Research Article

Pulmonary Circulation

Dynamic vascular changes in chronic thromboembolic pulmonary hypertension after pulmonary endarterectomy

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Abstract

Residual pulmonary hypertension is an important sequela after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Recurrent thrombosis or embolism could be a contributor to this residual pulmonary hypertension but the potential extent of its role is unknown in part because data on incidence are lacking. We aimed to analyze the incidence of new intravascular abnormalities after pulmonary endarterectomy and determine hemodynamic and functional implications. A total of 33 chronic thromboembolic pulmonary hypertension patients underwent routine CT pulmonary angiography before and six months after pulmonary endarterectomy, together with right heart catheterization and exercise testing. New vascular lesions were defined as (1) a normal pulmonary artery before pulmonary endarterectomy and containing a thrombus, web, or early tapering six months after pulmonary endarterectomy or (2) a pulmonary artery already containing thrombus, web, or early tapering at baseline, but increasing six months after pulmonary endarterectomy. Nine of 33 (27%) chronic thromboembolic pulmonary hypertension patients showed new vascular lesions on CT pulmonary angiography six months after pulmonary endarterectomy. In a subgroup of patients undergoing CT pulmonary angiography 18 months after pulmonary endarterectomy, no further changes in lesions were noted. Hemodynamic and functional outcomes were not different between patients with and without new vascular lesions. New vascular lesions are common after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension; currently their origin, dynamics, and long-term consequences remain unknown.

Keywords

hypertension, pulmonary, pulmonary embolism, venous thromboembolism, endarterectomy, pulmonary circulation

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by incomplete resolution of pulmonary embolism (PE) leading to organized thrombus, secondary remodeling of the distal vasculature, and microvascular disease.[1,2] If left untreated, chronic pressure overload will ultimately lead to right ventricular failure and death. CTEPH distinguishes itself from other groups of pulmonary hypertension (PH) by the possibility of potential curation through a pulmonary endarterectomy (PEA) in approximately 60% of patients.[3,4] Despite the excellent results and long-term survival after PEA,[4] residual PH after PEA is an important sequela occurring in 30–50% of patients.[5] Little is known about the mechanism and

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predictors of residual PH. Residual lesions, distal pulmonary vasculopathy, recurrent embolism, and in situ thrombosis (despite anticoagulation) after PEA could all contribute to residual PH. Large follow-up studies on recurrent perfusion defects after PEA have not been performed. Accurate estimations of the incidence of new thrombotic or embolic lesions after PEA are unavailable, although a recent cohort study showed recurrent PE in 6 of 356 patients after PEA.[5] Notably, all these six patients had a vena cava inferior (VCI) filter in situ and four had antiphospholipid syndrome, suggesting that new vascular lesions were caused by the intervention/surgery or resulted from in situ thrombosis. In the study, postoperative CT scans were only performed in symptomatic patients[5] and therefore the true incidence of new vascular lesions may have been underestimated.

Several relevant questions remain currently unanswered. First, how often can new (thrombotic) lesions be identified when CT pulmonary angiography (CTPA) is performed routinely after PEA? Second, which patients are at risk for recurrent lesions after PEA? And third, what are the clinical consequences of new vascular lesions, particularly with respect to the presence of residual PH?

In the current study, we evaluated a cohort of CTEPH patients who were routinely subjected to ECG-triggered CTPA six months after PEA. Our objective was to describe the incidence, morphology, and clinical implications of recurrent thrombotic lesions after PEA.

Methods

Study subjects

Patients with CTEPH undergoing PEA in the VU University Medical Center between October 2014 and July 2016 were screened for inclusion in this observational analysis. Inclusion criteria consisted of a diagnosis of CTEPH, and performance of ECG-triggered CTPA both before and six months after PEA (as part of standard clinical care). Patients with chronic thromboembolic disease without PH were excluded.

According to our center's clinical protocol at that time, all patients had a VCI filter implanted before PEA unless contra-indicated and were permanently anticoagulated. Postoperatively, intravenous heparin was started as soon as the chest tube production was <50 mL/h for 3 h. After the initial postoperative period, patients were restarted on vitamin K antagonists (VKA).

