The aftermath of acute pulmonary embolism: approach to persistent functional limitations

Boon, G.J.A.M.

10

Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH

N.J. Braams, G.J.A.M. Boon, F.S. de Man, J. van Es, P.L. den Exter, L.J.M. Kroft, L.F.M. Beenen, M.V. Huisman, E.J. Nossent, A. Boonstra, A. Vonk Noordegraaf, D. Ruigrok, F.A. Klok, H.J. Bogaard, L.J. Meijboom

Eur Respir J. 2021;2100699

ABSTRACT

Introduction: The pulmonary arterial morphology of patients with pulmonary embolism (PE) is diverse and it is unclear how the different vascular lesions evolve after initiation of anticoagulant treatment. A better understanding of the evolution of CTPA findings after the start of anticoagulant treatment may help to better identify those PE patients prone to develop CTEPH. We aimed to assess the evolution of various thromboembolic lesions on CTPA over time after the initiation of adequate anticoagulant treatment in individual acute PE patients with and without an ultimate diagnosis of CTEPH.

Methods: We analyzed the CTPA at diagnosis of acute PE (baseline) and at follow-up in 41 patients with CTEPH and 124 patients without an ultimate diagnosis of CTEPH, all receiving anticoagulant treatment. Central and segmental pulmonary arteries were scored by expert chest radiologists as normal or affected. Lesions were further sub-classified as: 1. central thrombus, 2. total thrombotic occlusion, 3. mural thrombus, 4. web or 5. tapered pulmonary artery.

Results: Central thrombi resolved after anticoagulant treatment, while mural thrombi and total thrombotic occlusions either resolved or evolved into webs or tapered pulmonary arteries. Only patients with an ultimate diagnosis of CTEPH exhibited webs and tapered pulmonary arteries on the baseline scan. Moreover, such lesions always persisted after follow-up.

Conclusion: Webs and tapered pulmonary arteries at the time of PE diagnosis strongly indicate a state of chronic PE and should raise awareness for possible CTEPH, particularly in patients with persistent dyspnea after anticoagulant treatment for acute PE.

INTRODUCTION

Acute pulmonary embolism (PE) is a potentially dangerous form of venous thromboembolism (VTE) and is the third most common cause of cardiovascular death.[1,2] It is characterized by thromboembolic occlusions of one or more pulmonary arteries and requires anticoagulant treatment for at least three months.[3] Despite effective anticoagulant treatment, approximately 1-3% of PE patients develop chronic thromboembolic pulmonary hypertension (CTEPH).[4,5] This is the most severe long-term consequence of PE and, if left untreated, may ultimately lead to right-sided heart failure and death.[6-8]

Signs of chronic thromboembolism are usually present on initial computed tomography pulmonary angiography (CTPA) of patients with an ultimate diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH).[9-11] However, without three months of adequate anticoagulant treatment a presumptive diagnosis is made of acute PE, even when chronicity is suspected. Of note, signs of chronicity are often overlooked in the setting of CTPA performed to diagnose acute PE in routine practice.[12] Webs, tapered vessels, mural thrombi and total thrombotic occlusions are generally associated with chronic thromboembolisms, while it is unknown whether these vascular lesions can dissolve after initiation of anticoagulant treatment.[9-11,13,14] In addition, particularly mural thrombi and total thrombotic occlusions may also be identified in acute PE patients who will not have signs of chronic thromboembolism at follow-up.[15]

The pulmonary arterial morphology of CTEPH patients is diverse and it is unclear how the different vascular lesions evolve after initiation of anticoagulant treatment. A better understanding of the evolution of CTPA findings after the start of anticoagulant treatment may help to better identify those acute PE patients prone to develop CTEPH. We aimed to assess the evolution of various thromboembolic lesions on CTPA over time after the initiation of adequate anticoagulant treatment in individual acute PE patients with and without an ultimate diagnosis of CTEPH.

METHODS

Study subjects

As CTEPH develops only in a small proportion of acute PE patients, we performed a case-cohort study. As cases, we selected patients with a documented history of acute PE who were diagnosed with CTEPH in the Amsterdam University Medical Center, location VUMC, between 2014 and 2019 (CTEPH@FU group). According to standard care, CTPA was repeated for the diagnostic work-up for CTEPH after the initial PE. As controls, we selected acute PE patients from a prospective multicenter cohort study, who were subjected to follow-up CTPA six months after their initial PE and who had no signs or symptoms of CTEPH in a period of 2,5 years following their initial PE (no-CTEPH@FU group).[16] Patients were excluded if 1) they had a prior history of oral anticoagulant treatment, 2) the acute PE had been treated with reperfusion therapy, 3) anticoagulation had been discontinued before the follow-up CTPA was performed or 4) follow-up CTPA had been performed <3 months after the initial CTPA. This selection resulted in a homogenous population of patients who all underwent a CTPA for a first episode of acute PE and who had a follow-up CTPA performed after at least 3 months of continuous anticoagulant treatment. We combined the two prospective cohorts and analyzed pulmonary vessel morphology at the CTPA at diagnosis of initial PE (baseline) and at follow-up in CTEPH@FU and no-CTEPH@FU. Anticoagulant treatment consisted of low-molecular-weight heparin (LMWH), direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA), according to standard care.[17]

In this study, CTEPH@FU patients did not fall within the scope of the Medical Research Involving Human Subjects Act, since the diagnostic procedures were performed for routine clinical purposes. This was confirmed by the Medical Ethics Review Committee of the VU University Medical Center (2017.313). No-CTEPH@FU patients were selected from a previous prospective multicenter study. In that study, institutional ethical review boards of all participating centers approved the study protocol and all participants had provided written informed consent.[16]

