Steady-State End-Tidal Alveolar Dead Space Fraction and D-Dimer*  
Bedside Tests To Exclude Pulmonary Embolism  
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Study objective: Less than 35% of patients suspected of having pulmonary embolism (PE) actually have PE. Safe bedside methods to exclude PE could save health-care resources and improve access to diagnostic testing for suspected PE. In patients with suspected PE, we sought to determine the sensitivity, specificity, and negative predictive value of (1) a steady-state end-tidal alveolar dead space fraction (AVDSf) of <0.15, (2) a negative D-dimer result, and (3) the combination of a steady-state end-tidal AVDSf of <0.15 and a negative D-dimer result. 
Study design: Prospective cohort study.  
Setting: Tertiary-care center in Ottawa, Ontario, Canada.  
Patients: Consecutive inpatients, outpatients, and emergency department patients with suspected PE referred to the Departments of Nuclear Medicine or Radiology for investigation of suspected PE.  
Interventions and measurements: All study patients had D-Dimer and alveolar dead space measurements prior to determining outcome (PE or no PE) with ventilation/perfusion scans and/or noninvasive leg vein imaging and/or pulmonary angiography.  
Results: Two hundred forty-six eligible and consenting patients underwent diagnostic imaging that excluded PE in 163 patients, diagnosed PE in 49 patients, and was indeterminant in 34 patients. A negative D-dimer result excluded PE with a sensitivity of 83.0% (95% confidence interval [CI], 69.2 to 92.4%), a negative predictive value of 91.2% (95% CI, 83.4 to 96.1%), and a specificity of 57.6%. A steady-state end-tidal AVDSf of <0.15 excluded PE with a sensitivity of 79.5% (95% CI, 63.5 to 90.7%), a negative predictive value of 90.7% (95% CI, 82.5 to 95.9%), and a specificity of 70.3%. The combination of a negative D-dimer result and a steady-state end-tidal AVDSf of <0.15 excluded PE with a sensitivity of 97.8% (95% CI, 88.5 to 99.9%), a negative predictive value of 98.0% (95% CI, 89.4 to 99.9%), and a specificity of 38.0%.  
Conclusion: This simple combination of bedside tests may safely rule out PE without further diagnostic testing in large numbers of patients with suspected PE. 

Key words: alveolar dead space; D-dimer; diagnosis; pulmonary embolism; reproducibility  
Abbreviations: AVDSf = alveolar dead space fraction; CI = confidence interval; PE = pulmonary embolism; PETCO₂ = end-tidal carbon dioxide pressure; RT = respiratory therapist; V/Q = ventilation/perfusion  

Pulmonary embolism (PE), the third-leading cause of cardiovascular mortality in North America, has an estimated annual incidence of 23 cases per 100,000 population per year.¹ Untreated PE has a hospital mortality rate as high as 30%.² This mortality falls to 8% if PE is appropriately diagnosed and treated.²  
The diagnosis of PE remains one of the most difficult problems confronting clinicians. PE is considered in the differential diagnosis of many clinical presentations, including chest pain, hemoptysis, or dyspnea, and in a wide variety of clinical settings, such as emergency departments, obstetrical units, surgical wards, and ICUs. However, <35% of pa-

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This study was conducted at the Ottawa Hospital - General Campus.  
Financial support was provided by the Ottawa General Hospital Research Fund and the Clinical Trials and Research Unit of the Division of Hematology, Ottawa Hospital- General Campus.  
Dr. Rodger was the recipient of the Thrombosis Interest Group of Canada Research Fellowship. Dr. Wells was the recipient of a Research Scholarship from the Heart and Stroke Foundation of Canada.  
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tients suspected of having PE are found to have PE. This leads to presumptive anticoagulation, hospital admission, and testing for a large number of patients without PE.

A bedside method that safely excludes PE would be desirable. For such a bedside method to be accepted into clinical practice, it must be near 100% sensitive (ie, very few false-negative findings). For a bedside method to be clinically useful, it must exclude a large proportion of the patients who do not have the disease (ie, it should have many true-negative findings).

