Diagnosis, management and prognosis of symptomatic and incidental pulmonary embolism

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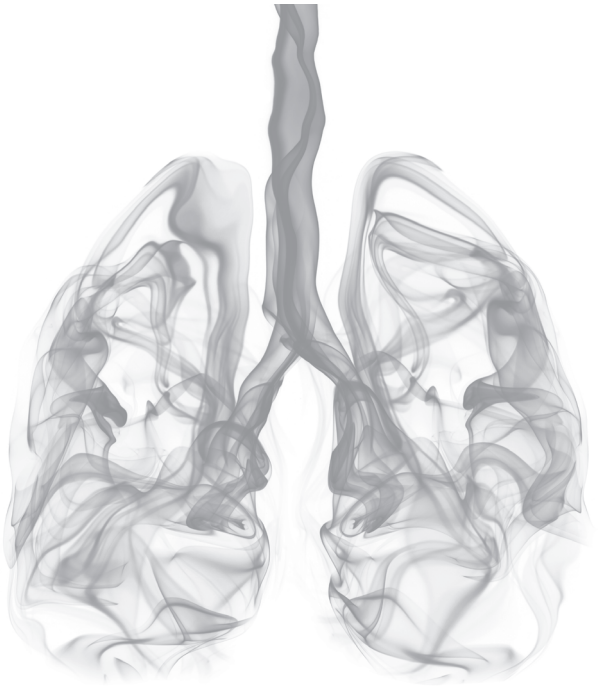
CHAPTER 8

Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism



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ABSTRACT

The systematic assessment of residual thromboembolic obstruction after treatment for acute pulmonary embolism (PE) has been understudied. This assessment is of potential clinical importance, should clinically suspected recurrent PE occur, or as tool for risk stratification of cardiopulmonary complications or recurrent venous thromboembolism (VTE). This study aimed to assess the rate of PE resolution and its implications for clinical outcome. In this prospective, multi-center cohort study, 157 patients with acute PE diagnosed by CT pulmonary angiography (CTPA) underwent follow-up CTPA-imaging after 6 months of anticoagulant treatment. Two expert thoracic radiologists independently assessed the presence of residual thromboembolic obstruction. The degree of obstruction at baseline and follow-up was calculated using the Qanadli obstruction index. All patients were followed-up for 2.5 years. At baseline, the median obstruction index was 27.5%. After six months of treatment, complete PE resolution had occurred in 84.1% of the patients (95% confidence interval (CI): 77.4-89.4%). The median obstruction index of the 25 patients with residual thrombotic obstruction was 5.0%. During follow-up, 16 (10.2%) patients experienced recurrent VTE. The presence of residual thromboembolic obstruction was not associated with recurrent VTE (adjusted hazard ratio: 0.92; 95% CI: 0.2-4.1). This study indicates that the incidence of residual thrombotic obstruction following treatment for PE is considerably lower than currently anticipated. These findings, combined with the absence of a correlation between residual thrombotic obstruction and recurrent VTE, do not support the routine use of follow-up CTPA-imaging in patients treated for acute PE.

INTRODUCTION

Although pulmonary embolism (PE) is traditionally considered to be an acute disease, and its treatment and medical follow-up is generally limited to approximately 3-6 months from diagnosis, it is now increasingly recognized that acute PE has serious impact on patients' long-term clinical outcomes and health status.[1] Not only do recurrent venous thromboembolic events (VTE) occur in over 20% of the patients during the initial five years of follow-up[2], more than half of the patients still report dyspnoea or an impaired physical performance 6 months to 3 years after an successfully treated acute event, for reasons that are as yet unclear.[3,4] Moreover, the quality of life of long-term survivors of acute PE is lower compared to control populations.[5] To provide more pathophysiologic, and perhaps prognostic, insight in the long-term course of acute PE, information on the resolution of PE has become of recent interest. Incomplete thromboembolic clearance has been proposed to be predictive for recurrent thromboembolic episodes, and may ultimately lead to chronic thromboembolic pulmonary hypertension (CTEPH).[6,7] The latter, although rare, may be considered the most severe end of the spectrum of long-term consequences of acute PE. Assessment of the presence of residual thrombotic obstruction after completion of anticoagulant treatment might also facilitate differentiation between residual and new emboli in the diagnostic work-up of patients with suspected recurrent PE.[8] This is of importance given the therapeutic consequences of prolonged or even lifelong anticoagulant treatment resulting from an incorrect diagnosis of recurrent PE, with its high costs, inconvenience and bleeding risk.[9]

