Complications and Validity of Pulmonary Angiography in Acute Pulmonary Embolism

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Background. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) addressed the value of ventilation/perfusion scans in acute pulmonary embolism (PE). The present study evaluates the risks and diagnostic validity of pulmonary angiography in 1,111 patients who underwent angiography in PIOPED.

Methods and Results. Complications were death in five (0.5%), major nonfatal complications in nine (1%), and less significant or minor in 60 (5%). More fatal or major nonfatal complications occurred in patients from the medical intensive care unit than elsewhere: five of 122 (4%) versus nine of 989 (1%) \((p<0.02)\). Pulmonary artery pressure, volume of contrast material, and presence of PE did not significantly affect the frequency of complications. Renal dysfunction, either major (requiring dialysis) or less severe, occurred in 13 of 1,111 (1%). Patients who developed renal dysfunction after angiography were older than those who did not have renal dysfunction: 74±13 years versus 57±17 years \((p<0.001)\). Angiograms were nondiagnostic in 35 of 1,111 (3%), and studies were incomplete in 12 of 1,111 (1%), usually because of a complication. Surveillance after negative angiograms showed PE in four of 675 (0.6%). Angiograms, interpreted on the basis of consensus readings, resulted in an unchallenged diagnosis in 96%.

Conclusions. The risks of pulmonary angiography were sufficiently low to justify it as a diagnostic tool in the appropriate clinical setting. Clinical judgment is probably the most important consideration in the assessment of risk. (Circulation 1992;85:462–468)

The collaborative study of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) addressed the value of ventilation/perfusion scans in acute pulmonary embolism (PE).\(^1\) Ventilation/perfusion scans combined with clinical assessment permitted an accurate noninvasive diagnosis or exclusion of PE, but only for a minority of patients: those with concordant clinical and ventilation/perfusion scan findings.\(^1\) In approximately one third of the patients, the diagnosis of PE based on ventilation/perfusion scans was indeterminate. The pulmonary angiogram is the definitive diagnostic test, but the risks and validity of pulmonary angiography were not evaluated in the original PIOPED report.\(^1\) The purpose of this communication is to determine, based on the PIOPED data, the risks and diagnostic validity of pulmonary angiography for the diagnosis of acute PE.

Methods

Patients in this study participated in the national collaborative study of the PIOPED.\(^1\) The project protocol and consent forms were approved by the institutional review boards of all participating centers. There were two arms of the study: One was composed of patients who, before the ventilation/perfusion scan, consented to pulmonary angiography provided that the ventilation/perfusion scan was abnormal. Among this group, 755 patients completed pulmonary angiograms and seven had started the catheterization procedure, but the angiogram was not completed. The value of the ventilation/perfusion scans in these patients has been reported.\(^1\) The second arm of the study was composed of patients with
suspected PE who had ventilation/perfusion scans and in whom the decision for obtaining a pulmonary angiogram was made by the attending physician on the basis of his clinical judgment. In this arm of the study, 346 patients completed pulmonary angiograms and one patient had an incomplete study. In total, 1,111 patients underwent cardiac catheterization for angiography. The patients were 57±17 years of age (mean±SD); 513 of 1,111 (46%) were men. Three patients in whom a catheter could not be introduced into a vein because of technical problems were excluded. In addition, one patient was excluded who underwent digital subtraction angiography but not standard angiography. Also, one patient was excluded because the study was discontinued on finding an elevated right ventricular end-diastolic pressure.

All of the patients underwent 1 year of surveillance after pulmonary angiogram. Any rehospitalization, new investigation for PE, complication of anticoagulation, or death triggered a detailed review of the patient's medical records by the PIOPED outcome classification committee. The review used all available clinical information including hospital and autopsy records, death certificates, and original radiographic studies. The outcome classification committee could reverse the reading of a negative angiogram if PE was found at autopsy or on repeat angiography or new perfusion scan defects interpreted as high probability for PE were observed.

