Normal D-Dimer Levels in Patients With Pulmonary Embolism

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**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, and 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, hypercoaguable 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.

Arch Intern Med. 1999;159:1569-1572

**Pulmonary Embolism** (PE) is a well-recognized event in acute care because of its frequency, various clinical presentations, and potential morbidity and mortality. The annual incidence is 69 per 100 000.1 Untreated patients with PE have mortality rates as high as 30%.² It is difficult to accurately and cost-effectively diagnose PE. We use ventilation-perfusion (V/Q) scans in addition to clinical suspicion to diagnose and then decide whether to treat patients with anticoagulation therapy. However, this is useful for only half of the patients with suspected PE.³ Ventilation-perfusion scans are not interpreted as normal or abnormal but rather across a spectrum as normal, low probability, intermediate or indeterminate probability, and high probability. Consequently, patients may undergo pulmonary angiograms (PAGs), the standard criterion, to confirm the diagnosis. Unfortunately, PAGs are not always readily accessible, are cumbersome, are expensive, and have documented rates of morbidity (5%) and mortality (0.5%).¹ Helical computed tomographic scans hold some promise, but are not the standard of care.

Research focuses on finding a cost-effective, noninvasive, diagnostic aid to rule out PE because 70% of V/Q scans are nondiagnostic.³ There is considerable interest in finding a blood test to expedite the exclusion of PE. D dimer is a specific fibrin degradation product released by a dissolving fibrin clot that can be measured in peripheral blood. Similar to troponin use in acute myocardial infarctions, D dimers have been extensively evaluated in venous thromboembolic disease, and specifically in PE.³-⁸

Numerous studies⁹-¹² have shown that normal D-dimer levels, as determined by enzyme-linked immunosorbent assay (ELISA) technique, have excellent negative predictive values (NPVs) of 91% to 98%, postulated to be adequate to ex-
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.7 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.

Angiograms were interpreted by 2 separate radiologists, both blinded to the D-dimer and V/Q scan results. If there was disagreement, a third radiologist was available to review the PAG.

Blood was drawn from patients into a citrated tube for LA D-dimer assays on the day of the PAG via the central venous catheter used for the PAG or a peripheral vein. The plasma was separated within 1 hour of venipuncture and then stored at −70°C. Batches of plasma were processed within 3 weeks of phlebotomy by a qualified laboratory technician blinded to the V/Q scan and PAG results. D-dimer assays were performed using a kit (Accuclot D-dimer kit; Sigma Diagnostics, St Louis, Mo), per manufacturer’s recommendations. Briefly, latex beads coated with monoclonal antibody to D dimer are added to serial dilutions of the patient’s plasma. Dilutions containing 250 ng/mL or more of D dimer produce agglutination. Ranges of concentration of D dimer are reported using the lowest concentration of plasma that produced agglutination and the next most dilute sample. A D-dimer level less than 250 ng/mL is the lowest level detected with this semiquantitative LA kit and is considered a negative or normal result—undiluted normal human plasma produces no agglutination. Negative and positive controls are provided in the kit for comparison with each batch assay.

A detailed medical record review was performed by 1 of 3 reviewers (I.K., S.B., or V.R.) who were blinded to the D-dimer results. The medical record review provided information about demographics; the patient’s status at the time of the PAG, including hypercoagulability status, surgery within 30 days, the presence of cancer or liver disease, and creatinine level; and the presence of disseminated intravascular coagulation.

Descriptive statistics, x2 tests, Wilcoxon t tests, and sensitivity and NPV tests were performed with a statistical software package (SAS 6.10; SAS Institute Inc, Cary, NC).

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 follow: 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-
patients' 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 studies2-10,13,14 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, χ² 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 levels 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.5,8,12,14-16 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

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

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Abnormal (n = 71)</th>
<th>Normal (n = 51)</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>
<th>&lt;250 ng/mL (n = 47)</th>
<th>&gt;250 ng/mL (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary angiogram</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Ventilation-perfusion scan</td>
<td>8</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Intermediate or indeterminate</td>
<td>6</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results According to D-Dimer Levels</th>
<th>&lt;500 ng/mL (n = 71)</th>
<th>&gt;500 ng/mL (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary angiogram</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Ventilation-perfusion scan</td>
<td>15</td>
<td>56</td>
<td>15</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>4</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Intermediate or indeterminate</td>
<td>10</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
assays in a prospective clinical manner. Two studies\textsuperscript{19,20} evaluated, with 2 main criteria in mind: rapidity and proximity 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 agglutination, and 1\textsuperscript{21} by an automated ELISA technique. The whole blood agglutination tests showed 94% to 100% sensitivity and 98% to 100% NPV. The automated ELISA technique demonstrated a sensitivity of 100% (95% CI, 92-100) and an NPV of 100% (95% CI, 93.3-100.0). In these 3 studies, PE was indirectly determined by lung scan results and/or lower extremity ultrasonography. Only a small proportion of the study patients had PAG data available. Additional information is necessary to prove the clinical use of these favorable assays.

Our study has several limitations. First, we recognize that LA tests are not standardized and, thus, the sensitivities of kits may vary. Although most kits are comparable, our results cannot be extrapolated to all latex kits. Second, we may have limited the generalizability of our findings by restricting the study to patients undergoing PAG following V/Q scanning. This preselects a population in which physicians' clinical suspicion conflicts with scan results. Therefore, it may have been useful to have documented clinical suspicions as part of our study. Last, fibrin 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 onset 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 treatment for PE and, therefore, cannot be used to rule out PE in acute care settings.

Accepted for publication December 2, 1998.


REFERENCES