Despite these potentially important clinical implications, to date, little is known on the natural resolution of PE following anticoagulant treatment. Although a systematic review suggested that 57% of all patients with PE have incomplete PE resolution 6 months after diagnosis,[10] the studies on which this pooled percentage was based were small and differed largely with respect to the duration of anticoagulant treatment, type of imaging test (i.e. CT-pulmonary angiography (CTPA) or VQ-scanning), and timing of the follow-up scan.[11-13] Moreover, prospective studies assessing residual thromboembolic obstruction with CTPA, which has emerged as the first-line imaging test for the detection of acute PE[14], are lacking.

In this prospective follow-up study we aimed to systematically assess the course of clot resolution, as well as the course of right ventricular dilatation, as assessed with CTPA in patients who completed six months of anticoagulant treatment for acute PE. Secondary objectives were to assess the predictive value of residual thrombotic obstruction for the development of recurrent VTE or CTEPH during 2.5 years of follow-up.

METHODS

Patients

In this prospective multi-center cohort study, patients with acute hemodynamically stable PE, objectively confirmed by CTPA, were included between September 2008 and October 2011 in four academic and two non-academic hospitals. Patients with first or recurrent PE, either provoked or unprovoked, and a planned regular treatment with anticoagulants for at least 6 months were eligible for this study. Exclusion criteria were refusal by patient to undergo a second CT scan, logistic reasons, age below 18 years, pregnancy, life expectancy less than 6 months, impossibility to return for follow-up, inserted vena cava filter, thrombolytic therapy, allergy to intravenous iodinated contrast agent, or severe renal insufficiency (estimated creatinine clearance < 30 ml/min). Institutional ethical review boards of all participating centers approved the study protocol and written informed consent was obtained from all patients.

All patients were treated with LMWH and vitamin K antagonists (VKA) according the standard care for patients with PE recommended by the Dutch CBO guideline. This consisted of dose-adjusted doses of LMWH for a duration of at least 5 days. When the international normalized ratio (INR) was 2.0 or more for two consecutive days, LMWH was discontinued. VKA were administered and dosed according to the national consensus of the Dutch Thrombosis Services with adjustments made using a standardized nomogram, aiming at an INR range of 2.0-3.0. Patients with active malignant disease received LMWH as mono-therapy for at least 3 months. Anti-Xa levels were not routinely monitored.

Procedure

Patients underwent a follow-up CTPA 6 months after the diagnosis of PE. Subsequently, a half yearly follow-up during the following two years was performed by telephone or clinical visits to assess their clinical outcome. Patients were instructed to contact the study center or treating physician in case of any complaints suggestive of recurrent PE or DVT. In case of a clinically suspected recurrent PE or DVT, objective imaging tests were performed, including CTPA or compression ultrasound, respectively. In case of death during follow-up, autopsy or an independent medical report was required to determine the cause of death. Deaths were classified as due to PE in case of confirmation by autopsy, in case of an objective positive test for PE prior to death or if PE could not be confidently excluded as the cause of death.

Patients with otherwise unexplained persistent dyspnea on exertion or at rest during follow-up, as assessed with a standardized questionnaire, were considered to have a suspicion of CTEPH. These patients underwent trans-thoracic echocardiography. If supportive findings were present, patients underwent further diagnostic workup

consisting of VQ-scanning and pulmonary angiography, with direct measurement of the pulmonary-artery pressure. CTEPH was considered to be present if the systolic and mean pulmonary-artery pressures exceeded 40 mm Hg and 25 mmHg, respectively; the pulmonary-capillary wedge pressure was normal; and there was angiographic evidence of pouching, webs, or bands with or without post-stenotic dilatation, intimal irregularities, abrupt narrowing, or total occlusion[7].

CTPA data acquisition and reconstructions

Standard CTPA was performed using a 16-slice, 64-slice or 320-slice CT scanner with acquisition of 0.5 - 1 mm slices (depending on the scanner) in transverse orientation of the entire chest for diagnosing or excluding PE. The tube current was 250-300 mA and the tube voltage 100 kV. Acquisitions were performed during a single breath-hold, lasting 10-12 seconds or less, depending on the type of scanner. 80-100 ml of contrast agent was injected in an antecubital vein with an injection rate of 4.0 ml/sec, with contrast timing for pulmonary artery enhancement. The effective radiation dose varied between 2.8-3.9 mSv.