CTPA data acquisition and assessment

Standard CTPA was performed as described in previous studies.[16,18] In short, CTPA was performed on multi-detector row CT scanners with at least 64-slices from different vendors. CTPAs were excluded for analysis if the available reconstructed slice thickness was more than 3 mm or if image quality was non-diagnostic. The presence of bronchial collaterals was defined as the presence of one or more bronchial collaterals with a diameter of more than 2mm.[19] Right ventricular (RV)/left ventricular (LV) ratio was measured in diastole on the transverse section by defining the widest point from inner wall to inner wall at valvular level of each chamber. Pulmonary artery diameter was measured at the level of the pulmonary trunk.

Pulmonary arterial morphology was assessed post-hoc as described previously.[18] In brief, 31 pulmonary arteries were evaluated in each patient, including 11 central pulmonary arteries (5 mediastinal and 6 lobar) and 20 segmental pulmonary arteries. Each artery was scored as normal or affected and was further sub-classified as: 1. central thrombus, 2. total thrombotic occlusion, 3. mural thrombus, 4. web or 5. tapered pulmonary artery. Morphological pulmonary artery characteristics were presented as percentage of the total central or segmental vasculature. All thrombotic pulmonary arteries were additionally scored for the presence of calcification. Furthermore, lumen size was measured in total thrombotic occlusions that did not resolve after anticoagulant treatment. Two investigators, including at least one expert chest radiologist with specific expertise in CTEPH, reviewed the images and final judgment was achieved by consensus.

Statistical analysis

Data are presented as mean (standard deviation, SD), or as percentage of the pulmonary vasculature. All variables were tested for normal distribution by carefully assessing the mean, median and standard deviation. Data that failed the normal distribution were log- or square root transformed for analysis. Comparison of characteristics between the groups was performed using independent t-test for continuous variables and chi-squared test for proportions. Comparison of baseline with follow-up characteristics was performed using dependent t-test. Differences in pulmonary arterial morphology changes over time between the groups were tested using two-way repeated measures ANOVA test. Missing data were not imputed. Values of $P < 0.05$ were considered to reflect statistical significance. Statistical analysis was performed using R version 3.6.3.

RESULTS

Patient characteristics

A total of 165 patients with acute PE were included (**Figure 1**). Of those, 41 patients were diagnosed with CTEPH (CTEPH@FU) and 124 patients had no signs suggestive of CTEPH during follow-up (no-CTEPH@FU). Baseline characteristics of the study patients are presented in **Table 1**. CTEPH@FU patients were older (63±14 vs. 54±16 years in no-CTEPH@FU; $p<0.001$), while the time between the initial CTPA and the follow-up CTPA was similar (185 [148 – 243] days in CTEPH@FU vs. 184 [176 – 194] days no-CTEPH@FU, NS). Anticoagulation treatment in CTEPH@FU consisted of either VKA or DOAC, while no-CTEPH@FU patients were predominantly treated with VKA. This could be explained by the fact that the no-CTEPH@FU group was diagnosed with acute PE before the introduction of the DOACs. All CTEPH@FU patients fulfilled the diagnostic criteria of pulmonary hypertension at follow-up and had a mean pulmonary artery pressure (mPAP) of 46±14 mmHg, a pulmonary vascular resistance (PVR) of 679±471 [dynes/sec/cm^{-5} and a cardiac index of 2.4±0.7 l/min/m^2 (**Table 2**).

Imaging analysis

Four segmental pulmonary arteries in a single CTEPH@FU patient could not be analyzed due to breathing artefacts. As a result, a total of 451 central pulmonary arteries and 816 segmental pulmonary arteries were scored at baseline and repeatedly at follow-

10

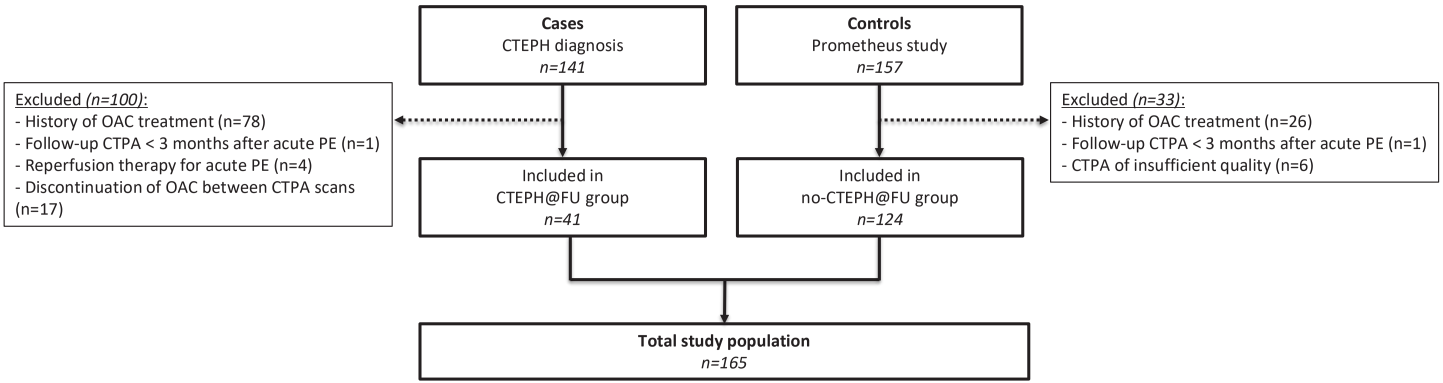

Figure 1: Flowchart

Note: CTEPH@FU: patients with an ultimate diagnosis of CTEPH at follow-up; no-CTEPH@FU: patients without an ultimate diagnosis of CTEPH at follow-up.

