Resolution of thrombo-emboli in patients with acute pulmonary embolism; a systematic review.

M. Nijkeuter, M.M.C. Hovens, B.L. Davidson, M.V. Huisman

Chest 2006; 129: 192-197

Palazzo dell'Archiginnasio, Bologna, Italia
Abstract

Study objectives
Much attention has been paid in recent years to optimizing the diagnosis of acute pulmonary embolism (PE). However, little is known about the changes in clot burden that occur at the level of the pulmonary arteries after documented PE. It is often problematic to distinguish between a new or residual defect on lung scintigraphy or helical computed tomography (CT). This may lead to falsely labeling patients with residual PE as having recurrent PE and consequent unnecessary treatment changes.

Design
We performed a systematic analysis of studies of imaging tests (radionuclide and computerized tomography) evaluating resolution rate of PE with independent assessment of predefined methodologic criteria by two investigators.

Results
We identified 29 clinical studies. Of these, 25 were excluded and 4 studies were included in our review. Because studies differed largely in patient selection, duration of anticoagulation, timing of follow up etc., the studies were not pooled but briefly described. The percentage of patients with residual pulmonary thrombi was 87% at eight days after diagnosis, 68% after six weeks, 65% after three months, 57% after six months and 52% after 11 months.

Discussion
This review shows that complete resolution of PE is not routinely achieved between 8 days and 11 months after diagnosis. More than 50% of patients with PE still have defects six months after diagnosis, after which resolution of thrombi appears to reach a plateau phase. Physicians should be aware of the high percentage of incomplete resolution of pulmonary emboli. Routine re-imaging after cessation of anticoagulant therapy in patients with PE to obtain a new baseline could be considered.
Resolution of thrombo-emboli in patients with acute pulmonary embolism; a systematic review.

Introduction

Much attention has been paid in recent years to optimizing the diagnosis of acute pulmonary embolism (PE). Helical computed tomography (CT) is increasingly preferred as a first-line test. However, little is known about the subsequent changes in clot burden that occur in pulmonary arteries after objectively documented PE. In patients with symptomatic objectively proven proximal deep vein thrombosis (DVT) of the leg veins, studies of sequential ultrasound examinations have demonstrated that persistent residual thrombosis is common after treatment with short-term anticoagulation and, according to one report, “normalization” of the image is achieved in 39% at 6 months, 58% after 12 months and 74% at 36 months, while other studies suggest other time ranges. Information regarding the rate of resolution of pulmonary thrombi after diagnosis of PE is important because it may facilitate objective diagnosis when patients with PE return with complaints possibly due to recurrent PE. It is often clinically difficult to determine whether defects suggesting pulmonary emboli on lung scintigraphy or helical CT are residual or represent a new event. In a prospective study, it has been shown that 4% of first, symptomatic pulmonary embolism patients develop symptomatic chronic thromboembolic pulmonary hypertension (CTPH) within 2 years. It would be desirable to avoid this outcome if possible and likewise to prevent the cascade of treatment consequent to falsely labeling patients with a recurrent PE. To better understand the natural history of pulmonary artery clot evolution after objectively documented PE, we performed a systematic analysis of published studies addressing this important clinical problem.

Methods

Search strategy

We used electronic search strategies to identify relevant studies. The following electronic databases were searched: PubMed (1966 to November 2004), EMBASE (1980-nov 2004), Cochrane, the Library Issue 1, 2005 and Web of Science using the search terms residual thrombosis or incomplete recovery or incomplete resolution or (resolving AND (clots OR clot)) or (Normalization OR Normalisation) AND (pulmonary arteries OR pulmonary artery)) or (((thrombi AND regression) or thrombus regression) AND (pulmonary embolism OR pulmonary embolic OR (pulmonary AND (embolism OR emboli OR embolus))) or (Scintigraphic AND control AND pulmonary embolism). We augmented our search by reviewing the reference lists of retrieved articles. Studies published in any language were used.