Diagnosis of PE and residual thrombotic obstruction

Pulmonary embolism was defined as the presence of at least one filling defect in the pulmonary artery tree. Residual thrombotic obstruction at the follow-up CTPA was defined as any of the following: 1) a complete obstruction by thrombus of a pulmonary artery that shows a decrease in diameter as compared to surrounding non-obstructed pulmonary arteries, or 2) an eccentric partial intraluminal filling defect with an obtuse angle to the vessel wall, or 3) an abrupt tapering of a vessel which is usually the consequence of recanalization of a previously completely obstructed pulmonary artery by thrombus, 4) a thickening, sometimes irregularly, of the pulmonary arterial wall, with narrowed lumen if recanalization had occurred, or 5) presence of intraluminal webs or bands, or 6) an intraluminal filling defect with the morphology of an acute PE present for > 3 months[15, 16]. The degree of pulmonary artery obstruction at baseline and at follow-up CTPA was quantified using the scoring system of Qanadli et al[17]. In summary, this index is defined as the number of segmental artery branches that are blocked, corrected by a factor of 1 for partial blockage, or a factor of 2 for complete obstructive PE. Using this scoring system, 40 is the highest possible score (thrombus completely obstructing the pulmonary trunk), corresponding with a 100% obstruction index.

Diagnostic and follow-up CTPA-scans were independently analyzed by two expert thoracic radiologists of different academic medical centers (LJMK and LFMB), who were unaware of clinical information, initial report of the scan and timing of the scan (i.e. diagnostic or follow-up CTPA). The radiologists were allowed to use post processing tools for optimal viewing as is used in clinical practice (e.g., zoom function, slab function,

window-with and window-level adaptations, orthogonal and multiplanar orientations). In case of disagreement, a consensus reading was carried out. Since the inter-observer agreement of the Qanadli score for the diagnosis of PE has previously reported to be excellent (r = 0.944),[17] we performed an interim analysis on the interclass coefficient (ICC) of the scans at baseline. If the ICC after one-third of the scans was >90%, we discontinued the consensus. All follow-up CT images were assessed by the two independent radiologists for the presence and the degree of residual thrombotic obstruction.

Right ventricular / left ventricular ratio

In all patients, parallel to the diagnosis of PE, right ventricular diameter in relation to left ventricular diameter (RV/LV ratio) was measured at CTPA, representing right ventricular function at time of diagnosis and after 6 months of treatment. Right and left ventricular diameters were measured on axial images by identifying the maximal distance between the ventricular endocardium and the intraventricular septum, perpendicular to the long axis. Previous studies have established an association between an RV/LV ratio > 1.0 and an unfavorable short-term clinical outcome.[18] We therefore assessed the proportion of patients with an RV/LV larger than 1.0 at baseline and follow-up.

Statistical analysis

The proportion of patients with residual thrombotic obstruction was calculated, with the corresponding 95% confidence intervals (CI). To assess the inter-observer agreement, the interclass correlation coefficient (ICC) was calculated for the degree of thrombotic obstruction and the multi-reader kappa (κ) coefficient for the presence of residual thrombotic obstruction at follow-up CTPA. Differences in patient demographics, comorbidities and PE characteristics between patients with and without residual thrombotic obstruction were tested for statistical significance with the use of the Chi-square-test or the Fisher's exact test for categorical data and the student-t test or Mann Whitney test for continuous variables. Univariate and multivariate regression analysis were performed for the assessment of significant independent predictors of residual thrombotic obstruction. Any variable achieving a p-value of less than 0.25 was included in an unconditional multivariate regression model.

The method of Kaplan and Meier was used to estimate the cumulative probability of recurrent VTE and mortality during follow-up. The patients were censored at time of recurrent VTE, death, or at the end of follow-up, whichever occurred first. With the use of a Cox proportional hazard model, hazard ratios (HR) were derived for the association between residual thrombotic obstruction and recurrent VTE. HRs were adjusted for age, gender, history of VTE and active malignancy. P-values < 0.05 were considered statistically significant. All analyses were conducted using statistical software SPSS, version 19.0; (SPSS Inc; Chicago, IL).

