Systematic Lung Scans Reveal a High Frequency of Silent Pulmonary Embolism in Patients With Proximal Deep Venous Thrombosis

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Background: A high frequency of asymptomatic pulmonary embolism (PE) has been reported in patients with deep venous thrombosis (DVT) in studies of a limited number of patients using varying criteria for lung scan assessment.

Objectives: To estimate the frequency of PE using systematic lung scans in a large group of outpatients with DVT and to compare the results using varying lung scan assessment criteria.

Methods: An international multicenter study comparing 2 different regimens of low-molecular-weight heparin nadroparin in DVT: perfusion lung scans were performed in 622 outpatients with no clinical indication of PE and with proximal DVT confirmed by venography. Three hundred seventy-nine of these patients underwent ventilation lung scans. High-probability (HP) scans for PE were assessed separately using either ventilation scans or chest radiographs to define mismatched perfusion defects.

Results: Perfusion scans showed abnormalities in 82% of the patients; 59% had segmental defects and 30% had normal scans or scans with a very low probability of PE. Depending on the criteria used, 32% to 45% had HP scans for PE; these percentages were higher in young patients. No relationship was found between extent of thrombosis and HP scans. The estimated frequency of silent PE was 39.5% to 49.5%. During a 3-month follow-up period during which the patients received therapy, the rate of PE recurrence was low (1.3%) and did not differ between patients with baseline HP scans and those with normal scans.

Conclusions: Regardless of what interpretative criteria are used for assessing lung scans in PE, the frequency of silent PE is 40% to 50% in patients with DVT. A baseline lung scan may easily detect PE in these patients but is not useful for predicting early thromboembolic recurrences that may occur during therapy. Arch Intern Med. 2000;160:159-164

Lung scintigraphic and angiographic abnormalities suggesting silent PE have been reported in 40% to 60% of patients with deep venous thrombosis (DVT). However, study criteria used to estimate the frequency of PE in patients with DVT vary. Except for 1 study performed in outpatients with DVT, all have involved only a limited number of patients with silent PE, many of whom had secondary DVT and multiple risk factors. Researchers frequently adopt different scintigraphic diagnostic criteria for PE, and the timing of scintigraphy has differed from one study to another.

The need to evaluate the presence of silent PE in patients referred for primary DVT is critical, particularly when outpatient treatment is considered. In this context, it is important to better assess the frequency of silent PE in a large number of patients and to define the role of pulmonary scintigraphy, which is a safe, non-invasive, and sensitive method that can exclude the presence of emboli in the lung. A lung scan is also potentially useful in evaluating the efficacy of different treatment modalities.

For editorial comment see page 145

In 651 consecutive outpatients with confirmed primary proximal DVT and no clinical suspicion of PE, we performed a prospective study to determine the incidence of silent PE using lung scans analyzed by various methods. These patients were included in a European multicenter trial comparing the efficacy of 2 low-molecular-weight heparin regimens.

Patients and Methods

General Protocol

Between November 1993 and August 1995, a European multicenter random...
ized double-blind trial was performed in patients with proximal DVT to compare the efficacy and the tolerability of the low-molecular-weight heparin nadroparin given either in a single daily injection of a double-concentration solution or at the same daily dose in 2 injections of the customary-concentration solution.13

Treatment was administered for at least 5 days, followed by oral anticoagulant therapy for 3 months. Patients were eligible for the study if they were 18 years of age or older and had acute asymptomatic proximal DVT defined as thrombosis in the popliteal vein or on venography scan as described above. Patients were not included if they had clinical symptoms at entry suggestive of PE, had a history of venous thromboembolism in the past 2 years, had thrombosis extending to the vena cava, had received a full dose of heparin for more than 24 hours, had surgery within the last 5 days, were actively bleeding, or had a hemorrhagic diathesis detected by the initial pretreatment coagulation tests. Other reasons for noninclusion were contraindication to anticoagulant therapy, uncontrolled hypertension, severe hepatic or renal failure, or a known short-term life expectancy.

All patients were hospitalized during the initial course of the treatment. Chest radiographs and perfusion or ventilation perfusion lung scans were performed within 48 hours of the start of treatment to allow comparison in case of subsequent symptomatic PE. A ventilation lung scan was recommended if the perfusion lung scan showed abnormalities.

Perfusion lung scans were obtained with either technetium Tc 99m albumin macroaggregates or albumin microspheres depending on where they were performed. A minimum of 4 views, including anterior, posterior, and right and left posterior oblique views, each acquired on a minimum of 400 000 K-counts, were performed. For ventilation lung scans, the method was one commonly practiced in the different centers using either radioactive gases (Xenon 133 or Krypton 81m) or radiolabeled aerosols.

