Pulmonary embolism: advances in diagnosis and prognosis
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Chapter 14
Clot resolution after three weeks of anticoagulation for pulmonary embolism: comparison of computed tomography and perfusion scintigraphy

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ABSTRACT

Introduction
Little is known about clot resolution of acute pulmonary embolism (PE) in patients treated with anticoagulation, and the performance of computed tomography (CT) compared to perfusion scintigraphy for its measurement. We performed a prospective non-randomized cohort study to compare pulmonary thromboembolic resolution measured with these two modalities.

Methods
Consecutive patients with PE confirmed by a CT- or a high probability ventilation/perfusion-scan were asked to participate. A repeat scan (CT- or perfusion scan, the same as performed at baseline) was employed after three weeks of anticoagulation. For each scan, the percentage of vascular obstruction (PVO) was calculated based on a weighted semi-quantitative estimation of obstruction. The percentage of reperfusion was assessed by calculating the mean relative change after three weeks relative to baseline.

Results
Of 165 patients included in the analysis, 127 patients were examined with CT- and 38 with ventilation/perfusion-scan, respectively. Clinical characteristics were comparable between the groups. At baseline, mean PVO was 20% (standard deviation, 11%) for CT- and 21% (14%), for perfusion-scan, respectively (p=0.536). After three weeks, PVO was 5.6% (6.9%) with CT-scan compared to 9.0% (9.4%) with perfusion-scan (p=0.016). The mean relative decrease in PVO was 73% (32%) for CT-scan compared to 59% (37%) for perfusion-scan (p=0.041), while complete resolution was seen in 43% (57/129; 95% confidence interval, 36-53%) of the patients with CT- and in 29% (11/38; 17-45%) with perfusion-scan (p-for-trend=0.028).

Conclusions
In patients with acute PE, three weeks anticoagulation leads to complete resolution of the clot in nearly half of the patients when analyzed with CT-scan and in 29% with perfusion-scan. These findings suggest that clot resolution occurs very early after starting treatment and that normalization may also be greater with CT-scan compared to current knowledge based on perfusion-scan.
INTRODUCTION

Ever since the landmark trial of Barritt and Jordan in 1960, anticoagulation is the designated treatment for patients with pulmonary embolism (PE) (1). If indicated, clot lysis can be accelerated with more aggressive thrombolytic therapy. Despite the beneficial effect of anticoagulation on clinical outcome, little is known about the natural history of clots in the pulmonary circulation, for instance the rate of clot resolution. In the available studies, perfusion scintigraphy has been the cornerstone to measure the degree of thromboembolic resolution and complete normalization is found in approximately 40% of patients after six months of treatment (2). However, incidental reports suggest discrepancies between the resolution of thrombi assessed with perfusion-scan and when measured with the current first-line imaging test for the diagnosis of PE, computed tomography (CT). In a recent small study of 25 consecutive patients, the agreement of perfusion scintigraphy and CT scanning to detect residual thromboemboli after at least six months of treatment was only minimal (kappa <0.2), and showed a discrepancy in two thirds of the patients (3). Although earlier studies revealed a good agreement between perfusion scintigraphy and pulmonary angiography (PA) (4,5), disagreement has also been found between these two tests. In a study by Ryan et al. in which the severity of vascular obstruction in the evaluation of chronic thromboembolic pulmonary hypertension (CTEPH) was evaluated, perfusion scintigraphy consistently underestimated the extent of vascular obstruction compared to PA (6). Clearly, the three imaging techniques are not identical. Whereas perfusion scintigraphy gives an indirect visualization of vascular obstruction (and may therefore be less specific in the presence of co-morbidity), CT-scanning and PA provide a direct visualization, offering more concrete evidence to support the presence or absence of thromboemboli. We, therefore, performed a prospective cohort study to compare the resolution of pulmonary thromboembolic obstruction after 3 weeks of anticoagulant treatment in patients with acute PE measured with either perfusion scan or a CT scan.

