Unexpected High Prevalence of Silent Pulmonary Embolism in Patients with Deep Venous Thrombosis*

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In patients presenting with clinically suspected deep vein thrombosis, symptomatic pulmonary embolism is rarely apparent. To assess the prevalence of silent pulmonary embolism in outpatients with proven deep vein thrombosis but without symptoms of pulmonary embolism, perfusion ventilation lung scans were performed in 101 consecutive patients at presentation. Fifty-one percent of these patients had a high probability lung scan at the initiation of treatment. In comparison, in patients referred with suspected venous thrombosis, but who on subsequent objective testing did not have venous thrombosis (n = 44), the prevalence of a high probability-scan for pulmonary embolus was only 5 percent. At repeat lung scanning, performed after one week of anticoagulant treatment, complete to partial improvement was observed in 68 percent of the patients with initially abnormal scans. Lung-scan detected asymptomatic pulmonary embolism occurs frequently in patients presenting with symptomatic deep venous thrombosis, and the majority of these emboli showed significant to complete resolution within one week of anticoagulant treatment. (Chest 1989; 95:495-502)

Usually, patients with symptomatic deep vein thrombosis (DVT) have symptoms for several days before they are seen by their family physician. In outpatients, the mean patient-doctor delay has been reported to vary between five and seven days.1-3 In studies employing objective methods to detect DVT, it has been shown that at presentation, approximately 90 percent of patients have evidence of proximal DVT.1,3 It is known that proximal venous thrombosis is associated with a high risk for pulmonary embolism.4-6 However, only very few patients presenting with clinically symptomatic DVT exhibit symptoms of pulmonary embolism. The precise prevalence of silent pulmonary embolism in these outpatients is unknown.

Once venous thrombosis is objectively diagnosed, prompt anticoagulant treatment should be initiated. Heparin is currently the drug of choice for the primary treatment of venous thrombosis. It is believed that by its ability to block directly the activated coagulation system, heparin can prevent extension of the thrombus, and thus, minimize the risk of pulmonary embolism. However, the effects of heparin in the prevention and resolution of pulmonary embolism in patients with DVT has not been formally studied.

Ventilation-perfusion lung scanning is a very sensitive, noninvasive method to detect pulmonary emboli.7,8 Based on the hypothesis that venous thrombosis and pulmonary embolism form a pathophysiologic continuum, we have performed ventilation-perfusion lung scanning in consecutive outpatients with proven DVT and without symptomatic pulmonary embolism to determine the prevalence of silent pulmonary embolism at presentation and to assess the effect of one week of intravenous heparin combined with oral anticoagulants on the scintigraphic findings.

METHODS

Patients

Outpatients with clinically suspected DVT in the Amsterdam region are referred to the Thrombosis Unit of the Academic Medical Center for objective testing. The diagnostic approach to these patients using repeated impedance plethysmography and the patients' characteristics have been reported earlier.2 The patients referred are representative of all patients with clinically suspected DVT in the Amsterdam region. In the present investigation, two groups of patients were studied. Group 1 consisted of 101 consecutive patients with DVT confirmed by venography and without clinically suspected pulmonary embolism. Group 2 consisted of 44 patients, a random sample of 150 consecutive patients, referred with clinically suspected DVT, but who had repeatedly normal impedance plethysmography tests. At presentation, the medical history with respect to chest symptoms (dyspnea, pleuritic pain, etc) and the presence of preexisting lung disease and smoking habits were recorded in all patients using a standard questionnaire. During the entire study, only one patient was excluded because of symptoms suggestive of pulmonary embolism at presentation to the Thrombosis Unit. All patients gave their informed consent before participation. The study was approved by the hospital ethics committee in accordance with the Helsinki declaration. The mean age was 60 years (range 18 to 89) in group 1 and 62 years (range 19 to 94) in group 2. The female: male ratio was 89:33 and 29:15, respectively.