At the time of six-month follow-up after PEA, six-minute walking test (6MWT) and cardiopulmonary exercise testing (CPET) were performed in addition to CTPA, as well as right heart catheterization (RHC). These tests were also performed before PEA in all patients.

This study did not fall within the scope of the Medical Research Involving Human Subjects Act, since a retrospective 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 Center (2017.313).

Procedures

All CT scans were obtained on a 256-MDCT scanner (Brilliance 256, Philips Healthcare) with retrospective ECG triggering with 0.625 slice thickness and 0.27 s/rotation. The tube voltage was set at 100 kV and the tube current was set at 600 mA with dose modulation to reduce radiation exposure. The injection protocol consisted of administration of 85 mL of non-ionic contrast agent (Iobitridol, Xenetix 300, Guerbet) through an antecubital vein at a flow rate of 5 mL per sec followed by injection of 40 mL saline solution. Automatic bolus tracking was applied with the region of interest (ROI) positioned in the truncus pulmonalis and a threshold for triggering data acquisition was set at 115 HU. The acquisition was performed during inspiration. The CT images were reconstructed at 75% of the R–R interval with 1.5 slice thickness at 1.0-mm intervals using standard algorithm. The CT images were digitally stored and analyzed at a dedicated workstation.

Changes in vascular morphology on ECG-triggered CTPA six months after PEA were assessed post-hoc using a scoring model designed to evaluate 31 pulmonary arteries including five mediastinal, six lobar, and 20 segmental arteries in every patient.[6] Each artery was scored as normal, containing thrombus, web(s), or early tapering before and six months after PEA. New vascular lesions were defined as (1) a normal pulmonary artery before PEA and containing a thrombus, web, or early tapering six months after PEA, or (2) a pulmonary artery already containing thrombus, web, or early tapering at baseline which had increased six months after PEA. Early tapering is the early narrowing of arteries on CTPA, comparable to subtotal lesions on angiography. Two investigators, including an experienced cardiothoracic radiologist with expertise in CTEPH, reviewed the images and final evaluations were achieved by consensus. Due to the nature of this analysis, inter-observer variability regarding the CTPA evaluation was not analyzed.

6MWT was performed according to the 2002 ATS statement.[7] CPET consisted of a symptom-limited maximal incremental exercise test up using a cycle ergometer.[8]

RHC was performed using a fluid-filled balloon-tipped 7 F Swan-Ganz catheter inserted via the jugular vein under local anesthesia, with positioning under continuous electrocardiographic monitoring, and recording of the following variables: mean pulmonary artery pressures (mPAP), right atrial pressures, pulmonary artery wedge pressure (PAWP), and heart rate. Cardiac output (CO) was determined by thermodilution or the direct Fick method (indexed for body surface area: cardiac index). Pulmonary vascular resistance (PVR) was calculated from $(80 \times [\text{mPAP} - \text{PAWP}]/\text{CO})$.

Study design and statistical analysis

Primary objective of this observational retrospective study was analysis of the incidence of new vascular (recurrent thrombotic or thromboembolic) lesions six months after PEA. The secondary objective was an analysis of clinical (hemodynamic and functional) implications of new vascular lesions.

The corresponding author had full access to all the study data and takes responsibility for its integrity and data analysis. Data are presented as mean (standard deviation (SD)), median (interquartile range), or number of patients (%). Based on the number of patients, non-parametric testing was performed, using Mann–Whitney test or Fisher's exact test where appropriate, to compare patients with or without new vascular lesions. Changes in CT morphology were assessed using Wilcoxon matched-pairs signed rank test. Missing data were not imputed. Values of $P < 0.05$ were considered to reflect statistical significance. Correlation analysis regarding the association between abnormal arteries and hemodynamic parameters were performed using Pearson correlation in data normally distributed and using Spearman correlation in data not normally distributed. Statistical analysis was performed using GraphPad Prism version 7.0b (GraphPad Software, La Jolla, CA, USA) and IBM SPSS Statistics version 24.

Results

As indicated in the flow chart (Fig. 1), 43 CTEPH patients underwent PEA in the time period between October 2014 and July 2016. After excluding 10 patients with absent or incomplete follow-up data, 33 patients with CTPA before and six months after PEA were included in this observational analysis. Patients characteristics and baseline (hemodynamic) parameters are shown in the first column of Table 1.

