Normal D-Dimer Levels in Patients With Pulmonary Embolism

Ilana Kutinsky, DO; Susan Blakley, MD; Vivyenne Roche, ML, MB

Background: Pulmonary embolism (PE) is frequently evaluated in acute care settings. Despite this, the clinical diagnosis of PE is difficult. Results of ventilation-perfusion (V/Q) scans may be inconclusive, and pulmonary angiograms (PAGs) are cumbersome, involve risk, and are often unavailable. Using PAG as the standard criterion, we evaluated the relationship between PE, V/Q scans, and semiquantitative latex agglutination (LA) D-dimer levels.

Methods: Ninety-eight patients who underwent V/Q scanning for suspected PE were enrolled; based on the results of the scans, the patients were scheduled for PAG. Blood samples were drawn for LA D-dimer assays during the PAGs at Saint Joseph Hospital, Denver, Colo, from January 1, 1996, to February 1, 1997. A detailed medical record review was performed for all enrollees.

Results: The mean ± SEM patient age was 56.6 ± 1.9 years; 52 (53%) were men, 13 (13%) had cancer, 23 (23%) had undergone surgery within 30 days of their PAG, and 13 (13%) were receiving warfarin sodium. There were no differences in warfarin therapy, hypercoagulable state, or cancer prevalence between patients with negative and positive PAGs (P = .53). Ventilation-perfusion scan results were available for all study patients. Eight (27%) of 30 patients who had positive angiogram results had LA D-dimer levels less than 250 ng/mL. Patients with positive PAGs (n = 30) had the following V/Q scan results: normal, 0; low probability, 7; intermediate or indeterminate probability, 22; and high probability, 1. In patients with low-probability V/Q scan results (n = 34), a positive D-dimer result for PE (>250 ng/mL) had a sensitivity of 71.4% (95% confidence interval: 0.29-0.97) and a negative predictive value of 87.5% (95% confidence interval: 0.62-0.98). We found a significant difference in D-dimer levels in patients with an abnormal angiogram result (mean, 750 ng/mL) compared with patients with a normal angiogram result (mean, 250 ng/mL) (P = .01, χ² test).

Conclusions: Eight patients had normal D-dimer levels with angiographic evidence of PE. Algorithms in acute care settings have been proposed; they exclude PE with normal D-dimer levels using the enzyme-linked immunosorbent assay technique. These cannot be extrapolated to the more widely used LA assays. A normal LA D-dimer level alone or with V/Q scan results is not recommended to preclude the treatment of PE.

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PATIENTS AND METHODS

The study was performed at Saint Joseph Hospital, Denver, Colo, a university-affiliated, tertiary referral community teaching hospital. Patients who were eligible for enrollment underwent V/Q scanning between January 1, 1996, and February 1, 1997, and were subsequently scheduled for PAGs because clinical suspicion required additional evaluation. A detailed medical record review was performed for each participating patient. The study protocol was reviewed and approved by the hospital’s institutional review board.

Lung scans were performed and interpreted using the same criteria as were used in the prospective investigation of pulmonary embolism diagnosis (PIOPED) study.9 The ventilation portion of the scan was performed using 1110 MBq (30 mCi) of xenon 133. Multiple images were obtained at 10-second intervals. Subsequently, the perfusion portion was performed using 6.2 mCi of technetium Tc 99m, which was injected peripherally. Images were obtained up to 2 minutes later and repeated in all 6 standard views. Lung scans were interpreted as follows: normal, low probability, intermediate or indeterminate probability, and high probability, per the PIOPED protocol. Each scan was interpreted by 1 of 5 board-certified radiologists blinded to the D-dimer results.

The radiologists performed the PAGs by catheterizing a femoral vein via the Seldinger technique with a 6F to 8F pigtail catheter. A small amount of nonionic contrast dye (Hexabrix, Cleveland, Ohio) was selectively injected into branches of the pulmonary arteries, as directed by findings on the V/Q scan. Multiple views were obtained in anterior and posterior projections. Pulmonary angiograms were interpreted according to hospital protocol, and the radiologist diagnosed PE when total occlusion of a vessel was seen and/or a filling defect of at least 3 mm was present.

