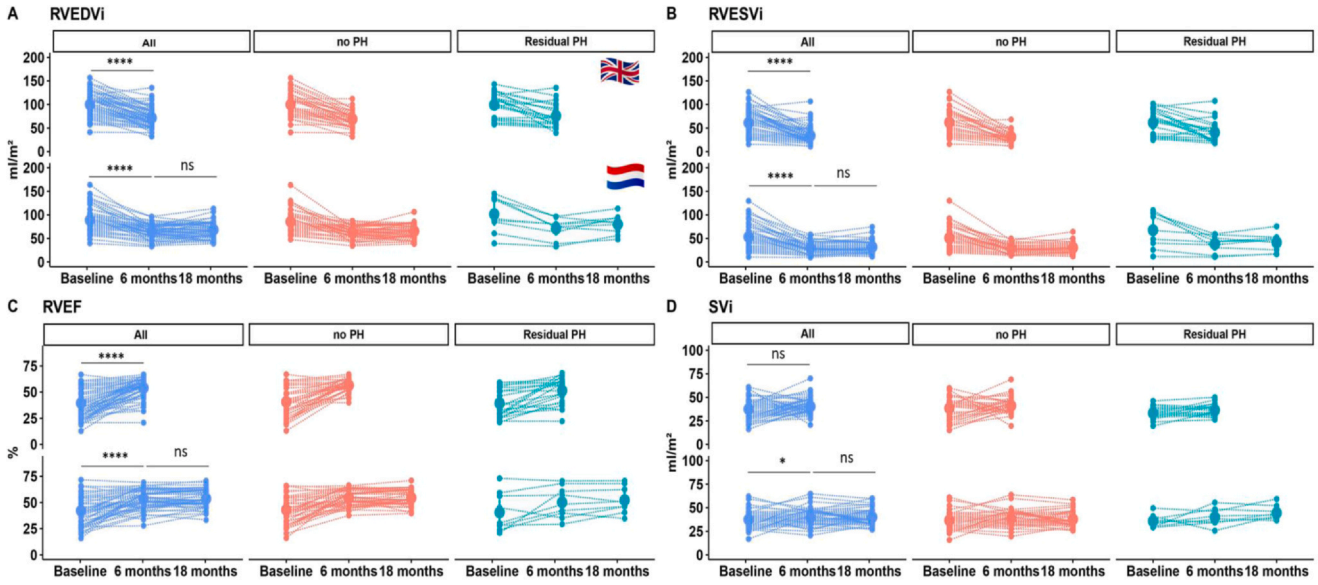

Figure 3 Long-term changes in CMR measures of RV function and morphology. Changes in (A) indexed RVEDV, (B) indexed RVESV, (C) RVEF (D) indexed SV. Data presented as individual data points. No PH: patients without residual pulmonary hypertension 6 months after PEA; residual PH: patients with residual pulmonary hypertension 6 months after PEA; PEA, pulmonary endarterectomy; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVEF, right ventricular ejection fraction; SV, stroke volume. Statistical tests are shown for the whole group: paired *t*-test with Bonferroni correction. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$.

Hg, but PVR < 2 WU) was observed in 4 of the 21 patients in Amsterdam (Table S2). At 18 months of follow-up, a moderate increase of PVR was observed, which resulted in 5 new-onset residual PH patients (patient 1 from 2.5 to 2.6 WU, patient 2 from 1.9 to 3.0 WU, patient 3 from 0.9 to 3.9 WU, patient 4 from 1.7 to 2.5 WU, and patient 5 from 1.5 to 2.7 WU). After baseline cardiopulmonary and functional measurements, PAH-targeted therapy was initiated in 25 patients (41%) in London and in 5 (9%) patients in Amsterdam. Between 6 and 18 months, 8 patients in the

