Continuing Risk of Thromboemboli Among Patients With Normal Pulmonary Angiograms*

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Purpose: The purpose of this investigation was to determine the frequency of future pulmonary embolism (PE) among patients in whom PE was suspected and excluded by pulmonary angiography.

Methods: Data are from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). The present investigation includes 380 patients in whom PE was excluded by pulmonary angiography and who received no anticoagulant therapy while in the hospital or after discharge. Patients were followed 1 year after their normal pulmonary angiograms.

Results: Pulmonary embolism occurred within 1 year in 6 of 380 (1.6%) (95% confidence interval [CI] 0.3 to 2.9%) patients with suspected PE and normal pulmonary angiograms. Four of six (67%) PE were nonfatal. Three of six (50%) PE occurred in the first 8 days and four of six (67%) PE occurred within the first month. Among patients who subsequently showed PE, a history of thrombophlebitis or an objective test suggestive of deep venous thrombosis was present in five of six (83%). Symptoms, signs, and radiographic abnormalities were similar among patients who showed PE on follow-up and those who did not, although the pulmonary artery mean pressure was higher among those with subsequent PE (34 ± 25 mm Hg vs 22 ± 10 mm Hg) (p<0.01).

Conclusion: The frequency of PE on follow-up among patients with normal pulmonary angiograms is small. There is, however, a real and measureable rate of clinically important PE over the subsequent 12 months that is higher than reported in the general population of hospitalized patients. Patients with suspected PE, therefore, even if their angiogram is normal, might benefit from definitive studies of the lower extremities to exclude deep venous thrombosis. The cost benefit ratio of this, however, has not been evaluated.

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Key words: deep venous thrombosis; pulmonary embolism; thromboembolism

Patients in whom pulmonary embolism (PE) was suspected and excluded by pulmonary angiography are a group likely to have conditions that predispose to PE, and such patients, therefore may be at continuing risk of PE. The purpose of this investigation was to determine the frequency of the development of future PE in such patients.

METHODS

Data were evaluated among patients who participated in the collaborative study of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) who were randomized to obligatory angiography if they had an abnormal ventilation/perfusion lung scan.\(^1\) In PIOPED, 380 patients had normal pulmonary angiograms and had anticoagulant treatment withheld or withdrawn if it had been commenced, and anticoagulants were not given after discharge from the hospital. This group was evaluated in the present investigation of PIOPED data. Techniques of recruiting, physical examination, ventilation/perfusion lung scans, and pulmonary angiography were reported in PIOPED.\(^1\) The protocol of PIOPED did not require laboratory tests of the legs for deep venous thrombosis. Twenty-nine untreated patients had such tests within 2 weeks of the normal pulmonary angiogram, and 12 patients had more than one test. Tests for deep venous thrombosis were Doppler ultrasound in 20 patients, impedance plethysmography in 16 patients, and venography in 5 patients.

Data on the history, physical examination, chest radiograph, and pulmonary artery mean pressure were measured in all of the 380 patients. The partial pressure of oxygen in arterial blood (PaO\(_2\)) and the alveolar arterial oxygen gradient while breathing room air were obtained in 287 of the 380 patients. The method for assessment of the alveolar arterial oxygen gradient was previously described.\(^2\)

Prospective follow-up in PIOPED was done to detect clinical events that could represent PE.\(^1\) This PIOPED follow-up protocol detected only symptomatic events. After discharge from the hospital, each patient was contacted by telephone at 1, 3, 6, and 12 months. The reporting of rehospitalization, any new investigation for PE, or death led to a detailed review of the patient’s medical records by the outcome classification committee. Diagnostic studies for PE during the period of follow-up were ordered by the attending physician on the basis of clinical suspicion and were not part of the study protocol. Pulmonary embolism during the period of follow-up was diagnosed on the basis of a clinical suspicion confirmed by an abnormal pulmonary angiogram, high-probability ventilation-perfusion lung scan, or autopsy.

Statistical Methods

A \(\chi^2\) with Yates’ correction was used to compare the prevalence of predisposing factors, symptoms, and characteristics of labora-

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tory tests. Comparisons of continuous variable means were made with Student’s t test. Data are reported as mean±SD. The 95% confidence interval (CI) was calculated using the method of Galen and Gambino.3

**RESULTS**

Among the 380 patients with normal pulmonary angiograms who received no anticoagulant therapy, the cumulative number of deaths from all causes at 1 month, 3 months, 6 months, 9 months, and 1 year was 35, 60, 75, 85, and 89, respectively. Only two deaths were related to PE, and both were in the first month. Four of the six (67%) episodes of PE were nonfatal. Three of six (50%) PE occurred in the first 8 days and four of six (67%) PE occurred within the first month (Table 1). Among 380 patients with normal pulmonary angiograms, six (1.6%) (CI, 0.3 to 2.9%) suffered clinical PE during the year of follow-up. Among 291 patients with normal pulmonary angiograms who survived the year of follow-up, nonfatal PE occurred in four (1.4%).