METHODS

Patients
Consecutive patients with PE confirmed either by a CT- or a high-probability ventilation/perfusion (V/Q) -scan, who were treated with conventional anticoagulant therapy (low molecular weight heparin (LMWH) followed by vitamin K antagonists) and who were at least 18 years of age, were asked to participate in the study. Patients with an impaired renal function (creatinine clearance <30 ml/min using the Cockroft-Gault formula) were not included. The institutional review board of the participating hospitals approved the study protocol and written informed consent was obtained from all included patients.
All patients were treated with vitamin K antagonists (International Normalized Ratio (INR) between 2.0 and 3.0). This was supplemented with LMWH until the INR was above the lower target range on two consecutive occasions, with a minimum of five days of LMWH administration. A follow up scan was performed in all patients after three weeks of anticoagulant therapy. Patients received the same type of scan for the follow-up as had been performed to confirm the diagnosis. If a V/Q scan was employed at diagnosis, a perfusion scan (without ventilation) was performed for the follow-up. The type of scan that was performed was based on availability in the study center and was not randomly assigned.

**Imaging protocols**

**CT-scanning**

Standard contrast enhanced CT scans were performed using a multi-detector row CT scanner according to state-of-the-art protocols for the diagnosis and evaluation of pulmonary embolism (7). Patients were scanned during a single breath-hold, in caudocranial direction, from the upper level of the diaphragm to a level slightly above the aortic arch (pitch of 1, 120 kV, 150-200 mAs). One hundred milliliters of contrast was administered intravenously (injection rate of 2.3 mL/sec for 40 seconds). An imaging delay of 20 seconds was used and overlapping images were reconstructed every 3 mm. PE was confirmed by the presence of a constant intraluminal defect in segmental or more proximal branches of a pulmonary artery.

**Ventilation-perfusion scintigraphy**

Ventilation/perfusion scintigraphy was performed following the guidelines of the Society of Nuclear Medicine (SNM 2004). Images were obtained in the upright position immediately after the administration of 75-150 MBq of technetium-99m macroaggregated albumin particles (MAA) after several deep breaths. Ventilation scintigraphy was also performed in the upright position immediately after inhalation of technetium-99m aerosols or xenon-133 or krypton-81m gases. Perfusion and ventilation planar images were acquired from multiple projections, including anterior, posterior, both posterior oblique and if possible both lateral and even both anterior oblique projections; at least four and up to eight imaging projections were acquired (500 kilocounts per view).

**Assessment of pulmonary vascular obstruction**

CT-scans and perfusion scans were analyzed and scored by two trained physicians and in case of discrepancy, a third observer was consulted. For each lobe, the vascular obstruction was first assigned a semi-quantitative obstruction score from 0 (no obstruction) to 1 (no perfusion) (0, 0.25, 0.5, 0.75 and 1), estimated visually based on the comparison of film density with an apparently normal perfused area (perfusion-scan) or based on the localization of obstruction in the vascular tree for that lobe (CT-scan). The percentage of vascular obstruction (PVO) was calculated, as described by Meyer et al. (5) and Wartski et al. (8) for both types of scans. Each
lobe was assigned a weight, based on regional blood flow distribution in the supine position: right lower lobe, 25%; right middle lobe, 12%; right upper lobe, 18%; left lower lobe, 20%; left upper lobe, 25% and lingula, 12%. Each lobar obstruction score was then calculated by multiplying the weight by the obstruction score. The overall PVO (%) was the sum of the six separate lobar scores (x100%).

**Statistical analysis**

PVOs were calculated for the scans at the moment of diagnosis and after three weeks of anticoagulant treatment. The percentage of reperfusion was assessed by calculation of the mean relative change after three weeks relative to baseline. Clinical characteristics of the study patients in the two groups were compared using a chi$^2$ test or Fisher’s exact test for qualitative variables, and a Student t-test for continuous variables.