RESULTS

A total of 166 patients with PE were included during the study period Figure 1. Six patients were excluded from analysis because either the diagnostic or the follow-up CTPA images were considered non-diagnostic for the definite presence of PE by the expert radiologists in consensus. Two patients were excluded because the initial PE diagnosis was refuted on expert reading in consensus, in one patient the filing defect was considered a motion artifact and in the other patient a beam-hardening artifact. One other patient was excluded because on both the baseline and the follow-up images, the filling defects were caused by infiltration of angiosarcoma in the pulmonary artery. The baseline characteristics of the remaining 157 participants are depicted in Table 1. Mean age was 55 years and 54% of the participants were male. Active malignant disease was present in 18% of the patients and 16% had a history of VTE.

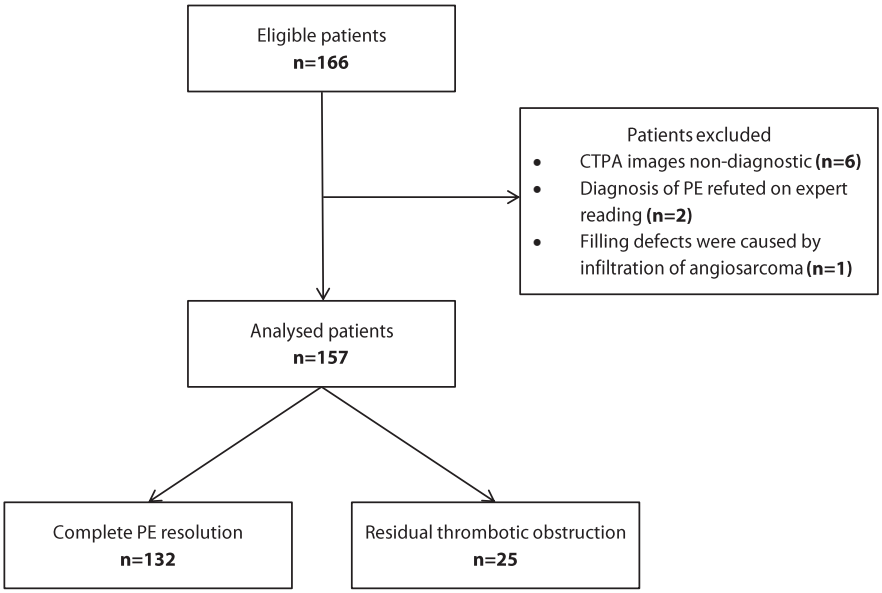

Figure 1. Flow of patients through the study
CTPA computed tomography pulmonary angiography, N, number, PE, pulmonary embolism

In the patients with complete clot resolution, 72.7% were treated for a maximum duration of 6 months. In patients with residual thrombotic obstruction, this rate was 68.0% (p=0.629). The remainder of patients were treated for a duration of one year or longer. Fifteen of the patients (11.3%) with complete clot resolution received long-term LMWH, versus one of the patients (4%) with residual thrombotic obstruction (p=0.264).

Table 1. Patient characteristics

	All patients (n=157)	Residual PE (n=25)	No residual PE (n=132)	*P*-value
Age (mean ± SD)	54.7 (15.7)	54.2 (18.5)	54.8 (15.2)	0.863
Male sex (n, %)	84 (53.5)	12 (48.0)	72 (54.5)	0.547
BMI (mean ± SD)	28.1 (5.9)	28.4 (9.4)	28.1 (5.1)	0.798
DVT at baseline (n, %)	24 (15.3)	6 (24.0)	18 (13.6)	0.211
VTE Risk factors:				
Known thrombophilia (n, %)	14 (8.9)	0 (0.0)	14 (10.6)	0.085
Previous VTE (n, %)	25 (15.9)	8 (32.0)	17 (12.9)	0.017
Active Malignancy (n, %)	28 (17.8)	1 (4.0)	27 (20.5)	0.049
Estrogen use, women (n, %)	14 (19.2)	3 (23.1)	11 (18.3)	0.715
Comorbidities				
COPD (n, %)	7 (4.5)	2 (0.8)	5 (0.4)	0.322
Heart failure (n, %)	1 (0.6)	0 (0.0)	1 (0.8)	1.000
Current smoker	29 (18.5)	5 (20.0)	24 (18.2)	0.722

PE, pulmonary embolism; BMI, body mass index; CHF congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT deep venous thrombosis; N, number; SD, standard deviation; VTE, venous thromboembolism.