Study selection

We attempted to identify all published clinical studies that evaluated patients with pulmonary embolism and the rate of resolution of pulmonary emboli visualized by follow up objective imaging tests. Of potential articles, abstracts were read to determine eligibility and in case of doubt, full-text articles were retrieved. To be included, a study had to 1) be prospective and involve consecutive patients; 2) objectively diagnose symptomatic...
Chapter 8

pulmonary embolism (pulmonary angiography or helical CT, high-probability ventilation/perfusion (VQ) lung scintigraphy or intermediate probability VQ scan with positive compression ultrasonography or venography); 3) use objective imaging tests at follow up; 4) describe the duration and type of treatment of PE with a minimum administration of anticoagulant therapy of 6 weeks and no allowance of vena cava ligation, femoral ligation or pulmonary embolectomy; 5) identify whether there was a prior history of venous thromboembolism; 6) provide a description of the method of follow-up.

Data extraction
Two investigators independently assessed studies for inclusion according to the predefined methodological criteria. Investigator disagreements were resolved by majority opinion of a third investigator. Study authors were contacted as required to retrieve missing information.

Table 1
Excluded studies

<table>
<thead>
<tr>
<th>Author (Ref)</th>
<th>Year</th>
<th>Diagnosis</th>
<th>N</th>
<th>Reason for exclusion</th>
<th>Time of FU scan</th>
<th>Follow up result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sautter (16)</td>
<td>1964</td>
<td>PA</td>
<td>2</td>
<td>2.5</td>
<td>25,128 d</td>
<td>100% normalisation</td>
</tr>
<tr>
<td>Fred (7)</td>
<td>1966</td>
<td>PA</td>
<td>7</td>
<td>1.25</td>
<td>7-19 d</td>
<td>6/7 normalisation</td>
</tr>
<tr>
<td>Poe (17)</td>
<td>1967</td>
<td>PA/VQ</td>
<td>20</td>
<td>2.3</td>
<td>7 d, 16 m</td>
<td>40% normalisation</td>
</tr>
<tr>
<td>Murphy (18)</td>
<td>1968</td>
<td>PA/VQ</td>
<td>25</td>
<td>2.3, 5.6</td>
<td>1-20 w</td>
<td>60% normalisation</td>
</tr>
<tr>
<td>Dalen (19)</td>
<td>1969</td>
<td>PA</td>
<td>15</td>
<td>2.5</td>
<td>1-34 d</td>
<td>3/15 normalisation</td>
</tr>
<tr>
<td>Paraskos (8)</td>
<td>1969</td>
<td>PA</td>
<td>43</td>
<td>1.5</td>
<td>1-7 y</td>
<td>65% normalisation</td>
</tr>
<tr>
<td>Mounts (20)</td>
<td>1969</td>
<td>PA</td>
<td>4</td>
<td>2.5</td>
<td>4 w - 3 m</td>
<td>0% normalisation</td>
</tr>
<tr>
<td>Sutton (9)</td>
<td>1969</td>
<td>PA/embolect</td>
<td>38</td>
<td>1.5</td>
<td>3-5 y (1-8)</td>
<td>45% normalisation</td>
</tr>
<tr>
<td>Tow (21)</td>
<td>1969</td>
<td>clinic/PA</td>
<td>69</td>
<td>2.3, 5</td>
