Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism

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Assessment of clot resolution following treatment of acute pulmonary embolism and its prognostic implications for recurrent venous thromboembolism

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Chapter 11

Abstract

Background: In patients with acute pulmonary embolism (PE), systematic assessment of residual thrombotic obstruction after long-term anticoagulation has been understudied. Nowadays physicians often order repeat CT-scans after six months of anticoagulant treatment without solid evidence for clinical relevance, because assessment of the presence of residual thrombotic obstruction is of clinical importance for these diagnostic baseline CT-scans, in case of clinically suspected recurrent PE or as a tool for risk stratification for recurrent venous thromboembolism (VTE). Information regarding residual thrombosis may be of clinical importance for assessing the need for repeat diagnostic baseline scans.

Methods: In this prospective, multi-center cohort study, consecutive patients with acute PE underwent baseline CT pulmonary angiography (CTPA) following 6 months of anticoagulant treatment. Two independent, expert thoracic radiologists systematically and independently assessed all CTPAs for the presence of residual thrombosis. The degree of pulmonary obstruction was calculated using the obstruction index of Qanadli. A two-year follow-up was performed to assess the correlation between residual thrombotic obstruction and recurrent VTE. Ethical approval and informed consent was obtained.

Results: A total of 141 patients were included. At time of diagnosis, the mean obstruction index was 30% (standard deviation (SD) 20). After six months of treatment, 95% of the patients had complete resolution of PE. Seven patients (5%; 95% CI 2-10%) had residual thrombosis in at least a segmental pulmonary artery, accounting for a mean obstruction index of 8% (SD 5). In another 14 patients (10%; 95% CI 6-16%), non-occlusive post-thrombotic webs or strictures were found. During follow-up, 13 (9.2%) patients experienced recurrent VTE. None of the patients with residual PE developed recurrent VTE.

Conclusion: This study reveals that the incidence of residual thrombotic obstruction following treatment for acute PE is considerably lower than currently assumed. These findings, combined with the absence of a correlation between residual thrombotic obstruction and the occurrence of recurrent VTE, do not support the use of baseline CTPA imaging in patients treated for acute PE.
INTRODUCTION

Acute pulmonary embolism (PE) is a potentially fatal disease with a high tendency to recur, with an incidence of 10-20% of patients in the first two years after cessation of anticoagulant therapy (1:2). The optimal duration of anticoagulant therapy is therefore a topic of ongoing debate. For the long-term management of acute PE, information on the resolution of PE has become of recent interest. Assessment of the presence of residual thrombotic obstruction appears to have two important clinical implications. First, baseline imaging may aid in the differentiation between residual and recurrent emboli in the diagnostic work-up of patients with suspected recurrent PE. This is of importance given the therapeutic consequences of prolonged or even lifelong anticoagulant treatment (3). Second, patients with residual thrombotic occlusion may be at increased risk of recurrent VTE or chronic thromboembolic pulmonary hypertension (4).

However, to date, little is known on the natural resolution of PE following anticoagulant treatment. Although a recent systematic review suggested that more than 50% of all patients with PE have incomplete PE resolution 6 months after diagnosis(5), the studies on which this pooled percentage was based were small and differed largely with respect to the duration of treatment, type of imaging test (i.e. CT-pulmonary angiography (CTPA) or VQ-scanning), and timing of the follow-up scan (6-8). Since CTPA, allowing direct thrombus visualization, has emerged as the first-line imaging test for the detection of acute PE, and considering the potential clinical implications of residual thrombus mentioned above, it would be important to study the natural history of PE and assess the degree of residual thrombotic obstruction with CT-scanning. However, prospective studies on the assessment of residual thrombotic obstruction with CTPA are scarce.

Therefore, this study investigated the course of clot resolution as assessed with CTPA, in patients treated with anticoagulants for six months for an episode of acute PE. Furthermore, this study investigated whether residual thrombotic obstruction is predictive for the development of recurrent VTE.
METHODS

Participants
This was a prospective multi-center cohort study of consecutive, in- and outpatients patients with PE, proven by CTPA. Patients were included in three academic and two non-academic hospitals, between September 2008 and October 2011. Patients with first or recurrent PE, either provoked or unprovoked, and a planned treatment with anticoagulant therapy of at least 6 months were eligible for this study. Exclusion criteria were age below 18 years, pregnancy, life expectancy less than 6 months, impossibility to return for follow-up, inserted vena cava filter or thrombolytic therapy, allergy to intravenous iodinated contrast, 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 included patients.

Procedure
Patients underwent a baseline CTPA 6 months after the diagnosis of PE. Subsequently, a half yearly follow-up during two years was performed by telephone or clinical visits at 12, 18 and 24 months to document the occurrence of recurrent PE, DVT as well as the occurrence of CTEPH. Demographic data and clinical information of the patients were collected on a case record form.