Assessment of CTPAs

Contrast delivery was suboptimal but still diagnostic in two diagnostic scans and three follow-up scans. In two other scans, motion artifacts had impaired image quality but were still diagnostic.

The ICC for the degree of thrombotic obstruction at baseline was 0.96, as derived from the first 56 CTPAs that were evaluated. Based on this observation, it was decided that a double reading was not required for the remainder of the baseline CTPAs. For the follow-up scans, which were all assessed by the two expert readers, the interobserver agreement for the dichotomous categories of whether residual thrombotic obstruction was present or not, as expressed by the Kappa, was 0.80.

Residual thromboembolic obstruction

After six months of treatment, consensus reading revealed that complete PE resolution had occurred in 132 patients (84.1%; 95% CI: 77.4-89.4%). Of the 25 patients (15.9%) with residual thrombotic obstruction, nine patients (5.7%; 95% CI: 2.7-10.6%) had residual arterial filling defects, 12 patients (7.6% 95% CI: 4.0-13.0%) had intraluminal webs or bands (Figure 2), three patients (1.9%; 95% CI: 4.0-5.5%) had an abrupt tapering of an artery that was (completely) obstructed at the baseline CTPA and one patient (0.6%; 95% CI: 0.02%-3.5%) had an eccentric partial intraluminal filling defect with an obtuse angle to the vessel wall. When considering only the 143 patients with a first episode of

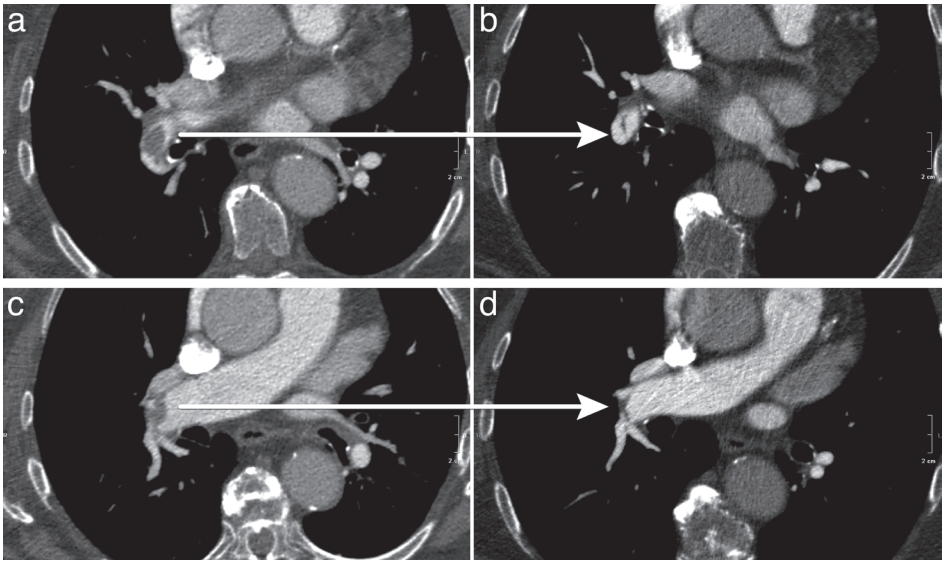

Figure 2. 79-year old female presenting with acute dyspnea on exertion. Computed tomography images, axial orientation. Acute pulmonary embolism in right lung interlobar pulmonary artery (a, c). After six months of anticoagulant treatment (b, d), note presence of band or web in interlobar pulmonary artery, indicating incomplete resolution of the emboli.

PE, complete PE resolution had occurred in 85.3%, compared to 71.4% in the 14 patients with a history of PE (p=0.18).