RESULTS

Of the 121 consecutive patients scheduled for PAGs by their physicians following lung scan results, 118 agreed to participate in the study. Blood samples to test for D-dimer levels, results of lung scans, and PAGs were available for 98 patients. The average age of the patients was 56.6 ± 1.9 years (mean ± SEM). Fifty-two (53%) of the patients were men, 13 (13%) had cancer, 23 (23%) had undergone surgery within the 30 days preceding their PAGs, and 25 (26%) had a history of thromboses. Thirteen patients (13%) were taking warfarin, 7 of whom had been receiving long-term anticoagulation therapy; and 8 patients had hypercoagulation. One patient was receiving long-term anticoagulation therapy with heparin, 1 had sepsis, and 5 had liver disease. Given the small numbers of patients with these diagnoses, no further subgroup analysis was attempted. The duration of heparin therapy before angiography ranged from 0 to 4 days, with a mean of 0.8 days when the patient receiving long-term heparin therapy was excluded. Patient characteristics did not differ between patients with normal and those with abnormal PAG results (P = .53) (Table 1).

Ventilation-perfusion scan results for the 98 enrollees were as follows: normal, 1; nondiagnostic, 91; and high probability, 6. The nondiagnostic scans were read as low probability (n = 34) and as intermediate or indeterminate probability (n = 57). Only 1 of the 6 patients with a high-probability lung scan result had an abnormal angiogram result (Table 2). This unexpected finding of high-probability V/Q scan results with normal angiogram results prompted a specific review of these 5 pa-
tients’ medical records. Two of these patients had moderate to severe pulmonary hypertension secondary to severe obstructive lung disease; 1 patient had chronic PE, as demonstrated by clinical evaluation and by the presence of webs on angiography; 1 patient had bronchial obstruction due to a tumor; and a cause was not identified in the remaining patient.

There was no disparity between any 2 radiological interpretations of an angiogram and, therefore, a third radiological interpretation was unnecessary. Thirty patients (30.6%) had positive PAG results. Seven of these patients had low-probability V/Q scan results, 22 had indeterminate or intermediate scan results, and 1 had a high-probability scan result. Table 2 provides D-dimer levels, less than and greater than 250 ng/mL, together with lung scan and subsequent angiogram results.

Forty-seven of the patients had D-dimer levels less than 250 ng/mL, which are considered normal. We chose to report D-dimer levels less than 250 ng/mL (Table 2) because this level had a sensitivity of 73.3% (95% confidence interval [CI], 0.58-0.89) and an NPV of 83% (95% CI, 0.72-0.94). As previous studies have used levels between 300 and 500 ng/mL as determined by either the ELISA or the LA method, Table 2 also illustrates our results using D-dimer levels greater than 500 ng/mL. The higher level of 500 ng/mL had poor sensitivity (50%; 95% CI, 0.32-0.68) and an NPV of only 78.9% (95% CI, 0.69-0.88).

Patients with abnormal angiogram results had higher mean D-dimer levels (mean, 750 ng/mL) compared with patients without angiographic evidence of PE (mean, 250 ng/mL) (P = .01, x² test). Despite the higher mean D-dimer levels found with abnormal angiogram results, a positive D-dimer level (>250 ng/mL) by itself had inadequate sensitivity to diagnose PE (73.3%; 95% CI, 0.58-0.89) and NPV inadequate to exclude PE (83%; 95% CI, 0.72-0.94).

Positive D-dimer levels (>250 ng/mL) combined with low-probability V/Q scan results changed the sensitivity to 71.4% (95% CI, 0.29-0.97) and the NPV to 88% (95% CI, 0.62-0.98). Nondiagnostic scans (low and intermediate or indeterminate) and positive D-dimer levels (>250 ng/mL) had a sensitivity of only 72.4% and an NPV of 81.4%.

Our study compares D-dimer levels with PAG results and shows that positive LA D-dimer levels (>250 ng/mL) were not sensitive (73.3%) enough to exclusively diagnose PE. When combined with low-probability lung scan results, the sensitivity and NPV of positive D-dimer levels did not improve. The combination of nondiagnostic scan results and positive D-dimer tests by LA also will not help decide whom to treat for PE. The sensitivity of high clinical suspicion and a low-probability scan result remains superior at 96%.5

This is the largest study to date, to our knowledge, that defines the relationship between LA-determined D-dimer tests and PAG. The main strength of this study is its design. In contrast to other studies in which angiograms were only available for a proportion of the study population, every patient in this study had a prospective D-dimer level, lung scan results, and the criterion standard, PAG.3,8,12,14-16 A detailed medical record review controlled for confounding variables, and the radiologists and medical record reviewers were blinded to the patients’ D-dimer levels.

The prevalence of PE in our study was 30.6%, which is comparable to that in other cohorts undergoing PAGs.3 Thirty-five percent of our V/Q scans were read as low probability, similar to that proportion found in the PIOPED study. Although every patient with a low-probability V/Q scan result in the PIOPED study did not undergo a subsequent angiogram, 20% of those who had angiographic evidence of PE compared with 21% in our study.

