Pulmonary Embolism Among Patients With a Nearly Normal Ventilation/Perfusion Lung Scan*

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Background: Among patients with nearly normal ventilation/perfusion (V/Q) lung scans in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), pulmonary embolism (PE) was diagnosed more frequently in those who underwent pulmonary angiography than in those in whom PE was diagnosed on the basis of an adverse outcome while receiving no anticoagulant therapy. This may suggest that an adverse outcome is not apparent in patients with PE of such mild severity that the V/Q scan is nearly normal. If this were the case, patients with mild PE might not require treatment.

Purpose: The purpose of this investigation was to evaluate patients in PIOPED with nearly normal V/Q lung scans. The V/Q scans and clinical characteristics of those in whom PE was diagnosed or excluded by pulmonary angiography (angiography group) were compared with those in whom PE was diagnosed or excluded by the presence or absence of an adverse outcome while not receiving anticoagulant therapy (outcome group). If the characteristics were the same, it would suggest that some patients with mild PE do well without treatment. If the characteristics were different, it would indicate that there is no evidence from these data that mild PE need not be treated.

Methods: Data from PIOPED were evaluated from patients with suspected acute PE who had V/Q scans interpreted as nearly normal. There were 75 patients in the angiography group and 90 patients in the outcome group. Patients with entirely normal V/Q scans were excluded.

Results: PE was more frequent in the angiography group than in the outcome group, 8 of 75 (11%) vs 0 of 90 (0%) (p<0.01). In patients with nearly normal V/Q scans who were in the outcome group in comparison to the angiography group, the V/Q scan showed fewer mismatched segmental perfusion defects, a lower percentage of low-probability V/Q interpretations by one of the two V/Q readers (compared with very low or normal probability), and a generally lower clinical assessment.

Conclusion: The observed lower frequency of PE in the outcome group in comparison to the angiography group can be attributed to a lower likelihood of PE in this group of patients with nearly normal V/Q scans in comparison to those who underwent pulmonary angiography. There is no evidence from these data that occasional patients with nearly normal V/Q scans who have PE do not require treatment.

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Key words: pulmonary angiography; pulmonary embolism; thromboembolism; ventilation/perfusion scintiscans

Abbreviations: NS=not significant; PE=pulmonary embolism; PIOPED=Prospective Investigation of Pulmonary Embolism Diagnosis; V/Q=ventilation/perfusion

In the national collaborative study Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), patients with a ventilation/perfusion (V/Q) lung scan interpretation of nearly normal were found to have pulmonary embolism (PE) in 5 of 131 (4%) scans. Among the patients with nearly normal V/Q scans, there were two methods of determining whether PE was present or absent. The first method was pulmonary angiography to diagnose or exclude PE. The second method did not employ pulmonary angiography, but the status of PE or no PE was determined by whether an adverse event occurred in patients not receiving anticoagulant therapy. The nearly normal V/Q scan of patients diagnosed by pulmonary angiography had a higher rate of PE detected than the nearly normal V/Q scan of patients whose conditions were diagnosed by outcome analysis. This difference suggested

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the possibility that patients with PE who had V/Q scans that were nearly normal may have no recurrences of PE or only subclinical recurrences, and therefore, may not require anticoagulant therapy. The possibility could not be excluded, however, that there may have been differences between the patients who underwent angiography compared with those who were assessed by outcome analysis, even though both groups had nearly normal interpretations of the V/Q scans.

The purpose of this investigation was to analyze the V/Q scan and clinical findings in patients with nearly normal V/Q scans to determine if a reason could be found for the difference in occurrence of PE in those who underwent pulmonary angiography vs those who underwent outcome analysis. If the two groups of patients have similar V/Q scan and clinical findings, this would provide support for the hypothesis that some patients with PE may not require anticoagulant therapy. We performed a prospective cohort analysis comparing the characteristics and outcomes of patients with nearly normal V/Q scans who had pulmonary angiography with those who also had nearly normal V/Q scans but did not undergo pulmonary angiography.

**Materials and Methods**

**Patients Studied**

In PIOPED, a V/Q scan interpretation of “near normal/normal” included readings of very low probability by one central scan reader and low probability by the other, very low probability by both readers, very low probability by one reader, and normal by the other. If the V/Q scan was read as normal by both readers, the V/Q scan was considered entirely normal. Pulmonary embolism did not occur in any patients in PIOPED with entirely normal V/Q scans, and a normal V/Q scan excluded PE in the experience of others. Therefore, we eliminated these patients from this investigation. The present study relates to patients with nearly normal V/Q scans. The criteria for V/Q scan interpretation of low, very low, and normal are shown in Table 1.