Dead space ventilation represents ventilation of those parts of the lung not involved in gas exchange. Dead space ventilation has two components: anatomic dead space and alveolar dead space. Anatomic dead space ventilation represents ventilation of the airways. The airways conduct air to the alveoli and are not involved in gas exchange. Alveolar dead space represents ventilation of those alveoli that are not involved in gas exchange (ie, alveoli that are unperfused or poorly perfused, as occurs in PE). Kline et al demonstrated the high negative predictive value of alveolar dead space measurement combined with a negative D-dimer result in ambulatory patients with suspected PE. This combination of bedside tests has only been tested in an ambulatory patient population and has yet to be validated. We sought to prospectively determine, in consecutive ambulatory and hospitalized patients with suspected PE, the sensitivity, specificity, and negative predictive value of (1) a steady-state end-tidal alveolar dead space fraction (AVDSF) of < 0.15, (2) a negative D-dimer result, and (3) the combination of both negative test results.

**Materials and Methods**

**Patients**

All inpatients and outpatients at the Ottawa Hospital - General Campus suspected of having PE and referred for a ventilation/perfusion (V/Q) scan or pulmonary angiogram from January 1996 to August 1998 were approached for consent to participate in the study. Patients were excluded from the study if they (1) were < 18 years of age, (2) were unable to give informed consent, (3) had a contraindication to pulmonary angiography, (4) were receiving mechanical ventilation, or (5) were in the final stages of terminal illness. Participating patients signed informed consent approved by our hospital ethics review board.

**Standardized Patient Assessment**

The referring physician first assigned an index of clinical suspicion of PE (ie, pretest percentage likelihood of PE) based on clinical gestalt. The respiratory therapist (RT) performed arterial blood gas analysis and alveolar dead space analysis. Two methods of end-tidal alveolar dead space measurement were used over the course of the study. Both methods were taught in separate 2-h training sessions to 40 RTs in our institution. From January 1996 to February 1998, the sitting patient breathed through a one-way valve (Hans Rudolph, Inc.; Kansas City, MO). A sidestream port on the valve was connected to a capnograph (Datex CD-102–27-00; Datex; Helsinki, Finland). The capnograph provided continuous expired CO2 vs time data. The capnograph was calibrated with room air (0.3% CO2) and 4.0% CO2 prior to each use. Once the patient was judged to be relaxed and breathing regularly by the RT, an arterial puncture was performed for arterial blood gas analysis. The blood gas was analyzed with an analyzer (Ciba-Corning 278; Ciba-Corning; San Diego, CA) that was calibrated twice daily with standard gases. The calibrations of the capnograph and the blood gas analyzer were cross-checked with a sample of expired gas. If a difference in the PCO2 measurements with the capnograph and the blood gas analyzer was > 2 mm Hg, the patient's dead space data were excluded from the study because small discrepancies in PCO2 can result in large differences in the AVDSF (see below). The steady-state end-tidal AVDSF was calculated as follows:

\[
\text{AVDSF} = \frac{\text{PaCO}_2 - \text{PETCO}_2}{\text{PaCO}_2},
\]

where PETCO2 = end-tidal carbon dioxide pressure concentration in last 10 breaths.

Because we were concerned with the importance of (1) patient stability at the time of arterial and end-tidal CO2 sampling, (2) late-emptying alveoli (with higher PCO2) being overrepresented with end-tidal PCO2 measurement with time-based capnograph, and (3) the accuracy of our end-tidal CO2 monitor, we modified our methods and equipment. From February 1998 to August 1998, the sitting patient breathed through an airway adapter attached to a mouthpiece. The airway adapter had a mainstream CO2 and volume sensor (CapnoSTAT and COSMO+; Novametrix Medical Systems; New Haven, CT). This device measures breath-by-breath CO2 vs volume with an accuracy of ± 50 mL and CO2 with an accuracy of ± 1 mm Hg. The calibration of the capnograph was verified prior to each use with a known gas (4% CO2). Once the patient's condition had stabilized (respiratory rate of plus or minus two breaths per minute over 2 min), the RT recorded this as the stable respiratory rate.