Primary outcome

Nine out of 33 patients (27%) were found to have new vascular lesions on CTPA six months after PEA. New vascular lesions mainly consisted of new or increased thrombus and early tapering of mainly the segmental pulmonary arteries (Table 2). Examples of new vascular lesions in different patients are shown in Fig. 2.

The mean percentage of normal vessels increased from 48% (SD: 20%, range: 6–87%) pre-PEA to 88% (SD: 9.8%, range: 68–100%) six months post-PEA; the percentages of arteries with thrombus, webs, or tapering all significantly decreased (Fig. 3).

Secondary outcomes

Correlations between number of remaining abnormal arteries and postoperative mPAP and PVR were absent (Spearman correlation r 0.32 ($p = 0.08$) and Pearson correlation r 0.18 ($p = 0.32$), respectively).

Subject characteristics and baseline hemodynamic and exercise parameters of nine patients with new lesions on CTPA (group 1) and 24 patients without new lesions (group 2) were comparable (Table 1), except for a higher prevalence of systemic hypertension in patients with new lesions.

The incidence of residual PH (as defined by mPAP $\geq$ 25 mmHg) six months after PEA was not different between patients with or without new vascular lesions (29% vs 48% in groups with and without new lesions on CTPA, respectively, Fisher's exact test $p = 0.43$) and hemodynamic and functional outcomes were similar (Table 3 and Table A (supplement)).

Anticoagulation parameters such as time to start of heparin after ICU admission and time to first adequate were similar in both groups (Table A in supplement). It can be noticed that the median time to the first adequate APTT was 11–12 h in both groups with a large range indicating an interval of suboptimal anticoagulation during which thrombus formation could occur. Direct oral anticoagulant instead of VKA was used in only two patients, both in the group without new lesions on CTPA. In a non-selective subgroup of 19 patients, CTPA was

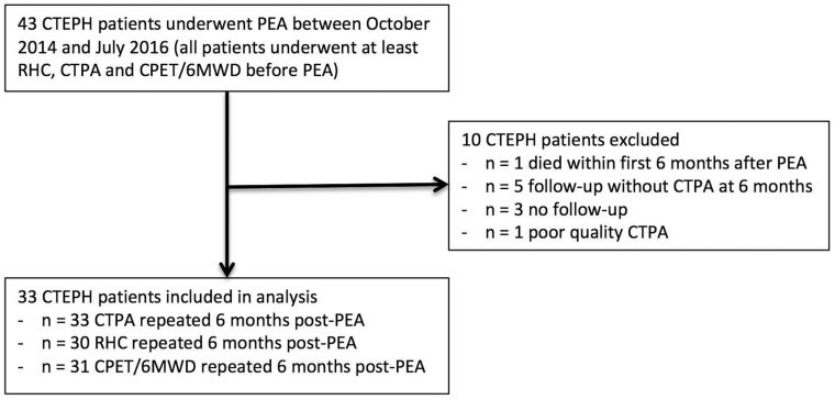

Fig. 1. Flowchart of included patients and reasons for exclusion.
CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy; RHC: right heart catheterization; CTPA: CT pulmonary angiography; CPET: cardiopulmonary exercise testing; 6MWD: six-minute walking distance.

Table 1. Subject characteristics and comparison of characteristics at baseline (before PEA).

