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# Diagnostic Accuracy of a Bedside D-dimer Assay and Alveolar Dead-Space Measurement for Rapid Exclusion of Pulmonary Embolism

## A Multicenter Study

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IN 1997, KLINE ET AL<sup>1</sup> SUGGESTED that the combination of a normal D-dimer assay result and a normal alveolar dead-space fraction could safely exclude the diagnosis of pulmonary embolism (PE) in emergency department (ED) patients. In a study of 170 patients at 1 center, this test combination was 100% sensitive and 65% specific for the diagnosis of PE. The rationale for the combined use of the D-dimer assay and alveolar dead-space fraction hinges on the concept that an abnormal D-dimer measurement suggests the presence of intravascular thrombus, and an elevated alveolar dead-space measurement suggests the presence of pulmonary vascular obstruction.

Alveolar dead-space volume occurs in areas of the lung that are ventilated but not perfused and that contain a very low partial pressure of carbon dioxide (PCO<sub>2</sub>). Exhaled dead-space volume dilutes the total amount of carbon dioxide (CO<sub>2</sub>) in exhaled breaths relative to the arterial partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>). Therefore, the alveolar dead-

**Context** A previous study suggested that the combination of a normal D-dimer assay and normal alveolar dead-space fraction is a highly sensitive screening test for pulmonary embolism (PE).

**Objective** To determine if the combination of a normal alveolar dead-space fraction (volume of alveolar dead space/tidal volume  $\leq$ 20%) and a normal whole-blood agglutination D-dimer assay can exclude PE in emergency department (ED) patients.

**Design** Prospective, noninterventional study conducted in 1998-1999. Study data were obtained prior to standard testing for PE, consisting of radionuclide lung scanning or contrast-enhanced computed tomography and 6-month follow-up plus selective use of venous ultrasonography and pulmonary angiography. Imaging studies were interpreted by blinded observers.

**Setting** Six urban teaching hospitals in the United States.

**Patients** A total of 380 hemodynamically stable ED patients aged 18 years or older with suspected acute PE.

**Main Outcome Measures** Sensitivity and specificity for PE with a positive test defined as having either alveolar dead-space fraction or D-dimer assay results abnormal. Alveolar dead-space fraction was determined by subtracting airway dead space from physiological dead space (determined using the modified Bohr equation) and D-dimer assay, assayed at bedside using 20  $\mu$ L of arterial blood.

**Results** Pulmonary embolism was diagnosed in 64 patients (16.8%), of those 20 had an abnormal D-dimer assay result, 3 had an abnormal alveolar dead-space fraction, 40 had abnormal results in both, and 1 had normal results for both tests. The sensitivity for diagnosis of PE was 98.4% (95% confidence interval [CI], 91.6%-100.0%). Among the 316 patients without PE, both D-dimer and dead-space results were normal in 163, for a specificity of 51.6% (95% CI, 46.1%-57.1%). Posterior probability of PE with normal results on both tests was 0.75% (95% CI, 0%-3.4%).

**Conclusion** In this multicenter study of ED patients, a normal D-dimer assay result plus a normal alveolar dead-space fraction was associated with a low prevalence of PE.

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space volume can be estimated by simultaneously measuring carbon dioxide in exhaled breaths and the PaCO<sub>2</sub>. The previous study used a lower sensitivity latex D-dimer assay<sup>2,3</sup> and used the end-tidal CO<sub>2</sub> (measured with standard capnometry) with PaCO<sub>2</sub> to estimate the alveolar dead-space fraction. In our study, from the multicenter

Rapid Exclusion of Pulmonary Embolism (REPE) collaborative, we used a whole blood D-dimer assay (SimpliRED, Agen Inc, Brisbane, Australia), the

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See also Patient Page.

most extensively studied D-dimer assay,<sup>2</sup> and volumetric capnometry with PaCO<sub>2</sub>.<sup>4</sup> Volumetric capnometry simultaneously measures expired CO<sub>2</sub> and breath volume, which can be used with the PaCO<sub>2</sub> to make a more precise quantitation of the alveolar dead-space fraction than can be made with conventional capnometry.<sup>5</sup> We hypothesized that use of these 2 minimally invasive bedside tests could exclude the diagnosis of PE with a high degree of certainty in a prospective multicenter trial.