Reading of venograms, lung scans, chest radiographs, and pulmonary angiograms was first performed by the hospital radiologist or the nuclear medicine physician. Then a centralized blind reading was performed by 2 independent experts from the study validation committee.

During the 3-month follow-up period, patients with clinically suspected PE underwent a new perfusion or ventilation-perfusion lung scan and PE was diagnosed if the scan showed a new segmental perfusion defect compared with the baseline assessment. In case of uncertainty, pulmonary angiography was performed.

Perfusion Scans

Perfusion defects were classified as segmental if they involved more than 75% of a segment. Their location in the lungs was noted. All other perfusion defects were defined as subsegmental. Among these defects, perfusion scans with 3 or less than 3 small defects (ie, less than 25% of the segment) were identified.

Ventilation Scans

Ventilation and perfusion scans were compared. Segmental perfusion defects were classified as matched if they were abnormally ventilated and mismatched if they had normal ventilation in the same area. Matching was not attempted when the defects were subsegmental. The frequency with which matched and mismatched defects occurred was related to their location in the lung and to the age of the patient.

Chest Radiographs

Chest radiographs were compared with perfusion lung scans. Segmental perfusion defects were classified as matched if both the chest radiographs and the perfusion lung scan demonstrated abnormalities in the same region or mismatched if the chest radiograph showed no abnormalities in the region of the perfusion defect. Matching was not attempted when the defects were subsegmental.

LUNG SCAN ABNORMALITIES AND EXTENT OF DVT

The association of segmental perfusion defects and of segmental ventilation-perfusion mismatched defects to the location of the thrombosis (limited to popliteal vein or extending above) was also analyzed.

Estimates of the Lung Scan Probability of PE and of Frequency of PE

Four different scintigraphic categories corresponding to different estimates of the lung scan probability of PE were defined: (1) normal scans; (2) scans showing a very low probability of PE; (3) scans showing intermediate probability of PE; and (4) scans showing a high probability of PE. Scans were considered normal when perfusion was normal, and very low probability if the abnormalities were limited to 3 or less than 3 small perfusion defects.16-17 High-probability scans were assessed in different ways: by the presence of at least 2 segmental defects associated with either normal ventilation and normal chest radiographs (ventilation-perfusion mismatched) or with normal chest radiograph alone (chest radiograph/perfusion mismatched). This is the highest cut-off point criteria for Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) high probability applied to either ventilation perfusion scans in the PIOPED study16-21 or to comparing chest radiographs and perfusion scans, as proposed by Stein et al14; presence of at least 1 mismatched ventilation-perfusion segmental defect associated with a normal chest radiograph which was Hull et al’s definition of a high-probability scan22,23 and was the highest cut-off point in Biello et al’s high-probability criteria.13

Intermediate probability scans were classified as those that could not be placed in the normal-very-low probability or the high-probability categories.

As in previous studies,7 the PE frequency was approximated by combining the frequencies of high-probability, intermediate-probability, and
very-low-probability scans found in our study with the positive predictive values for PE reported for each scan category. When high probability was defined by the presence of at least 2 mismatched ventilation-perfusion segmental defects, these values were 0.84 for high-probability and 0.03 for very-low-probability categories. In the absence of reported values for the intermediate scan as defined by our criteria, we used values given for the PIOPED intermediate category; ie, 0.3. When high probability was defined by at least 2 mismatched chest radiographs or perfusion segmental defects, in the absence of reported values using our criteria, we used for high-probability and intermediate-probability scans the values given by Stein, ie, 0.93 and 0.37 respectively. When high-probability was defined by the presence of at least 1 mismatched ventilation-perfusion segmental defect, the value was 0.86 for high-probability and 0.27 for a category which included the sum of intermediate- and very low-probability categories of our study.

Recurrence of Thromboembolic Events in Patients With Different Lung Scan Categories

During the 3-month study, the recurrence of thromboembolic events with treatment and the number of sudden deaths in patients without associated disease and in whom PE could not be excluded were compared in patients with high- or intermediate-probability baseline lung scans and in patients with normal or very low-probability baseline scans.

RESULTS

Six hundred and fifty-one patients (mean age, 60 years; range, 18-94 years) from 70 centers in 11 European countries were included in the study. Deep venous thrombosis extension above the popliteal vein was present in 82.5% of the patients. All other patients had popliteal thrombosis.

PERFUSION SCANS

Perfusion scans were performed in 622 patients and were coupled to a ventilation scan in 379 patients. Ventilation scans were performed with 133Xe, 81mKr, or aerosols in 20%, 22%, and 57% of the patients, respectively.