Angiography

The femoral vein–Seldinger technique with a multiple side-hole, 6F to 8F pigtail catheter was used. Small amounts of contrast material (5–8 ml) were injected by hand to check the patency of the inferior vena cava by fluoroscopy. The catheter was directed into the proximal portion of the pulmonary artery of the lung with the greatest V/Q scan abnormality. Initial filming was in the anteroposterior projection. Seventy-six percent iodinated (ionic) contrast material was injected at a rate of 20–35 ml/sec for a total of 40–50 ml over 2 seconds. Film rates were three per second for 3 seconds, followed by one per second for 4–6 seconds. Depending on the size of the lungs, filming was not magnified or was given a low magnification of 1.4. A 12:1 grid was used, and roentgenographic factors were in the range of 70–80 kV (peak) and 0.025–0.040 seconds at 1,000 mA, with a focal spot of 1.2–1.5 mm. If emboli were not identified, injections were repeated and magnification (×1.8–2.0) oblique views were obtained of the areas suspicious for PE. Films were obtained with an air-gap technique (i.e., no grid was used). Roentgenographic factors were in the range of 78–88 kV (peak) and 0.040–0.080 seconds at 160 mA, with a focal spot 0.3–0.6 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. Angiograms were usually completed within 24 hours of the onset of clinical symptoms.

Interpretation of Angiograms

Criteria for the diagnosis of PE were the identification of an embolus obstructing a vessel or the outline of an embolus (filling defect) within a vessel. Angiograms were randomly assigned to pairs of angiographers from clinical centers other than the originating hospital. The angiograms were interpreted with the lung scans. If two readers disagreed whether PE was present, absent, or uncertain, the interpretations were adjudicated by readers who were randomly selected from the remaining clinical centers. If adjudicating readers did not agree with either of the first two readers, angiograms went to panels of angiography readers.

Definitions of Complications

Complications were identified prospectively. All tabulated complications were reviewed and assessed by the authors. In addition, complications of hospitalization were tabulated and evaluated in relation to complications of angiography. Summary descriptions of all patients were evaluated to determine whether late complications of angiography may have occurred. All deaths that occurred within 24 hours of catheterization were reviewed for consideration of their relation to catheterization. Major complications were those that were life threatening and did not respond promptly to pharmaceutical therapy or required intensive or prolonged treatment within the hospital. Patients who required cardiopulmonary resuscitation, endotracheal intubation, dialysis, or blood transfusion were defined as having major complications. Patients who required prolonged monitoring of a complication that spontaneously regressed with no apparent residual damage were considered to have nonmajor or minor complications. In some instances, such complications were important, potentially dangerous events and may have prolonged the hospital stay. Only one complication (the most severe complication) was listed for any patient.

Statistical Methods

Comparisons of the prevalence of clinical features were made with a χ² test. Continuous variables among patients with major, minor, or no complications were evaluated with a one-way analysis of variance using α=0.05. Comparisons of continuous variables among two groups were made with an unpaired Student's t test. Probability values of less than 0.05 were considered significant. Analyses of data were made at Henry Ford Heart and Vascular Institute, based on data obtained from a data tape supplied by the PIOPED Data and Coordinating Center.

Results

Among 1,111 patients who underwent pulmonary angiography for suspected PE, death occurred in five (0.5%), nonfatal major complications occurred in nine (1%), and minor complications occurred in 60 (5%).
Complications

Major complications are listed in Table 1, circumstances associated with death are outlined in Table 2, and circumstances associated with respiratory decompensation in the four patients who required endotracheal intubation or cardiopulmonary resuscitation are outlined in Table 3.

One of the two patients who had hematomas of the groin with bleeding severe enough to require two units of blood was receiving anticoagulant therapy.

After angiography, three patients developed renal dysfunction, presumably acute tubular necrosis, which required dialysis. Serum creatinine in one patient increased from 1.2 mg/100 ml to 6.0 mg/100 ml, and in one patient it increased from 2.4 mg/100 ml to 6.0 mg/100 ml. One patient developed a serum creatinine of 2.7 mg/100 ml, which was associated with pulmonary edema caused by fluid overload: This patient required endotracheal intubation.

Minor Complications

Minor complications are listed in Table 4. Two patients had bronchospasm after the injection of contrast material that was severe enough to discontinue the procedure. One required subcutaneous epinephrine. Two patients developed angina during the catheterization and were transferred to the coronary care unit for monitoring. Two patients (in addition to one patient whose most prominent problem was angina) became hypotensive.

Ten patients developed elevation of serum creatinine and were treated with fluid balance, diuretics, and in one patient, dopamine. These patients did not require dialysis. Among these patients, five with previously normal serum creatinine developed levels that ranged from 2.1 to 5.9 mg/100 ml. Five patients with previously abnormal serum creatinine that ranged from 1.5 to 2.7 mg/100 ml developed a further increase ≥2 mg/100 ml.