Table 2 Baseline characteristics of Patients With Residual PH post-PEA

	Residual PH ($n = 50$)	No PH ($n = 66$)[a]	p value
Age (years)	61 (12)	52 (15)	0.001
Male gender, *n* (%)	25 (50)	42 (64)	0.20
BMI (kg/m^2)	28 (6)	28 (5)	0.84
Comorbidities, *n* (%)			
DM	3 (6)	5 (8)	1.0
Hypertension	16 (32)	9 (14)	0.031
Ischemic heart disease	3 (6)	3 (5)	1.0
Renal disease	2 (3)	1 (2)	1.0
COPD	2 (4)	3 (5)	1.0
History of cancer	3 (6)	6 (9)	0.73
Thrombophilic disorder	4 (8)	4 (6)	0.72
NYHA Fc (*n*)			0.11
I/II/III/IV	1/12/36/1	0/22/38/6	
6MWD (m)	276 [180-388]	389 (122)	0.001
DLCO (%)	62 (12)	67 (11)	0.035
BNP (ng/ml) - *(London cohort)*	149 [64-597]	98 [28-354]	0.23
NT-proBNP (pg/ml) - *(Amsterdam cohort)*	344 [142-1,392]	428 [109-1,364]	0.92
RHC			
mPAP (mm Hg)	44 (11)	40 (13)	0.31
PVR (WU)	7.9 [4.9-12.9]	7.1 [4.4-11.0]	0.18
Cardiac index (liter/min/m^2)	2.3 (0.6)	2.4 (0.7)	0.29
PAWP (mm Hg)	10 (3)	10 (3)	0.53
mRAP (mm Hg)	9 [6-13]	9 [6-11]	0.68
SvO_2 (%)	64 (7)	65 (9)	0.58
CMR			
LVEF (%)	63 (9)	60 (9)	0.071
RVEDVi (ml/m^2)	96 (30)	95 (26)	0.84
RVESVi (ml/m^2)	60 (30)	58 (27)	0.82
RVEF (%)	40 (14)	41 (14)	0.67
SVi (ml/m^2)	35 (7)	37 (11)	0.20
CPET			
VO_{2max} (% pred)	55 (15)	55 (20)	0.93
VO_2 (ml/kg/min)	13 (4)	14 (5)	0.17
RER	1 (0.1)	1.1 (0.1)	0.06
Peak O_2 pulse (% pred)	64 (15)	62 (19)	0.42
VE/VCO_2 at AT	51 (10)	49 (12)	0.35
Peak work load (% pred)	41 (17)	38 [26-55]	0.79
Peak heart rate (% pred)	85 (14)	86 (13)	0.63
SpO_{2max} (%)	92 (5)	92 (4)	0.39

6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DLCO, diffusing capacity for carbon monoxide; DM, diabetes mellitus; mPAP, mean pulmonary arterial hypertension; mRAP, mean right atrial pressure; *n*, number of patients; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA Fc, New York Heart Association Functional Classification; O_2 pulse, oxygen pulse; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RER, respiratory exchange ratio; RHC, right heart catheterization; RVEDVi, indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVi, indexed right ventricular end-systolic volume; SpO_2, maximum peripheral saturation; SVi, indexed stroke volume; SvO_2, mixed venous oxygen saturation; VE/VCO_2 at AT, minute ventilation/carbon dioxide production atanaerobic threshold; VO_{2max}, maximum oxygen uptake.

Data are presented as mean (SD), median [interquartile range], or %.

Statistical tests: unpaired *t*-test.

[a]Total of 116 patients instead of 118 due to missing invasive hemodynamic data (mPAP and/or PVR) at 6 months in 2 patients in the Amsterdam cohort.

London cohort were treated with PAH therapy, while in Amsterdam, 5 patients were on therapy. None of the patients underwent repeated surgery or balloon pulmonary angioplasty (BPA) during the entire follow-up.

Long-term cardiopulmonary exercise test results after PEA exercise tolerance improved 6 months after PEA (Figure 4, Table S6, Figure S3). Patients achieved a significantly higher peak oxygen uptake (peak VO_2) and peak work load and, as well as a higher peak oxygen pulse (O_2 pulse). In addition, ventilatory efficiency and gas exchange improved, reflected by a significant decrease in the ventilatory equivalents for carbon dioxide at the anaerobic threshold (VE/VCO_2 at AT from 52 [11] to 41 [7] in London and from 47 [11] to 35 [7] in Amsterdam, both $p < 0.0001$) and an increase in peak saturation