Variable	Overall baseline characteristics for total cohort of 33 patients	Group 1: with new vascular lesions on CTPA six months post-PEA (9 patients)	Group 2: without new vascular lesions on CTPA six months post-PEA (24 patients)
Age at PEA (years)	63 (range 22–79)	65 (range 45–78)	62.5 (range 22–79)
Male gender (*n*, %)	21 (64%)	6 (67%)	15 (63%)
Time CTEPH diagnosis to PEA (days)	154 (109–254)	153 (94–472)	154 (119–260)
BMI at baseline (kg/m^2)	26.4 (24.3–29.8)	25.4 (22.8–27.4)	26.6 (24.4–30.4)
Acute VTE in previous history	30 (91%)	8 (89%)	22 (92%)
DVT in previous history	9 (27%)	1 (11%)	8 (33%)
Blood group non-O	23 (70%)	5 (56%)	18 (75%)
Myeloproliferative disease (*n*, %)	1 (3%)	0 (0%)	1 (4%)
Diabetes mellitus (*n*, %)	2 (6%)	2 (22%)	0 (0%)
Obstructive lung disease (*n*, %)	3 (9%)	2 (22%)	1 (4%)
Systemic hypertension (*n*, %)	12 (36%)	6 (67%)	6 (25%)
Splenectomy (*n*, %)	2 (6%)	1 (11%)	1 (4%)
Known significant coronary artery disease (*n*, %)	0 (0%)	0 (0%)	0 (0%)
Known thyroid disease/thyroid replacement therapy (*n*, %)	1 (3%)	1 (11%)	0 (0%)
Current or former smoker (*n*, %)	18 (69%) ($n=26$)	4 (80%) ($n=5$)	14 (67%) ($n=21$)
Baseline hemodynamic parameters			
mPAP pre-PEA (mmHg)	39 (34–48)	39 (33–46)	40 (35–48)
PVR pre-PEA (dynes.s.cm^{-5})	469 (346–690) ($n=32$)	503 (346–720) ($n=8$)	469 (338–638)
PAWP pre-PEA (mmHg)	11 (9–13) ($n=32$)	9.5 (6.8–11.8) ($n=8$)	12 (9.3–13)
CI pre-PEA (L/min/m^2)	2.5 (2.0–3.1) ($n=32$)	2.8 (1.9–3.1) ($n=8$)	2.4 (2.0–3.1)
Other parameters pre-PEA			
PAH-specific medication pre-PEA	11 (33%)	3 (33%)	8 (33%)
VCI-filter pre-PEA in situ	31 (94%)	9 (100%)	22 (92%)
NT-proBNP (ng/L)	489 (114–1305)	316 (119–1003)	725 (112–1715)
NYHA class III–IV (*n*, %)	15 (48%) ($n=31$)	3 (33%)	12 (55%) ($n=22$)
6MWD (m)	449 (363–511) ($n=30$)	482 (439–560)	416 (321–480) ($n=21$)
DLCO (% predicted)	66.5 (61.3–78.3) ($n=28$)	70.5 (65–80.5) ($n=8$)	65.5 (61–76) ($n=20$)

CTPA: CT pulmonary angiography; PEA: pulmonary endarterectomy; BMI: body mass index; VTE: venous thromboembolism; DVT: deep vein thrombosis; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; CI: cardiac index; PAH: pulmonary arterial hypertension; VCI: vena cava inferior; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; 6MWD: six-minute walking distance; DLCO: transfer factor for carbon monoxide; CTEPH: chronic thromboembolic pulmonary hypertension.
Notes: Data presented as median (IQR) or absolute number of patients (%) unless otherwise stated. Data apply to all 33 (9 plus 24) patients unless otherwise stated. Statistical tests: Mann–Whitney test (numeric variables) and Fisher's exact test (categorical variables).

performed 18 months after PEA. This subgroup included seven patients with new lesions six months after PEA and in all these patients, lesions remained unchanged 18 months after PEA.

Discussion

This is the first report on the results of a structured follow-up with CTPA after PEA. In this observational study, 27% of patients had new vascular lesions on CTPA six months after PEA. Morphology of new vascular lesions after surgery varied from new or increased thrombus to new webs or new/increased tapering (this consisted of at least one completely new abnormality in all nine patients, with three patients with an additional increase in thrombus or tapering). Hemodynamic and functional outcomes after PEA were not influenced by these lesions, and had no effect on the incidence of residual PH.

Few studies have addressed recurrent thromboembolism after PEA. Most studies on the role of CTPA in residual PH after PEA used preoperative CT imaging to predict hemodynamic results after PEA.[9,10] One case series from almost two decades ago performing follow-up CT in 21 patients within three months to one year after PEA, described complete absence of new vascular lesions.[11] At the time of that study, CTPA imaging quality was inferior compared to

Table 2. Description of new vascular lesions on CTPA in nine patients six months after PEA.