Normal scans were observed in only 18% of the 622 patients. Twelve percent had 3 or less than 3 small defects. A high percentage (59%) of patients had segmental defects. At least 2 segmental defects were present in 49% of the patients. The highest proportion of normal perfusion scans was observed in patients less than 30 years old (40%); the lowest proportion occurred in patients older than 60 (12%).

VENTILATION SCANS

Ventilation scans were normal in 57% of the 379 patients with ventilation studies. This percentage reached 91% in patients 30 years of age or younger and was 67% in patients older than 60 years. Mismatched segmental defects were observed in 45% of the patients; 32% of these had 2 or more mismatched segmental defects. Four percent of the patients had 6 or more mismatched segmental defects. Matched segmental defects were observed in 23% of the patients. Fifty-eight percent of the mismatched segmental defects and 59% of the matched segmental defects were located in both lower lobes of the lung. Of the patients 30 years of age or younger with segmental defects, 76% had only mismatched defects. Of the patients older than 60 years, 52% had only mismatched defects.

CHEST RADIOGRAPHS

Of the entire group, 57% of patients had normal chest radiographs. When chest radiographs were compared with perfusion scans, 43% of patients had 1 or more segmental perfusion defects and 34% had 2 or more segmental perfusion defects with normal chest radiographs in the region of the defect.

ESTIMATES OF THE LUNG SCAN PROBABILITY OF PE AND OF THE FREQUENCY OF PE

The distribution of the different lung scan categories according to the different criteria used for patients with ventilation-perfusion scans is reported in Table 1. According to these data the PE frequency was 39.5% (ie, 0.84 x 0.32 + 0.30 x 0.41 + 0.03 x 0.12) when high-probability scans were defined by at least 2 mismatched ventilation-perfusion defects. When high-probability scans were defined by at least 1 mismatched ventilation-perfusion defect, PE frequency was 49.5% (ie, 0.86 x 0.45 + 0.27 x 0.40). When chest radiographs instead of ventilation scans were compared with perfusion scans, PE frequency was 45.3% (ie, 0.93 x 0.34 + 0.37 x 0.36 + 0.03 x 0.12).

LUNG SCAN ABNORMALITIES RELATED TO DVT EXTENSION

Similar proportions of popliteal DVT and popliteal DVT with suprapopliteal extension were observed in patients with and without perfusion defects (Table 2). No difference was observed between patients with 1 or more mismatched defects and 2 or more mismatched defects in terms of proximal DVT location (Table 3).

RECURRENCE OF THROMBOEMBOLIC EVENTS

The incidence of recurrent thromboembolic events in the group of patients who underwent ventilation-perfusion scan was not significantly different in patients with high-probability baseline scans (13 patients) and intermediate-probability baseline scans (275 patients), and
in patients with normal- (3 patients) and very-low-probability (104 patients) scans. Recurrent PE was observed in 4 patients with high-probability and intermediate-probability baseline lung scans. Sudden deaths where PE could not be excluded was observed in 2 patients. No such events occurred in patients with normal- or very-low-probability baseline scans. However, in the whole group in which 9 patients had recurrent PE, 2 had normal- or very-low-probability baseline scans and only 3 had high-probability scans. Among the 4 patients with intermediate-probability baseline scans, 2 had fatal PE. In these 9 patients, the diagnosis of recurrence was confirmed in only 5 cases by lung scan.

**COMMENT**

This prospective European multicenter study assessed the frequency of lung scan abnormalities in 622 outpatients with primary proximal DVT confirmed by venography and without any sign of PE. The main finding is that a high percentage of these patients have lung scans that fulfill the criteria for a high probability of PE regardless of the criteria used for scan analysis. Depending on the criteria applied, this percentage varied between 32% and 45%. These results confirm, on a larger scale, the results of Huisman et al in 89 consecutive outpatients and of Moser et al in a multicenter study of 37 patients with DVT and without lung symptoms. Others studies using the criteria of Biello et al or PIOPED for ventilation perfusion scan analysis have reported similar results, but they differed from our study by the type of DVT, location of the thrombosis, and methods used for diagnosing DVT.

In addition, our study underlines that, among patients who have abnormal scans, the proportion of high-probability scans is higher in patients younger than 30 years. Evaluating various methods of scan analysis, our study also indicates that the frequencies of high-probability patients in this population are similar when the perfusion scans are compared with chest radiographs or with ventilation scans. In a subgroup of patients from the PIOPED study, Stein et al demonstrated that chest radiographs could be used instead of ventilation scans for PE diagnosis.