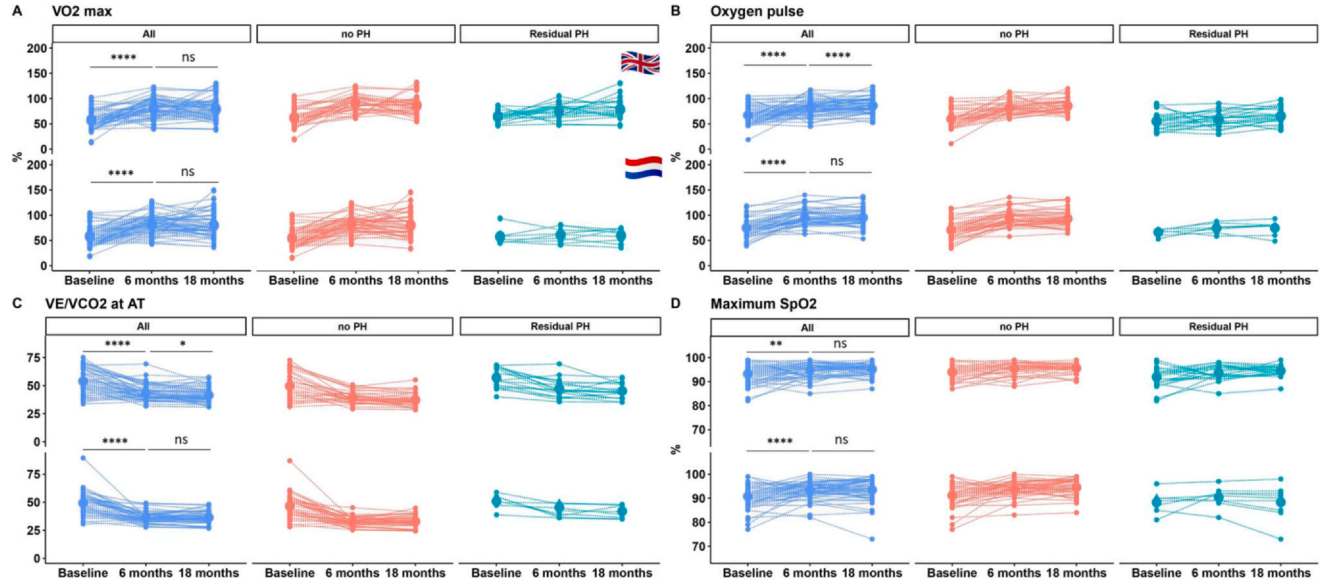

Figure 4 Long-term changes in exercise capacity. Changes in (A) VO_{2max}, (B) oxygen pulse, (C) VE/VCO_2 on anaerobic threshold, (D) maximum SpO_2. No PH: patients without residual pulmonary hypertension 6 months after PEA; PEA, pulmonary endarterectomy; residual PH: patients with residual pulmonary hypertension 6 months after PEA; VO_{2max}, maximum oxygen uptake; VE/VCO_2, minute ventilation/carbon dioxide production; SpO_2, maximum peripheral saturation. Statistical tests are shown for the whole group: paired *t*-test with Bonferroni correction. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $***p < 0.0001$.

(SpO_{2max} increased from 93 [4] to 95 [3] $\%p = 0.007$ in London and from 91 [5] to 93 [4], $\%p = 0.002$ in Amsterdam). Between 6 and 18 months, after PEA, further restorations were observed in peak work load (from 60 [17] to 71 [24], $\%p = 0.002$), O_2 pulse (from 75 [16] to 84 [17], $\%p < 0.0001$), and VE/VCO_2 at AT (from 41 [7] to 39 [7], $p = 0.048$) in London patients. Persistent exercise intolerance (defined as $VO_{2max} < 80\%$ pred) was present in 61 (52%) of 118 patients at 6 months and increased to 70 (59%) patients at 18 months after surgery (Table 2). Patients with persistent exercise intolerance had worse baseline cardiopulmonary hemodynamics and lower DLCO compared with patients without exercise intolerance at 18 months (Table 2). Residual PH was present in 35 (50%) of 70 patients with persistent exercise intolerance compared to 15 (32%) of 48 patients without persistent exercise intolerance (Table 4, $p = 0.057$). In addition, 6 months after PEA, patients with long-term exercise limitation still displayed worse hemodynamics, right ventricular function, and functional impairment. Complications postsurgery were not different between patients with or without long-term exercise limitation. Reperfusion edema was present in 8 patients, resurgery in 7 patients, and respiratory tract infection in 11 patients (Table 4).