The average interval between the onset of symptoms and diagnosis was 6.9 days (range 0 to 31) in group 1 and 7.1 days (range 0 to 27) in group 2 patients.

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Silent Pulmonary Embolism (Huisman et al)
Study Protocol

Group 1 and 2 patients underwent a chest roentgenogram and a perfusion lung scan within 24 hours after diagnosis of deep vein thrombosis or after the second normal impedance plethysmography test respectively. If the perfusion defect was segmental or larger and the chest roentgenogram was normal, a ventilation lung scan was performed within 24 hours after the perfusion scan. Patients in whom the perfusion scans were performed more than 24 hours after diagnosis of DVT (and start of heparin treatment) were excluded from the analysis because patient’s own fibrinolytic mechanisms have been documented to change lung scan patterns.

The group 1 patients with venographically-proven DVT were treated with a continuous infusion of heparin (adjusted individually, aiming at 1.5 to 2 fold prolongation of the pretreatment kaolin-cephalin clotting time) and concomitant start of oral anticoagulants (adjusted individually, aiming at a thrombostat between 5 and 10 percent). Heparin therapy was discontinued after seven days when the thrombostat was in the therapeutic range for at least 24 hours. At day 7 ± 1 of anticoagulant treatment, all group 1 patients underwent a repeat perfusion lung scan but no ventilation scan. None of the group 2 patients was treated with anticoagulants and no repeat lung scans were performed in this group.

Pulmonary angiography, to confirm the presence of pulmonary embolism, was considered not to be ethically justified in asymptomatic patients, in particular because of the invasive nature of the procedure and the potential morbidity.

Perfusion-Lung Scanning

Perfusion studies were performed after the injection of 75 mBq of $^{99m}$Tc labelled albumin macroaggregates (Pulmolite) on a large field gamma camera mounted with a low energy collimator. Six views of 300 K counts each were obtained in the upright position: anterior, posterior, right and left lateral and right and left anterior oblique. For each anatomic view, the perfusion images were presented on roentgenographic films. The perfusion lung scan was considered abnormal if a perfusion defect was present in two or more of the six views. The findings were coded as normal, segmental or greater, subsegmental, or inadequate for interpretation.

Ventilation-Lung Scanning

Ventilation studies were performed employing $^{13}$N Kr. The patient was examined in upright position, and after proper window setting, inhaled from the generator system up to 300 K counts. For the combined perfusion-ventilation studies, a medium energy collimator was used because of the 190 KeV energy of $^{13}$N Kr. Ventilation scanning was not repeated on day seven.

Ventilation-Perfusion Lung Scan Findings

A ventilation-perfusion lung scan was called high probability for pulmonary embolism if the perfusion scan showed a segmental or larger defect and both the ventilation scan (mismatch) and the chest roentgenogram were normal. All other lung scan abnormalities were called nonhigh probability.

Effects of Anticoagulant Treatment

To assess the resolution of lung scan findings in the presence of anticoagulant treatment, the distribution pattern of perfusion lung scan findings (ie, normal, segmental or larger and subsegmental) performed at day 1 and day 7 of treatment in patients with thrombosis, were compared. In addition, for each patient, the changes in perfusion lung scans after seven days of treatment were coded as normalized, improved (area of perfusion defect decreased by 20 percent or more), remained normal, unchanged, or deteriorated (area of perfusion defect increased by 20 percent or more).

All scans were read by a panel of three experienced observers, who were unaware of the patient’s clinical condition as well as the

IPG results and venogram results.

For the comparison of perfusion lung scans, the observers were informed whether the set of scans was performed on the first or the seventh treatment day.

Statistical Analysis

Statistical Analysis and Sample Size Considerations: Data on the prevalence of asymptomatic lung scan abnormalities were, at the start of this study, rather scarce. Based on the 60 percent prevalence of high-probability scan defects as found by Doyle et al in 30 untreated patients with proximal DVT and a postulated prevalence of 20 percent in patients without documented DVT we calculated, using chi-square approximation for nonuniform allocation, that a sample size of at least 30 patients in the thrombosis group and 20 patients in the control group would be needed to detect a statistically significant difference with a type 1 error of 0.05 and a type 2 error of 0.1.