Relation of Complications to Clinical Characteristics

Major complications occurred more frequently among patients sent for angiography from the medical intensive care unit than in patients from elsewhere: five of 122 (4%) versus nine of 989 (1%) (p<0.02). Minor complications occurred with a similar frequency among patients sent from the medical intensive care unit and from elsewhere: four of 122 (3%) versus 56 of 989 (6%).

<table>
<thead>
<tr>
<th>TABLE 1. Major Complications of Angiography Among 1,111 Patients With Suspected Acute Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Respiratory distress (CPR or intubation)</td>
</tr>
<tr>
<td>Renal failure (dialysis)</td>
</tr>
<tr>
<td>Hematoma (transfusion, two units)</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Only one complication per patient is listed.

CPR, cardiopulmonary resuscitation.

<table>
<thead>
<tr>
<th>TABLE 2. Deaths From Pulmonary Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

PA, pulmonary artery; PE, pulmonary embolism; F, female; CA, carcinoma; ND, not done; RA, right atrium; HTN, hypertension; MR, mitral regurgitation; CHF, congestive heart failure; VT, ventricular tachycardia; resp, respiratory; RV, right ventricle; M, male; CHD, coronary heart disease; angio, angiogram; MI, myocardial infarction; EF, ejection fraction; VF, ventricular fibrillation.
In general, complications were not related to age, although renal complications occurred more often in elderly patients. Patients with major, minor, and no complications were 61±17 years, 58±19 years, and 57±17 years of age, respectively (NS). Patients with either major or less severe renal dysfunction, in comparison with patients with no renal dysfunction, were 74±13 years versus 57±17 years of age (p<0.001).

Complications were unrelated to sex. Major complications occurred in six of 513 men (1%) and in eight of 598 women (1%) (NS). Minor complications occurred in 26 of 513 men (5%) and in 34 of 598 women (6%) (NS).

The frequency of complications was not related to the presence or absence of PE. Major complications occurred in four of 383 (1%) with PE and in seven of 681 (1%) who did not have PE (NS). Minor complications occurred in 22 of 383 (6%) with PE and in 32 of 681 (5%) with no PE (NS).

The frequency of complications was not related to pulmonary artery mean pressure. Pulmonary artery mean pressure was measured in patients with major, minor, and no complications; among 13, 56, and 1,010 patients, it was 22±14 mm Hg, 19±9 mm Hg, and 23±11 mm Hg, respectively. Patients with major or minor complications had right atrial mean pressures that were no higher than in patients with no complications. Measurements were obtained in 13, 56, and 1,079 patients and were 6±4 mm Hg, 6±4 mm Hg, and 7±5 mm Hg, respectively.

The volume of contrast material injected was not significantly larger in patients with major or minor complications than in patients with no complications: 106±73 ml, 185±84 ml, and 181±61 ml, respectively. Even among patients with major or minor renal dysfunction (n=13), the volume of contrast material injected was not significantly greater than that among those who had no complications: 207±53 ml versus 181±61 ml (NS).

The frequency of complications was not related to whether patients were obligated by PIOPED protocol to undergo pulmonary angiography or whether their attending physicians requested angiograms. Major complications occurred in eight of 762 (1%) who were obligated by protocol versus six of 349 (2%) who were physician referred (NS). Nonmajor/minor complications occurred in 44 of 762 (6%) obligated by protocol and in 16 of 349 (5%) who were physician referred.

**Validity of Pulmonary Angiograms**

Among 1,111 patients who underwent catheterization for angiography, 383 (35%) had positive angiograms and 681 (61%) had negative angiograms. In 35 (3%), the angiogram was nondiagnostic, and in 12 (1%), the angiogram was not completed, usually because of complications. Among completed angiograms, therefore, 35 of 1,099 (3%) were nondiagnostic.

Among the 681 patients with negative angiograms, the diagnosis of no PE was reversed by the outcome
classification committee in four (1%). Each of these patients died within 6 days of the angiogram, and PE was found in each at autopsy. The validity of positive angiograms could not be assessed from the data collected in PIOPED. 