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 a suspected (recurrent) 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 ventilation–perfusion (V-Q) lung 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.

**Imaging protocols**

**MDCT data acquisition and reconstructions**

Standard contrast enhanced MDCT was performed using a 16-slice or 64-slice MDCT scanner with acquisition of 0.5 or 1 mm sections (depending on the weight of the subject) of the entire chest for diagnosing or excluding PE. The rotation time was 0.4 s and the pitch factor 1.4; 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 the antecubital vein with an injection rate of 4.0 ml/sec. The acquisition of the static pulmonary angiography scan was started after automated threshold enhancement detection in the pulmonary trunk. A threshold difference of 100 Hounsfield units was selected for starting the acquisition. The effective radiation dose varied between 2.8-3.9 mSv.

**Diagnosis of PE and obstruction index on CTPA**

Images at baseline and 6 months after the diagnosis of PE were stored on CD-Rom or comparable storage. Diagnostic and follow-up CT-scans were 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). In case of disagreement, a consensus reading was carried out to come to an agreement. Since the inter-observer agreement of the Qanadli score for the diagnosis of PE has previously reported to be excellent ($r=0.944$) (9), 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. However, as we are the first to use the Qanadli index to assess the degree of residual thrombotic obstruction all follow-up CT images were reviewed by the two trained, independent radiologists to assess its inter-observer variability, as expressed by the Kappa coefficient for the presence and the ICC for the degree of residual thrombotic obstruction.

PE at baseline and residual thrombotic occlusion were classified at two levels of thrombus occlusion, i.e. central or peripheral (including lobar, segmental and
subsegmental vessels) using the scoring system of Qanadli et al (9). 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.

**Right ventricular dysfunction**

In all patients, parallel to the diagnosis of PE, right ventricular function was assessed at time of diagnosis and after 6 months treatment by determining right ventricular to left ventricular (RV/LV) diameter ratio on CTPA. Right ventricular dysfunction was considered present when the RV/LV ratio was larger than 1.0 (10).

**Statistical analysis**

Dependent on normal or skewed distribution, quantitative baseline data were presented as mean and standard deviation (SD) or medians and interquartile ranges (IQR), and qualitative data as frequencies.

The proportion of patients with residual thrombosis was calculated, with 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 PE at follow-up. Logistic regression analysis was used to assess the association between baseline characteristics and the presence of residual obstruction. In addition, we assessed whether residual thrombotic obstruction correlated with persistent right ventricular dysfunction.

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 event, at time of death, or at time of the end of follow-up, whichever came 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 148 patients with PE were included. Six patients were excluded from analysis because either the diagnostic scan or the follow-up scan was considered non-interpretable for the definite presence of PE. One other patient was excluded because during follow-up the filling defects were considered to represent infiltration of angiosarcoma in the pulmonary artery. The baseline characteristics of the remaining 141 participants are depicted in Table 1. Mean age was 60 years and 37% of the participants were female. In 13% of the patients, PE was located centrally, and approximately one-third had a history of VTE.

Table 1. Baseline characteristics of patients with pulmonary embolism (PE).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value N=141</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>66 (46.8)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>56 (15)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>28 (5.6)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>History of DVT or PE, n (%)</td>
<td>25 (18)</td>
</tr>
<tr>
<td>History of DVT</td>
<td>11 (7.8)</td>
</tr>
<tr>
<td>History of PE</td>
<td>11 (7.8)</td>
</tr>
<tr>
<td>History of DVT + PE</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Active malignancy, n (%)</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Known thrombophilia, n (%)</td>
<td>12 (8.5)</td>
</tr>
<tr>
<td>Centrally located PE, n (%)</td>
<td>23 (16)</td>
</tr>
<tr>
<td>Estrogen containing drugs, n (%)</td>
<td>13 (9.2)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>26 (18)</td>
</tr>
<tr>
<td>Duration anticoagulant therapy</td>
<td></td>
</tr>
<tr>
<td>6 months, n (%)</td>
<td>89 (63)</td>
</tr>
<tr>
<td>&gt; 6 months, n (%)</td>
<td>38 (30)</td>
</tr>
<tr>
<td>unknown, n (%)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Time span in months between initial CT for acute PE and control CTPA, mean (SD)</td>
<td>5.8 (2.1)</td>
</tr>
</tbody>
</table>

BMI body mass index, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, DVT deep venous thrombosis; IQR interquartile range, N number, SD standard deviation, VTE venous thromboembolism.
Assessment of the CTPAs

Based on the first 56 CTPAs that were evaluated, the ICC for the degree of thrombotic obstruction at baseline was 0.96. 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, the ICC was 0.24. The interobserver reliability for the dichotomous categories of whether residual thrombosis was present or not, was moderate (κ=0.58). After consensus reading, the mean obstruction index at baseline was 30.3% (SD 20.0). After six months, this decreased to 1% (SD 3.7).