## METHODS

### Patient Enrollment

Patients were enrolled during 1998-1999 at 6 urban academic EDs: Carolinas Medical Center, Charlotte, NC, July 15, 1998, to August 1, 1999; Barnes Hospital, St Louis, Mo, November 21, 1998, to May 17, 1999; Detroit Medical Center and Affiliated Hospitals, Detroit, Mich, September 15, 1998, to April 20, 1999; St Vincent Mercy Medical Center, Toledo, Ohio, October 24, 1998, to August 16, 1999; Northwestern Memorial Hospital, Chicago, Ill, May 27, 1999, to November 22, 1999; and Henry Ford Hospital, Detroit, Mich, October 5, 1998 to April 10, 1999. The institutional review boards at each center approved the study protocol.

Patients were prospectively enrolled during times the investigators or study associates were available. All patients were ED patients older than 18 years who were not transferred from another medical care facility. Patients were eligible for enrollment when the ED physician had suspected PE enough to order a pulmonary vascular imaging study. Eligible patients did not have to present with specific historical or physical findings classically associated with PE. Patients were not preselected based on results of a prior D-dimer test or on the results of any other objective test for PE. Exclusion criteria were clinical signs of circulatory shock (systolic blood pressure <90 mm Hg, base deficit <-4 mEq/L), inability to breathe room air and maintain pulse oximetry reading of at least 90%, or inability to cooperate with

volumetric capnometry measurement and D-dimer collection.

### Dead Space and D-dimer Measurement

Study associates were notified of potential candidates when an ED physician ordered a lung vascular imaging study. Study associates included this article's 6 authors, 6 emergency medicine residents, 2 registered nurses, 2 respiratory therapists, and 3 medical students. After written informed consent was obtained, each subject was enrolled, and all measurements were completed at the bedside prior to the completion of pulmonary vascular imaging. Clinical and demographic data were assessed using a computerized database (Access, Microsoft Corp, Redmond, Wash). This database, consisting of 75 fields, recorded historical, physical, and risk-factor data to allow pretest clinical probability stratification. Associates were not given any specific instructions regarding how these data would be used for risk stratification.

After the patient had been breathing room air for 5 minutes and while seated in a semi-Fowler position, volumetric capnograms and arterial blood were collected. Patients breathed through a snorkel-like rubber mouthpiece with an airtight seal to the CO<sub>2</sub>-flow sensor (Novamatrix Medical Systems, Wallingford, Conn) and wore nostril-occluding nose-clips to ensure that their entire inspiratory and expiratory volume crossed the flow sensor. Spontaneous tidal respirations were captured and analyzed by a commercially available device (CosmoPLUS!, Novamatrix Medical Systems). In addition to measuring standard time-based capnograms, this instrument can also measure multiple respiratory parameters, including tidal volume (VT), mixed-expired CO<sub>2</sub> (PECO<sub>2</sub>), and airway dead-space volume (VDSaw), the latter of which is determined from the method described by Fletcher and Jonson.<sup>6</sup> Respiratory parameters were output via serial connection from the capnograph to a portable computer

(Monorail Corp, Atlanta, Ga), which was equipped with software (CosmoPLUS! for Windows) that permits real-time viewing of CO<sub>2</sub>-flow capnograms on the computer screen, and digital archiving of all respiratory data. We have previously shown that volumetric capnograms can be obtained with minimal interobserver variability using this technique.<sup>7</sup> Volumetric capnograms were recorded for 2 minutes.

Within 5 minutes of collecting the volumetric capnograms, arterial puncture was performed in an anesthetized radial artery to obtain at least 1.0 mL of arterial blood in a syringe containing lyophilized heparin lithium. Twenty microliters of arterial blood was then pipetted from the blood gas syringe for D-dimer analysis, and the remaining blood sample was immediately subjected to blood gas analysis. D-dimer testing was performed at the bedside using a whole-blood agglutination assay (SimpliRED). Briefly, 10 µL of arterial blood was pipetted into each test well, the reagents were added and mixed, and the test well was read after 2 minutes by holding it in front of a radiographic view box to inspect for agglutination. The same study associate who collected the capnometry data interpreted the D-dimer assays. The D-dimer interpretation was performed and recorded before the alveolar dead-space fraction or arterial blood gas results were available. All study associates received a standardized, 90-minute training session on these methods before starting patient enrollment. Additionally, all study associates viewed the same training videotape for the assay, and each had a copy of a booklet of 10 standard photographs (supplied by the manufacturer) to assist in deciding 1 of 3 results: strong-positive, weak-positive, or negative agglutination. Both strong-positive and weak-positive test interpretations were considered abnormal.