Data of the lung scans performed at the day of presentation were analyzed using the chi-square test. Patients with proven deep vein thrombosis were compared with patients without deep vein thrombosis.

RESULTS

Prevalence of Lung Scan Defects

In 89 of the 101 patients in group 1 (88 percent) with proven venous thrombosis, both the perfusion- and ventilation lung scans were adequate for analysis. The 12 patient exclusions were because a perfusion lung scan was performed more than 24 hours after diagnosis (three patients), the ventilation lung scan was obtained more than 24 hours after the perfusion scan (three patients), the perfusion/ventilation lung scan was inadequate for interpretation (five patients), and because one patient refused to undergo scanning. Of the 89 remaining patients, venography revealed proximal vein thrombosis in 78 patients (88 percent), while the other 11 patients had isolated calf vein thrombi.

Of the 44 patients in group 2, the perfusion ventilation lung scans were adequate for analysis in 39 patients (87 percent). In two patients, the perfusion or ventilation scan was performed after the 24 hour limit and the scan was inadequate for interpretation in three patients. All 39 patients had a repeatedly normal impedance plethysmography test (four tests over a ten-day period). The prevalence of lung scan findings, ie, normal, high probability, and nonhigh probability, in patients with proven DVT and patients without DVT is shown in Table 1.

Table 1 — Prevalence of Lung Scan Defects in Symptomatic Patients With and Without DVT at Day of Presentation

<table>
<thead>
<tr>
<th>Perfusion/Ventilation Lung Scan Result</th>
<th>Patients With Proven DVT (n = 89)</th>
<th>Patients Without DVT (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>24 (27)*</td>
<td>24 (62)</td>
</tr>
<tr>
<td>High probability</td>
<td>45 (51)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Nonhigh probability</td>
<td>20 (22)</td>
<td>13 (33)</td>
</tr>
</tbody>
</table>

*Percentages in parentheses
Patients with and without venous thrombosis were comparable with respect to age, sex, smoking habits, duration of leg symptoms, and cardiopulmonary diseases.

In 73 percent of patients with proven thrombosis, the lung scan was abnormal. At the initiation of anticoagulant treatment, the lung scan showed a high probability for pulmonary embolism in 51 percent (45 patients) of the patients with documented venous thrombosis. None of these patients had symptoms of pulmonary embolism.

In contrast, in patients referred by the same pattern but without venous thrombosis, the prevalence of high probability lung scan defects was 5 percent (p<0.001, chi-square analysis). Only 24 patients with documented venous thrombosis (27 percent) had a completely normal perfusion scan, while 62 percent of the patients without venous thrombosis had a normal perfusion scan (p<0.001, chi-square analysis). Of the 11 patients with calf vein thrombosis, three had an abnormal lung scan of whom two patients had a high-probability scan and one patient a nonhigh probability scan. In the 78 patients with proximal vein thrombosis, a high probability lung scan was observed in 43 patients (55 percent) and a nonhigh probability lung scan in 19 patients.

Effects of Anticoagulant Treatment

Out of the 101 patients with proven DVT, the perfusion scans performed at the initiation of treatment were adequate for analysis in 95 patients (94 percent). Six patients were excluded because the perfusion lung scan was performed more than 24 hours after diagnosis (three patients), the perfusion lung scan was inadequate for interpretation (two patients), and because one patient refused to undergo scanning. Table 2 shows that at the first day of treatment, one half of the patients had segmental or larger defects on their perfusion lung scan, while in 27 patients (28 percent), the perfusion lung scan was normal. The distribution pattern of perfusion lung scan defects is closely similar to the results obtained using the combination of ventilation and perfusion scans (Table 1).