Abbreviations: OAC, oral anticoagulant; CTPA, computed tomography pulmonary angiography.

Table 1: Baseline characteristics

	Total (n=165)	No-CTEPH@FU (n=124)	CTEPH@FU (n=41)	P-value
Age (years)	56±16	53±16	63±14	<0.01
Male gender (n, %)	84 (51%)	62 (50%)	22 (54%)	NS
Anticoagulation (n,%)				
- VKA	137 (83%)	111 (90%)	26 (63%)	<0.001
- DOAC	15 (9%)	0 (0%)	15 (37%)	
- LMWH	13 (8%)	13 (10%)	0 (0%)	
Anticoagulation time (days)	184 [173 – 199]	184 [176 – 194]	185 [148 – 243]	NS

Note: Data are presented as mean±SD, median [IQR] or number (%). No-CTEPH@FU: patients without an ultimate diagnosis of CTEPH at follow-up; CTEPH@FU: patients with an ultimate diagnosis of CTEPH at follow-up.
Statistics: independent t-test for continuous variables and chi-squared for proportions.
Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin.

Table 2: Pulmonary hemodynamics

	No-CTEPH@FU (n=124)			CTEPH@FU (n=41)		
	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value
RV/LV ratio	1.0±0.3	0.9±0.2	<0.001	1.5±0.5	1.5±0.5	NS
PA diameter	28±4	26±3	<0.001	34±5	33±5	NS
Bronchial collaterals (n,%)	10/122 (8%)	10/122 (8%)	NS	19/38 (50%)	19/38 (50%)	NS
mPAP (mmHg)					46±14	
PVR (dynes/sec/cm^{-5})					679±471	
mRAP (mmHg)					9±4	
Cardiac index (l/min/m^2)					2.4±0.7	
SvO2 (%)					62±8	

Note: Data are presented as mean±SD or number (%). No-CTEPH@FU: patients without an ultimate diagnosis of CTEPH at follow-up; CTEPH@FU: patients with an ultimate diagnosis of CTEPH at follow-up.
Abbreviations: RV, right ventricular; LV, left ventricular; PA, pulmonary artery; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; SvO2, mixed venous oxygen saturation.

up in this group. In the no-CTEPH@FU group, all 1364 central pulmonary arteries and 2480 segmental pulmonary arteries were scored at baseline and at follow-up. Central and segmental pulmonary arteries were scored as normal or affected and was further sub-classified as: 1. central thrombus, 2. total thrombotic occlusion, 3. mural thrombus, 4. web or 5. tapered pulmonary artery. Morphological pulmonary artery characteristics were presented as percentage of the total central or segmental vasculature. We observed no calcifications in thrombotic pulmonary arteries.

Bronchial collaterals could not be analyzed in 5/165 patients due to suboptimal contrast timing. Baseline scans from the remaining 160 patients were scored for the presence of bronchial collaterals. We observed more bronchial collaterals in CTEPH@FU patients compared to no-CTEPH@FU (50% vs. 8%; p<0.001). In both groups, the presence of bronchial collaterals did not change after anticoagulant treatment (**Table 2**). RV/LV ratio at acute PE diagnosis was higher in CTEPH@FU compared to no-CTEPH@FU (1.5±0.5 vs. 1.0±0.3; p<0.001; **Table 2**) and did not change after anticoagulant treatment in CTEPH@FU. In contrast, in no-CTEPH@FU, RV/LV ratio decreased significantly after anticoagulant treatment (1.0±0.3 vs. 0.9±0.2; p<0.001; **Table 2**). Accordingly, pulmonary artery diameter at acute PE diagnosis was higher in CTEPH@FU compared to no-CTEPH@FU (34±5 vs. 28±4; p<0.001; **Table 2**) and did not change after anticoagulant treatment in CTEPH@FU. In contrast, in no-CTEPH@FU, the pulmonary artery diameter decreased significantly after anticoagulant treatment (28±4 vs. 26±3; p<0.001; **Table 2**).

Pulmonary arterial morphology at acute PE diagnosis

The different types of morphology of central and segmental vessels at the time of the initial acute PE diagnosis are presented in **Figure 2**. CTEPH@FU patients had significantly fewer normal central vessels (55 vs. 71%; p<0.01) and central thrombi (13 vs. 27%; p<0.01) at the time of the initial PE diagnosis. In contrast, they showed more total thrombotic occlusions (9 vs. 2%; p<0.001), mural thrombi (21 vs. 1%; p<0.001) and webs (3 vs. 0%; p<0.05) in the central vessels. No tapered pulmonary arteries were observed in the central pulmonary arteries. Regarding the morphology of segmental