<td>4-120 d</td>
<td>48% normalisation</td>
</tr>
<tr>
<td>McDonald (22)</td>
<td>1970</td>
<td>PA</td>
<td>9</td>
<td>2</td>
<td>17-48 h</td>
<td>0% normalisation</td>
</tr>
<tr>
<td>Walker (10)</td>
<td>1970</td>
<td>VQ</td>
<td>74</td>
<td>1.2, 3.5, 6</td>
<td>3-277d</td>
<td>32.5% normalisation</td>
</tr>
<tr>
<td>Winebright (23)</td>
<td>1970</td>
<td>VQ</td>
<td>70</td>
<td>2.5, 6</td>
<td>3m - 1y</td>
<td>27% normalisation</td>
</tr>
<tr>
<td>UPET (24)</td>
<td>1973</td>
<td>PA+VQ</td>
<td>105</td>
<td>2.5, 6</td>
<td>1-14d, 3.6, 12m</td>
<td>77% normalisation</td>
</tr>
<tr>
<td>Hall (11)</td>
<td>1977</td>
<td>PA/embolect</td>
<td>88</td>
<td>1.2, 5</td>
<td>5 y (1-9 y)</td>
<td>42% normalisation</td>
</tr>
<tr>
<td>Fredin (25)</td>
<td>1982</td>
<td>VQ</td>
<td>23</td>
<td>2.45</td>
<td>10-14 d</td>
<td>Partial/compl norm, 22/23</td>
</tr>
<tr>
<td>Riedel (12)</td>
<td>1982</td>
<td>PA,VQ/+CUS</td>
<td>76</td>
<td>1.27</td>
<td>1-15 y</td>
<td>22/49 normalisation</td>
</tr>
<tr>
<td>Schwarz (26)</td>
<td>1985</td>
<td>PA</td>
<td>7</td>
<td>2</td>
<td>6 d + 15 m</td>
<td>6/7 normalisation</td>
</tr>
<tr>
<td>Palla (30)</td>
<td>1986</td>
<td>VQ</td>
<td>69</td>
<td>3</td>
<td>7,30,180 d</td>
<td>0% normalisation</td>
</tr>
<tr>
<td>Prediletto (27)</td>
<td>1990</td>
<td>VQ/PA</td>
<td>33</td>
<td>2</td>
<td>7, 30, 6 m</td>
<td>28% normalisation</td>
</tr>
<tr>
<td>Pacho (28)</td>
<td>1996</td>
<td>VQ</td>
<td>13</td>
<td>2.7</td>
<td>4, 5 m</td>
<td>18% normalisation</td>
</tr>
<tr>
<td>Nauffal (13)</td>
<td>1997</td>
<td>VQ+/VA</td>
<td>116</td>
<td>1.2</td>
<td>7,10 d, 6 m</td>
<td>28% normalisation</td>
</tr>
<tr>
<td>Otero (29)</td>
<td>1997</td>
<td>VQ,PA,VA</td>
<td>70</td>
<td>2.5,7</td>
<td>6 m</td>
<td>23% normalisation</td>
</tr>
<tr>
<td>Menendez (14)</td>
<td>1998</td>
<td>PA,VQ+/VA</td>
<td>96</td>
<td>1</td>
<td>7-10 d, 6 m</td>
<td>68% normalisation</td>
</tr>
<tr>
<td>Ribeiro (31)</td>
<td>1999</td>
<td>VQ</td>
<td>67</td>
<td>5</td>
<td>6 w, 1 y</td>
<td>34% normalisation</td>
</tr>
<tr>
<td>Gotthardt (15)</td>
<td>2002</td>
<td>VQ</td>
<td>129</td>
<td>1</td>
<td>0-10 y</td>
<td>70% normalisation</td>
</tr>
</tbody>
</table>

PA: pulmonary angiography; VQ: lung scintigraphy; VA: venography of the legs; CT: computed tomography; 1: retrospective study; 2: non-consecutive patients; 3: no objective diagnosis; 4: asymptomatic patients; 5: improper treatment (embolectomy or vena cava or femoral ligation or no treatment); 6: anticoagulant therapy < six weeks; 7: no description of history of VTE; h: hours; d: days; w: weeks; m: months; y: years
Resolution of thrombo-emboli in patients with acute pulmonary embolism; a systematic review.