Another strength of this study is that D-dimer levels were calculated by LA rather than the ELISA technique. Latex agglutination is widely available and is often preferred to ELISA because of its low cost and accessibility. In a telephone survey, we found that all 17 metropolitan Denver hospitals use the LA method automatically to determine D-dimer levels in their acute clinical care settings. Although ELISA assays are available if

### Table 1. Patient Characteristics in Groups With Abnormal and Normal Angiogram Results

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Abnormal</th>
<th>Normal</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>50.0</td>
<td>55.9</td>
<td>.59</td>
</tr>
<tr>
<td>Surgery within 30 days</td>
<td>26.7</td>
<td>22.1</td>
<td>.62</td>
</tr>
<tr>
<td>Receiving heparin</td>
<td>70.0</td>
<td>66.2</td>
<td>.71</td>
</tr>
<tr>
<td>Receiving warfarin sodium</td>
<td>16.7</td>
<td>10.3</td>
<td>.50</td>
</tr>
<tr>
<td>Cancer</td>
<td>10.0</td>
<td>14.7</td>
<td>.75</td>
</tr>
<tr>
<td>Previous deep vein thrombosis</td>
<td>23.3</td>
<td>26.9</td>
<td>.71</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>10.0</td>
<td>7.5</td>
<td>.70</td>
</tr>
</tbody>
</table>

*Values are given as percentage of patients.
†There were no differences in patient characteristics between the normal and abnormal angiogram groups (P = .53).

### Table 2. Results of D Dimers, Pulmonary Angiograms, and Ventilation-Perfusion Scans for the Entire Sample

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results According to D-Dimer Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;250 ng/mL (n = 47)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Pulmonary angiogram</td>
<td>8</td>
</tr>
<tr>
<td>Ventilation-perfusion scan</td>
<td>15</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>4</td>
</tr>
<tr>
<td>Intermediate or indeterminate</td>
<td>10</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results According to D-Dimer Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;500 ng/mL (n = 71)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Pulmonary angiogram</td>
<td>15</td>
</tr>
<tr>
<td>Ventilation-perfusion scan</td>
<td>10</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>4</td>
</tr>
<tr>
<td>Intermediate or indeterminate</td>
<td>10</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
</tr>
</tbody>
</table>

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assays in a prospective clinical manner. Two studies\textsuperscript{19,20} promising studies are those that have evaluated the new
ated, with 2 main criteria in mind: rapidity and proxim-
angiographic results. Different assays are being evalu-
ted, with 2 main criteria in mind: rapidity and proxim-
ity to the standard criterion ELISA. On review, the most
promising studies are those that have evaluated the new
assays in a prospective clinical manner. Two studies\textsuperscript{19,20}
determined D-dimer levels by whole blood agglutina-
tion, and 1\textsuperscript{21} by an automated ELISA technique. The whole
blood agglutination tests showed 94\% to 100\% sensitiv-
ity and 98\% to 100\% NPV. The automated ELISA tech-
nique demonstrated a sensitivity of 100\% (95\% CI, 92-
100) and an NPV of 100\% (95\% CI, 93.3-100). In these
3 studies, PE was indirectly determined by lung scan re-

dults and/or lower extremity ultrasonography. Only a small
proportion of the study patients had PAG data avail-
able. Additional information is necessary to prove the clin-
cal use of these favorable assays.

Our study has several limitations. First, we recog-
ize that LA tests are not standardized and, thus, the sen-
sitivities of kits may vary. Although most kits are compa-
bale, our results cannot be extrapolated to all latex kits.

Second, we may have limited the generalizability of our find-
ings by restricting the study to patients undergoing PAG
following V/Q scanning. This preselects a population in
which physicians' clinical suspicion conflicts with scan re-

results. Therefore, it may have been useful to have docu-
mented clinical suspicions as part of our study. Last, fi-
brin degradation products have a short half-life, causing D-
dimer levels to decrease over time; therefore, it might
have been helpful to have recorded the time from the on-
set of symptoms to PAG and blood sample draw.

In summary, we agree with the American College of
Chest Physicians\textsuperscript{22} consensus panel opinion regarding
the diagnosis and management of PE, and strongly
recommend that LA D dimers not be used to evaluate the
condition of patients with suspected PE. Recently, it has
been suggested that a normal D-dimer level can be used to
preclude treatment of PE in an acute care setting.\textsuperscript{3} These
algorithms used ELISA methods to determine D-dimer
levels, and cannot be extrapolated to settings in which
D-dimer levels are usually determined by the latex method.
A normal D-dimer level alone or in conjunction with a
nondiagnostic lung scan result should not preclude treat-
ment for PE and, therefore, cannot be used to rule out
PE in acute care settings.

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