At time of PE diagnosis, the median obstruction index of the patients was 27.5%. After six months, this had decreased to 0.7% (Table 2). The median obstruction index of the patients with residual thrombotic obstruction was 5.0%. The change in obstruction

Table 2. Assessment of CT-images

	All patients (n=157)	Residual PE (n=25)	No residual PE (n=132)	*P*-value
Median obstruction index at baseline (median, IQR)	27.5 (12.5 - 50.0)	40 (20.0 - 50.0)	25.0 (12.5 - 50.0)	0.186
Obstruction index at baseline >50% (n, %)	41 (26.1)	7 (28.0)	34 (25.8)	0.831
Median obstruction index at follow-up (median, IQR)	0.69 (0.0 - 0.0)	5.0 (2.5 - 5.0)	NA	NA
Decrease in obstruction index	NA	35.0 (13.8 - 46.3)	25.0 (12.5 - 50.0)	0.665
RV/LV ratio at baseline (mean ± SD)	1.02 (0.29)	1.09 (0.27)	1.01 (0.29)	0.179
RV/LV > 1.0 at baseline* (n, %)	64 (40.8)	14 (56.0)	50 (37.9)	0.097
RV/LV ratio at follow-up (mean ± SD)	0.91 (0.13)	0.94 (0.14)	0.90 (0.13)	0.209
RV/LV ratio >1.0 at follow-up* (n, %)	31 (19.7)	7 (28.0)	24 (18.2)	0.258

PE, pulmonary embolism; IQR, inter-quartile range; N, number, SD, standard deviation, RV/LV, right ventricular/left ventricular

*RV/LV ratio >1

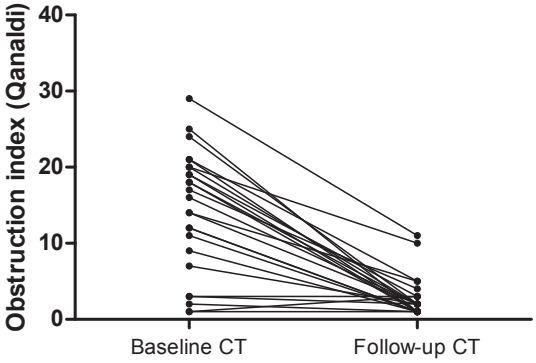

Figure 3. Change in pulmonary thromboembolic obstruction over time for patients with incomplete PE resolution

index over time in each patient with residual PE is depicted in figure 3. There was no difference in the obstruction index at baseline between patients with and without residual thrombotic obstruction. The obstruction index at baseline correlated with BMI (Pearson r=0.199, p=0.02) but with no other patient characteristics.

Predictors of residual thrombotic obstruction

Patients with residual thrombotic obstruction more frequently had a history of VTE compared to those patients with complete PE resolution (32.0% vs. 12.9%, p= 0.017, table 1). In addition, patients with residual thrombotic obstruction less frequently had malignant disease at baseline (4.0% vs 20.5%, p=0.049). No significant differences were observed between these groups for all other baseline characteristics. On multivariate analysis, only previous VTE remained independently associated with the presence of residual thrombotic obstruction: OR: 3.0 (95% CI: 1.1-8.2).

Right ventricular enlargement

The mean RV/LV diameter ratio at baseline was 1.0 (SD 0.29), which significantly reduced to 0.9 (SD 0.13) after 6 months of treatment (P < 0.001). An association was found between RV/LV diameter ratio at baseline and the initial thrombotic obstruction index (Pearson r= 0.44, p<0.001). There was, however, no correlation between the RV/LV ratio and the obstruction index after six months.

At baseline, 64 patients (40.8%) presented with an RV/LV ratio >1.0. After six months of anticoagulant therapy, this number had decreased to 31 patients (19.7%) (P <0.0001). Of the latter patients, 23 (74.2%) already had RV enlargement at baseline. Patients with and without residual thromboembolic obstruction did not differ with regard to the RV/LV ratio and the proportion of patients with an RV/LV ratio > 1.0 (Table 2).

Table 3. Recurrent VTE during follow-up

	Recurrent VTE (n= 16)	No recurrent VTE (n = 141)	*P*-value
Median obstruction index at baseline (median, IQR)	36.25 (13.23 - 52.50)	27.5 (12.5 - 49.38)	0.456
Obstruction index at baseline >50% (n, %)	6 (37.5)	35 (24.8)	0.282
Incomplete PE resolution (n, %)	2 (12.5)	23 (16.3)	0.693
RV/LV ratio at baseline (mean ± SD)	1.08 (0.21)	1.02 (0.29)	0.407
RV/LV > 1.0 at baseline* (n, %)	10 (62.5)	54 (38.3)	0.065
RV/LV ratio at follow-up (mean ± SD)	0.94 (0.18)	0.90 (0.13)	0.354
RV/LV ratio >1.0 at follow-up* (n, %)	5 (31.2)	25 (17.7)	0.223