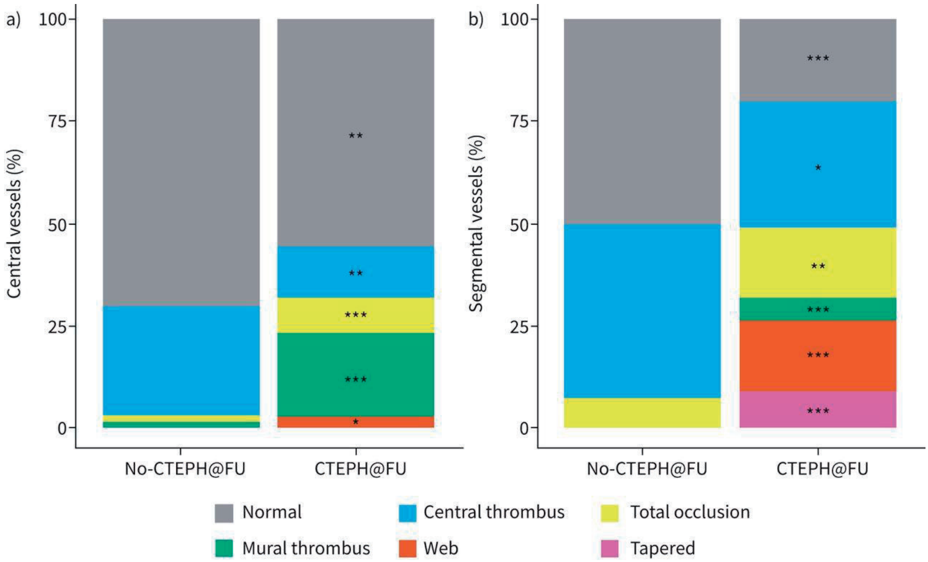

Figure 2: Pulmonary arterial morphology at acute pulmonary embolism diagnosis

Note: A) Pulmonary arterial morphology of all central pulmonary arteries for no-CTEPH@FU and CTEPH@FU. B) Pulmonary arterial morphology of all segmental pulmonary arteries no-CTEPH@FU and CTEPH@FU. CTEPH@FU: patients with an ultimate diagnosis of CTEPH at follow-up; no-CTEPH@FU: patients without an ultimate diagnosis of CTEPH at follow-up.

Statistics for the differences between no-CTEPH@FU and CTEPH@FU group: independent t-test with Bonferroni correction. *:p<0.05; **:p<0.01; ***:p<0.001.

vessels at the time of the initial acute PE, CTEPH@FU patients had significantly fewer normal vessels (20 vs. 50%; $p<0.001$) and central thrombi (31 vs. 42%; $p<0.05$) too. In contrast, CTEPH@FU patients had more total thrombotic occlusions (17 vs. 7%; $p<0.01$), mural thrombi (5 vs. <1%; $p<0.001$), webs (18 vs. <1%; $p<0.001$) and tapered pulmonary arteries (9 vs 0% $p<0.001$).

Central pulmonary arterial morphology after anticoagulant treatment

Changes in central pulmonary morphology after anticoagulant treatment are presented in **Figure 3** (and **Appendix A**). Although both groups showed a significant improvement in the percentage of affected vessels, significantly more vessels remained affected after follow-up in the CTEPH@FU group (24 vs. 1% in the no-CTEPH@FU group, $p<0.001$). In both groups, almost all central thrombi had resolved after follow-up. In addition, the number of total thrombotic occlusions and mural thrombi significantly decreased after oral anticoagulant treatment in both groups (p-interaction: NS). However, CTEPH@FU had a higher number of residual total thrombotic occlusions (4 vs. <1%; $p<0.01$) and mural thrombi (15 vs. <1%; $p<0.001$) at follow-up. Although residual total thrombotic occlusions were observed at follow-up, the lumen size of these total occlusions had decreased (13.1±5.1 vs. 11.8±4.1 mm; $p<0.001$). The number of webs at follow-up was higher in CTEPH@FU (5 vs. <1% in no-CTEPH@FU, $p<0.01$) and these webs originated from webs already present at baseline, or from central thrombi, total thrombotic occlusions and mural thrombi. None of the central pulmonary arteries were tapered.

Segmental pulmonary arterial morphology after anticoagulant treatment

Changes in segmental pulmonary morphology after anticoagulant treatment are presented in **Figure 4**. In line with findings in the central pulmonary vasculature, both groups showed a decrease in percentage of affected vessels. However, more affected vessels persisted after follow-up in CTEPH@FU (58 vs. 2%; $p<0.001$). After follow-up, almost no central thrombi (<1%) or total thrombotic occlusions (<1%) had persisted, regardless of group. In addition, the lumen size of residual total thrombotic occlusions at follow-up decreased (6.3±2.5 vs. 5.6±2.1 mm at follow-up; $p<0.05$). However, mural thrombi did not change their morphology and were mainly observed in CTEPH@FU patients at follow-up (5 vs. <1%: $p<0.001$).

Remarkably, none of the webs or tapered pulmonary arteries observed at baseline in CTEPH@FU had resolved after follow-up (**Figure 5**). In fact, the total number of webs and tapered pulmonary arteries increased in CTEPH@FU despite anticoagulant treatment (resp. from 18 to 33% and 9 to 19%; both $p<0.001$). **Figure 6** represents the origin of webs and tapered vessels detected at follow-up. Webs at follow-up originated either from webs already present at baseline (54% in CTEPH@FU and 6% in no-CTEPH@FU), or