With the patient breathing at the stable respiratory rate, the end-tidal CO2 was recorded if it was stable (± 1 mm Hg over 2 min). Arterial blood gas was obtained by a single arterial blood gas puncture only if the patient was breathing at the stable respiratory rate and had stable end-tidal PCO2. Subsequently, the RT calculated the steady-state end-tidal AVDSF as follows:

\[
\text{AVDSF} = \frac{\text{PaCO}_2 - \text{PETCO}_2}{\text{PaCO}_2},
\]

We have shown that this technique has excellent reproducibility (unpublished data submitted for publication). The dead space measurements were not provided to the referring physician or to the interpreting nuclear medicine physician.

**D-Dimer**

A latex D-dimer (Accuclot; Sigma Diagnostics; St. Louis, MO) or a whole-blood agglutination D-dimer (SimpliRED; AGEN Biomedical Limited; Brisbane, Australia) was performed on venous blood within 24 h of the V/Q scan or pulmonary angiogram.

**Outcome Measure**

The presence or absence of PE was determined independent of the standardized patient assessments. After the V/Q scan,
patients with a posttest probability of PE of < 5% were considered for study purposes, not to have PE. This group was defined by (1) patients with normal or near-normal V/Q scan results, (2) patients with a low index of pretest clinical suspicion who had low probability V/Q scan results, and (3) patients with low-probability scan results with a negative leg vein ultrasound result at presentation. After V/Q scan, patients with a posttest probability of ≥ 88% were considered for study purposes to have PE. This was defined as patients with a high or intermediate index of pretest clinical suspicion who had high-probability V/Q scan results. We recommended that other patients proceed to pulmonary angiography, but this decision was left to the patient’s treating physician. Those patients with indeterminant scan results who did not undergo angiography were excluded from the analysis.

Analysis

Sensitivity, specificity, negative predictive were calculated with 95% exact binomial confidence limits.

RESULTS

We approached 293 patients, of whom 282 were eligible for participation in the study. Of these 282 patients, 246 consented. Of the 246 consenting patients, 49 patients (19.9%) had PE, 163 patients (66.3%) did not have PE, and 34 patients (13.8%) could not be classified with “gold standard” outcome measures (Table 1). Female patients were less likely to have PE. Patients with PE were significantly older (mean age, 58.9 years) than patients without PE (mean age, 50.6 years). More than 94% of our patients presented with chest pain or dyspnea.

A negative D-dimer result excluded PE with a sensitivity of 83.0% (95% confidence interval [CI], 69.2 to 92.4%), a negative predictive value of 91.2% (95% CI, 83.4 to 96.1%), and a specificity of 57.6% (Table 2). The two D-dimer assays had comparable sensitivity (latex, 70%; whole-blood agglutination, 81%).

The mean steady-state end-tidal AVDSf in the patients without PE was 0.11 (95% CI, 0.09 to 0.13). The mean steady-state end-tidal AVDSf in the patients with PE was 0.27 (95% CI, 0.23 to 0.32). We performed a receiver operating characteristics analysis (ie, sensitivity vs 1 − specificity curve) to determine the optimal cut-off point for AVDSf. A cut-off point of 0.15 resulted in optimal sensitivity and specificity. A steady-state end-tidal AVDSf < 0.15 excluded PE with a sensitivity of 79.5% (95% CI, 63.5 to 90.7%), a negative predictive value of 90.7% (95% CI, 82.5 to 95.9%), and a specificity of 70.3% (Table 3).

The combination of a negative D-dimer result and a steady-state end-tidal AVDSf of < 0.15 excluded PE with a sensitivity of 97.8% (95% CI, 88.5 to 99.9%), a negative predictive value of 98.0% (95% CI, 89.4 to 99.9%), and a specificity of 38.0%. In subgroup analyses, the sensitivity and specificity of this combination were similar in patients with lung disease (sensitivity, 100%; specificity, 31.4%) and patients without lung disease (sensitivity, 96.4%; specificity, 38.4%). The sensitivity of this combination was slightly better in patients with tachypnea (100%) than patients without tachypnea (94.1%). The specificity was slightly worse in patients with tachypnea (18.9%) compared to those without tachypnea (39.6%). The sensitivity of the combination was not influenced by the technique of alveolar dead space analysis (old technique of alveolar dead space measurement, 97%; new technique of alveolar dead space measurement, 100%; Table 4).