Table 2—Distribution Pattern of Perfusion Lung Scan Findings in Patients With Proven DVT at Initiation and After Seven Days of Heparin/Oral Anticoagulant Treatment

<table>
<thead>
<tr>
<th>Perfusion Lung Scan Result</th>
<th>Patients at Initiation of Treatment (n = 95)</th>
<th>Patients After Heparin Treatment (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27 (29)*</td>
<td>30 (44)</td>
</tr>
<tr>
<td>Segmental or larger</td>
<td>48 (51)</td>
<td>29 (33)</td>
</tr>
<tr>
<td>Subsegmental</td>
<td>20 (21)</td>
<td>21 (23)</td>
</tr>
</tbody>
</table>

*Percentages in parentheses

In 89 of the 95 patients (94 percent) with adequate perfusion scans at the start of treatment, the repeat perfusion scans after 7 ± 1 days of anticoagulation were adequate for comparative analysis. Repeat scanning was refused by three patients, and the repeat scan was performed beyond eight days after the initial scan in another three patients. After seven days of a combined treatment of intravenous heparin and oral anticoagulants, 44 percent of all patients had a normal perfusion scan, subsegmental defects were still present in 29 patients (33 percent), and segmental defects were observed in the remaining 21 patients (23 percent) (Table 2).

To obtain a more precise estimation of the individual changes in perfusion ventilation scans during treatment, the first and seventh day perfusion ventilation scan of the 89 patients (with adequate scans) were compared at both days (Table 3). Normalization or improvement of the initial perfusion defect was observed in 42 of 62 patients (68 percent). The scan deteriorated in seven of 89 patients (8 percent).

**DISCUSSION**

It is generally believed that symptomatic DVT is a separate clinical entity from symptomatic pulmonary embolism. Indeed, the overwhelming majority of patients presenting with clinically suspected and objectively confirmed DVT do not have symptoms suggesting pulmonary embolus. Using perfusion-ventilation lung scanning, a sensitive method to detect pulmonary embolism, this study demonstrates a surprisingly high prevalence of silent pulmonary embolism in outpatients with proven DVT. Fifty one percent of these patients had a high probability lung scan at presentation (Table 1). It is known from studies in patients with symptomatic pulmonary embolism that at least 86 percent of the patients with a high probability perfusion-ventilation scan have pulmonary emboli on angiography,7,8 and that in patients with nonhigh probability scan, pulmonary angiography confirms emboli in approximately 30 percent. Extrapolating these findings to the present study population indicates that if pulmonary angiography had been performed.
performed at presentation in all patients with proven venous thrombosis, 45 of the 89 patients (51 percent) would have had pulmonary emboli shown on their angiograms (86 percent of the patients with high probability scans and 30 percent of the patients with nonhigh probability scans). Although in the present study emboli were documented by ventilation perfusion scintigraphy, only its accuracy could be debated. However, it was felt impossible to endorse pulmonary angiography in these asymptomatic patients. Moreover, well designed prospective studies have revealed the clear correlation between abnormal scans and pulmonary angiography.5

In contrast, in patients in the control group without venous thrombosis, as documented by repeated normal impedance plethysmography tests, a high probability scan was observed in only two patients (5 percent). This figure is in agreement with that obtained in studies performed in clinically asymptomatic volunteers and preoperative patients, in which the prevalence varied between 0 and 12 percent.10-13

We observed lung scan abnormalities in three of the 11 patients with isolated calf vein thrombi, two of whom had high-probability defects. Although the number patients with calf vein thrombosis in the present study is small, the high probability lung scan rate is in agreement with that observed by Doyle et al9 (33 percent) but in contrast with the observations of Moser and colleagues14 who found no scan abnormalities among 21 patients with calf vein thrombosis.