**RESULTS**

**Patients**

In total, 185 patients with CT- or perfusion-scan confirmed PE were eligible for the present analysis. The imaging test at follow up differed from the imaging test at baseline in 10 patients and follow up imaging was incomplete or absent in another 10 patients; these patients were excluded. Of the remaining 165 patients, the baseline and follow-up scan was performed with CT-scan in 127 patients (77%) and with perfusion-scan in 38 patients (23%). The clinical characteristics of the two study groups are described in Table 1 and were comparable. The mean time between the baseline and follow-up examination was similar for patients examined with CT- or perfusion-scan: 22 days (standard deviation (SD), 2.7 days) for CT-scan, versus 23 days (SD, 5.6 days) with perfusion-scan (p=0.325). During this period, none of the patients experienced recurrent PE and the quality of anticoagulant therapy was similar (data not shown).

**Percentage of vascular obstruction**

At baseline, the mean PVO on CT-scan was comparable to perfusion-scan: 20% (SD, 11%) and 21% (SD, 14%) with CT- and perfusion-scan, respectively (p=0.536). After three weeks of anticoagulant treatment, PVO decreased to 5.6% (SD 6.9%) with CT-scan and to 9.0% (SD 9.4%) with perfusion-scan (p=0.016), see Figure 1. The mean absolute decrease of PVO did not differ between the two groups: 14% (SD, 9.8%) and 12% (SD, 9.5%) for CT- and perfusion-scan groups, respectively (p=0.297). However, the mean relative decrease of PVO after three weeks of anticoagulant treatment was significantly greater with CT-scan compared to perfusion-scan: 73% (SD 32%) and 59% (SD 37%) for CT- and perfusion-scan groups, respectively (p=0.041). The relative decrease in PVO was not related to the PVO at baseline (data not shown).
### Table 1. Clinical characteristics of the two study groups at baseline*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CT-scan</th>
<th>Perfusion-scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>127 (77)</td>
<td>38 (23)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>59 (46)</td>
<td>24 (61.5)</td>
</tr>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>57 (17.5)</td>
<td>60 (14.6)</td>
</tr>
<tr>
<td>Idiopathic PE, n (%)#</td>
<td>67 (53)</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Recent surgery or trauma, n (%)</td>
<td>20 (16)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Immobilization, n (%)</td>
<td>16 (13)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Use of estrogen containing drugs, n (%)</td>
<td>14 (10.3)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Active cancer, n (%)</td>
<td>12 (8.8)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Previous episode of VTE, n (%)</td>
<td>27 (21)</td>
<td>11 (29)</td>
</tr>
<tr>
<td>Known thrombophilic condition, n (%)</td>
<td>8 (6.3)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Venous insufficiency, n (%)</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

* No significant difference in baseline characteristics between two study groups; # No other risk factor

### Normalization of the pulmonary artery obstruction

Complete resolution was seen in 43% of patients examined with CT-scan (57/129; 95% CI, 36-53%) compared to 29% of patients evaluated with perfusion-scan (11/38; 95% CI, 17-45%), while on the other hand, no relevant change was seen in 9.3% of patients undergoing CT-scan (12/129; 95% CI, 5.4-16%) compared to 21% of patients examined with perfusion-scan (8/38; 95% CI, 11-36%; Table 2). This difference between the two imaging techniques in distribution according to the three categories (total resolution, partial resolution, or no relevant change) almost reached statistical significance (p=0.077), yet significance was observed for trend (p=0.028). Patients in whom no relevant change was seen, did not have a higher mean PVO at baseline compared to patients with complete resolution: mean PVO at baseline was 15% (SD, 8.8%) in patients with complete resolution and 15% (SD, 7.6%) for patients with no relevant change after three weeks, respectively (p=0.910).

### Table 2. Thrombus resolution after three weeks of anticoagulation for pulmonary embolism

<table>
<thead>
<tr>
<th></th>
<th>CT-scan</th>
<th>Perfusion-scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>127 (45, 36-53)</td>
<td>38 (29, 17-45)</td>
</tr>
<tr>
<td>Complete resolution</td>
<td>57 (45, 36-53)</td>
<td>11 (29, 17-45)</td>
</tr>
<tr>
<td>Partial resolution</td>
<td>58 (46, 34-54)</td>
<td>19 (50, 35-65)</td>
</tr>
<tr>
<td>No relevant change</td>
<td>12 (9.5, 5.0-16)</td>
<td>8 (21, 11-36)</td>
</tr>
</tbody>
</table>