Relation between clinical characteristics and residual PH and exercise intolerance

Baseline demographics, comorbidities, and cardiopulmonary hemodynamics were identified in univariate logistic regression to be correlated with residual PH and with long-term exercise intolerance (Tables S3-S5). According to the revised hemodynamic definition proposed at the 6th World Symposium on Pulmonary Hypertension (mPAP > 20 mm Hg and PVR ≥3 WU)[33] and in line with previous literature, age, female sex, history of hypertension, presurgical PVR, and DLCO were multivariate predictors for residual PH after PEA.[34-36] By applying the latest 2022 ESC definition of PH[1] (mPAP > 20 mm Hg and PVR ≥2 WU), only age and baseline DLCO remained multivariate predictors for residual PH after PEA (Table S3). Baseline predictors of long-term exercise intolerance were DLCO and SvO_2 (Table S4). Interestingly, postoperative correlate with long-term exercise limitation was RVEF (Table S5).

Discussion

In this binational, prospective study, we explored the long-term cardiopulmonary exercise testing and cardiopulmonary hemodynamic outcomes after PEA. The main findings were:

1. Long-term exercise intolerance is common after PEA, affecting 59% of patients. Among preoperative variables, DLCO and SvO_2 predicted long-term exercise intolerance. Of the postoperative variables, RV function was independently associated with long-term exercise intolerance.
2. Pulmonary hemodynamics, RV function, and dimensions all improve 6 months after PEA, resulting in improved exercise capacity. Between 6 and 18 months after PEA, no substantial changes in cardiopulmonary hemodynamics occurred.

Overall, residual PH 6 months after surgery was present in 42% of patients. Older age and lower DLCO were baseline predictors of residual PH post-PEA.

Table 3 Baseline Characteristics of Patients With Long-Term Exercise Limitation

	VO_2 < 80% at 18 months (n = 70)	VO_2 > 80% at 18 months (n = 48)	p value
Age (years)	56 (15)	55 (14)	0.71
Male gender, n (%)	42 (60)	26 (54)	0.57
BMI (kg/m^2)	27 (6)	28 (4)	0.45
Current or previous smoker, n (%)	30 (43)	21 (44)	1.0
Comorbidities, n (%)			
DM	5 (7)	4 (8)	1.0
Hypertension	18 (26)	10 (21)	0.51
Ischemic heart disease	3 (4)	3 (6)	0.69
Renal disease	2 (3)	1 (2)	1.0
COPD	3 (4)	3(6)	1.0
History of cancer	4 (9)	5 (7)	1.0
Thrombophilic disorder	2 (4)	6 (9)	0.47
PH medication (n)	20	5	0.009
β-blockers (n)	6 (9)	4 (8)	1.0
NYHA Fc, (n)			0.12
I/II/III/IV	0/17/49/4	1/19/25/3	
6MWD (m)	299 (141)	438 (102)	< 0.001
DLCO (%)	62 (11)	69 (12)	0.001
BNP (ng/ml) - *(London cohort)*	150 [56-555]	106 [24-440]	0.43
NT-proBNP (pg/ml) - *(Amsterdam cohort)*	459 [240-1,410]	132 [57-1,051]	0.021
RHC			
mPAP (mm Hg)	43 (13)	41 (12)	0.21
PVR (WU)	7.9 [5.1-11.6]	6.1 [3.5-10.9]	0.10
Cardiac index (liter/min/m^2)	2.2 (0.6)	2.5 (0.6)	0.015
PAWP (mm Hg)	10 (3)	10 (3)	0.32
mRAP (mm Hg)	10 [6-13]	7 [5-10]	0.013
SvO_2 (%)	63 (8)	67 (8)	0.009
CMR			
LVEF (%)	59 (9)	64 (9)	0.005
RVEDVi (ml/m^2)	101 (28)	86 (25)	0.003
RVESVi (ml/m^2)	63 [42-87]	43 [30-63]	0.001
RVEF (%)	38 (13)	45 (16)	0.011
SVi (ml/m^2)	37 (9)	37 (10)	0.51
CPET			
VO_{2max} (% pred)	48 (13)	65 (21)	< 0.001
VO_2 (ml/kg/min)	12 (4)	16 (5)	< 0.001
RER	1.1 (0.1)	1.1 (0.1)	0.26
Peak O_2 pulse (% pred)	59 (14)	69 (20)	0.005
VE/VCO_2 at AT	51 (10)	47 (13)	0.09
Peak work load max (% pred)	36 (16)	53 (21)	< 0.001
Peak heart rate (% pred)	82 (13)	91 (12)	< 0.001
SpO_{2max} (%)	92 (4)	93 (4)	0.24

