Value of the Ventilation/Perfusion Scan in Acute Pulmonary Embolism

Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED)

The PIOPED Investigators

To determine the sensitivities and specificities of ventilation/perfusion lung scans for acute pulmonary embolism, a random sample of 933 of 1493 patients was studied prospectively. Nine hundred thirty-one underwent scintigraphy and 755 underwent pulmonary angiography; 251 (33%) of 755 demonstrated pulmonary embolism. Almost all patients with pulmonary embolism had abnormal scans of high, intermediate, or low probability, but so did most without pulmonary embolism (sensitivity, 98%; specificity, 10%). Of 116 patients with high-probability scans and definitive angiograms, 102 (88%) had pulmonary embolism, but only a minority with pulmonary embolism had high-probability scans (sensitivity, 41%; specificity, 97%). Of 322 with intermediate-probability scans and definitive angiograms, 105 (33%) had pulmonary embolism. Follow-up and angiography together suggest pulmonary embolism occurred among 12% of patients with low-probability scans. Clinical assessment combined with the ventilation/perfusion scan established the diagnosis or exclusion of pulmonary embolism only for a minority of patients—those with clear and concordant clinical and ventilation/perfusion scan findings.

For editorial comment see p 2794.

PERFUSION lung scans have been reported to be sensitive in detecting pulmonary emboli, but many other conditions such as pneumonia or local bronchospasm cause perfusion defects. Ventilation scans were added to perfusion scans with the idea that ventilation would be abnormal in areas of pneumonia or local hypoventilation, but that in pulmonary embolism ventilation would be normal. A number of investigators have attempted to make ventilation/perfusion (V/Q) scans more useful for diagnosing pulmonary embolism by classifying them not just as normal or abnormal, but if abnormal, as indicating high probability, intermediate probability (indeterminate), or low probability of pulmonary embolism. Under the auspices of the National Heart, Lung, and Blood Institute, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) investigators have assessed the diagnostic usefulness of V/Q lung scans in acute pulmonary embolism. The project protocol and consent forms were approved by the institutional review boards of all participating centers. (Participating centers and investigators are listed at the end of the article.)

METHODS
Patient Enrollment

From January 1985 through September 1986 in each of six clinical centers, all patients for whom a request for a V/Q scan or a pulmonary angiogram was made were considered for study entry. The eligible study population consisted of patients, 18 years or older, inpatients and outpatients, in whom symptoms that suggested pulmonary embolism were present within 24 hours of study entry and without contraindications to angiography such as pregnancy, serum creatinine level greater than 260 μmol/L, or hypersensitivity to contrast material. Once approached for the study, patients with recurrences were not approached for recruitment a second time.

Recruitment

A total of 5587 requests for V/Q scans were recorded in the six PIOPED clinical centers from January 1985 through September 1986 (Figure). Although
some patients could not be thoroughly evaluated prior to completion of the V/Q scan, clinical investigators made every effort to record their individual clinical impressions as to the likelihood of pulmonary embolism prior to learning the results of V/Q scans and angiography. Impressions were based on an agreed on set of information—history, results of physical examination, arterial blood gas analyses, chest roentgenograms, and electrocardiograms—but without standardized diagnostic algorithms. The medical records of a random sample of patients who refused or were ineligible for study entry (refuser/ineligible patients) were evaluated retrospectively for comparison with study patients.

**Lung Scan**

The protocol directed ventilation and perfusion studies with the subject in the upright position, but other positions were acceptable. Ventilation studies were performed with 5.6 x 10^6 to 11.1 x 10^6 Bq of xenon 133 using a 20% symmetric window set over the 80-keV energy peak. They started with a 100 000-count, posterior-view, first-breath image and then posterior equilibrium (wash-in) images for two consecutive 120-second periods. Washout consisted of three serial 45-second posterior views, 45-second left and right posterior oblique views, and a final 45-second posterior view. Then, perfusion scans were obtained with 1.5 x 10^8 Bq of technetium Tc 99m macroaggregated albumin that contained 100 000 to 700 000 particles using a 20% symmetric window set over the 140-keV energy peak. Particles were injected into an antecubital vein over 5 to 10 respiratory cycles, with the patient supine or at most semirecumbent. The perfusion images consisted of anterior, posterior, both posterior oblique, and both anterior oblique views, with 750 000 counts per image for each. For the lateral view with the best perfusion, 500 000 counts per image were collected; the other lateral view was obtained for the same length of time. Scintillation cameras with a wide field of view (38.1 cm in diameter) were used with parallel-hole, low-energy, all-purpose collimators. Perfusion scans were satisfactory or better in 96% of cases, ventilation scans adequate or better in 95%.