After six months of treatment, consensus reading showed complete resolution PE to have occurred in 95% of the patients. Seven patients (5%; 95% CI 2-10%) had residual arterial filling defects in at least a segmental pulmonary artery, accounting for a mean obstruction index of 8% (SD 5). In another 14 patients (10%; 95% CI 6-16%), non-occlusive post-thrombotic webs (n=5, 3.5%) or strictures (n=9, 6.3%) were identified.

The degree of thrombotic obstruction at baseline was associated with the degree of thrombotic obstruction index at follow-up (Spearman r=0.19, p=0.002). No correlation was found between the obstruction index at baseline or follow-up and age, gender, malignancy, BMI, history of VTE, COPD, smoking habits or centrally located PE.

The mean RV/LV diameter ratio at baseline and after six months of anticoagulant treatment was 1.0 (SD 0.30) and 0.9 (SD 0.14), respectively (p=0.22). The interobserver reliability of the RV/LV diameter ratio was both good (ICC=0.86 and ICC=0.75, respectively) (Table 2). An association was found between RV/LV diameter ratio at baseline and the initial thrombotic obstruction index (Pearson r=0.81, p < 0.02). There was, however, no correlation between the RV/LV ratio and the thrombotic obstruction after six months (Spearman r=-0.04, p<0.61).

At baseline, 48 patients presented with right ventricular dysfunction (RV/LV >1.0). After six months of anticoagulant therapy, this number had decreased to 24 patients (p < 0.0001). Residual thrombotic obstruction did not correlate with RV dysfunction at follow-up.

Clinical outcome during follow-up

During two years of follow-up, 23 (16%, 95% CI 11-23) patients presented with suspected recurrent PE. Of those, PE was ruled out in 15 (11%, 95% CI 6.6-17) patients, either with the use of a D-dimer testing or with CTPA. In the remaining 8 (5.7%, 95% CI 2.9-11) patients, CTPA confirmed recurrent PE. An additional 5 (3.5%, 95% CI 1.6-8.0) patients were diagnosed with DVT during follow-up. Thus, a total of 13 (9.2%, 95% CI
5.5-15) patients developed recurrent VTE during follow-up, accounting for a cumulative risk of 13.2%. In 7 (5.0%, 95% CI 2.5-9.9) patients, additional testing was performed for the suspicion of CTEPH. In all 7 patients, the presence of CTEPH was considered unlikely based on either echocardiography or VQ-scanning. A total of 6 (4.2%, 95% CI 2.0-8.9) patients died during follow-up, the cumulative risk for mortality was 6%. In all six patients, death was caused by a malignancy, none was suspected for recurrent PE.

Neither recurrent VTE nor death was correlated with the obstruction index at baseline or after six months. None of the patients with residual PE developed recurrent VTE. The hazard ratio (HR) for recurrent VTE was not significantly different for patients with residual thrombosis versus patients without residual thrombosis (HR: 0.45 95% CI 0.01-14.5), p=0.7. Adjustment for age, gender, and malignant disease did not materially influence the HR.

Table 2. Interobserver reliability of the obstruction index, measured by the Qanadli score (9) at baseline and after six months of anticoagulant therapy, the presence of residual thrombosis in the pulmonary arteries, and the right ventricular to left ventricular (RV/LV) diameter ratio.

<table>
<thead>
<tr>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Interobserver reliability (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus</td>
<td>Quanadli</td>
<td></td>
</tr>
<tr>
<td>Obstruction index (SD) by Qanadli baseline</td>
<td>30 (20)</td>
<td>32 (20)</td>
</tr>
<tr>
<td>Obstruction index (SD) by Qanadli after six months</td>
<td>1.1 (3.7)</td>
<td>0.9 (2.8)</td>
</tr>
<tr>
<td>Number of patients with residual thrombotic obstruction, n (%)</td>
<td>8 (6)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>RV/LV baseline, mean (SD)</td>
<td>1.0 (0.30)</td>
<td>0.99 (0.28)</td>
</tr>
<tr>
<td>RV/LV baseline, mean (SD)</td>
<td>0.90 (0.14)</td>
<td>0.87 (0.21)</td>
</tr>
</tbody>
</table>

CI confidence interval, N number, SD standard deviation.