The scintigraphic abnormalities observed in our study suggest a high prevalence of asymptomatic PE in outpatients with DVT. As pulmonary angiography was not performed for ethical reasons, this frequency can only be an estimate computed from our data and the PE prevalence reported in various scan categories in other studies and gives a frequency of silent PE ranging from 39.5% to 49.5%. The lowest value is obtained by considering the frequency of high-probability scans defined on at least 2 segmental mismatched ventilation-perfusion defects and the positive predictive values for PE reported in PIOPED studies for each scan category. This frequency of 39.5% is probably an underestimate for the following reasons: (1) The guidelines of the Adjudication Committee were restricted in scope to be compatible with the routine scanning practices of the centers who participated. Because of this, we only considered the large mismatched defects, which are the easiest to assess, in defining the high-probability category. We did not include the moderate mismatched defects in the intermediate category in our study. (2) In our study, 60% of the matched defects (included in the intermediate scan) were located in the base of the lung, which is known as the primary location of PE. Therefore, the prevalence of PE in the intermediate-probability scans is probably higher in our study than in the PIOPED study. This suggests that the PE frequency is probably closer to the highest value (49.5%) computed in our study by using the analysis of lung scan and the positive predictive values for PE reported by Hull et al. By the same analysis of lung scans, Huisman et al computed a 51% frequency of PE in a study performed on 89 patients with DVT and demonstrated that more than 50% of these patients improved on scans after 7 days of anticoagulant treatment.

We found no relationship between the extension of the thrombosis and frequency of a high-probability scan, which suggests that thromboses limited to the popliteal vein give rise to as many embolic events as those with suprapopliteal extension. This finding is in accordance with that of a recent study from Lusiani et al who showed that there is no relationship between the risk of PE and the degree of thrombotic involvement of the lower limbs. Our results contrast with those of Monreal et al; in their study, the majority of patients had multiple risk factors; 88 of 434 patients with symptoms of PE were included; and only 64 of 434 patients had idiopathic DVT.
Many authors have stressed the usefulness of a baseline lung scan in patients with DVT as well as a control scan after 6 to 8 weeks of therapy. However, the cost-effectiveness of performing a lung scan in patients with DVT is not clear, and must be discussed in light of the new treatment modalities for thromboembolic diseases and of the relatively low incidence of recurrent thrombotic events. Recent studies have demonstrated that submassive embolism can be effectively treated with the same dosage of low-molecular-weight heparin as that used for the treatment of DVT. In the present study, the number of PEs in patients undergoing therapy was 1.4%. Recurrent thromboembolic events were observed in only 5.7%, However, a recent literature analysis of the risk of fatal PE in patients treated for venous thromboembolism reported that patients with symptomatic PE have a 5.6% rate of recurrent PE and a 1.8% rate of fatal events. These values are higher than those observed in patients with DVT. Our findings do not support this analysis for asymptomatic PE as there was no difference in the rate of recurrence of PE or the rate of fatal PE after 3 months of therapy between the patients with high- or indeterminate-probability baseline scans and those with normal- or very-low-probability baseline scans.

At this time, perfusion lung scans are the most useful screening test to rule out PE. No other method has been proven to have the same efficacy in detecting silent PE and in noninvasively quantitating lung flow reduction. Its effectiveness is highest in young patients in whom nondiagnostic scans are less frequent and in whom the use of perfusion scans alone may be employed to diagnose PE. When DVT is present, d-dimer measurements cannot be used to exclude PE, as their levels are high. Finally, according to the outcome of our study, the risk of PE in patients with DVT cannot be predicted from thromboembolism location.

Despite these advantages, it appears from our results that routine baseline lung scans for diagnosing asymptomatic PE in patients with DVT may not be necessary. The abnormalities observed may be of no clinical significance, as they seem nonpredictive of PE recurrence, at least after 3 months of therapy. This could not be true for delayed events and for long-term evolution. It has been reported that patients with symptomatic PE had a 27% frequency of previous thromboembolism and that chronic PE occur in some patients in whom embolic events were unrecognized. Extensive pulmonary occlusion has been reported in asymptomatic patients. Six percent of our patients had more than 6 large perfusion defects. However, the frequency of these events has not yet been assessed. Finally, even if the baseline scan can serve as a comparison when a recurrence of PE is suspected and is not interpreted as a therapeutic failure, the cost restriction makes its usefulness questionable owing to the low incidence of PE recurrence in patients with DVT during therapy. This may be reconsidered in the future as recent studies have demonstrated that there is a high percentage of recurrences in patients with a first episode of venous thromboembolism when anticoagulant therapy is discontinued after 3 months. Accepted for publication April 15, 1999.

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