Patient number	Location new lesion	Preoperative CTPA	CTPA six months after PEA
1	Superior segmental artery left lower lobe (segment A6)	Normal	Tapering
2	Superior segmental artery lingula (segment A4) (Fig. 2e)	Normal	Tapering
3	Superior segmental artery lingula (segment A4) (Fig. 2a)	Normal	Tapering
4	Superior segmental artery right lower lobe (segment A6)	Tapering	Increase in tapering
	Anterobasal segmental artery right lower lobe (segment A8) (Fig. 2f)	Normal	Thrombus
5	Anterobasal segmental artery right lower lobe (segment A8) (Fig. 2d)	Normal	Thrombus
	Lateral segmental artery middle lobe (segment A4)	Tapering	Increase in tapering
6	Lingula	Thrombus	Increase in thrombus
	Superior segmental artery left lower lobe (segment A6)	Normal	Thrombus
	Left lower lobe artery (Fig. 2c)	Normal	Thrombus
7	Lateral segmental artery middle lobe (segment A4) (Fig. 2b)	Normal	Web
	Superior segmental artery left lower lobe (segment A6)	Normal	Web
8	Posterior segmental artery left upper lobe (segment A10)	Normal	Tapering
9	Apical segmental artery right upper lobe (segment A1)	Normal	Thrombus

CTPA: CT pulmonary angiography; PEA: pulmonary endarterectomy.