Results

We identified 29 clinical studies. Of these, 25 were excluded because of 1) retrospective design; 7-10,13,16-29, 2) non-consecutive patients; 7,10-13,16-29, 3) lack of objective verification of the diagnosis; 10,17,18,21,30, 4) asymptomatic patients; 25, 5) treatment with inferior vena cava ligation or femoral ligation, embolectomy or no treatment in some patients; 7-11,16-18,21,23-25,29,31, 6) anticoagulant therapy for less than 6 weeks; 10,18,23,24, and 7) no description of history of VTE; 12,28,29. The excluded studies and reason for exclusion are listed in table 1. Four studies remained for inclusion in our review of rate of resolution of thrombi in patients with PE (table 2)12-15. Two studies used VQ lung scintigraphy as the follow up test and two studies used helical CT. The included studies differ not only in objective diagnostic tests used at follow up, but also in duration of follow up and duration of treatment. Therefore, we decided not to pool data statistically, but to describe the studies briefly.

Table 2
Included studies

<table>
<thead>
<tr>
<th>Ref</th>
<th>Test at Diagnosis</th>
<th>Test at FU</th>
<th>n</th>
<th>History VTE</th>
<th>Therapy</th>
<th>FU scan</th>
<th>Follow up result</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>VQ</td>
<td>VQ</td>
<td>30</td>
<td>No</td>
<td>OAT 3 m</td>
<td>6 m</td>
<td>43% normalization</td>
</tr>
<tr>
<td>33</td>
<td>VQ</td>
<td>VQ</td>
<td>157</td>
<td>43</td>
<td>OAT 3 m</td>
<td>8 d, 3 m</td>
<td>13% d8, 35% 3 m normalization</td>
</tr>
<tr>
<td>34</td>
<td>PA/CT</td>
<td>CT</td>
<td>62</td>
<td>3</td>
<td>OAT ⩾6 m/filter/FT mean 10.5 m</td>
<td>48% normalization</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>PA/VQ</td>
<td>CT</td>
<td>19</td>
<td>No</td>
<td>OAT 6 w</td>
<td>6 w</td>
<td>32% normalization</td>
</tr>
</tbody>
</table>

PA: pulmonary angiography; VQ: ventilation/perfusion lung scintigraphy; CT: computed tomography; VA: venography of the legs; FU: follow up; FT: fibrinolytic therapy; OAT: (oral) anticoagulant therapy; d: days; w: weeks; m: months

Studies using VQ scintigraphy at follow up

Hvid-Jacobsen et al. re-examined 30 consecutive patients 6 months after diagnosis of PE32. All had repeat V/Q scans and chest X-rays and all had been treated for 3 months. Six months after diagnosis, 13 patients (43%) had normalized scans, 9 (30%) had minor defects, 6 (20%) had persistent defects and 2 had new defects. None of the patients had developed symptoms of recurrent PE. In this early study, the authors concluded that defects could not be assumed to have resolved 6 months after diagnosis of PE and that re-scanning after treatment should be done to obtain a new baseline. A limitation of this study is the 3-month time interval between cessation of anticoagulant treatment and follow-up scan. The time course of natural resolution of pulmonary thrombi with anticoagulant therapy in this study may be confounded by the asymptomatic recurrence of pulmonary embolism in the 3-month period without treatment. Wartski et al.13 included 157 patients from the THESEE study, a multicenter, randomized, comparison of continuous, adjusted-dose intravenous heparin versus once-daily, subcutaneous, low-molecular weight heparin followed by oral anticoagulants for 3 months in 612 patients with acute pulmonary embolism.13,36 The results of THESEE showed both initial therapies to be equally effective. The 2 treatment groups did not significantly differ in age, sex, weight or percentage of vascular obstruction (PVO) and were therefore pooled. Of 157 patients at study entry, 145 had high-probability lung scans and 12 had intermediate lung scans with deep vein
thrombosis confirmed by venography or compression ultrasonography. In all patients, routine follow-up perfusion lung scintigraphy was obtained after eight days and after three months. The degree of PVO was calculated for each scan by assigning a weight to each lobe, based on regional blood flow distribution, and subsequently estimating a quantitative score from 0 (no perfusion) to 1 (normal perfusion) on the basis of gamma count defects seen in each lobe. Lobar perfusion score was calculated by multiplying the assigned weight of each lobe by the perfusion score. The overall score is the sum of the six separate lobar scores (the lingula is counted as a separate lobe) and PVO (%) is calculated as follows: (1 - total perfusion score) × 100%. Three months after diagnosis, fifty-three patients (34%) had normalized perfusion lung scans; 21 of these (13% of the total) had already normalized perfusion by day 8. Of the 157-patient cohort, 16 (10%) had no resolution of perfusion defects whatsoever after 3 months. An additional 28 (18%) of the total cohort had some improvement by day 8 but no further resolution by 3 months. These authors also concluded that follow-up scintigraphy serves as a new baseline for the diagnosis of recurrent PE. Furthermore, they suggest that a follow-up scan may help to identify patients who are likely to progress to chronic thromboembolic pulmonary hypertension on the basis of extensive residual defects.