6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DLCO, diffusing capacity for carbon monoxide; DM, diabetes mellitus; mPAP, mean pulmonary arterial hypertension; mRAP, mean right atrial pressure; n, number of patients; NT-proBNP, N-terminalpro-brain natriuretic peptide; NYHA Fc, New York Heart Association Functional Classification; O_2 pulse, oxygen pulse; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RER, respiratory exchange ratio; RHC, right heart catheterization; RVEDVi, indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVi, indexed right ventricular end-systolic volume; SpO_2, maximum peripheral saturation; SVi, indexed stroke volume; SvO_2, mixed venous oxygen saturation; VE/VCO_2 at AT, minute ventilation/carbon dioxide production atanaerobic threshold; VO_{2max}, maximum oxygen uptake.

Data are presented as mean (SD), median [interquartile range], or %.

Statistical tests: unpaired t-test.

Table 4 Postoperative (6-Month) Characteristics of Patients With Long-Term Exercise Limitation

	VO_2 < 80% at 18 months (n = 70)	VO_2 > 80% at 18 months (n= 48)	p value
Residual PH post-PEA	35 (50)	15 (31)	0.05
Postoperative complications			0.07
Reperfusion edema	3	5	
Reoperation due to bleeding	1	6	
Respiratory tract infection	6	5	
Acute kidney failure	4	0	
Other	3	2	
NYHA Fc (n)			0.004
I/II/III/IV	14/42/13/1	24/19/5/0	
6MWD (m)	346 (125)*	491 (102)	< 0.001
RHC			
mPAP (mm Hg)	24 (8)	22 (5)	0.069
PVR (WU)	2.3 [1.6-3.7]*	1.9 [1.4-2.7]	0.033
Cardiac index (liter/min/m^2)	2.8 (0.7)	3 (0.7)	0.19
PAWP (mm Hg)	10 (4)	10 (3)	0.83
mRAP (mm Hg)	5 [3-8]	5 [4-6]	0.32
SvO_2 (%)	69 (6)	70 (5)	0.76
CMR			
LVEF (%)	61 (7)	63 (7)	0.13
RVEDVi (ml/m^2)	72 (19)*	63 (17)	0.021
ΔRVEDVi	-24 [-43 to -12]	-19 [-35 to -9]	0.15
RVESVi (ml/m^2)	35 (16) *	28 (10)	0.009
ΔRVESVi	-23 [-51 to -10]	-14 [-24 to -4]	0.05
RVEF (%)	52 (10) *	57 (7)	0.003
ΔRVEF	13 [3-22]	7 [1-23]	0.23
SVi (ml/m^2)	39 (8)	39 (8)	0.61
CPET			
VO_{2max} (% pred)	69 (16)	94 (15)	< 0.001
VO_2 (ml/kg/min)	16 (5)	20 (4)	< 0.001
RER	1.1 (0.1)	1.1 (0.1)	0.26
Peak O_2 pulse (% pred)	74 (15)	91 (14)	< 0.001
VE/VCO_2 at AT	40 (8)	36 (6)	0.006
Peak work load max (% pred)	54 (15)	83 (17)	< 0.001
Peak heart rate (% pred)	81 (11)	92 (9)	< 0.001
SpO_{2max} (%)	94 (4)	94 (3)	0.66

6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DLCO, diffusing capacity for carbon monoxide; DM, diabetes mellitus; mPAP, mean pulmonary arterial hypertension; mRAP, mean right atrial pressure; n, number of patients; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA Fc, New York Heart Association Functional Classification; O_2 pulse, oxygen pulse; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RER, respiratory exchange ratio; RHC, right heart catheterization; RVEDVi, indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVi, indexed right ventricular end-systolic volume; SpO_2, maximum peripheral saturation; SVi, indexed stroke volume; SvO_2, mixed venous oxygen saturation; VE/VCO_2 at AT, minute ventilation/carbon dioxide production atanaerobic threshold; VO_{2max}, maximum oxygen uptake.