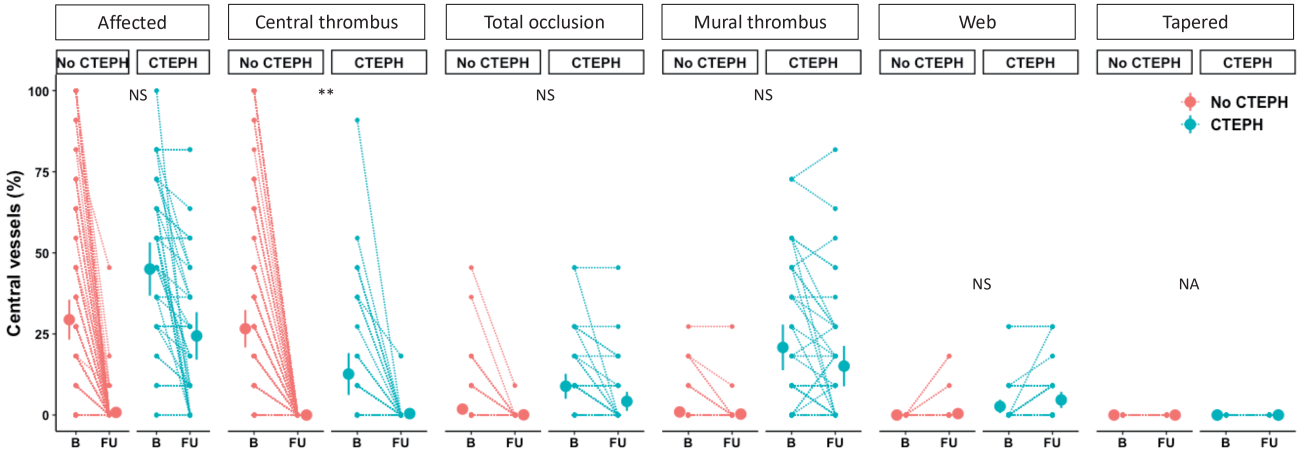

Figure 3: Effect of anticoagulant treatment on central pulmonary arterial morphology

Note: Data are presented as mean±SE. CTEPH: patients with an ultimate diagnosis of CTEPH at follow-up; no CTEPH: patients without an ultimate diagnosis of CTEPH at follow-up.

Statistics: two-way ANOVA repeated measurements. **:p<0.01.

Abbreviations: B, baseline; FU, follow-up; NS, not significant; NA, not applicable.

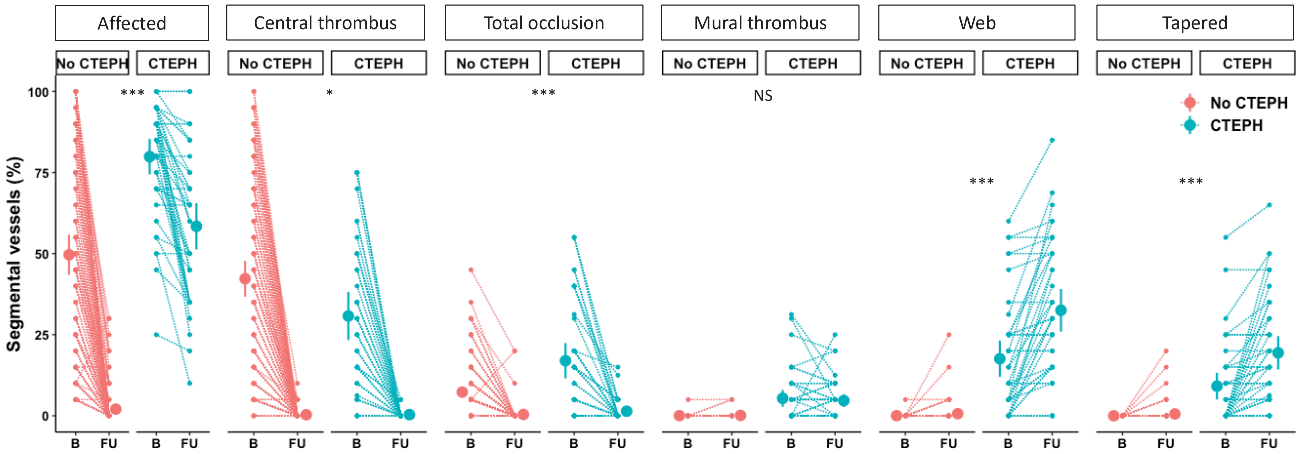

Figure 4: Effect of anticoagulant treatment on segmental pulmonary arterial morphology

Note: Data are presented as mean±SE. CTEPH: patients with an ultimate diagnosis of CTEPH at follow-up; no CTEPH: patients without an ultimate diagnosis of CTEPH at follow-up.

Statistics: two-way ANOVA repeated measurements. ***:p <0.001; *:p <0.05.