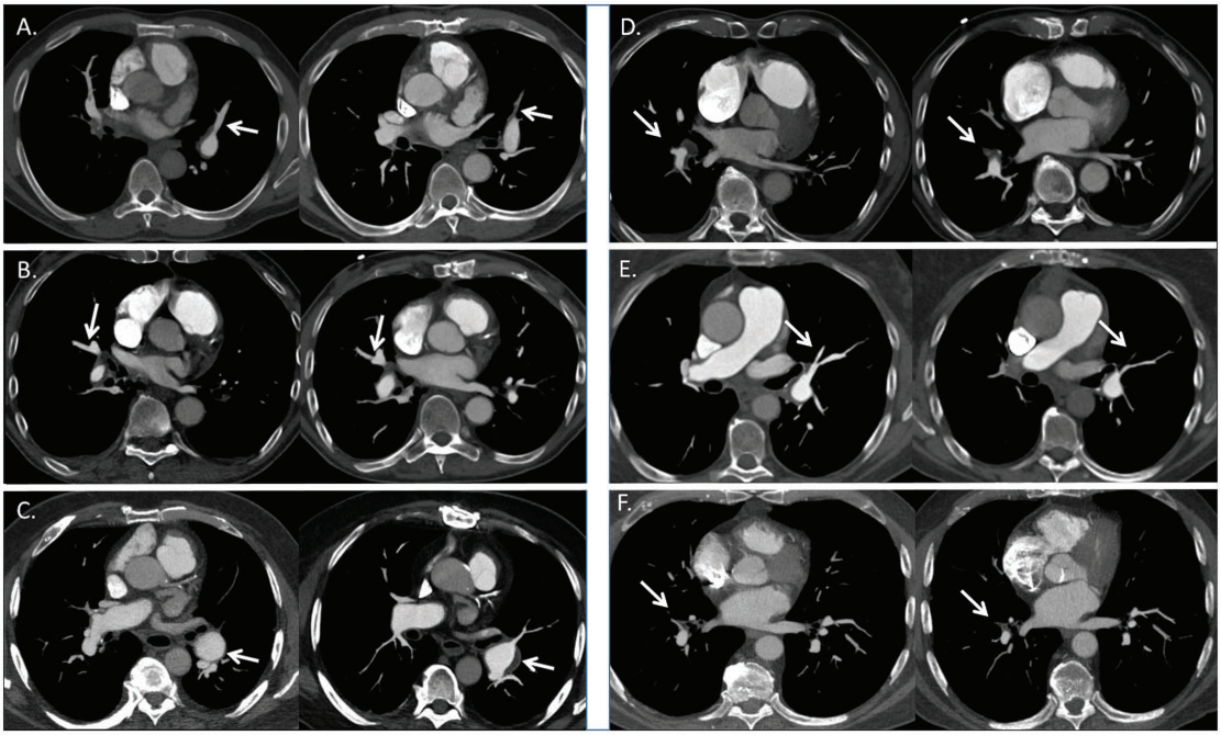

Fig. 2. Examples of new vascular lesions six months after PEA. (a) Superior segmental artery lingula (segment A4): normal before PEA (left panel), tapering six months after PEA (right panel). (b) Lateral segmental artery middle lobe (segment A4): normal before PEA (left panel), new web six months after PEA (right panel). (c) Left lower lobe artery: normal before PEA (left panel), new thrombus six months after PEA (right panel). (d) Anterobasal segmental artery right lower lobe (segment A8): normal before PEA (left panel), new thrombus six months after PEA (right panel). (e) Superior segmental artery lingula (segment A4): normal before PEA (left panel), tapering six months after PEA (right panel). (f) Anterobasal segmental artery right lower lobe (segment A8): normal before PEA (left panel), thrombus six months after PEA (right panel).

imaging accuracy in the current era.[12,13] A recent large prospective cohort study reported recurrent thromboembolic lesions in 1.7% of patients after PEA.[5] However, only symptomatic patients underwent CTPA, while our cohort is unique because CTPA was performed in all patients irrespective of symptoms. This explains the large difference in incidence of new vascular lesions between the two cohorts (27 vs 1.7%).

Although the timing of new lesion development cannot be firmly established on the basis of our data, the fact that no new lesions developed after six months in a subset of 19 patients who underwent CTPA 18 months after surgery suggests that new lesions probably developed in the early postoperative period. The dissected pulmonary endothelium and media layer can be considered very prone to platelet aggregation and in situ thrombus formation in the early postoperative phase, after removal of the endothelial and intimal layer of the vessel, is likely to occur. Superimposed on this are (short) time periods of suboptimal anticoagulation especially in the early postoperative phase where new thrombus formation can occur. Second, besides the formation of new thrombus, this study also illustrated that some vessels showed increased tapering after surgery, possibly explained by residual intimal flaps and local disruptions of the media layer directly related to surgery. To our knowledge, the exact mechanism of tapering has not been described before and might also be a consequence of mechanical stimulation/injury eliciting a vasoconstrictive response of the vascular smooth muscle. Recurrent venous thromboembolism is less likely unless suboptimal anticoagulation is present but cannot be excluded by the presence of VCI filters since small thrombi may pass the filters, as illustrated by two prospective trials indicating recurrent PE in 3% of patients despite retrievable VCI filters.[14,15] In only one patient, new webs were found, making it difficult to hypothesize on the origins of new webs in this single patient.

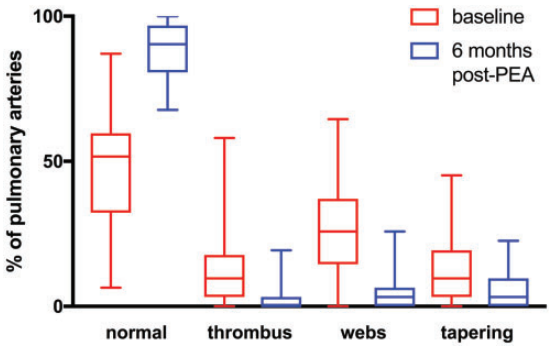

Fig. 3. Changes in vascular morphology of pulmonary arteries before and after PEA. Boxplots of percentages of (ab)normal pulmonary arteries for 33 patients. Red boxplots indicate data at baseline, blue boxplots indicate data six months after PEA. Changes in all morphological groups (normal, thrombus, webs, and tapering) between baseline and six months after PEA were statistically significant ($p < 0.001$, Wilcoxon matched-pairs signed rank test). PEA: pulmonary endarterectomy.

Importantly, new vascular lesions were not associated with the hemodynamic outcome after PEA in this cohort. Because only one patient died before CTPA was performed, it seems unlikely that a survival bias explains the lack of correlation between new vascular lesions and the presence of residual PH. However, the relatively small number of patients might under power the detection of a potential hemodynamic effect. Additionally, we observed no symptomatic or functional consequences of new vascular lesions. Our findings are in line with the current hypothesis that residual PH is caused by either incomplete removal of more distal thrombi and/or concomitant small-vessel disease, while recurrent PH is thought to be rare and presumed to be associated with new thrombus.[16] Possibly the potential negative hemodynamic effects of new thromboembolic lesions are too small in relation to the major vascular improvements made after surgery (the mean percentage of remaining abnormal arteries decreased from 52% to 12%). Correlation between number (or fraction) of remaining abnormal arteries and PVR (or its fractional delta) was absent, similar to the absent relation in previous studies between pulmonary vascular obstruction (based on perfusion scintigraphy) and total pulmonary resistance in untreated CTEPH.[17] Incomplete resection of removable chronic thromboembolic lesions is unlikely or at least no more likely than in other centers since hemodynamic and functional outcomes are comparable to other PEA centers, and the PEA surgeon checked every segment for residual lesions before closing the pulmonary artery, to ensure complete endarterectomy.