Data are presented as mean (SD), median [interquartile range] or *n (%)*.

Statistical tests: unpaired *t-test*.

Persistent long-term exercise intolerance is common after PEA

Although PEA results in early improvements in pulmonary hemodynamics and RV dimensions in CTEPH, less is known about the long-term effects. In this study, we harnessed the availability of combined data sets on hemodynamics, CMR imaging, and exercise testing before and after PEA at 2 tertiary referral centers for CTEPH patients. Here, we confirm a significant early functional and hemodynamic improvement and show that such improvement does not progress beyond 6 months after PEA. Apparently contrasting these results, a 2006 longitudinal analysis of hemodynamic and functional outcomes after PEA showed a significant and progressive improvement of peak VO_2 1 month and 1 year postsurgery, without significant further improvement at 2 years.[37] However, the first time point earlier after surgery might explain the further significant increase in peak VO_2 up until the first year postoperatively.

Despite significant improvements in central hemodynamics and RV function, persistent exercise intolerance was quite common in our cohort, affecting 59% of patients at 18 months.

Interestingly, among exercise-intolerant patients, half of them had residual PH. Long-term exercise intolerance in our cohort could not be explained by differences in demographics nor comorbidities. However, patients with exercise limitation displayed a lower preoperative DLCO compared to patients without exercise limitation at 18 months. In addition, baseline DLCO and SvO_2 emerged as independent predictors of long-term exercise intolerance. DLCO may be considered as a surrogate marker of distal vasculopathy, not amenable to surgery. As such, it can be hypothesized that vasculopathy/vascular remodeling in these patients can lead to increased RV afterload, thus partly explaining the ongoing functional impairment. In addition, we found that postoperative RV function was an independent predictor of persistent exercise intolerance. In line with our study, Ruigrok et al[38] highlighted a significant increase in peak VO_2 6 months after surgery on 68 operated CTEPH. In keeping with our findings, 66% of patients had exercise intolerance, and among these, only 40% displayed residual PH. Interestingly, DLCO emerged as a predictor of exercise intolerance. Here, we confirm this finding in 2 independent cohorts and show that this relationship remains present after a longer duration of follow-up. This would suggest that the distal vasculopathy in CTEPH is irreversible, also after long duration.

Recently, Howden et al. explored the pathophysiology of exercise intolerance after pulmonary vascular interventions (PEA or BPA) using exercise CMR with simultaneous invasive hemodynamic monitoring. In the context of an overall improved postoperative oxygen delivery, the ongoing exercise intolerance was partly explained by persistent impairment of peripheral oxygen extraction.[39] Skeletal muscle dysfunction, including atrophy and capillary bed rarefaction, has indeed been described in pulmonary arterial hypertension.[40-42] In this context, an emerging body of evidence has highlighted the beneficial effects of physical activity and rehabilitation programs on exercise capacity, quality of life, as well as on RV function and pulmonary hemodynamics.[43] In a recent randomized controlled trial, it was demonstrated that exercise training is safe and yields a significant improvement in terms of peak VO_2, 6MWD, and quality of life in both patients with PAH and CTEPH.[44] Although assessment for residual disease and suitability for BPA should be considered in patients with sufficiently symptomatic PH following surgery, it can be hypothesized that targeting peripheral oxygen extraction, instead of, or in addition to, pulmonary vasculopathy by means of structured rehabilitation programs might be beneficial in attaining a long-term recovery of exercise capacity. Further studies are warranted to test such hypothesis.

Improvements of cardiopulmonary hemodynamics and function after PEA are maintained during long-term follow-up

This multinational study confirms the results of previous monocentric studies on long-term cardiopulmonary effects of PEA. We demonstrated that PEA leads to improvement of invasively measured pulmonary hemodynamics and restoration of RV volumes and RV function at 6 months after PEA.[5,7-11] Long-term follow-up at 18 months showed no further improvement of pulmonary hemodynamics, RV dimensions, and function.