Interestingly, one third of the patients in the control group showed a nonhigh probability lung scan. However, the majority of these subjects exhibited subtle defects, the origin of which is unknown. Possibly some of the scan defects in this group may be explained by small pulmonary emboli originating from calf thrombi, which went undetected by serial impedance plethysmography. However, it has been shown by long-term follow-up studies1-3 that these possible emboli are not clinically relevant for the patient’s outcome. Moreover, the prevalence of nonhigh probability scans in normal volunteers has been reported to vary between 1 and 50 percent.10-13 Of the 15 patients without DVT but with abnormal scans, three were known to have chronic obstructive lung disease and six patients were moderate (>15 cigarettes per day) or heavy smokers (>25 cigarettes per day). Previously published studies on silent pulmonary embolism in DVT patients are few, of variable design and concern a limited number of selected in and outpatients.15 The present study involving 101 consecutive patients permits a more accurate estimation of the prevalence of asymptomatic pulmonary embolism in outpatients with documented DVT. It is likely these findings are generalizable for outpatients who are referred with clinically suspected DVT, since the characteristics of the patients in the present study (age, delay between onset of symptoms and diagnosis, underlying diseases, including pulmonary diseases, distribution of proximal and distal vein thrombosis and smoking habits, etc) are consistent with the patient profiles reported by other centers.1,2,13 Therefore, this study demonstrates that venous thrombosis and pulmonary embolism form one disease entity.

The second aim of this study was to observe the rate of resolution during treatment—one week of intravenous heparin combined with oral anticoagulants—on the initial lung scan findings. In 68 percent of the patients with initially abnormal scans, the lung scan showed complete to partial improvement (Table 3). Although no other studies evaluating the effects of treatment for DVT on lung scan abnormalities are available, the improvements found in the present study are considerable and indeed suggest that the initial lung scan defects were caused by pulmonary embolism. The importance of resolution of scintigraphic defects is underlined by the results of studies showing a beneficial effect of significant resolution on pulmonary function and clinical status of patients with pulmonary embolism.16,17 Moreover, the observed high prevalence of significant lung scan abnormalities at the time of diagnosis of DVT may be relevant for the understanding of the so-called heparin treatment failures. Patients who develop pleuritic chest pain several days into anticoagulant therapy frequently are considered to have failed on heparin. This actually might just be the clinical manifestations due to pleuritic irritation of the previously occult pulmonary embolus. Finally, the observed marked changes in lung scan abnormalities may make the perfusion scan a potentially useful instrument in the evaluation of different treatment modalities for DVT, which are currently under clinical investigation, eg, fibrinolytic therapy and short-term heparin treatment (five to seven days).

A number of methodologic issues require comment. In patients presenting with clinically suspected DVT, symptoms of pulmonary embolism are rarely encountered. In fact, only one patient was excluded from this study because of transient pleuritic chest pain. The high probability lung scan abnormalities did not give rise to chest symptoms.

A possible explanation for the high prevalence of silent pulmonary embolism might be found in the diagnostic approach used for DVT, in particular, patient delay on repeated testing with impedance plethysmography. However, the delay between onset of symptoms and diagnosis, (mean 6.9 days) and the proportion of patients with proximal and distal thrombosis is consistent with that reported by others.1,2,14

Moreover, the lung scan defects were equally observed in patients with a short and prolonged period of leg symptoms. Furthermore, the majority of patients
with DVT (87 percent) had their abnormal impedance plethysmogram at the day of presentation. Therefore, only a small fraction of the lung scan abnormalities may be explained by patients with abnormal impedance plethysmograms on day 2, 5, and 10. Finally, the marked improvements observed with the individual comparisons of perfusion lung scans (Table 3) may have been overestimated as a result of reader bias, because the assessors were aware whether the scan was performed on the first or seventh treatment day. In order to minimize this potential bias, predetermined criteria were used to assess the effects of treatment.

It is concluded that by using sensitive methods to detect pulmonary embolism, this study reveals a 50 percent prevalence of clinically asymptomatic pulmonary embolism in patients presenting with objectively proven DVT, and that after one week of anticoagulant treatment, major improvement of lung scan abnormalities occurs in 68 percent of the patients.

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