Lack of power represents the main limitation of this study, together with its retrospective nature resulting in

Table 3. Comparison of hemodynamic outcomes six months post-PEA.

Hemodynamic parameter six months post-PEA	Group 1: with new vascular lesions on CTPA six months post-PEA Nine patients	Group 2: without new vascular lesions on CTPA six months post-PEA 24 patients	*P*-Values
mPAP (mmHg)	22 (16–31) ($n = 7$)	24 (18–27) ($n = 23$)	0.857
PVR (dynes.s.cm^{-5})	216 (154–283) ($n = 7$)	160 (99–227) ($n = 23$)	0.156
PAWP (mmHg)	6 (4.8–12.5) ($n = 6$)	11 (8–12) ($n = 23$)	0.256
CI (L/min/m^2)	2.9 (2.5–3.4) ($n = 7$)	3.2 (2.7–3.7) ($n = 23$)	0.292

CTPA: CT pulmonary angiography; PEA: pulmonary endarterectomy; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; CI: cardiac index.
Notes: Data presented as median (IQR). Data apply to the number of patients stated per variable. Statistical test: Mann–Whitney test.

some missing data, especially regarding thrombophilia factors. However, since structured follow-up after PEA is often limited by logistical issues (such as travel distance), and CTPA is only rarely part of follow-up programs, larger patient numbers are probably not to be expected. The exclusion of 23% of eligible patients, mainly because of missing follow-up CTPA, represents a potential source of bias. Unfortunately, the quality of long-term anticoagulation and time in the therapeutic range (TTR) of vitamin K antagonist therapy could not be quantified; however, the current system of local thrombosis services in the Netherlands offers high quality and adequacy of vitamin K anticoagulant treatment, and therefore major differences in TTR are not expected to be a relevant determinant of our main outcome. And last, classification of new vascular lesions was based on the occurrence of new lesions or an increase of pre-existing abnormalities according to the information provided by CTPA; this is in contrast to a more detailed classification of lesions based on pulmonary angiography, such as proposed by Kawakami et al.[18]

Based on the quite high incidence of new lesions and lack of hemodynamic consequences in this cohort, we do not recommend follow-up CTPA after PEA in CTEPH as part of standard clinical care unless new symptoms occur. Potentially the remaining abnormal arteries after PEA, whether old or new, represent new therapeutic targets for balloon pulmonary angioplasty in the case of significant remaining symptoms or residual PH.

In conclusion, we showed new vascular lesions on CTPA six months after PEA in 27% of patients despite anticoagulation and VCI filters. These findings should be regarded as hypothesis generating: the origin, dynamics, and long-term outcome of these vascular changes after PEA are currently unknown, although the time course suggests a relation with the surgical procedure.

Author contributions

All authors were involved in the development of the manuscript: D.R., N.J.B., H.-J.B., and L.J.M. were involved in conception, design, analysis and interpretation of data, and drafting of the manuscript. E.J.N., P.I.B., A.B., R.J.L., F.A.K., A.V.N., and P.S. were involved in revising the manuscript critically for important intellectual content. Final approval of the manuscript submitted applies to all authors.

Conflict of interest

The author(s) declare that there is no conflict of interest. R.J.L. reports personal fees from BTG and Philips outside the submitted work. A.V.N. reports grant support from Actelion, GlaxoSmithKline, Bayer, and Pfizer outside the submitted work. H.-J.B. reports grant support from Actelion, GlaxoSmithKline, Therabel, Pfizer, and Bayer outside the submitted work.

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Supplemental material

Supplemental material for this article is available online.

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