**Studies using helical CT at follow up**

Remy-Jardin et al. were among the first to use helical CT as a follow-up test to evaluate the resolution of acute pulmonary embolism. In 62 consecutive patients who had been referred to an intensive care unit with massive acute PE, a follow up CT scan was performed a mean of 11 months after onset to analyze the outcome of endoluminal clots after at least 6 months of anticoagulation therapy. The diagnosis of acute PE was made with pulmonary angiography (n=43) or helical CT (n=19). For 59 of the 62 patients, the massive acute PE was their first episode of thromboembolism; three of 62 had a history of chronic thromboembolic disease. Complete resolution of thrombi at a mean of 11 months (range, 1-53 months) was shown in 48% of patients and endovascular abnormalities were present in 52%. Within this follow-up period there were no clinical episodes of recurrent PE. Follow-up scans were categorized as showing resolution of thrombi (group 1) or endovascular abnormalities (group 2). Group 1 patients showed no cardiopulmonary symptoms or echocardiographic abnormalities, while 6 of 32 (9.7% overall) group 2 patients had dyspnea on exertion and 5 group 2 patients (8.1% overall) had echocardiographic findings of pulmonary hypertension. Furthermore, group 2 patients were categorized into a) patients with partial resolution of initial thrombi (n=24) and b) patients with CT features of chronic PE, defined as severe arterial narrowing of more than 50% of the arterial diameter developing between the time of the initial diagnosis and the post-therapeutic follow-up. A striking finding was that 8 patients (13%) had CT signs of chronic PE over a median follow-up of 8.5 months (range 2-30 months) despite an anticoagulant course of at least six months and no symptomatic recurrences. The authors conclude that helical CT might help in understanding changes within central pulmonary arteries after massive acute PE, enabling not only the in vivo surveillance of organized and recanalized clots, but also of arterial narrowing (a sign of chronic PE) in asymptomatic patients.
Van Rossum et al. described the helical CT appearance of clots 6 weeks after acute PE. Clots on the initial and follow-up scan were divided into five categories: (1) central filling defect or complete occlusion (the established CT criteria for acute PE); (2) eccentric clot contiguous with the vessel wall at the site of acute PE on the initial scan; (3) filling defect with central contrast material indicating recanalization; (4) severe arterial luminal narrowing or vessel occlusion of a stenosed artery (the established criteria for chronic PE); and (5) normally enhancing vessels at follow-up indicating complete resolution of clots. At the initial CT scan, all patients (n=19) had type (1) clots, signs of acute PE. Normalization of pulmonary arteries at 6-week follow-up was seen in 6 patients (32%). Of the 13 (68%) patients with residual abnormalities, two patients still had solely type (1) clots. In the 11 remaining patients, most emboli had disappeared but some residual emboli were present as eccentric emboli contiguous with the vessel wall (22% of initial 153 clots) or filling defects with central contrast material (3% of initial 153 clots) representing recanalization (i.e., type 2 and 3 clots). In one of these patients, signs of chronic PE at the initial scan remained unchanged at follow-up. The authors of this study wondered whether existing CT criteria for chronic PE are as specific as assumed since this study showed that eccentric emboli contiguous with the vessel wall and evidence of recanalization are already present at six weeks follow-up in 22% and 3% of clots, respectively. No vascular narrowing or stenosis with occlusion was found, which may be more specific criteria for chronic PE.