PE, pulmonary embolism; IQR, inter-quartile range; N, number, SD, standard deviation, RV/LV, right ventricular/left ventricular
*RV/LV ratio >1

Clinical outcome during follow-up

During two years follow-up, 25 patients presented with suspected recurrent PE. Of those, CTPA confirmed recurrent acute PE in 10 patients (6.4%, 95% CI: 3.1 – 11.4%) patients. An additional 6 (3.8%, 95% CI 1.4-8.1%) patients were diagnosed with acute DVT during follow-up. Thus, a total of 16 (10.1%, 95% CI 5.9-16.0%) patients developed recurrent VTE during follow-up, accounting for a cumulative risk of 12.8%. No patients died because of PE during follow-up. The cumulative risk of death was 4.7%.

In 7 patients (4.5%), additional testing was performed for the clinical suspicion of CTEPH during follow-up. In all 7 patients, the presence of CTEPH was considered unlikely based on the results of either echocardiography or VQ-scanning. However, two (29%) of these patients did have intravascular webs on follow-up CT. Only one of these patients had an RV/LV ratio >1.0 on follow-up CT.

Recurrent VTE occurred in 14 (10.6%) of the patients with complete PE resolution and in two patients (8.0%) with residual thrombotic obstruction. The crude HR for recurrent VTE was not significantly different for patients with residual thrombosis versus patients without residual thrombosis (HR: 0.84; 95% CI: 0.19-3.7, p=0.82). After adjustment for age, gender, history of VTE, and malignant disease, this HR was 0.92 (95% CI: 0.2-4.1). In a second analysis, we excluded all patients with a history of VTE, since this may be associated with both the presence of residual PE as the occurrence of recurrent VTE. Taking into account only those patients with a first episode of PE, the crude HR and adjusted HR were 1.1 (95% CI: 0.3-5.1) and 1.1 (95% CI: 0.2 – 4.8), respectively.

Neither recurrent VTE nor death was associated with the obstruction index at baseline or after six months (data not shown). In addition, the RV/LV ratio at baseline or after six months was not significantly different for patients with an uneventful clinical course versus those who experienced recurrent VTE or death.

DISCUSSION

This prospective cohort study, which systematically investigated the natural course of clot resolution in patients treated for acute PE and its impact on their clinical outcome indicates that complete PE resolution occurs in a substantially higher proportion of patients than currently anticipated. Second, the presence of residual thrombotic obstruction did not appear to be of predictive value for the occurrence of recurrent VTE in patients treated for PE.

The rate of residual thrombotic obstruction that we found (16%) is substantially lower and in contrast with previous studies. A systematic review reported residual PE to be present in more than 50% of the patients six months after PE diagnosis.[10] An explanation for this difference may come from the type of imaging test used. Previously, VQ-scanning has been the land-mark tool to assess the presence of residual perfusion defects.[13,19,20] CTPA principally differs from VQ-scanning in detecting PE in that it allows direct embolus visualization, whereas VQ-scans provide an indirect indication for the presence of emboli derived from perfusion defects. Residual perfusion defects detected on VQ-scans may not always reflect the actual presence of residual thrombus, but may be caused by other pulmonary comorbidities.[21] Also, residual perfusion defects may persist even after complete resolution of the emboli. A recently published safety analysis from the EINSTEIN PE study, where 347 patients with acute PE, confirmed by CTPA (n=264) or VQ-scan (n=83) underwent a repeat scan after three weeks of anticoagulant treatment, indeed pointed towards a higher rate of clot resolution assessed with CT-scan (44%) compared to Q-scan (31%).[22] Previous studies that did use CTPA to assess the presence of residual thrombotic obstruction, were designed retrospectively and conducted CTPA after a limited duration of follow-up,[12,23] included a limited sample of patients[12], or only included patients with central PE[11], or did not account for sequelae of chronic PE.[23] The findings of our study are however in line with a recent study by Pesavento et al, who performed follow-up CTPA after 6 months in 113 patients with acute PE and found complete thrombus resolution in 85% of the patients.[24]