**Angiography**

The femoral-vein Seldinger technique with a multiple side-holed, 6F to 8F pigtail catheter was used. Small amounts of contrast material (5 to 8 mL) were injected by hand, to check the patency of the inferior vena cava by fluoroscopy. The catheter was directed into the main pulmonary artery of the lung with the greatest V/Q scan abnormality. Initial filming was in the anteroposterior projection. Seventy-six percent iodinated contrast material was injected at a rate of 20 to 35 mL/s for a total of 40 to 50 mL (2-second injection). Film rates were three per second for 8 seconds, followed by one per second for 4 to 6 seconds. Depending on the size of the lungs, filming was not magnified or given a low magnification of 1.4. A 12:1 grid was used and roentgenographic factors were in the range of 70 to 80 kilovolts (peak) and 0.025 to 0.040 seconds at 1000 mA (large focal spot of 1.2 to 1.5 mm in diameter). If emboli were not identified, injections were repeated and magnification (1.8 to 2.0 times) oblique views were obtained of the areas suspicious for pulmonary embolism. Films were obtained with an air-gap technique (ie, no grid used). Roentgenographic factors were in the range of 78 to 88 kV (p) and 0.040 to 0.080 seconds at 100 mA (small focal spot of 0.3 to 0.6 mm in diameter). If no emboli were found in the first lung, or if bilateral angiography in the clinical center was routine, identical techniques were used for the second lung. Angiography was completed within 24 hours, and usually within 12 hours of V/Q scans. Pulmonary angiograms were adequate or better in 85% of cases.
Central Scan and Angiogram Interpretations

Two nuclear medicine readers, not from the center that performed the scan, independently interpreted the lung scans with chest roentgenograms according to preestablished study criteria (Table 1). Angiograms were likewise randomly assigned to pairs of angiographers from clinical centers other than the originating hospital. The angiogram readers interpreted the angiograms with lung scans as having acute pulmonary embolism present—which required the identification of an embolus obstructing a vessel or the outline of an embolus (filling defect) within a vessel—absent, or uncertain. If two readers disagreed, the interpretations were adjudicated by readers who were selected randomly from the remaining clinical centers. If adjudicating readers did not agree with either of the first two readers, scans or angiograms went to panels of nuclear medicine or angiography readers. The final adjudicated V/Q scan readings consisted of four categories—high probability, intermediate probability (indeterminate), low probability, and very low probability through normal (near normal/normal). The near-normal/normal category includes readings of very low probability by one reader and low probability by the other, very low probability by both, very low probability by one and normal by the other, and normal by both. Refuser/ ineligible patients’ scans were read in each clinical center by the clinical center’s PIOPED nuclear medicine reader(s) and not reread.

Follow-up and Outcome Classification

Patients were contacted by telephone at 1, 3, 6, and 12 months after study entry. Deaths, new studies for pulmonary embolism, and major bleeding complications were reviewed by an outcome classification committee using all available information. Only 23 (2.5%) of the 931 patients had incomplete (16) or no (7) follow-up. Angiograms, follow-up data, and outcome classifications were used to determine pulmonary embolism status as positive for patients with angiograms that showed pulmonary embolism and for patients for whom outcome review established the presence of pulmonary embolism at the time of PIOPED recruitment. Pulmonary embolism status was determined as positive for patients with angiograms that did not show pulmonary embolism and no contrary outcome review and for patients who lacked a definite angiogram reading who were discharged from the hospital without a prescription for anticoagulants and in whom no outcome event suggested pulmonary embolism. Pulmonary embolism status could be determined as positive or negative for 902 patients. A clinical assessment of the likelihood of pulmonary embolism was available for 887 (98%) of these patients.