**Reader Agreement**

Overall agreement on all three categories of interpretation (both readers agreed that PE was present, PE was absent, or PE was uncertain) was $81 \pm 2\%$ (±95% confidence interval) (Table 5). There was closer agreement on the presence of PE than on the absence of PE. Both agreed that PE was present or both agreed that PE could not be diagnosed with certainty in $92 \pm 2\%$. Both readers agreed that PE was absent or both agreed that PE could not be excluded with certainty in $82 \pm 2\%$.

The quality of the angiograms had a greater impact on the agreement on negativity than on positivity (Tables 4, 5, and 6). Agreement on positivity with good, fair, and poor quality angiograms (see Tables 7 and 8) was $93 \pm 2\%, 90 \pm 3\%$, and $98 \pm 4\%$, respectively. Agreement on negativity was $88 \pm 2\%, 77 \pm 4\%$, and $54 \pm 14\%$, respectively.

Readers agreed with each other more often on angiograms with embol in lobar arteries than on angiograms in which the largest emboli were in segmental or subsegmental arteries. Average copositivity (average agreement of reader 1 with reader 2 and of reader 2 with reader 1) was $98\%$ with lobar PE, $90\%$ with segmental PE, and $66\%$ with subsegmental PE.

**Discussion**

Although five deaths were attributed to pulmonary angiography, the cause of death in patients 1, 3, and 5 (Table 2) may not have been due to the catheterization procedure or pulmonary angiography. At least one of the patients was practically moribund (patient 5), and the four others (patients 1–4) had severe underlying cardiac or respiratory diseases.

Most of the patients who died or suffered major nonfatal cardiopulmonary complications were in critical condition with severely compromised cardiopulmonary function before angiography. The severity of the clinical condition usually was not due to massive PE. Only four of 11 patients with major complications, in whom a diagnosis was established, had PE. The severity of the underlying condition rendered these patients vulnerable to the procedure. Such critically ill patients often present the most vexing diagnostic dilemmas, which require precise information for their optimal management, but the risk of angiography is higher in these patients. Clinical judgment is paramount in this situation.

The frequency of death that we report (0.5%) is similar to the pooled value reported by others: nine of 3,074 (0.3%).

**Table 5. All Angiograms**

<table>
<thead>
<tr>
<th>Reader 1</th>
<th>PE+</th>
<th>PE−</th>
<th>PE?</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE+</td>
<td>331</td>
<td>35</td>
<td>8</td>
<td>374</td>
</tr>
<tr>
<td>PE−</td>
<td>37</td>
<td>544</td>
<td>60</td>
<td>641</td>
</tr>
<tr>
<td>PE?</td>
<td>12</td>
<td>58</td>
<td>14</td>
<td>84</td>
</tr>
<tr>
<td>Total</td>
<td>380</td>
<td>637</td>
<td>82</td>
<td>1,099</td>
</tr>
</tbody>
</table>

PE+, pulmonary embolism present; PE−, pulmonary embolism absent; PE?, pulmonary embolism uncertain.

**Table 7. Fair Quality Angiograms**

<table>
<thead>
<tr>
<th>Reader 1</th>
<th>PE+</th>
<th>PE−</th>
<th>PE?</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE+</td>
<td>76</td>
<td>11</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>PE−</td>
<td>15</td>
<td>181</td>
<td>25</td>
<td>221</td>
</tr>
<tr>
<td>PE?</td>
<td>7</td>
<td>32</td>
<td>5</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>98</td>
<td>224</td>
<td>33</td>
<td>355</td>
</tr>
</tbody>
</table>

PE+, pulmonary embolism present; PE−, pulmonary embolism absent; PE?, pulmonary embolism uncertain.

**Table 6. Good Quality Angiograms**

<table>
<thead>
<tr>
<th>Reader 1</th>
<th>PE+</th>
<th>PE−</th>
<th>PE?</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE+</td>
<td>246</td>
<td>23</td>
<td>3</td>
<td>272</td>
</tr>
<tr>
<td>PE−</td>
<td>20</td>
<td>355</td>
<td>20</td>
<td>395</td>
</tr>
<tr>
<td>PE?</td>
<td>5</td>
<td>18</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>271</td>
<td>396</td>
<td>24</td>
<td>691</td>
</tr>
</tbody>
</table>

PE+, pulmonary embolism present; PE−, pulmonary embolism absent; PE?, pulmonary embolism uncertain.