All calculations were performed within a computer algorithm embedded in a computer spreadsheet (Excel 97 visual basic macro, Microsoft Corp), applied to the stored capnometry breath

data. Prior to dead-space calculations, respiratory data were processed with a macro designed to eliminate breaths with erroneously recorded data (ie, usually the first 5-6 breaths that were recorded as having a mixed-expired CO<sub>2</sub> of 0, or breaths with 0 phase 2 slopes on the flow-CO<sub>2</sub> capnogram). The mean of all remaining breaths obtained during the 2-minute period was computed for each patient, and mean data were used to calculate VADS/VT. The alveolar dead-space fraction (VADS/VT) was calculated in 2 steps. First, the physiological dead-space fraction (VDSphys/VT) was calculated from the Enghoff<sup>8</sup> modification of the Bohr equation:

$$VDS_{phys}/VT = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

Second, because the VDSphys/VT measures the fraction of each tidal volume that is wasted on alveolar and airway dead space (ie, VDSphys = VADS + VDSaw), the airway dead-space fraction was subtracted from VDSphys/VT to yield the alveolar dead-space fraction, multiplied by 100%:

$$VADS/VT = (VDS_{phys}/VT - VDS_{aw}/VT) \times 100\%$$

Normal alveolar dead-space fraction was defined as VADS/VT of 20% or less.<sup>1</sup> For simplicity hereafter, VADS/VT is referred to as *dead space*.

### Diagnosis and Exclusion of Pulmonary Embolism

Radiographic examinations used for the standard criteria were interpreted by radiologists who were unaware of study results. All subjects underwent at least 1 pulmonary vascular imaging procedure, either a ventilation-perfusion scintillation lung scan (V/Q scan) or a contrast-enhanced helical computed tomography (CT) scan of the chest. The V/Q scans and helical CT scans were initially interpreted at each study site by board-certified nuclear medicine radiologists or by radiologists with specialization in body CT imaging, respectively. The V/Q scans were interpreted according to established criteria.<sup>9</sup> The V/Q read as either normal or high prob-

ability were considered diagnostic for the absence or presence of PE, respectively.

For subjects with nondiagnostic V/Q scans (low, intermediate, or indeterminate probability), the decisions to order further imaging was at the discretion of the attending physician who was not aware of study results. Subjects with nondiagnostic V/Q scans and higher suspicion for PE, including all subjects with intermediate probability V/Q scans, underwent bilateral lower-extremity venous duplex ultrasonography. A subject with a nondiagnostic V/Q scan and sonographic evidence of deep venous thrombosis was diagnosed with PE. Subjects with nondiagnostic V/Q scans, no deep venous thrombosis, but with a high clinical probability of PE underwent pulmonary angiography.

Results of pulmonary angiography were considered diagnostic. Contrast-enhanced helical CT scans of the chest were performed using local image acquisition protocols. Helical CT scans were interpreted using standard criteria for PE (presence of an intraluminal filling defect or vascular occlusion).<sup>10</sup> The final reading dictated by the radiologist was used to determine whether the CT was positive or negative for PE.

Subjects with no evidence of PE on their CT scans underwent additional testing if the clinical suspicion for PE remained high. All subjects were followed up by telephone call approximately 6 months later and asked a structured set of questions regarding their state of health, presence of continuing chest pain or dyspnea, and whether they had been diagnosed with PE or deep venous thrombosis since study enrollment. Subjects were considered to be free of PE when, at follow-up, the subject reported the same or better state of health and had no interval diagnosis of PE or deep venous thrombosis. For subjects who died during the 6-month follow-up period, PE was diagnosed if death occurred during the hospitalization attendant to the time of study entry in a subject without a normal V/Q scan or normal pulmonary angiogram result; subjects were deemed as nega-

tive for PE if autopsy results were negative for PE or if death occurred more than 3 months after study entry in a subject with a known end-stage disease and with no autopsy performed.

### Clinical Probability Assessment

To help quantitate the pretest clinical probability for PE, a clinical probability score was calculated post hoc using a modification to a system previously reported by Susec et al.<sup>11</sup> This system considers 5 symptoms (dyspnea, chest pain, syncope, hemoptysis, anxiety), 6 risk factors (previous PE or deep venous thrombosis, malignancy or other hypercoagulable state, total body or limb immobility for more than 48 hours, recent surgery requiring general anesthesia, pregnant or postpartum status, obesity) and 4 signs (respiratory rate >22/min, heart rate >100/min, PaO<sub>2</sub> <80 mm Hg while breathing room air, and unilateral leg swelling). Those considered low-risk had the combination of 2 or fewer symptoms, 1 or no risk factor(s), and 1 or no sign(s). Those considered high-risk had 2 or more elements in each category. All other patients were considered at moderate risk for PE. When study associates filled out the clinical database, they were not aware of this scoring system.