Statistical Methods

Probability values for the comparison of percentages and proportions and 95% confidence intervals (CIs) were calculated using standard z tests. 1 A χ² test for homogeneity of proportions was used to compare distributions. 2 Sensitivity is defined as the proportion of cases of pulmonary embolism correctly diagnosed and specificity as the proportion of diagnoses that pulmonary embolism is absent for patients without pulmonary embolism. Sensitivity, specificity, and percent agreement have been calculated according to standard methods for proportions. 3 Analyses were performed with the Statistical Package for the Social Sciences statistical software package. 4 Recruitment of 900 to 1000 patients in the random sample for PIOPED angiography was planned to obtain estimates of sensitivity and specificity with 95% CIs not wider than ±10%. To determine the sensitivity and specificity of V/Q lung scans without the biases associated with haphazard patient selection (ie, convenience sampling), 5 a 933-patient sample of the 1493 patients who consented to PIOPED participation was selected according to random sampling schedule created separately by the data and coordinating center for each clinical center. The PIOPED protocol required these 933 patients to undergo angiography if their scans were abnormal. Of the 933 patients selected for angiography, 1 patient died before the V/Q scan could be completed and 1 other patient’s V/Q scan was determined to be uninterpretable. These 2 patients are not further reported herein.

RESULTS

Of the 3016 patients eligible for PIOPED, 1493 (60%) gave consent to

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Table 1. —PIOPED Central Scan Interpretation Categories and Criteria*

<table>
<thead>
<tr>
<th>Probability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High probability</td>
<td>≥2 Large (&gt;75% of a segment) segmental perfusion defects without corresponding ventilation or roentgenographic abnormalities or substantially larger than either matching ventilation or chest roentgenogram abnormalities</td>
</tr>
<tr>
<td>Moderate segmental (≥75% to &lt;95%) segmental perfusion defects without matching ventilation or chest roentgenogram abnormalities and l large mismatched segmental defect</td>
<td></td>
</tr>
<tr>
<td>Moderate segmental (≥75% to &lt;95%) segmental perfusion defects without ventilation or chest roentgenogram abnormalities</td>
<td></td>
</tr>
<tr>
<td>Intermediate probability (indeterminate)</td>
<td>Not falling into normal, very-low-, low-, or high-probability categories</td>
</tr>
<tr>
<td>Borderline high or borderline low</td>
<td>Difficult to categorize as low or high</td>
</tr>
<tr>
<td>Low probability</td>
<td>Nonsegmental perfusion defects (eg, very small effusion causing blunting of the costophrenic angle, cardiomegaly, enlarged aorta, hila, and mediastinum, and elevated diaphragm)</td>
</tr>
<tr>
<td>Single moderate mismatched segmental perfusion defect with normal chest roentgenogram</td>
<td></td>
</tr>
<tr>
<td>Any perfusion defect with a substantially larger chest roentgenogram abnormality</td>
<td></td>
</tr>
<tr>
<td>Large or moderate segmental perfusion defects involving no more than 4 segments in 1 lung and no more than 3 segments in 1 lung region with matching ventilation defects either equal to or larger in size and chest roentgenogram abnormality or normal with abnormalities substantially smaller than perfusion defects</td>
<td></td>
</tr>
<tr>
<td>Small segmental perfusion defects (&lt;25% of a segment) with a normal chest roentgenogram</td>
<td></td>
</tr>
<tr>
<td>Very low probability</td>
<td>Nonsegmental perfusion defects</td>
</tr>
<tr>
<td>≤3 Small segmental perfusion defects with a normal chest roentgenogram</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*PIOPED indicates Prospective Investigation of Pulmonary Embolism Diagnosis.