Abbreviations: B, baseline; FU, follow-up; NS, not significant

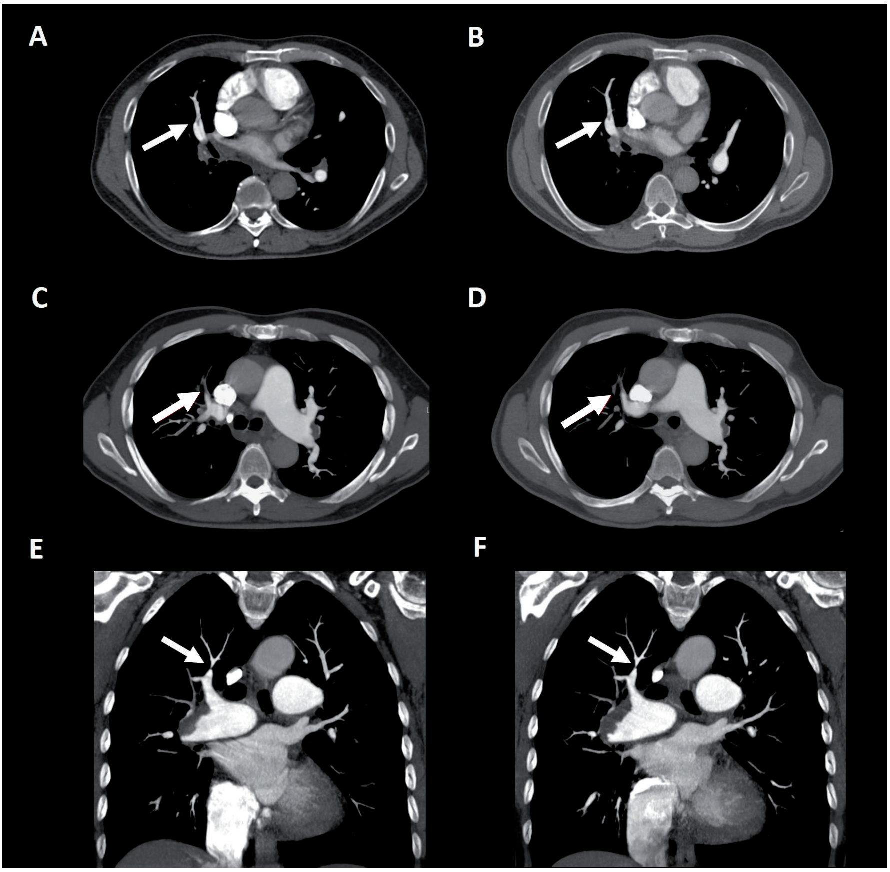

Figure 5: Webs and tapered pulmonary arteries did not change morphology after anticoagulant treatment
Note: CTPA of a CTEPH patient showing a web in the right middle lobe medial segmental pulmonary artery at baseline (A) that was unchanged after anticoagulant treatment at follow-up (B). Tapered pulmonary artery detected in the right anterior segmental pulmonary artery at baseline (C) that was unchanged after anticoagulant treatment at follow-up (D). A web detected in the right posterior segmental pulmonary artery at baseline (E) that was unchanged after anticoagulant treatment at follow-up (F).

from central thrombi (32% in CTEPH@FU and 69% in no-CTEPH@FU), total thrombotic occlusions (9% in CTEPH@FU and 25% in no-CTEPH@FU) and mural thrombi (5% in CTEPH@FU and 0% in no-CTEPH@FU). Tapered pulmonary arteries at follow-up were either already present at baseline (47% CTEPH@FU and, 0% no-CTEPH@FU), or evolved from central thrombi (7% CTEPH@FU and, 14% no-CTEPH@FU) and total thrombotic occlusions (46% CTEPH@FU and 86% no-CTEPH@FU).

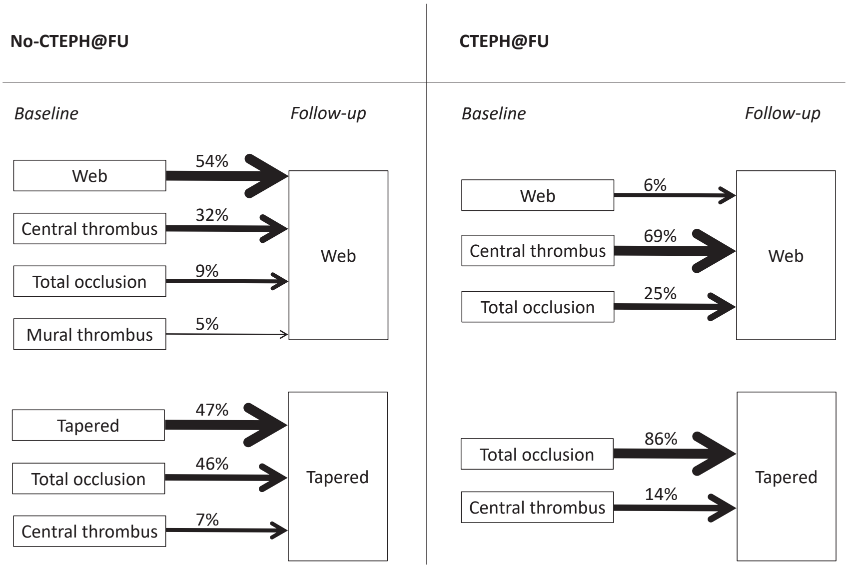

Figure 6: Origin of detected webs and tapered pulmonary arteries at follow-up
Note: Data are presented as percentage of segmental webs or tapered pulmonary arteries at follow-up. CTEPH@FU: patients with an ultimate diagnosis of CTEPH at follow-up; no-CTEPH@FU: patients without an ultimate diagnosis of CTEPH at follow-up.

DISCUSSION

To the best of our knowledge, this is the first study describing the morphological changes in pulmonary arteries after anticoagulation therapy for acute PE in patients with and without an ultimate diagnosis of CTEPH. Our study demonstrates that: 1) central thrombi usually resolve during anticoagulant treatment for PE, while mural thrombi and total thrombotic occlusions either resolve or evolve into a web or tapered pulmonary artery; 2) webs and tapered pulmonary arteries observed at baseline do not resolve after anticoagulant treatment; 3) more webs and tapered pulmonary arteries are observed at follow-up than at baseline, because a proportion of central thrombi and total thrombotic occlusions evolve into webs and tapered pulmonary arteries; 4) patients who later on develop CTEPH present with more total thrombotic occlusions, mural thrombi, webs and tapered pulmonary arteries at their initial CTPA than patients who do not develop CTEPH.