**Table 8. Poor Quality Angiograms**

<table>
<thead>
<tr>
<th>Reader 1</th>
<th>PE+</th>
<th>PE−</th>
<th>PE?</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE+</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>PE−</td>
<td>1</td>
<td>8</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>PE?</td>
<td>0</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>15</td>
<td>21</td>
<td>46</td>
</tr>
</tbody>
</table>

PE+, pulmonary embolism present; PE−, pulmonary embolism absent; PE?, pulmonary embolism uncertain.
nonlocal complications in 12 of 122 patients (10%) with suspected PE or other pulmonary disorders. Two remote deaths occurred that probably were not a direct result of pulmonary arteriography. Ranniger and associates reported nonlocal complications in eight of 241 patients (3%). There were no deaths. Novelline and associates reported only minor arrhythmias in three of 302 patients (1%) who underwent pulmonary angiography. They reported no major complications and no deaths.

The largest series of patients who underwent pulmonary angiography was reported by Mills and associates. They reported major complications (including death) in 43 of 1,350 patients (3%). Three deaths occurred (0.2%), and each was in a patient with cor pulmonale, elevated right ventricular end-diastolic pressure, and elevated pulmonary artery pressures. Nonfatal major complications among these 1,350 patients included cardiac perforation in 14 (1%), major arrhythmias in 11 (1%), successfully treated cardiac arrest in six (0.4%), myocardial injury in six (0.4%), and significant contrast reaction in four (0.3%).

Hull and associates reported two reactions to contrast media but no deaths among 104 patients. Marsh and associates reported one death and one nonfatal perforation of the right ventricle among 106 patients. Dalen and associates reported significant complications in 13 of 367 patients (4%) who underwent angiography because of suspected PE. There was one death (0.3%).

In the PIOPED study, the potential complication of myocardial perforation was specifically monitored, and not a single instance was observed. This group reflects the use of angiographic catheters with a "pigtail" shaped tip. Such catheters also have markedly reduced the incidence of major cardiac arrhythmias occurring during the passage of the catheter through the right ventricle.

The risk of pulmonary hypertension has been emphasized by previous investigators; however, procedural modifications diminished the risk in this study. In the past, most deaths and serious complications were reported in patients with pulmonary hypertension and an elevated right ventricular end-diastolic pressure. In this setting, an injection of contrast material into the main pulmonary artery may result in death. In the PIOPED study, the protocol called for selective contrast injections into the right or left pulmonary artery rather than into the main pulmonary artery. Furthermore, in patients with elevated pulmonary artery pressures, the protocol permitted a reduction of the flow rate and the total amount of contrast injected. The precautions taken in the PIOPED study, however, cannot be viewed as a guarantee for the prevention of serious or fatal complications in patients with pulmonary hypertension. In this regard, we note that Marsh and associates reported death in a patient with severe pulmonary hypertension after a hand injection of 10 ml of contrast.

Renal insufficiency induced by contrast material was a problem, particularly among elderly patients. All pulmonary angiograms in the PIOPED study were performed with a standard ionic, high-osmolar contrast agent. Whether the frequency of renal insufficiency would have been lower after the use of a low-osmolar contrast agent is undetermined. There is no evidence that the incidence of pronounced renal toxicity is different after the intravascular use of high-versus low-osmolar contrast agents. Also, the potential clinical advantages regarding cardiac function have not yet been clearly demonstrated.

The percent of nondiagnostic angiograms that we report in PIOPED, 35 of 1,099 (3%), is similar to the 5% of poor angiograms reported by Dalen and associates after an injection in the main pulmonary artery. The angiographic interpretations that we report, however, were consensus readings, adjudicated if necessary by a panel of readers. Overall agreement between readers was 81%, and individual readers were uncertain of the diagnosis in 8% of patients. Individual angiographers in a clinical environment may not achieve the accuracy of these consensus readings.

Techniques that augment standard angiography might be used to reduce the volume of contrast material that is needed and enhance the visualization of small PEs. Such techniques include digital subtraction angiography, cineangiography, balloon-occlusion cineangiography, and superselective angiography including wedge arteriography. These methods might increase the diagnostic validity of angiograms in patients in whom PE is not apparent by standard techniques.

Conclusions

On the basis of the data from the PIOPED study, we conclude that the risks of pulmonary angiography are sufficiently low to justify pulmonary angiography as a diagnostic tool in the appropriate clinical setting. We emphasize, however, the importance of clinical judgment in the selection of patients and the assessment of risk.

Acknowledgment

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