### Retrospective Survey of Eligible Patients Who Were Not Enrolled

A retrospective search of medical records was performed at each institution to locate records of ED patients who underwent V/Q scanning or contrast-enhanced helical CT examination during the study enrollment period but who were not recruited. The chief objective of this portion of the study was to collect demographic and diagnostic data on intent-to-study patients for comparison with subjects enrolled in REPE to identify potential selection bias. Each institution identified a number of intent-to-study patients equal to the number of subjects actually enrolled at that site.

### Statistical Analysis

A positive criterion standard was PE defined by the parameters described above. A positive diagnostic test was defined as

**Table 1.** Summary of Criteria Used to Diagnose Pulmonary Embolism (PE)\*

PE Diagnosis Criteria	No. of Patients
<b>Exclusion</b>	
Normal $\dot{V}/\dot{Q}$ scan	65
Negative helical computed tomography result confirmed by 2 radiologists, no clinical or sonographic evidence of deep venous thrombosis, and negative follow-up result at 6 months	32; Concomitant $\dot{V}/\dot{Q}$ scans: 8 low, 1 moderate, and 3 indeterminate probability
Low-probability $\dot{V}/\dot{Q}$ scan and negative follow-up result	171; 45 with negative lower extremity venous ultrasound examination
Indeterminate $\dot{V}/\dot{Q}$ scan, no clinical or sonographic evidence of deep venous thrombosis, and negative follow-up result	20
Pulmonary angiography negative for PE	27
Death within 1 month of study entry with negative autopsy results for PE	1
<b>Inclusion</b>	
High-probability $\dot{V}/\dot{Q}$ scan	25
Contrast-enhanced helical chest computed tomography read as positive for PE	6
Pulmonary angiography positive for PE	15
Nondiagnostic $\dot{V}/\dot{Q}$ scan and diagnosed deep venous thrombosis	10
Nondiagnostic $\dot{V}/\dot{Q}$ scan and death during hospitalization with suspicion for PE	2
Nondiagnostic $\dot{V}/\dot{Q}$ scan and follow-up result that found a new diagnosis of PE or deep venous thrombosis	6

\* $\dot{V}/\dot{Q}$  indicates ventilation-perfusion.

either an abnormal D-dimer assay result or an abnormal dead-space result, or both the D-dimer and dead space results abnormal. Continuous data were compared with a 2-tailed unpaired *t* test and proportions were compared with a 95% confidence interval (CI) for differences.<sup>12</sup> The 95% CIs calculated for the positive predictive value and for 100 negative predictive value were applied to the calculated posterior probability positive and negative, respectively. Diagnostic indexes, likelihood ratios (LRs), and posterior probabilities were calculated from standard equations.<sup>13</sup> For sample-size calculation, based on previous work<sup>1</sup> and a similar study,<sup>14</sup> we estimated that the pretest prevalence of PE would be 15% to 20% and that the LR negative for the test combination would be lower than 0.05. Therefore, at least 400 patients would be required to generate a negative posterior probability less than 1.0% with an upper limit of the 95% CI less than 4.0%.<sup>15</sup>

## RESULTS

During the enrollment period at each institution, approximately 1384 ED pa-

tients underwent pulmonary vascular imaging procedures in total. From this group, 401 (28.9%) were enrolled. Out of the 401, required data were not obtained in 21 (no arterial blood gas in 9, no pulmonary vascular imaging in 8, and software failure leading to complete data loss in 4). The final study sample comprised 380 subjects. None of the 21 patients who were excluded were diagnosed with PE. The mean (SD) age of the 17 excluded patients was 55 (16) years; 14 were women. At centers where arterial blood gas testing was available in the ED, both the D-dimer assay and the dead-space measurement were completed in less than 30 minutes by study associates who were fully trained (mean [SD], 16 [7] minutes).