Regarding the two patients who died of PE, one patient, a 33-year-old woman, had underlying primary pulmonary hypertension with right ventricular failure (Tables 1 and 2). Organized and fresh PE were shown at autopsy 6 days after a pulmonary angiogram that failed to show PE. Whether this death resulted from PE at the time of the normal pulmonary angiogram or recurrent PE is uncertain. The other patient who died, a 36-year-old woman, had carcinoma of the breast with metastasis and drug-induced cardiomyopathy. A repeated pulmonary angiogram 6 days after the initial normal pulmonary angiogram showed PE (Table 1). Whether this represented a recurrent PE following a PE that was inapparent or a first PE is uncertain.

Patients who developed PE compared with those who did not were 49±19 years of age vs 57±17 years (not significant [NS]). Among patients who developed PE vs those who did not, two of six (33%) were men vs 154 of 374 (41%) (NS).

The symptoms among patients with normal angiograms who developed subsequent PE did not differ to a statistically significant extent from symptoms among patients who did not develop PE, nor did the signs or chest radiographic abnormalities (Table 3). The partial pressure of oxygen in arterial blood (PaO₂) among patients with subsequent PE vs patients with no subsequent PE was 70±20 mm Hg vs 69±17 mm Hg (NS). The alveolar arterial oxygen gradient among patients with subsequent PE vs patients with no subsequent PE was 51±19 mm Hg vs 37±17 mm Hg (NS). The pulmonary artery mean pressure, however, was higher in patients who had a subsequent PE compared with patients who did not, 34±25 mm Hg vs 22±10 mm Hg (p<0.01).

Among patients in whom there was a history of thrombophlebitis, compared with those in whom there was no history of thrombophlebitis, a trend suggested that future PE was more likely, 3 of 40 (7%) vs 3 of 340 (0.9%), but the difference was not statis-

**Table 1—Ventilation/Perfusion Lung Scans on Study Entry and Subsequent Findings Among Patients With PE at Follow-up**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Entry V/Q Prob</th>
<th>Days to Follow-up PE</th>
<th>Follow-up V/Q Prob</th>
<th>Follow-up Angio</th>
<th>Death</th>
<th>Autop</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
<td>8</td>
<td>High</td>
<td>ND</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>51</td>
<td>High</td>
<td>ND</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Int</td>
<td>28</td>
<td>High</td>
<td>ND</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>6</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Int</td>
<td>6</td>
<td>High</td>
<td>PE</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Int</td>
<td>110</td>
<td>High</td>
<td>ND</td>
<td>No</td>
<td>—</td>
</tr>
</tbody>
</table>

*V/Q=ventilation/perfusion lung scan; Prob=probability; Angio=angiogram; ND=not done; Int=intermediate; Autop=autopsy.

**Table 2—Antiplatelet Agents, Evidence of Deep Venous Thrombosis, and Associated Illness Among Patients With PE at Follow-up**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Antiplatelet Therapy</th>
<th>History DVT</th>
<th>Leg Signs</th>
<th>Leg Test</th>
<th>Assoc Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>ND</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>ASA, Dipyridamole</td>
<td>Yes</td>
<td>No</td>
<td>ND</td>
<td>Recent MI</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Neg</td>
<td>Cholangitis</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Pos</td>
<td>Primary Pulm Htn</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>±↑</td>
<td>CA breast, drug-induced cardiomyopathy</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>ND</td>
<td>Bronchitis</td>
</tr>
</tbody>
</table>

*ND=not done; Neg=negative; Pos=positive; DVT=deep venous thrombosis; Assoc=associated; ASA=aspirin; CA=carcinoma; MI=myocardial infarction; Pulm Htn=pulmonary hypertension.

†Impedance plethysmogram abnormal, doppler ultrasound normal.
Among patients who developed PE, 3 of 6 (50%) vs 37 of 374 (10%) (p<0.02). Thrombophlebitis in the three patients who showed PE on follow-up had been diagnosed 1 to 2 years prior to study entry. These patients did not have objective tests for deep venous thrombosis (Tables 1 and 2).

Among patients who had measurements of the calf circumference as well as physical examination, one or more abnormalities of the lower extremities were shown in 164 of 351 (47%) untreated patients. These included tenderness, edema, erythema, palpable cord, Homan’s sign, or ≥1 cm asymmetry of the circumference of the calves. The calves were measured 10 cm below the tibial tuberosity. Among patients who had any abnormality of the lower extremities on physical examination compared with those who had no abnormality, PE on follow-up occurred in 3 of 164 (1.8%) vs 3 of 187 (1.6%) (NS). Among those who had a subsequent PE compared with those who had no subsequent PE, 3 of 6 patients (50%) compared with 161 of 345 (47%) patients had one or more abnormalities of the lower extremities (NS). Calf asymmetry ≥1 cm was seen in 2 of 6 (33%) patients with a subsequent PE compared with 129 of 345 (37%) patients with no subsequent PE (NS). Among patients who developed PE, ≥2 cm asymmetry was seen in 1 of 6 (17%) patients compared with 40 of 345 (12%) patients who did not develop PE (NS). Calf asymmetry ≥3 cm was seen in 0 of 6 (0%) patients with subsequent PE compared with 11 of 345 (3%) patients with no subsequent PE (NS).