To determine the relevance of follow-up CTPA imaging for clinical practice, its benefits should be weighed against its high costs, additional burden for patients, and potential harms, including radiation exposure with its associated lifetime risk of cancer.[25] An important clinical rationale to perform follow-up imaging would be to aid in the differentiation between new and residual PE, in case a patient presents with suspected recurrent PE. Indeed, a recent study suggested that follow-up imaging performed after treatment for either DVT or PE, was associated with an increased diagnostic certainty in patients investigated for suspected recurrent VTE.[8] However, the number of patients with suspected recurrent PE included in this analysis was low (n=38), and in these patients the proportion of diagnostic non-classifiable patients did not differ significantly

between patients with and without baseline imaging. Second, V/Q-scanning was used as follow-up imaging test. In clinical practice CTPA has currently largely replaced VQ-scanning in the diagnostic work-up of patients with suspected (recurrent) PE. The most important advantage of CTPA over VQ-scanning is the low number of inconclusive test results (0.0-3.0% vs. 28-40%).[26] The implementation of CTPA as first-line imaging test for suspected PE makes information on the level of clot resolution using this imaging test relevant, in order to allow valid comparison between images obtained at time of suspected recurrent PE and at time of completion of anticoagulant treatment. The high rate of complete clot resolution that we found may suggest that correctly diagnosing recurrent PE with the use of CTPA is less complicated than currently anticipated.

A second rationale to investigate the presence of residual PE would be its potential prognostic value for subsequent cardiovascular complications. In DVT patients, it has been demonstrated that assessment of residual thrombotic obstruction may aid in the differentiation of patients at risk for recurrent VTE.[27] As the majority of recurrent events included thrombosis in the initially unaffected leg or isolated PE, it has been postulated that residual thrombosis represents a hypercoagulable state. Considering that DVT and PE represent two expressions of a similar clinical pathological process, a similar prothrombotic tendency might be expected in patients with incomplete PE resolution. In the present study, however, no association was found for the presence of residual thrombotic obstruction and the occurrence of recurrent VTE. Given the low number of recurrent events during follow-up and the small proportion of residual PE, it cannot be excluded that our study was underpowered to detect this association. Still, the fact that residual PE was present in a minority of patients and that only two of these patients developed recurrent VTE, does not indicate that implementing follow-up CTPA imaging on a large scale may be useful to identify a subgroup of patients at high risk of recurrences.

Six months after diagnosis, 20% of the patients still had evidence of right ventricular enlargement according to a previously specified margin (RV/LV-ratio > 1.0). The majority of these patients (74%) already had RV enlargement at baseline. A previous study that used serial echocardiograms also indicated that 25% of the hemodynamically stable PE patients still had signs of right ventricular dysfunction six months after diagnosis.[28] Unfortunately, the absence of patients who developed CTEPH during follow-up, does not allow us to draw conclusions on the potential relation between residual PE, persistent or progressive RV enlargement and CTEPH.

The findings of our study are strengthened by its multi-center and prospective design. Furthermore, a pre-specified protocol was used to systematically identify residual thrombotic obstruction with a validated tool after a consistent duration of follow-up, and all scans were analyzed by a central expert adjudication committee. The clinical characteristics of the patients, embolic burden and mean RV/LV ratio at baseline com-

pare well with previous cohorts.[29-31] This may imply that our findings are applicable in a wide range of clinical settings.

This study has some limitations that require comment. Most importantly, its sample size was, although being the largest study up to date in this setting, relatively limited and the incidence of recurrent VTE (12.8%) during follow-up was somewhat lower than reported in previous studies.[32] Although being the largest study in assessing residual thrombotic obstruction with CTPA up to date, the moderate sample size and limited event rate during follow-up do not allow us to draw definite conclusions on the prognostic value of residual thrombotic obstruction. In addition, a larger cohort and longer duration of follow-up are required to assess whether patients with residual thrombotic obstruction are at risk of developing CTEPH. Another limitation that the patients were at a relatively young age at baseline, therefore it is uncertain whether these results also apply to older patients.

In conclusion, this study demonstrates that complete thromboembolic resolution assessed with CTPA following six months of treatment for acute PE, occurs in 84% of the patients. The embolic burden of filling defects that did remain was small and most reflected signs of chronic PE. Follow-up CTPA imaging may therefore be of limited value to improve the diagnostic work-up of patients with suspected recurrent PE. Together with the absence of a clear predictive value for recurrent VTE and the costs and potential harms associated with CTPA, our data do not support routine implementation of follow-up CTPA imaging in clinical practice following treatment of acute PE. Future studies are required to definitely close the gap between incomplete PE resolution and persistent signs of RV enlargement and the development of CTEPH.

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