**DISCUSSION**

The present study, which systematically investigated the natural course of clot resolution and its impact on the outcome of patients with PE, demonstrates that the proportion of patients with residual thrombotic obstruction after six months of anticoagulant treatment is 5%, substantially lower than currently assumed. Second, the presence of residual thrombotic obstruction did not appear to correlate with the occurrence of recurrent VTE in patients with PE.
The rate of residual thrombotic obstruction that we found (5%) is 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 (5). An explanation for our low incidence of residual PE may arise from the type of imaging test used. Up to date, most studies used V/Q-scanning to assess the presence of residual perfusion defects (11-13). CTPA principally differs from V/Q-scanning in detecting PE in that it allows direct embolus visualization, whereas V/Q-scans provide an indirect indication for the presence of emboli derived from perfusion defects. Residual perfusion defects detected on V/Q-scans may not always reflect the actual presence of residual thrombus, but may be caused by other pulmonary comorbidities (14). Also, residual perfusion defects may persist even after complete resolution of the emboli. In a retrospective study in which comparable patients with PE underwent either CTPA or V/Q-scanning after at least 3 months of anticoagulation, the proportion of residual thrombotic obstruction was almost two-fold higher in patients who underwent V/Q-scanning (28% vs. 15%) (15). A recently published safety analysis from the EINSTEIN PE study (16), where 347 patients with acute PE, confirmed by CTPA (n=264) or perfusion scintigraphy (n=83) underwent a repeat scan after three weeks of anticoagulant treatment (17), also pointed towards a higher rate of clot resolution assessed with CT-scan (44%) compared to perfusion scintigraphy (31%) (17). Still, our proportion of residual thrombotic obstruction is also lower compared to previous studies that did use CTPA to assess the presence of residual thrombotic obstruction. However, these studies were designed retrospectively and conducted CTPA after a limited duration of follow-up (18), included a limited sample of patients (8), or only included patients with central PE (7).

To determine the relevance of baseline CTPA imaging for clinical practice, its benefits should be weighed against its high costs and potential harms, including radiation exposure with its associated risk of cancer (19). The most important reason to perform baseline imaging following treatment for acute PE 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 by the REVERSE investigators demonstrated that baseline imaging performed after treatment for either DVT or PE, was associated with an increased diagnostic certainty in patients investigated for suspected recurrent VTE (20). 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 baseline-imaging test. Although it
should be stated that the golden standard for the assessment of residual PE is unknown, CTPA has currently largely replaced V/Q scanning in the diagnostic work-up of patients with suspected (recurrent) PE. The most important advantage of CTPA over V/Q scanning is the low number of inconclusive test results (0.0-3.0% vs. 28-40%) (21). 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, to assess its incremental value in managing patients with suspected recurrent PE. The high rate of complete clot resolution that we found suggests that the correct diagnosis recurrent PE with the use of CTPA is less complicated than currently anticipated, which does not support the routine use of baseline CTPA imaging.

A second rationale to routinely investigate the presence of residual PE would be the potential prognostic value. In patients with DVT, it has been demonstrated that assessment of residual thrombotic obstruction may aid in the differentiation of patients at risk for recurrent venous thrombosis (22). Considering that DVT and PE represent two expressions of a similar clinical pathological process, a similar prothrombotic tendency might be expected in PE patients with residual PE. In the present study, however, no correlation was found for the presence of residual thrombotic obstruction and the occurrence of recurrent VTE. It should be noted that given the low number of recurrent events during follow-up and the small proportion of residual PE, this study may have been underpowered to detect this correlation. However, the fact that residual PE was present in only 7 patients and none of these patients developed recurrent VTE, does not indicate that implementing baseline CTPA on a large scale may be useful to identify a subgroup of patients at high risk of recurrences. The absence of patients who developed CTEPH during follow-up, does not allow us to draw conclusions on the potential relation between residual PE and CTEPH.

The findings of this study are strengthened by its multi-center and prospective design. Furthermore, a pre-specified protocol was used to systematically identify residual thrombotic obstruction after a consistent duration of follow-up.

A limitation of this study includes the fact that we studied a relative healthy population of PE patients. Compared to previous studies on this topic, our patients are relatively young with low prevalence of comorbidities. This may be explained by the fact the fact patients were only eligible for this study if they survived the first 6 months following PE and were healthy enough to undergo baseline CTPA. This is a potential source of selection bias that may limit the extrapolation of our findings. Also, the incidences of recurrent VTE (13%) and mortality (6%) during follow-up were lower
than reported in previous studies assessing the outcome of PE patients (23). The relative large number of patients continuing anticoagulant therapy six months after diagnosis might have contributed to the observed low incidence of recurrent VTE. 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 conclusion, this study demonstrates that complete thrombus clot resolution assessed with CTPA following six months of treatment for acute PE, occurs in 95% of the patients. Baseline 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 predictive value for recurrent VTE and the costs and potential harms associated with CTPA, our data do not support implementation of baseline CTPA imaging in clinical practice following treatment of acute PE.

**REFERENCE LIST**


Clot resolution after six months of treatment