Pulmonary embolism was diagnosed in 64 subjects and excluded in 316 (16.8% pretest probability of PE). TABLE 1 summarizes the criteria used to diagnose or exclude PE. Pulmonary vascular imaging studies included  $\dot{V}/\dot{Q}$  scanning in 349 subjects, contrast-enhanced CT in 40, and pulmonary angiography in 42. The most frequent cri-

terion for diagnosis of PE was the high probability  $\dot{V}/\dot{Q}$  scan, whereas the most frequent criterion for exclusion of PE was the low-probability  $\dot{V}/\dot{Q}$  scan in a subject without evidence to suggest deep venous thrombosis, no pulmonary angiography, and a negative follow-up report. Telephone follow-up was successful in 96% (165/171) of subjects in the latter group, and none of the 6 subjects who were not reached by telephone had a death certificate filed or was diagnosed with PE or deep venous thrombosis at the same hospital of study entry during the follow-up interval. Fourteen subjects died during the follow-up period: 8 who had PE and 6 who did not. Among the 8 deceased subjects with PE, 6 had the diagnosis of PE confirmed prior to death and 2 subjects died during attendant hospital stay after a nondiagnostic  $\dot{V}/\dot{Q}$  scan. Both were awaiting more definitive imaging procedures at the time of death. Both had documented respiratory distress prior to cardiac arrest with pulseless electrical activity. No autopsy was performed in either subject, apparently because of advanced age (80 and 85 years). Among the 6 deceased subjects without PE, 1 had an autopsy that showed no evidence of PE and the remaining 5 died more than 3 months after enrollment (4 with end-stage cancer, 1 during coronary artery bypass graft surgery).

## Clinical Characteristics of Enrolled Patients

TABLE 2 shows the clinical characteristics of the study population. The only significant differences between subjects with and without PE were that those with PE were older and less likely to report a sensation of dizziness. When the explicit clinical probability assessment was applied to subjects with PE, 13 were classified as low risk, 45 as moderate risk, and 6 as high risk. Among subjects without PE, 102 were classified as low risk, 192 as moderate risk, and 22 as high risk.

When the respiratory data from subjects with PE were compared with subjects without PE, several differences

were observed. Those with PE had a lower arterial oxygen tension than those without PE (mean [SD], 73.5 [19.9] vs 79.9 [20.7] mm Hg, respectively;  $P=.03$ ) and lower oxygen saturation (94.3% [4.2%] vs 95.6 [4.6%], respectively;  $P=.04$ ). Larger differences were observed for end-tidal CO<sub>2</sub> tension (30.6 [6.9] vs 36.1 [6.3] mm Hg, respectively;  $P<.001$ ) and VADs/VT (23.9% [12.7%] vs 13.5% [9.5%], respectively;  $P<.001$ ). These data suggest that the ventilation-perfusion mismatch caused by acute PE had a greater impact on indices of CO<sub>2</sub> elimination than indices of oxygenation.

### Diagnostic Performance of the D-dimer and the Dead Space

The D-dimer assays and the dead-space measurements were both normal in 164 (43%) of 380 subjects and were both abnormal in 66 subjects (17%). In 150 subjects (40%), only 1 test was abnormal, including 52 subjects (14%) with only an abnormal dead-space measurement and 98 (20%) with only an abnormal D-dimer assay result.

Among the 64 subjects with PE, 63 had at least 1 abnormal test result, leading to a sensitivity of 98.4% (95% CI, 91.6%-100%) (TABLE 3). The test results for the 64 subjects with PE included 20 subjects with an abnormal D-dimer assay result, 3 with an abnormal dead-space fraction, and 40 with both tests with abnormal results (ie, 63 true-positives), and 1 with both tests normal (ie, 1 false-negative). Among the 316 patients without PE, 163 had both tests normal, leading to a specificity of 51.6% (95% CI, 46.1%-57.1%) for this test combination. Thus, if both the D-dimer assay and the dead space had normal results, the negative predictive value for PE was 99.4% (95% CI, 96.6%-100%). The LR negative ( $LR^- = [1 - \text{sensitivity}] / \text{specificity}$ ) of both tests normal was 0.03. Therefore, if the D-dimer assays and dead-space measurements were both normal in a population with a pretest probability of PE equal to that of subjects enrolled in REPE (16.8% [95% CI, 13.1%-20.6%]), the posterior probab-