Table 2. —Recruitment of Patients and Completion of Angiography*

<table>
<thead>
<tr>
<th>Clinical Center</th>
<th>% of Eligible Patients Recruited</th>
<th>Lung Scans Who Were Selected for Angiographic Pursuit</th>
<th>Angiograms Obtained, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke University</td>
<td>46</td>
<td>137</td>
<td>115 (84)</td>
</tr>
<tr>
<td>Henry Ford Hospital</td>
<td>62</td>
<td>228</td>
<td>177 (76)</td>
</tr>
<tr>
<td>Massachusetts General Hospital</td>
<td>33</td>
<td>140</td>
<td>120 (86)</td>
</tr>
<tr>
<td>University of Michigan</td>
<td>52</td>
<td>102</td>
<td>65 (64)</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>70</td>
<td>168</td>
<td>134 (80)</td>
</tr>
<tr>
<td>Yale University</td>
<td>43</td>
<td>156</td>
<td>144 (92)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>931</td>
<td>755 (81)</td>
</tr>
</tbody>
</table>

*PIOPED indicates Prospective Investigation of Pulmonary Embolism Diagnosis.
participate in PIOPED (Figure). The clinical centers varied in the percentage of eligible patients for whom consent could be obtained, from 39% to 70%, and in the percentage of patients for whom angiograms were obtained among those selected to determine the sensitivity and specificity of V/Q lung scans (PIOPED angiographic pursuit), from 64% to 96% (Table 2). The PIOPED patients resembled refuser/ineligible patients in a variety of clinical characteristics (Table 3). The PIOPED patients and refuser/ineligible patients were different, however, in their lung scan abnormalities ($P<.01$). Although they had similar frequencies of high-probability scans (18% among PIOPED patients and 11% among refuser/ineligible patients), the PIOPED patients had intermediate-probability scans almost twice as often as refuser/ineligible patients (39% vs 22%). The PIOPED study had a smaller proportion of patients with low-probability and near-normal/nor¬mal lung scans. Of the 931 patients who were selected for mandatory angiography in PIOPED, 755 (81.1%) completed angiography; 69 (7.4%) did not complete angiography because their V/Q scans were interpreted locally as normal; and 107 (11.5%) did not complete angiography in spite of the requirements of the protocol.

**Reader Agreement**

Agreement among scan readers was excellent for high-probability (95%), very-low-probability (92%), and normal (94%) scan categories. For intermediate-probability (indeterminate) and low-probability scan categories, the readers agreed less frequently (75% and 70%, respectively). In only 24 (2.6%) of 901 scans was panel adjudication necessary. Agreement among angiogram readers was excellent for the presence of pulmonary embolism (92%). For the absence of pulmonary embolism and pulmonary embolism uncertain, independent readers agreed on 83% and 89% of angiograms, respectively. In only 13 (1.7%) of 755 angiograms was panel adjudication necessary.

**Scan Findings**

Most (676) of the 931 patients had intermediate- or low-probability V/Q scan readings (39% and 34%, respectively) (Table 4). Only 131 (14%) had near-normal/normal V/Q scans and 124 (13%) had high-probability scans. The 176 patients who did not undergo angiography, in spite of their selection for mandatory angiography, had less severe scan abnormalities than those who completed angiography ($P<.01$).

**Angiogram and Outcome Findings**

Among the 755 patients who completed angiography, 251 (33%) had thromboemboli seen on the angiogram, 480 (64%) had no thromboemboli seen, and 24 (3%) had angiograms in which the presence of thromboemboli was uncertain (Table 4). For the vast majority of patients, 1 year of follow-up revealed clinical courses entirely consistent with angiographically established diagnoses. The outcome classification committee disagreed with central angiography interpretations for 4 patients with pulmonary angiograms free of signs of acute embolism who had pulmonary embolism at autopsies performed 2 to 6 days after angiography. The scan interpretations were of low probability for 3 and of intermediate probability (indeterminate) for 1 of these 4 patients.

**Scans Compared With Angiograms**

One hundred two of 251 patients with angiograms that showed thromboemboli had high-probability V/Q scans. The sensitivity, therefore, was 41% (95% CI, 34% to 47%) (Tables 4 and 5). If the patient had either a high- or intermediate-probability V/Q scan, the sensitivity for thromboemboli on angiography increased to 207 (82%) of 251 (95% CI, 78% to 87%). If the patient had either a high-, intermediate-, or low-probability V/Q scan, then 246 of 251 had thromboemboli on angiography, a sensitivity of 98% (95% CI, 96% to 100%).