Figure 1 summarizes our findings regarding the percentage of patients with residual thrombi in patients who presented with acute PE in the four studies described.
Chapter 8

Discussion

This review shows that complete resolution of pulmonary thrombo-embolism is not routinely achieved between 8 days and 11 months after acute PE. Overall, more than 50% of patients with PE have persistent defects at their follow up scan six months after diagnosis (figure 1). Afterward, resolution of thrombi seems to reach a plateau phase since complete resolution is found in 43% of patients after six months and in nearly the same percentage of patients (48%) after eleven months. Of interest is the wide variation in resolution of thrombi in individual patients. Complete resolution of pulmonary thrombi was already present in 13% of patients 8 days after diagnosis of PE while in 10% of patients no change in thrombotic occlusion was seen after three months. The pathophysiological mechanisms of resolution of thrombi and the risk factors and clinical consequences of partial resolution remain largely unknown.

There are several methodological issues within the included studies in our review. First, the timing of follow-up was not standardized between the studies, varying from 8 days to 6 months. In the study of Remy-Jardin there was no pre-specified timing of follow-up and hence follow-up ranged from 1 to 53 months. Similarly, the duration of anticoagulation therapy differed in length and in timing related to the follow up scan, varying from 6 weeks to more than 6 months. Also, there is no current standard technique for imaging resolution of PE. Two studies used VQ scintigraphy and two used CT as a follow up diagnostic method, but it is apparent that these two techniques are not interchangeable. Perfusion scintigraphy is a functional test but is reported to underestimate the presence of thromboembolic disease and also the severity of angiographic and hemodynamic compromise in CTPH. Helical CT depicts the morphology of the pulmonary arteries but contains no information regarding pulmonary functional status. Moreover, no uniform criteria are used in defining chronic imaging defects, even when similar imaging methods were used. Last, a confounding but unavoidable fact in prior or future studies is that for patients diagnosed with a first PE, it cannot be confidently ruled out that imaging defects were already present before the diagnosis since the majority of patients have no scan before their first thromboembolic event. With radionuclide scans, physicians cannot be certain, even with the aid of concomitant chest CT scans, that persistent defects represent residual thrombi rather than other defects responsible for decreased perfusion.

What are the implications of our findings for the future management of PE? First, physicians should be aware that complete resolution of pulmonary thrombi is not achieved in more than 50% of patients six months after diagnosis of PE and that this fact may complicate the objective and accurate diagnosis of recurrent pulmonary embolism. Second, an attempt should be made to generate an international consensus among physicians caring for PE patients, including radiologists and nuclear medicine physicians, regarding the optimal way of imaging, interpreting and reporting of resolution of pulmonary emboli and diagnosing chronic PE. Third, routine re-imaging after cessation of anticoagulant
Resolution of thrombo-emboli in patients with acute pulmonary embolism; a systematic review.

treatment in patients with PE to obtain a new baseline could be considered. Finally, in patients with persisting thrombo-embolic obstruction or with persisting cardiopulmonary complaints, one should be alert for chronic PE and the development of chronic thromboembolic pulmonary hypertension.

In conclusion, resolution of pulmonary thrombi is not routinely achieved after an acute PE. The pathophysiologic mechanisms, risk factors and clinical implications of incomplete resolution are not well established. There is a clear need for prospective well-designed follow-up studies to more accurately define the resolution rate after documented PE and related prognostic factors.
Chapter 8

Reference List

Resolution of thrombo-emboli in patients with acute pulmonary embolism; a systematic review.

18 Murphy ML, Bulloch RT. Factors influencing the restoration of blood flow following pulmonary embolization as determined by angiography and scanning. Circulation 1968; 38:1116-1126.
Chapter 8