Doppler ultrasound, impedance plethysmography, or venograms of the lower extremities were obtained in 29 patients, and one or more tests indicated deep venous thrombosis in three (10%). One patient had both a Doppler ultrasound and impedance plethysmogram interpreted as indicative of deep venous thrombosis. One patient had an impedance plethysmogram interpreted as indicative of deep venous thrombosis, but a Doppler ultrasound interpreted as normal, and one patient had a Doppler ultrasound interpreted as showing deep venous thrombosis, but a venogram interpreted as normal. Pulmonary embolism was more frequent among patients with at least one leg test interpreted as showing deep venous thrombosis than among patients with leg studies consistently interpreted as normal, 2 of 3 (67%) compared with 0 of 26 (0%) (p<0.01). Among patients who had a history of thrombophlebitis or at least one leg test interpreted as showing deep venous thrombosis compared with those who had neither, PE on follow-up occurred in 2 of 5 (40%) vs 0 of 24 (0%) (p<0.05). Among patients who showed PE on follow-up, five of six (83%) had a history of deep venous thrombosis or at least one objective test suggestive of deep venous thrombosis (Table 2).

**DISCUSSION**

Pulmonary embolism during the year of follow-up of patients who had a normal pulmonary angiogram was uncommon in our experience (1.6%) and it was uncommon in the experience of others.4 Cheeley and associates4 followed up 144 patients with normal pulmonary angiograms an average of 13 months. There were 32 deaths from unrelated illnesses. Nonfatal PE occurred in 3 of 112 (2.7%) survivors and PE was observed 3 of 11 patients in whom autopsies were performed. The total frequency of PE, therefore, was 6 of 144 (4.2%). Among 44 patients with normal pulmonary angiograms, Hull and associates5 observed one fatal PE (2.3%) that occurred in 2 weeks in a patient with untreated calf vein thrombosis. Novelline and associates6 followed up 167 untreated patients with normal pulmonary angiograms a minimum of 6 months. Twenty patients died of unrelated illnesses, and incidental PE was observed in three of ten patients who underwent autopsy. There was no evidence of PE among 147 survivors. The frequency of any PE during follow-up was 3 of 167 (1.8%). The frequency of PE on follow-up that we observed in untreated patients with normal pulmonary angiograms was comparable to the frequency of PE reported by Hull and associates7 among untreated patients with normal results of serial leg tests for deep venous thrombosis, 1.9%.

Whether PE after a normal pulmonary angiogram represents a recurrent PE in patients in whom the prior PE could not be definitively diagnosed or
whether the PE was the first PE in a patient with a prior normal pulmonary angiogram is uncertain. Many of the patients were at risk of PE and had clinical findings suggesting deep venous thrombosis.

Even though the frequency of PE was low during 1 year of follow-up of patients with a normal pulmonary angiogram, the frequency of PE in this group was higher than in the general population of hospitalized patients. During the 21-month period of recruitment for PIOPED, among patients in whom PE was diagnosed on the basis of the same criteria as used in the follow-up of patients in the PIOPED study, (a clinical suspicion confirmed by pulmonary angiography, a high-probability interpretation of the ventilation-perfusion lung scan, or confirmed at autopsy), PE was diagnosed in 0.3% (P.D.S. and J.W.H., May 1994, personal communication). Using the same criteria, Huber and associates\(^8\) reported an identical prevalence.

One or more objective leg tests suggestive of deep venous thrombosis was observed in 10% of the patients who had such tests. This was comparable to the frequency of 18% observed by Hull and associates\(^9\) among patients with normal pulmonary angiograms. Patients with at least one test indicative of deep venous thrombosis, although such tests may have been inconsistent, showed PE on follow-up more frequently than patients with normal studies. A history of thrombophlebitis or an abnormal result of a leg test in 83% of patients who developed PE after a normal pulmonary angiogram suggests that deep venous thrombosis may have been present in these patients.

In conclusion, the frequency of clinically important PE developing within 1 year in patients with a normal pulmonary angiogram is small. Even so, the frequency was higher than is reported in the general population of hospitalized patients and probably could be reduced further by studies of the lower extremities for deep venous thrombosis. A cost-benefit analysis of this approach, however, has not been assessed.

REFERENCES

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