**Table 2.** Clinical Characteristics of Subjects With and Without Pulmonary Embolism (PE)\*

Characteristics	Subjects Diagnosed With PE (n = 64)	Subjects Without PE Diagnosed (n = 316)
Age, mean (SD), y†	55.6 (16.9)	49.2 (16.2)
Men, %	24 (37.5)	89 (28.2)
Systolic blood pressure, mean (SD), mm Hg	136 (23)	141 (20)
Heart rate, mean (SD), beats/min	90.3 (16.5)	88.2 (20)
Body weight, mean (SD), kg	92.1 (38.7)	88.5 (26.2)
<b>Symptoms Reported</b>		
Pleuritic chest pain	25 (35.9)	144 (45.5)
Substernal chest pain	11 (17.2)	111 (35.1)
Dyspnea	52 (81.2)	245 (77.5)
Hemoptysis	5 (8.0)	14 (4.4)
Syncope	3 (4.8)	14 (4.4)
Dizziness†	10 (15.6)	97 (30.7)
Anxiety	12 (18.7)	91 (28.7)
<b>Predisposing Conditions and Comorbid Conditions</b>		
Previous DVT or PE	15 (23.4)	76 (24.1)
Malignancy	15 (23.4)	44 (13.9)
Recent surgery or trauma	12 (18.8)	34 (10.7)
Immobility	13 (20.3)	52 (16.4)
Estrogen therapy	10 (15.6)	35 (11.1)
Pregnant or postpartum	1 (1.6)	9 (2.8)
Coronary artery disease	14 (21.8)	35 (11.0)
Congestive heart failure	9 (14.0)	31 (9.8)
COPD/asthma	13 (20.3)	84 (25.9)
Cigarette use	23 (35.9)	119 (37.6)

\*Data are presented as number (percentage) unless otherwise indicated. DVT indicates deep venous thrombosis; COPD, chronic obstructive pulmonary disease.  
†Significantly different between groups by unpaired *t* test for continuous variables or 95% confidence intervals for proportions.

ity of PE would be 0.75% (95% CI, 0%-3.4%). With the LR<sup>-</sup> equal to 0.03, the posterior probability of PE with both tests normal would reach 1.0% in an individual from a population with a pretest probability of PE equal to 25%.

Several observations suggested that the measured dead space was greater in subjects who had larger or more severe PE. First, the dead space was significantly greater in subjects with a high probability  $\dot{V}/\dot{Q}$  scan (mean [SD], 26.0% [11.4%]) compared with patients with other  $\dot{V}/\dot{Q}$  readings (13.9% [9.4%]). Second, subjects with PE who died within a month of study entry had a significantly higher dead-space measurement ( $n=8$ , 33% [13%]) compared both with subjects with PE who survived ( $n=56$ , 23% [13%]) and with subjects without PE who died during the follow-up interval of causes other than PE ( $n=6$ , 11% [10%]). Only 1 deceased

subject with PE had a history of intrinsic lung disease that might have caused nonspecific elevation of the dead space.

### Characteristics of Patients Who Were Not Enrolled

A random sample of 401 charts of patients who underwent a  $\dot{V}/\dot{Q}$  scan ( $n=355$ ) or a contrast-enhanced helical CT of the chest ( $n=46$ ) but who were not enrolled in REPE was reviewed for pertinent information. This retrospective comparison group comprised 84 men (21%) and 317 women (79%). The mean (SD) age of this group was 49 (16) years. Pulmonary embolism was diagnosed or excluded based on criteria established in Table 1 for the diagnosis of PE, except that no follow-up was performed. With those criteria, 48 (12.0%, 95% CI, 8.8%-15.1%) of 401 patients were diagnosed with PE during their hospital stay. These data indicate that

**Table 3.** Diagnostic Performance of the Alveolar Dead-Space Fraction and D-dimer Measurement Combined and When Each Test Is Considered Individually for Pulmonary Embolism (PE)

	No. of Patients Diagnosed		% (95% Confidence Interval)		Likelihood Ratio	
	With PE	Without PE	Sensitivity	Specificity	Negative	Positive
Combined test performance						
Positive result*	63	153	98.4 (91.6-100.0)	51.6 (46.1-57.1)	0.03	2.03
Negative result†	1	163				
Individual test performance						
Abnormal alveolar dead-space fraction						
Yes	43	75	67.2 (52.7-77.1)	76.3 (71.6-81.0)	0.43	2.83
No	21	241				
Abnormal D-dimer concentration						
Yes	60	104	93.8 (84.8-98.3)	67.1 (61.9-72.3)	0.09	2.85
No	4	212				

\*Positive test results were based on abnormal alveolar dead-space fraction, abnormal D-dimer concentration, or both.