**Table 3.—Patient Characteristics**

<table>
<thead>
<tr>
<th>Category</th>
<th>PIOPED (N = 931)</th>
<th>Refuser/Ineligible (N = 326)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean)</strong></td>
<td>56.1</td>
<td>56.4</td>
</tr>
<tr>
<td>Male, %</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Service, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/CCU</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>Surgical</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Emergency dept/clinic</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>ICU</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

*PIOPED indicates Prospective Investigation of Pulmonary Embolism Diagnosis; CCU, coronary care unit; and ICU, intensive care unit.

**Table 4.—Comparison of Scan Category With Angiogram Findings**

<table>
<thead>
<tr>
<th>Scan Category</th>
<th>Pulmonary Embolism Present</th>
<th>Pulmonary Embolism Absent</th>
<th>Pulmonary Embolism Uncertain</th>
<th>No Angiogram</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>High probability</td>
<td>102</td>
<td>14</td>
<td>1</td>
<td>7</td>
<td>124</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>105</td>
<td>217</td>
<td>9</td>
<td>33</td>
<td>364</td>
</tr>
<tr>
<td>Low probability</td>
<td>39</td>
<td>199</td>
<td>1</td>
<td>62</td>
<td>312</td>
</tr>
<tr>
<td>Near normal/normal</td>
<td>5</td>
<td>50</td>
<td>2</td>
<td>74</td>
<td>131</td>
</tr>
<tr>
<td>Total</td>
<td>251</td>
<td>480</td>
<td>24</td>
<td>175</td>
<td>931</td>
</tr>
</tbody>
</table>

**Table 5.—Comparison of Scan Category With Angiogram Findings, Sensitivity and Specificity**

<table>
<thead>
<tr>
<th>Scan Category</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>High probability</td>
<td>41</td>
<td>97</td>
</tr>
<tr>
<td>High or intermediate probability</td>
<td>82</td>
<td>52</td>
</tr>
<tr>
<td>High, intermediate, or low probability</td>
<td>98</td>
<td>10</td>
</tr>
</tbody>
</table>
embolism was only 74% (14/19), compared with 91% (88/97) for those without a history of pulmonary embolism (P < .05). This difference in positive predictive values reflects a loss of specificity in the high-probability V/Q scan diagnosis for patients with histories of pulmonary embolism (88%) vs those with no prior pulmonary embolism (98%) (P < .01).

The percentage of patients whose angiograms showed thromboemboli was less in the intermediate-probability (indeterminate), low-probability, and near-normal/normal scan categories—33%, 16%, and 9%, respectively (Table 4). The frequency of angiographically demonstrable emboli among patients with low-probability scans (39 [16%] of 238) and near-normal/normal scans (5 [9%] of 55) is influenced by the relatively large numbers of patients (74 patients and 76 patients, respectively) for whom angiography was not completed or interpretations were uncertain in these scan categories (Table 4). Since none of these patients received anticoagulants and none developed clinically evident pulmonary embolism during follow-up, important pulmonary embolii did not occur in this group. If all 150 patients were regarded as not having had pulmonary emboli, then the frequency of clinically important pulmonary emboli in patients with low-probability scans could be no less than 39 (12%) of 312, and in patients with near-normal/normal scans, 5 (4%) of 131.

There were 21 patients whose V/Q scans were read centrally as normal on first reading by both readers. Three underwent angiography and none showed thromboemboli. None of the remaining 15 patients received anticoagulants and none had clinically evident pulmonary embolism on follow-up.

**Clinical Assessment of the Likelihood of Pulmonary Embolism**

The clinician's assessment of the likelihood of pulmonary embolism recorded before the scan was performed ("prior probability") was compared with pulmonary embolism status as determined by angiography and follow-up information (Table 6) for 887 patients with prior probability assessments and definite pulmonary embolism status. A clinical assessment of 80% to 100% likelihood of pulmonary embolism was made in 90 patients (10%) and was correct in 61 (68%) of 90. A clinical assessment of 0% to 19% likelihood of pulmonary embolism was made in 225 (26%) and was correct in 207 (91%) of 228. Clinical assessment, therefore, was more often correct in excluding pulmonary embolism than in identifying pulmonary embolism. In the majority of patients (569 [64%]), clinical assessments were noncommittal (20% to 79% likelihood of pulmonary embolism).