According to PIOPED protocol, patients whose V/Q scans were interpreted as normal by the local physician at the site of recruitment were not to undergo pulmonary angiography, but were to be followed up for outcome analysis. Some patients with nearly normal V/Q scans withdrew from the protocol before pulmonary angiography was performed, and these patients were also followed up for outcome analysis. The decision of whether a pulmonary angiogram was performed was made by the local physician, based on his or her interpretation of the V/Q lung scan. Patients with final readings of “nearly normal” V/Q scans may have been assessed as normal by the local readers and, therefore, excluded from the requirement for angiography. Such patients would have been followed up for outcome analysis.

For patients who lacked a definitive pulmonary angiogram, PE was considered absent if they were discharged from the hospital without anticoagulant therapy and had no outcome event suggestive of PE. Patients were contacted by telephone at 1, 3, 6, and 12 months after study entry. Deaths, new studies for PE, and major bleeding complications were reviewed by an outcome classification committee using all available information. Patients were not randomly selected to either the pulmonary angiography or the outcome analysis group.

We evaluated nearly normal V/Q scans of patients in two arms of PIOPED: (1) patients with suspected PE who were randomly selected for obligatory pulmonary angiography provided their V/Q lung scans were abnormal; and (2) patients with a suspicion of PE who were referred for angiography at the request of their physicians. These patients were not randomly selected for pulmonary angiography. Only the randomly selected group was included in the original PIOPED report. The rate of PE in patients with nearly normal V/Q scans in randomly selected vs referred patients was 5 of 195 (5%) vs 3 of 60 (5%) (not significant [NS]). Because there was no difference between the positive predictive values of nearly normal V/Q scans in the randomly selected vs referred groups, in the present investigation we combined groups.

Among patients with nearly normal V/Q scans, 75 underwent pulmonary angiography. We define this group as the “angiography group.” Among patients with nearly normal V/Q scans, 90 were assessed by outcome analysis. We define this as the “outcome group.” (The methods for obtaining V/Q lung scans and pulmonary angiograms have been described.)

**Statistical Methods**

The $x^2$ test was used to compare various findings among patients who underwent angiography vs patients whose conditions were diagnosed by outcome analysis. A Student’s unpaired $t$ test was used to compare continuous variables.

**Results**

PE was detected by angiography at the time of presentation in 8 of 75 patients in the angiography group (11%; 95% confidence interval, 4.7 to 9.9%). On follow-up, none of the 90 patients in the outcome group had clinically evident PE (95% confidence interval, 0 to 4.0%). No patient in the angiography group had clinically evident PE on follow-up. Thus, PE was detected more frequently in the angiography group than
in the outcome group, 8 of 75 (11%) vs 0 of 90 (0%) (p<0.01).

Categorization of V/Q Lung Scan Interpretations

The angiography group in comparison to the outcome group was more likely to have one of the two readers interpret the V/Q scan as low probability rather than very low, 49 of 75 (65%) vs 37 of 90 (41%) (p<0.01) (Table 2). The angiography group in comparison to the outcome group was less likely to have one reader interpret the V/Q scan as low probability and the other reader interpret the V/Q scan as normal, 15 of 75 (20%) vs 37 of 90 (41%) (p<0.01) (Table 2). Of the eight patients with PE in the angiography group, six had a low-probability V/Q scan interpretation by one reader and a very low interpretation by the other reader. Only two patients with PE in the angiography group had V/Q scan interpretations of very low by one reader and normal by the second reader.

Table 3—Detailed Findings in Patients With Nearly Normal V/Q Scans Comparing Patients With Conditions Diagnosed by Angiography or Outcome Analysis*

<table>
<thead>
<tr>
<th>V/Q Scan Finding</th>
<th>Angiography Group, No. (%) (n=75)</th>
<th>Outcome Group, No. (%) (n=74)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mismatched perfusion defects</td>
<td>5 (7)</td>
<td>0 (0)*</td>
</tr>
<tr>
<td>Matched defects</td>
<td>24 (32)</td>
<td>12 (16)*</td>
</tr>
<tr>
<td>Any small segmental perfusion defects</td>
<td>56 (75)</td>
<td>60 (81)</td>
</tr>
<tr>
<td>Nonsegmental defects</td>
<td>20 (27)</td>
<td>5 (7)*</td>
</tr>
</tbody>
</table>

*Patients may have had more than one defect.
†Information regarding V/Q scan defects was available in only 74 patients.
‡p<0.05 (angiography group vs outcome group).
§p<0.01 (angiography group vs outcome group).