The frequency of residual PH was slightly higher in the London cohort (48%) than in the Amsterdam cohort (37%). Although the London patients were younger on average, they had a higher preoperative PVR and lower DLCO, as well as being functionally more limited as assessed by exercise capacity and functional class. Residual PH can sometimes result from incomplete PEA due to surgical inexperience; however, this does not appear to be the case in both the London[45] and Amsterdam study population. Patients were discussed at the multidisciplinary PEA team/PH team in both cohorts and were operated on by an experienced PEA surgeon who confirmed complete endarterectomy. Additionally, in accordance with previous literature, the prevalence of residual PH in this cohort was 42%[14,16,46] and was associated with older age and low preoperative DLCO.[34-36]

Although several efforts have been made to define a hemodynamic threshold for clinically relevant residual PH after surgery,[16] the understanding of postsurgery cardiopulmonary hemodynamics and optimal treatment strategies is incomplete.[47] In our cohort, postoperative cardiopulmonary hemodynamics in patients with residual PH and persistent exercise limitation were on average quite mild, and functional class in these patients was mostly favorable, which probably explains why the majority of our patients were not treated with PAH-targeted therapy, nor received BPA between 6 and 18 months.

In addition, both long-term hemodynamic spontaneous improvement (4 of 21) or deterioration (5 of 36) rarely occurred beyond 6 months after PEA. Our study confirmed earlier findings of the few monocentric studies on long-term effects of PEA, in which a fast early remodeling phase was followed by a more stabilized phase.[9,11,22,48-50] While early improvements in pulmonary hemodynamics and RV dimensions after PEA are mainly the result of RV pressure unloading, it can be hypothesized that other mechanisms play a role in the long-term recovery, such as inflammation, RV fibrosis, or decreased pulmonary arterial compliance.[51-56] Taken together, we confirm that restoration of cardiopulmonary hemodynamics after PEA occurs within 6 months. Further improvement or deterioration is rarely observed between 6 and 18 months. These findings suggest that close long-term invasive follow-up may only be required in individual cases.

Limitations

Our study is limited by minor baseline differences between the 2 cohorts of CTEPH patients. Nevertheless, patients were included from 2 large tertiary referral centers, generating a unique data set based on a structured multimodal (RHC, CMR, and CPET) follow-up for up to 18 months. In addition, despite the diversity between the 2 cohorts, we showed similar results in cardiopulmonary hemodynamics and exercise capacity. Moreover, long-term invasive hemodynamic data were only available for the Dutch cohort of patients. Finally, part of both cohorts did not have long-

term follow-up, which could cause selection bias. Despite this limitation, the London patients represent a national cohort of operated patients, safeguarding the homogeneity of the therapeutic approaches.

Clinical implications

This study shows that the majority of operated CTEPH patients still experience exercise intolerance 18 months postsurgery. In line with previous literature on the subject, we also confirm that pulmonary hemodynamics, RV dimensions and function, and exercise capacity all improve 6 months after PEA, with residual PH affecting approximately one-third of patients. No further improvements or deterioration were observed between 6 and 18 months. These findings suggest that invasive measurements beyond 6 months post-PEA may not be required in most patients. At the same time, different treatment strategies, other than targeting PVR, might have beneficial effects on exercise capacity, such as physical rehabilitation.

Conclusion

Long-term exercise intolerance after PEA is common, and postoperative RV function and residual PH predict exercise capacity. Restoration in cardiopulmonary hemodynamics and exercise capacity occurs within 6 months from surgery. Between 6 and 18 months after PEA, no further changes in cardiopulmonary hemodynamics can be expected.

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Author Contributions

L.J.M., H.J.B., L.H., F.M., A.V.N., A.A., J.T.M., A.K., A.B., N.J.B., and S.A. designed the study. L.J.M., H.J.B., L.H., A.A., F.M., A.V.N., J.T.M., A.K., J.W., L.R.C., A.B., A. Boonstra, J.N.W, S.A, R.D, F.L.G, B.V. D.G., P.S., J.A.W. and N.J.B. wrote the manuscript. N.J.B., A.E.V., A.K., J.W., J.N.W., L.R.C., A.B., S.A., E.J.N., C.B., R.D., F.L.G., G.H., R.F.R., B.V., D.G., P.S., J.A.W., and A. Boonstra. collected the data. A.K., J.W., J.N.W., A.A., A.B., E.J.N., C.B., L.J.M., H.J.B., F.M., M.J.G., J.T.M., A.E.V., A.V.N., and L.H. performed data analyses and interpretation. All authors provided critical comments on the manuscript.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2023.11.011.

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