Combining clinical assessments with the V/Q scan interpretations improved the overall chance of reaching a correct diagnosis of acute pulmonary embolism (Table 6). Among patients in whom the clinical impression and the scan interpretation were both of high probability for pulmonary embolism, 28 (96%) of 29 had pulmonary embolism. If the high-probability scan interpretation was paired with an intermediate-likelihood clinical assessment or a low-likelihood clinical assessment, then the probability that the patient had pulmonary embolism fell to 70 (88%) of 80 and 5 (50%) of 9, respectively. The addition of the clinical evaluation also helped in the low-probability and in the near-normal/normal scan categories. A low-probability clinical assessment (0% to 19% likelihood of pulmonary embolism based on clinical judgment), when paired with a low-probability V/Q scan, correctly excluded the diagnosis of pulmonary embolism in 86 (95%) of 90 patients. The near-normal/near-normal V/Q scan category, when paired with a low-likelihood clinical assessment, correctly excluded pulmonary embolism in 60 (98%) of 61 patients.

**COMMENT**

The PIOPED study was conducted as a multicenter, prospective effort to estimate the sensitivity and specificity of the V/Q lung scan for the diagnosis of pulmonary embolism. Other retrospective and prospective studies have focused on positive predictive values, which are influenced by prevalence of pulmonary embolism and patient selection. Sensitivity and specificity, however, are fundamental characteristics of a diagnostic test and are not affected by the prevalence of disease.10

In PIOPED, almost all patients (98%) with clinically important pulmonary embolism had lung scans that fell into one of the three abnormal categories—high, intermediate (indeterminate), or low probability. If all three abnormal categories are combined into one, the lung scan is sensitive enough to serve as a screening test for the diagnosis of pulmonary embolism, but the specificity is limited. The high-probability scan lacked sensitivity in diagnosing pulmonary embolism, since it failed to identify 59% of patients with this disorder.

Only 14 (3%) of 480 patients who did not have evidence of acute pulmonary embolism on angiography had high-probability scans (Table 4). Therefore, the specificity of a high-probability scan was 97%. For patients with histories of pulmonary embolism, the specificity of the high-probability scan was reduced. This finding is consistent with other reports of previous pulmonary embolism as a cause of V/Q scan abnormality that may be confused with acute pulmonary embolism.12-14 The specificity of scans of intermediate or low probability was much less than the specificity of the high-probability scan.

The PIOPED study design included patient enumeration and recruitment prior to scan completion to avoid bias in patient selection. Nonetheless, patients who ultimately had high- and intermediate-probability scans were more often
successfully recruited for PIOPED. If anything, this selection bias would suggest that PIOPED tends to overestimate V/Q scans' sensitivities and underestimate specificities.

Clinical decisions are often made on the basis of the predictive values, which depend not only on the test's sensitivity and specificity, but also on the prevalence of disease in the population studied. Based on angiogram results, the prevalence of pulmonary embolism in PIOPED was 33\% (251/755) (Table 4); based on pulmonary embolism status—derived from angiogram evaluation and/or clinical evaluation—the prevalence was 28\% (Table 6), similar to the prevalences described in previous reports.\textsuperscript{13,14} In PIOPED, the positive predictive value of the high-probability scan was 88\%, whereas the negative predictive value of a low-probability scan was 84\%. The negative predictive value of the near-normal/near-normal scan category was better at 91\%. Estimates of negative predictive values increased when analyses took into account patients who did not undergo angiography, did not receive anticoagulants, and had no evidence of pulmonary embolism occurring during 1 year of follow-up. Including these patients among those not having pulmonary embolism in the analysis improved the negative predictive value of the low-probability scan from 84\% to 88\% and of the near-normal/near-normal scan from 91\% to 96\%. Because some instances of acute pulmonary embolism may not have been detected among these patients, the true negative predictive values may be less than 88\% for low-probability scans and 96\% for near-normal/near-normal scans, but still ought to be closer to these latter values than to the 84\% and 91\%, which did not apply for patients without angiography results.