V/Q Scan Findings

The angiography group was more likely to have mismatched segmental perfusion defects than the outcome group, 5 of 75 (7%) vs 0 of 74 (0%) (p<0.05) (Table 3). Among the 5 patients with mismatched segmental perfusion defects, 3 patients had a single moderate (25 to 75% of a segment) segmental mismatch, 1 patient had a single large (>75% of a segment) segmental mismatch, and 1 patient had 1 large and 1 moderate mismatched segmental perfusion defect. In addition, the angiography group was more likely to have nonsegmental defects (defined as perfusion defects due to enlarged aorta, hila, mediastinum or heart, or elevated hemidiaphragm) than the outcome group, 20 of 75 (27%) vs 5 of 74 (7%) (p<0.01) (Table 3). Small pleural effusions, also defined as nonsegmental perfusion defects in PIOPED, were analyzed separately. In the angiography group, small pleural effusions were observed in 3 of 75 (4%) patients and in the outcome group small pleural effusions were observed in 2 of 74 (3%) (NS).

Matched defects (defined as perfusion defects smaller than the chest radiographic defect or perfusion defects equal or smaller than the ventilation defect with a normal regional chest radiograph) in the angiography group were observed in 24 of 75 (32%) vs 12 of 74 (16%) in the outcome group (p<0.05). Data on matched defects were not available in 16 patients in the outcome group.

Table 4—Clinical Likelihood Among Patients With Nearly Normal V/Q Scans Comparing Patients With Conditions Diagnosed by Angiography or Outcome Analysis*

<table>
<thead>
<tr>
<th>Clinical Likelihood of PE (%)</th>
<th>Angiography Group, No. (%) (n=73)</th>
<th>Outcome Group, No. (%) (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (80-100)</td>
<td>3 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intermediate (20-79)</td>
<td>45 (62)</td>
<td>40 (45)*</td>
</tr>
<tr>
<td>Low (0-19)</td>
<td>25 (34)</td>
<td>49 (55)*</td>
</tr>
</tbody>
</table>

*p<0.05 (angiography group vs outcome group).
§p<0.01 (angiography group vs outcome group).

*Clinical likelihood of PE was not assessed in three patients.

Table 5—Clinical Likelihood Among Patients With Nearly Normal V/Q Scans Comparing Patients With Conditions Diagnosed by Angiography or Outcome Analysis*

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Angiography Group, No. (%) (n=74)</th>
<th>Outcome Group, No. (%) (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2, mm Hg, on room air</td>
<td>76±18 (n=63)</td>
<td>82±18 (n=68)</td>
</tr>
<tr>
<td>PaCO2, mm Hg, on room air</td>
<td>35±5 (n=63)</td>
<td>34±5 (n=68)</td>
</tr>
<tr>
<td>pH on room air</td>
<td>7.5±0.1 (n=63)</td>
<td>7.4±0.1 (n=68)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>133±23 (n=74)</td>
<td>130±21 (n=75)</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>88±20 (n=75)</td>
<td>87±17 (n=70)</td>
</tr>
<tr>
<td>Respiratory rate, min⁻¹</td>
<td>20±5 (n=75)</td>
<td>21±7 (n=70)</td>
</tr>
</tbody>
</table>

*All differences NS (angiography group vs outcome group).
Clinical Assessment

The angiography group was more likely to have an intermediate (indeterminate) clinical likelihood of PE than the outcome group, 45 of 73 (62%) vs 40 of 89 (45%) (p<0.05) (Table 4). The angiography group was less likely to have a low clinical likelihood than the outcome analysis group, 25 of 73 (34%) vs 49 of 89 (55%) (p<0.01) (Table 4). Clinical assessment was not available in three patients.

Clinical Findings

The angiography group had a similar PaO2 while breathing room air as patients whose condition were diagnosed by outcome analysis, 76±18 mm Hg vs 82±18 mm Hg (NS) (Table 5). Other clinical findings such as PaCO2, pH, systolic BP, heart rate, and respiratory rate were also similar between the two groups.

Discussion

More V/Q scan abnormalities and higher likelihood clinical assessments were observed among patients with nearly normal V/Q scans in the angiography group than the outcome group.

Patients with mild PE sometimes do well without treatment.6,7 We cannot exclude, therefore, that some patients in the outcome group may have had PE that did not recur or, if it recurred, was subclinical. The present study cannot determine if the finding of no PE in the outcome group was due to a low prevalence of venous thromboembolism from the outset, or due to the fact that some PE, which were undetected at presentation, do well without treatment. Distinguishing between these two possibilities could be done by randomly allocating patients with nondiagnostic lung scans and adequate cardiorespiratory reserve to be managed either using pulmonary angiography or using serial noninvasive leg testing.7 Such a trial would provide important data for the practical management of suspected PE, as well as further data testing the concept that some PE do not require antithrombotic treatment if proximal-vein thrombosis has been excluded by noninvasive leg testing.

References

1 A Collaborative Study by the PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990; 263:2753-59