†Negative test results were based on normal alveolar dead-space fraction and normal D-dimer concentration.

subjects enrolled in the REPE study were similar demographically but had a slightly higher prevalence of PE compared with patients not enrolled.

#### COMMENT

Evaluation of patients with suspected acute PE is a challenge for clinicians who practice in acute care settings. Available methods of pulmonary vascular imaging often require hours to perform, add substantial cost to the evaluation, and expose the patient to ionizing radiation. Moreover, pulmonary vascular imaging tests may not be available quickly 24 hours per day in many facilities. Several recent studies have suggested that the D-dimer assay can be used together with other clinical information to exclude the diagnosis of pulmonary embolism.<sup>2,16-18</sup> In the REPE study, we investigated the utility of a rapid D-dimer assay, together with a bedside measurement of alveolar dead space to evaluate patients with suspected acute PE in 6 urban EDs.

We used a commercially available whole blood agglutination D-dimer assay, which is supported by published diagnostic performance data and with characteristics that are well suited for use in the ED setting.<sup>2</sup> In a recent meta-analysis, Kline et al<sup>2</sup> reported the diagnostic performance of available D-dimer assays based on analysis with the

summary receiver operating characteristic curve.<sup>2</sup> The whole blood agglutination D-dimer assay demonstrated the highest composite sensitivity and specificity of all rapid D-dimer assays. Additionally, the whole blood agglutination assay is the most extensively studied rapid D-dimer assay. The whole blood agglutination D-dimer assay can be performed at the bedside within minutes. In our study, the whole blood agglutination D-dimer assay demonstrated an overall sensitivity of 93.8% and specificity of 67.1%, leading to an LR negative that was equal to 0.09. This level of diagnostic sensitivity suggests that a normal whole-blood D-dimer assay significantly reduces the probability of PE, but the findings also underscore the importance of using the D-dimer assay in conjunction with other clinical data to safely obviate pulmonary vascular imaging in patients with suspected PE.<sup>19</sup> In particular, previous studies have concluded that the D-dimer assay can be safely used to exclude PE only in patients at low risk for PE by clinical probability assessment.<sup>18</sup> However, in our study population, only 115 (30%) of 380 subjects were considered to be at low risk for PE by the clinical probability assessment used in this study. Out of these 115 low-risk subjects, 78 had a negative D-dimer test result. Thus, if the D-dimer assay were restricted to screening only

low-risk patients, then pulmonary vascular imaging would have been avoided in 21% of ED patients. On the other hand, the dead-space/D-dimer combination assessment was normal in 164 of 380 subjects, suggesting that this screening strategy could have obviated pulmonary vascular imaging in 43% of hemodynamically stable ED patients with suspected PE.

Observers in our study interpreted the D-dimer test results in the ED prior to pulmonary vascular imaging and independent of knowledge of the calculated alveolar dead-space fraction. The high sensitivity was therefore not a result of bias that could occur with knowledge of these other results. Immediate use of heparinized arterial blood at the bedside may have helped increase the sensitivity of readings, because the use of citrate-anticoagulated venous blood has been shown to reduce the sensitivity of the whole blood agglutination assay.<sup>20</sup> Likewise, manufacturers have suggested that warfarin sodium anticoagulation may reduce the sensitivity of the D-dimer assay (Louis Montford, NZ Dip MLS, Agen Inc, written communication, September 20, 2000). Prior use of warfarin was not an exclusion to study entry. Seven subjects with PE reported that they were taking warfarin at the time of enrollment. One of these 7 had a normal D-dimer assay and a normal dead-space measurement and was the only false-negative case in this study.

In this study, measured alveolar dead-space fraction functioned well as an adjunctive bedside test when interpreted together with the D-dimer assay. First, when the requirement of a normal dead-space measurement is added to a normal D-dimer assay, the sensitivity increases from 93.8% to 98.4% and the posterior probability of PE decreases to 0.75%. This posttest probability is similar to the frequency that PE is discovered on a long-term follow-up basis in patients with suspected PE and a normal  $\dot{V}/\dot{Q}$  scan, or a pulmonary angiogram that is negative for PE.<sup>21-23</sup> Second, assuming that PE could be excluded when both results are normal and that definitive pulmonary vascular imaging