Although pulmonary emboli did occur in patients with scans classified in the categories between low probability and normal, pulmonary embolism was documented in only 5 (4\%) of 131 of such patients. The true proportion of patients with pulmonary embolism must be inferred with caution, because large numbers of patients with near-normal/near-normal scans were not successfully recruited for the study. Only 42\% of the 131 PIOPED patients in this category completed angiography. Only 3 of the 21 patients with lung scans read as normal by both readers on the final reading completed angiography; all 3 had normal pulmonary angiograms. None of the remaining 18 had clinically evident pulmonary emboli on follow-up. This finding is consistent with the findings of Kipper et al.\textsuperscript{12}

The value of combining clinical judgment with the interpretation of the scan is supported by the PIOPED study. The predictive value of the high- and low-probability lung scans improved when supported by similar clinical assessments. For 90 patients, the negative predictive value of the low-probability scan rose to 96\% when accompanied by clinical assessment of low likelihood. In 29 patients, the positive predictive value of a high-probability scan increased to 96\% if supported by a high-likelihood clinical assessment. In the PIOPED experience, combining a lung scan interpretation with a strong clinical suspicion as to whether acute pulmonary embolism is present is a sound diagnostic strategy, as previously suggested by McNeil and colleagues.\textsuperscript{2,3} But is sufficient for only a minority of patients (Table 6). For a substantial number of patients in the PIOPED study, angiography was required for a definitive diagnosis of pulmonary embolism.

The PIOPED study employed pulmonary angiography, which proved to be a safe and accurate method of diagnosing pulmonary embolism, although it is invasive. The four patients (0.5\%) for whom the outcome classification committee disagreed with blinded angiogram interpretations that showed acute pulmonary embolism to be absent must be considered carefully in light of the angiographic criteria's design for acute pulmonary embolism, the variable time between angiographic evaluation and the patients' deaths, and the variability in pathophysiology and pathological interpretation of thromboemboli in evolution. In the PIOPED study, a normal angiogram almost excluded the possibility of pulmonary embolism, confirming the results of two previous studies.\textsuperscript{13,14} The PIOPED findings extend observations made by other investigators,\textsuperscript{1,3,10,19} from whom the PIOPED investigators derived study criteria for angiogram and V/Q scan interpretation. Although predictive values for patients with high-probability scans and patients with low-probability scans in previous series are generally consistent with the PIOPED findings, the under-representation of patients with low-probability scans in previous studies has in the past led to an exaggerated impression of the sensitivity of the high-probability lung scan.

The findings of Hull and colleagues,\textsuperscript{17,18} in the Hamilton District Thromboembolism Programme are particularly interesting in comparison with the PIOPED results. Of the 306 patients with suspected pulmonary embolism and abnormal perfusion lung scans in their study, 173 (57\%) had adequate ventilation scans and adequate pulmonary angiograms. Ninety-five patients (31\%) had pulmonary emboli demonstrated on angiography. The predictive values from their study are similar to PIOPED results in the high-probability and intermediate-probability (indeterminate) scan categories. The PIOPED study, like the one from the Hamilton District Thromboembolism Programme, compared estimates of sensitivity and specificity between the two studies are not possible.

The PIOPED results lead to a number of conclusions that settle controversies about the diagnostic value of the lung scan in pulmonary embolism.\textsuperscript{2,3,8,9} A high-probability scan usually indicates pulmonary embolism, but only a minority of patients with pulmonary embolism have a high-probability scan. A history of pulmonary embolism decreases the accuracy of diagnoses based on high-probability scans. A low-probability scan with a strong clinical impression that pulmonary embolism is not likely makes the possibility of pulmonary embolism remote. Near-normal/near-normal lung scans make the diagnosis of acute pulmonary embolism very unlikely. An intermediate-probability (indeterminate) scan is not of help in establishing a diagnosis. In PIOPED, the scan combined with clinical assessment permitted a noninvasive diagnosis or exclusion of acute pulmonary embolism for a minority of patients.

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