DISCUSSION

In this study, we have demonstrated that a negative D-dimer result and a steady-state end-tidal
AVDSf of < 0.15 is a potentially safe method for excluding PE in patients with suspected PE. These bedside methods are simple, noninvasive, and inexpensive. Since both the D-dimer measurement and the steady-state end-tidal alveolar dead space measurement require minimal expertise and inexpensive equipment, these tests could be made available in all hospitals. The negative predictive value of this combination of bedside tests (98.0%; 95% CI, 94.1 to 99.9%) is near that of a normal V/Q scan result (98.8%; 95% CI, 97.0 to 99.7%),5 is comparable to that of a near-normal V/Q scan result (96.1%; 95% CI, 91.1 to 98.7%),3 and is clearly better than that of a low-probability V/Q scan result (86%; 95% CI, 82 to 90%).3 Unfortunately, on a daily basis, clinicians use low-probability scan results alone to exclude PE.6

The diagnosis and exclusion of PE remain problematic. The diagnostic “gold standard” is pulmonary angiography. Pulmonary angiography is an invasive and expensive procedure, with limited availability and potentially serious complications. Despite being the “gold standard,” pulmonary angiograms are imperfect. A patient with a normal pulmonary angiogram can still expect a 2.2% (95% CI, 0.3 to 8.0%) venous thromboembolic event rate at 1-year follow-up.7 V/Q scan results provide a definitive diagnosis in < 40% of cases.3 Furthermore, a normal/near-normal V/Q scan result has a negative predictive value of only 96.4% (95% CI, 91.1 to 97.7%).3 Finally, more recent experience has shown that a patient with a normal V/Q scan result can expect a 1.2% (95% CI, 0.3 to 3.0%) chance of having a venous thromboembolic event (PE or deep vein thrombosis) diagnosed over a 3-month follow-up period.5

Kline et al4 recently demonstrated the high negative predictive value of end-tidal alveolar dead space measurement combined with a negative D-dimer result in ambulatory patients with suspected PE. The derivation set of Kline et al4 only included ambulatory patients, thereby limiting generalizability.

Clinical decision rules often do not perform as well in validation studies as they do in derivation studies.8 This may be due to differences in surveillance strategies and definitions of outcome between the original studies and the validation studies.8 It is plausible that our bedside techniques to exclude PE will not perform as well in validation studies. This possibility is minimized by the fact that we utilized validated reference standards as outcome measures and that we developed the bedside techniques in consecutive inpatients and outpatients suspected of having PE. Furthermore, we have shown that with minimal training (2 h), a large number of RTs can be taught our technique with excellent reproducibility (unpublished data submitted for publication). We caution, however, that care must be taken to ensure that the equipment (blood gas analyzer and capnograph) is properly calibrated prior to each use, as small errors in PaCO₂ measurement may result in large differences in the steady-state end-tidal AVDSf. We also recommend using our new technique of alveolar dead space measurement, given that we have demonstrated its reproducibility in a “real world” setting (unpublished data submitted for publication).

The “excluded proportion” reflects the proportion of patients suspected of having PE who are safely excluded. The excluded proportion is a measure of the proportion of patients who can be excluded without further testing. Hence, the excluded proportion reflects the clinical and economic impact a bedside technique will have once validated and adopted into clinical practice. An excluded propor-

### Table 2—Two-by-Two Table of D-Dimer in Suspected PE*

<table>
<thead>
<tr>
<th>D-Dimer Result</th>
<th>PE</th>
<th>No PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive†</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>83</td>
</tr>
</tbody>
</table>

*Sensitivity, 83% (95% CI, 69.2 to 92.4%); specificity, 57.6% (95% CI, 49.1 to 65.9%); negative predictive value, 91.2% (95% CI, 83.4 to 96.1%).

†Latex D-dimer > 250 μg/dL or positive results on whole-blood agglutination assay.