CTEPH patients have a different pulmonary arterial morphology at acute PE

Little is known about the morphological evolution of acute and chronic PE over time under the influence of anticoagulant treatment. Previous studies reported on the prediction of CTEPH on the CTPA at the time of the initial PE. We previously showed that the presence of webs and tapered pulmonary arteries at the initial PE are the only independent predictors for CTEPH.[9] In an attempt to find additional CTPA-biomarkers predicting CTEPH, a recent study excluded all PE CTPAs with webs and tapered pulmonary arteries and observed that total thrombotic occlusions were also predictive of CTEPH.[11] These findings are in line with our observations, as we found that patients who develop CTEPH have more mural thrombi, total thrombotic occlusions, webs and tapered pulmonary arteries already at the time of their first PE diagnosis. What our study adds to the current literature is a detailed description of the evolution of specific types of vascular morphologies in individual patients from PE diagnosis to 6-7 months of follow-up after initiation of anticoagulant treatment. Our analysis may lead to a better and earlier identification of patients at risk for CTEPH.

Only webs and tapered pulmonary arteries indicate chronic PE

Although chronic PE lesions were mainly observed in CTEPH@FU, we also observed some chronic lesions in no-CTEPH@FU after anticoagulant treatment. This is in line with our previous studies, where we observed that 16% of all acute PE patients have chronic PE after six months of anticoagulant treatment.[16] Chronic PE lesions in CTEPH are thought to result from incomplete clot resolution after acute PE.[20] However, around 25% of CTEPH patients do not have a history of documented acute PE.[21] This begs the question whether CTEPH is a true long-term complication of acute PE. Alternative explanations for the origin of CTEPH include one or more episodes of "clinically silent PE", and *in situ* thrombosis.[22] In accordance with our observations, it was previously suggested that the chronic PE lesions in CTEPH are often already present at the time of the presumptive first episode of acute PE.[4,10] In these studies, chronic PE was deemed proven when webs, tapered pulmonary arteries, mural thrombi and total thrombotic occlusions were observed. Webs and tapered vessels are usually associated with chronic PE, central thrombi are regarded to indicate acute PE, whereas mural thrombi and total thrombotic occlusions have been described to occur in acute as well as chronic PE.[13,23] By analyzing the natural evolution of CTPA findings in individual patients, our study demonstrated that webs and tapered pulmonary arteries do not resolve after anticoagulation treatment and sometimes arise from other vascular lesions. Therefore, webs and tapered pulmonary arteries always indicate chronic PE. We also demonstrated that while some mural thrombi and total occlusions persist after anticoagulant treatment, others do resolve after anticoagulant treatment. Therefore, mural thrombi and total thrombotic occlusions cannot be exclusively categorized as chronic lesions.

Strengths and limitations

Strengths of our study are the unique dataset and design leading to a better understanding of the evolution of acute and chronic PE after anticoagulant treatment. Ideally, a prospective study in all acute PE patients would have avoided a potential selection bias. However, since only 1-3% of acute PE patients develops CTEPH, an enormous number of acute PE patients would need a follow-up CTPA to include sufficient cases of CTEPH, which is practically infeasible.[4] Therefore, we decided to perform a case-cohort study, resulting in a homogenous group of acute PE patients with a follow-up CTPA performed after continuous anticoagulant treatment, resulting in patients with and without CTEPH at follow-up. The no-CTEPH@FU was selected earlier in time compared to the CTEPH@FU group. Due to changes in the guideline for acute PE treatment strategy, more patients were treated with VKA in no-CTEPH@FU group.[3,24] However, we assume that different oral anticoagulant treatment would not affect pulmonary vascular morphology differently, as DOACs are shown to be non-inferior to VKAs in the treatment of acute PE.[25]

The no-CTEPH@FU group did not undergo a right heart catheterization to exclude CTEPH. In this group, the presence of CTEPH was considered unlikely during the 2,5 years following initial PE based on either the absence of persistent dyspnea or the absence of signs of CTEPH on echocardiography or VQ-scanning.[16]

Clinical implications

The presence of webs and tapered pulmonary arteries after at least three months of anticoagulant treatment is one of the diagnostic criteria for CTEPH according current guidelines. With this study we demonstrate that webs and tapered pulmonary arteries do not resolve after anticoagulant treatment for acute PE. Therefore, in patients who present with persistent dyspnea after PE and who had webs and tapered pulmonary arteries at the diagnostic CTPA, careful attention for the presence of CTEPH is required.

Conclusion

During anticoagulant treatment for acute PE almost all central thrombi completely resolved, whereas mural thrombi and total thrombotic occlusions either resolved or evolved into a web or tapered pulmonary artery. Interestingly, none of the webs and tapered pulmonary arteries resolved after anticoagulant treatment. Therefore, webs and tapered pulmonary arteries at the time of PE diagnosis strongly indicate a state of chronic PE and should raise awareness for possible CTEPH, particularly in patients with persistent dyspnea after anticoagulant treatment for acute PE.