is required when both results are positive, the D-dimer assay plus the dead-space test could clarify the short-term clinical plan for 60% of all ED patients with suspected PE. Moreover, in 13 out of 27 subjects who were subjected to pulmonary arteriography to rule out PE, both tests results were normal. The use of the D-dimer–dead-space combination might therefore lead to a net reduction in ED length of stay for patients who are evaluated for PE and possibly reduce the number of pulmonary arteriograms required for definitive diagnosis. Finally, the magnitude of the dead-space measurement had some predictive value of severity of PE, given that patients with PE who died during the follow-up period had a significantly higher dead-space measurement. We have previously shown that the dead-space measurement correlates with the size of the perfusion defect and the pulmonary arterial pressure in subjects with PE.<sup>4</sup> Although the dead-space measurement did appear to enhance the diagnostic performance of the D-dimer assay, it should be emphasized that our data do not support the use of the dead space as a sole screening test for PE, in view of the finding that the dead-space measurement was normal in almost one third of patients with PE.

The finding of a pretest probability for PE of 16.8% is the same as the pretest probability reported in other recent studies of outpatients with suspected PE,<sup>18,24</sup> but it is substantially lower than the probabilities reported in other studies of PE in outpatients.<sup>25</sup> The retrospective data in our study indicate that the subjects who were enrolled in REPE had a higher probability of PE (16.8%) compared with patients who were not enrolled (12.0%), suggesting some selection or workup bias in the enrollment process. However, the ratio of women to men in the retrospective group and the mean age were similar to the study group. When the 401 prospectively enrolled subjects are added to the 401 retrospective patients, the 802 total represents 58% of the total number of ED patients (1384) who were eligible for the study during the times of enrollment at

each hospital. The clinical probability data indicate that 62.3% of the subjects had a set of risk factors for PE that put them at a moderate risk for PE and only 7.4% had a high risk for PE. All 6 study centers were academic teaching hospitals, with high-volume EDs. The findings of a 16.8% pretest probability of PE and that most patients had a moderate risk of PE are both consistent with the practice at teaching hospitals. Attending ED physicians in this setting are likely to make liberal use of pulmonary vascular imaging to work up possible PE. At the same time, the data suggest that the physicians exercised some degree of restraint in ordering these imaging studies, given that only 30% of subjects had a low risk for PE. In total, 6 out of 64 subjects had a final diagnosis of PE based on the follow-up diagnosis of either PE or deep venous thrombosis within 6 months after study entry. Two other subjects died during hospitalization within 2 weeks of study entry; both had documented respiratory distress prior to cardiac arrest with pulseless electrical activity. None of these 8 subjects were treated for thromboembolism. Thus, although the physicians were judicious in their decisions to work up PE, the follow-up data indicate that the initial evaluation for PE was not adequate in 8 (12.5%) of 64 subjects.

This study has several limitations. The follow-up protocol was designed to recognize any situation consistent with PE that might have clinical significance within 6 months after study entry. This time frame was chosen based on the concept that if a negative ED evaluation can reduce the probability of PE to less than 1% for 6 months, then such testing strategy would fulfill the standard of care expected of ED physicians in most communities.<sup>15,26</sup> The follow-up criteria may have overclassified the diagnosis of PE in a few cases. For example, subjects were classified as having PE if they were diagnosed with deep venous thrombosis during follow-up, even if PE was not diagnosed (as in the case of 3 subjects). Also, subjects with nondiagnostic  $\dot{V}/Q$  scans who died during hospitalization were considered to have PE, even if no

autopsy was performed ( $n=2$ ). We reasoned that these subjects had to be considered to have PE for practical reasons. We submit that most local standards of care would hold an ED physician culpable for missing the diagnosis of PE if the physician evaluated a patient for PE but later discharged the patient and the patient soon experienced sudden death with circumstances strongly suggestive of PE.<sup>27</sup> Also, we diagnosed 6 subjects with PE on the basis of a positive contrast-enhanced helical CT scan which raises the possibility of false-positive assignment of PE in this subgroup. When compared with angiography, the specificity of the helical CT scan has been reported as low as 78%.<sup>28</sup> Finally, the REPE study only evaluated the diagnostic performance of the D-dimer assay and dead-space measurement compared with standard diagnostic criteria. Future multicenter work will be required to determine the safety of this test combination in ruling out PE in other settings and patient populations.

In summary, this study demonstrates that the combination of a negative whole blood agglutination D-dimer assay plus a normal alveolar dead-space fraction was associated with a probability of PE below 1% in this multicenter study of ED patients. This test combination was observed in 43% of hemodynamically stable ED patients with suspected PE.

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