### Table 3—Two-by-Two Table of Steady-State End-Tidal AVDSf in Suspected PE*

<table>
<thead>
<tr>
<th>AVDSf</th>
<th>PE</th>
<th>No PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.15</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>&lt; 0.15</td>
<td>8</td>
<td>78</td>
</tr>
</tbody>
</table>

*Sensitivity, 79.5% (95% CI, 63.3 to 90.7%); specificity, 70.3%; negative predictive value, 90.7% (95% CI, 82.5 to 95.9%).

### Table 4—Two-by-Two Table of the Combination of D-Dimer and Steady-State End-Tidal AVDSf in Suspected PE*

<table>
<thead>
<tr>
<th>Combinations</th>
<th>PE</th>
<th>No PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. D-Dimer positive†</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>or II. Steady-state end-tidal AVDSf of &gt; 0.15 (suggests PE possible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. D-Dimer negative†</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>and II. Steady-state end-tidal AVDSf of &lt; 0.15 (rule out PE)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Sensitivity, 97.8% (95% CI, 88.5 to 99.9%); specificity, 38.0%; negative predictive value, 98.0% (95% CI, 89.4 to 99.9%).

†D-Dimer positive = latex D-dimer > 250 μg/dL or positive whole-blood agglutination assay result. D-Dimer negative = latex D-dimer < 250 μg/dL or negative whole-blood agglutination assay result.
tion of > 25% for our study represents significant numbers of patients who could be safely excluded at the bedside without further testing if our methods are validated and adopted.

There are limitations in our study. First, the CIs for sensitivity and negative predictive value are too wide to allow for widespread adoption of these bedside methods without further validation. Second, ideally, all patients would have had the reference standard (pulmonary angiography or a normal V/Q scan result). Unfortunately, in clinical practice, it is not uncommon that clinicians do not pursue pulmonary angiography or other tests in patients with indeterminant V/Q scan results. The reluctance of clinicians, even in the setting of a clinical trial (as we experienced), to use the “gold standard” (pulmonary angiography) necessitates that investigators must use imperfect outcome measures. Even if a group of investigators were able to convince clinicians to obtain pulmonary angiograms on all patients with suspected PE, as was done in the Prospective Investigation of Pulmonary Embolism Diagnosis study, it is likely that a highly selected study group would remain, as occurred in that study (1,493 patients consenting out of 3,016 eligible patients). This degree of selection almost certainly results in a biased study sample. In our study, we attempted to minimize selection bias and maximize the accuracy of diagnosis by utilizing the reference standard where possible (normal V/Q scan result and pulmonary angiograms) and otherwise using validated combinations of V/Q scan results and pretest probability or leg vein imaging. All imaging was interpreted by physicians unaware of patient presentation and outcomes, minimizing interpretation bias. Thirdly, not all patient data sets were complete, including 34 patients who were unclassified. The result of incomplete data sets may be that the study population is not representative of the total population of patients suspected of having PE. Reassurance that the unclassified and classified patients are comparable is given by the fact that these groups were not significantly different in gender or age. However, other important differences between these groups may exist. The fact that 14% of our population, in the context of a study, were unclassified provides further evidence that alternate diagnostic approaches, more acceptable to clinicians and patients, must be developed. Finally, it should be emphasized that this combination of tests is useful in excluding PE, not diagnosing PE. These tests individually and in combination have insufficient positive predictive value to diagnose PE.

If validated and adopted, the application of these bedside tests may safely exclude PE. Excluding PE at the bedside with these tests would eliminate the need for unnecessary presumptive treatment and further diagnostic testing in a large proportion of patients with suspected PE. This would save healthcare resources and avoid inconveniencing and placing these patients at risk from presumptive therapy and further diagnostic testing.

ACKNOWLEDGMENT: We are grateful to Dr. Alan Karovitch and the clinicians who completed data collection forms, including Dr. Jim Quinn and Dr. Mark Reardon. Many thanks to Dr. Francois Raymond and the staff of the Nuclear Medicine Department for their cooperation, Denise Blanchette and the R.T.s who provided valuable input to the alveolar dead space analysis, Jane Browning and Ted Tabort from Novametrix for valuable input and support with alveolar dead space measurement, and Michelle Willson for assistance in preparing this article.

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