REFERENCES

1. Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circulation Research 2016; 118(9): 1340-7.
2. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nature Reviews Disease Primers 2018; 4: 18028.
3. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. European Heart Journal 2019; 40(42): 3453-5.
4. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. European Respiratory Journal 2017; 49(2): 1601792.
5. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. The New England Journal of Medicine 2004; 350(22): 2257-64.
6. Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. Circulation 2014; 130(6): 508-18.
7. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. European Heart Journal 2016; 69(2): 177.
8. Delcroix M, Torbicki A, Gopalan D, et al. ERS Statement on Chronic Thromboembolic Pulmonary Hypertension. European Respiratory Journal 2021;57(6):2002828.
9. Ende-Verhaar YM, Meijboom LJ, Kroft LJM, et al. Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study. The Journal of Heart and Lung Transplantation 2019; 38(7): 731-8.
10. Guerin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thrombosis and Haemostasis 2014; 112(3): 598-605.
11. Lorenz G, Saeedan MB, Bullen J, et al. CT-Based Biomarkers for Prediction of Chronic Thromboembolic Pulmonary Hypertension After an Acute Pulmonary Embolic Event. AJR American Journal of Roentgenology 2020; 215(4): 800-6.
12. Rogberg AN, Gopalan D, Westerlund E, Lindholm P. Do radiologists detect chronic thromboembolic disease on computed tomography? Acta Radiologica 2019; 60(11): 1576-83.
13. Nijjer SS, Pabari PA, Stegemann B, et al. The limit of plausibility for predictors of response: application to biventricular pacing. JACC Cardiovascular Imaging 2012; 5(10): 1046-65.
14. Gopalan D, Blanchard D, Auger WR. Diagnostic Evaluation of Chronic Thromboembolic Pulmonary Hypertension. Annals of the American Thoracic Society 2016; 13 Suppl 3: S222-39.
15. Hoang JK, Lee WK, Hennessy OF. Multidetector CT pulmonary angiography features of pulmonary embolus. Journal of Medical Imaging and Radiation Oncology 2008; 52(4): 307-17.
16. den Exter PL, van Es J, Kroft LJ, et al. Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. Thrombosis and Haemostasis 2015; 114(1): 26-34.
17. De richtlijnen database: Antithrombotisch beleid. 2015. https://internisten.nl/files/Richtlijn%20 Antitrombotisch%20beleid_def.pdf.
18. Braams NJ, Ruigrok D, Schokker MGM, et al. Pulmonary vascular imaging characteristics after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. The Journal of Heart and Lung Transplantation 2020; 39(3): 248-56.

19. Walker CM, Rosado-de-Christenson ML, Martinez-Jimenez S, Kunin JR, Wible BC. Bronchial arteries: anatomy, function, hypertrophy, and anomalies. Radiographics 2015; 35(1): 32-49.
20. Pepke-Zaba J, Ghofrani HA, Hoeper MM. Medical management of chronic thromboembolic pulmonary hypertension. European Respiratory Review 2017; 26(143).
21. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011; 124(18): 1973-81.
22. Klok FA, Couturaud F, Delcroix M, Humbert M. Diagnosis of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. European Respiratory Journal 2020;55(6):2000189.
23. Castaner E, Gallardo X, Ballesteros E, et al. CT diagnosis of chronic pulmonary thromboembolism. Radiographics 2009; 29(1): 31-50; discussion -3.
24. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e419S-e96S.
25. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. Journal of Thrombosis and Haemostasis 2014; 12(3): 320-8.

Appendix A: Effect of anticoagulant treatment on central and segmental pulmonary arterial morphology

	Total (n=165)			**CTEPH@FU (n=41)**			**No-CTEPH@FU (n=124)**			P-interaction
	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value	
Central (%)										
Affected	33%	7%	***	45%$^{\#\#}$	24%†††	***	29%	1%	***	NS
Central thrombus	23%	<1%	***	13%$^{\#\#}$	<1%	***	27%	0%	***	<0.01
Total thrombotic occlusion	4%	1%	***	9%$^{\#\#\#}$	4%††	**	2%	<1%	**	NS
Mural thrombus	6%	4%	**	21%$^{\#\#\#}$	15%†††	*	1%	<1%	*	NS
Web	1%	1%	**	3%$^{\#}$	5%††	*	0%	<1%	NS	NS
Tapered	0%	0%	NA	0%	0%	NA	0%	0%	NA	NA
Segmental (%)										
Affected	57%	16%	***	80%$^{\#\#\#}$	58%†††	***	50%	2%	***	<0.001
Central thrombus	39%	<1%	***	31%$^{\#}$	<1%	***	42%	<1%	***	<0.05
Total thrombotic occlusion	10%	<1%	***	17%$^{\#\#}$	1%	***	7%	<1%	***	<0.001
Mural thrombus	1%	1%	NS	5%$^{\#\#\#}$	5%†††	NS	<1%	<1%	NS	NS
Web	4%	8%	***	18%$^{\#\#\#}$	33%†††	***	<1%	1%	*	<0.001
Tapered	2%	5%	***	9%$^{\#\#\#}$	19%†††	***	0%	<1%	*	<0.001

Note: Data are presented as percentage of central or segmental pulmonary arteries. CTEPH@FU: patients with an ultimate diagnosis of chronic thromboembolic pulmonary hypertension at follow-up; No-CTEPH@FU: patients without an ultimate diagnosis of chronic thromboembolic pulmonary hypertension at follow-up; n: number; NA: not applicable NS: not significant; Statistics: Differences between baseline and follow-up measurements were performed using dependent t-test with Bonferroni correction (***:p <0.001, **:p <0.01, *:p <0.05). Differences between the groups at one time point were tested using independent t-test with Bonferroni correction. Differences in baseline morphology between the groups: $^{\#\#\#}$:p <0.001, $^{\#\#}$:p <0.01, $^{\#}$:p <0.05. Differences in follow-up morphology between the groups: †††:p <0.001, ††:p <0.01, †:p <0.05. Differences over time between the groups were tested using two-way ANOVA with interaction testing.