P-value for the difference between CT- and Q-scan (chi²): 0.075; p-for trend: 0.028.
DISCUSSION

In this exploratory analysis the relative decrease in vascular obstruction after three weeks of anticoagulation was greater in patients examined with CT (73%) compared to patients examined with perfusion scintigraphy (59%). Furthermore, normalization was observed in no less than 43% of patients evaluated with CT, compared to 29% of patients evaluated with perfusion scintigraphy. Since the two groups did not differ in baseline clinical characteristics and degree of obstruction, and had a comparable quality of anticoagulation, this implies that CT-scan and perfusion-scan differ in their ability to detect thromboembolic resolution. Conceivably, this difference may be explained by the character of the two tests. With CT-scan thromboemboli can be directly visualized, whereas with perfusion scintigraphy, these defects are indirectly visualized; the test may therefore be less specific, particularly in the presence of co-morbidity. For instance, it is known that small perfusion defects may occur with increasing age and that they are probably due to the occurrence of chronic obstructive pulmonary disease (9).

Donadini and colleagues (3) directly compared CT- and Q-scanning six months after diagnosis in 25 patients with acute PE. Complete clot resolution was seen in 32% of the patients with CT-scan and in 44% with perfusion-scan. Although this difference was not significant, it seems contrary to our results. The reason for this difference is not clear.
The normalization of vascular obstruction we observed (45% and 27%) is comparable to earlier studies. However, our study demonstrates that improvement and normalization is already present three weeks after anticoagulation treatment is started. For comparison: van Rossum et al. (10) found normalization in 32% of patients after six weeks of treatment with CT-scanning, while after three to 11 months of treatment, normalization of vascular obstruction ranged from 32% to 48%, with both perfusion-scan and CT-scan (3,8,9,11). Although in some of these studies the included patients had a much higher level of vascular obstruction (8,11), which has been shown to influence clot resolution (12), the obstruction at baseline in the present analysis did not influence the improvement of PVO.

There are two important clinical consequences of our study. First, the high resolution of clots is of importance to make a correct diagnosis of recurrent PE, especially considering the possible implications for therapeutic management of a PE recurrence. Furthermore, the residual thrombosis of the pulmonary vasculature could lead to pulmonary hypertension. It has been generally accepted that after six months of treatment, over 50% of patients have residual thrombosis despite adequate anticoagulant therapy (2). However, the studies on which this percentage is based showed a large heterogeneity in duration of anticoagulation, type of patients included, severity of vascular obstruction and imaging techniques. The studies had a small study size (3,10), used perfusion scintigraphy (9) or included patients with massive PE only (11). If normalization is already observed with CT-scanning in nearly half of the PE patients after just three weeks of anticoagulation, it can be expected that a larger proportion of patients will have complete normalization after six months, much higher than what is presently assumed.

Our study is the first to prospectively compare perfusion scintigraphy with CT-scanning in a large group of consecutive patients. However, the study has some limitations which must be addressed. First, patients were not randomized to undergo either CT- or perfusion-scanning; this was based on the availability of the study center. Since CT-scan is the most widely used diagnostic test, only 23% of the patients had a perfusion scan. However, the baseline characteristics and the degree of vascular obstruction at baseline were comparable between the two groups, which we believe makes the comparison of scan outcomes in the two groups valid. Second, there is more experience with measuring the percentage of vascular obstruction with perfusion scintigraphy (5,8), than with CT-scanning (3). Estimating the vascular obstruction of an artery with CT-scanning would, however, more likely overestimate the obstruction. Third, information on the presence of co-existing cardiopulmonary disease was not collected, therefore we cannot rule out a difference between the two groups. Finally, we cannot exclude that perfusion defects may have already been present before the diagnosis.

In conclusion, this prospective study showed greater thrombus resolution with CT-scan compared to perfusion scintigraphy after three weeks of conventional anticoagulant treatment.
for acute PE, with normalization in nearly half of the patients undergoing CT-scanning. This implies that clot resolution occurs early after PE and challenges the high number of patients with persistent clots found in earlier studies.

**REFERENCE LIST**