D-Dimer and Exhaled CO_2/O_2 to Detect Segmental Pulmonary Embolism in Moderate-Risk Patients

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***Rationale*: Pulmonary embolism (PE) decreases the exhaled end-tidal ratio of carbon dioxide to oxygen ($etCO_2/O_2$).**

***Objectives*: To test if the $etCO_2/O_2$ can produce clinically important changes in the probability of segmental or larger PE on computerized tomography multidetector-row pulmonary angiography (MDCTPA) in a moderate-risk population with a positive D-dimer.**

***Methods*: Emergency department and hospitalized patients with one or more predefined symptoms or signs, one or more risk factors for PE, and 64-slice MDCTPA enrolled from four hospitals. D-dimer greater than 499 ng/ml was test(+), and D-dimer less than 500 ng/ml was test(−). The median $etCO_2/O_2$ less than 0.28 from seven or more breaths was test(+) and $etCO_2/O_2$ greater than 0.45 was test(−). MDCTPA images were read by two independent radiologists and the criterion standard was the interpretation of acute PE by either reader. PE size was then graded.**

***Measurements and Main Results*: We enrolled 495 patients, including 60 (12%) with segmental or larger, and 29 (6%) with subsegmental PE. A total of 367 (74%) patients were D-dimer(+), including all 60 with segmental or larger PE (posterior probability 16%). The combination of D-dimer(+) and $etCO_2/O_2$(+) increased the posterior probability of segmental or larger PE to 28% (95% confidence interval [CI] for difference of 12%, 3.0–22%). The combination of D-dimer(+) and $etCO_2/O_2$(−) was observed in 40 patients (8%; 95% CI, 6–11%), and none (0/40; 95% CI, 0–9%) had segmental or larger PE on MDCTPA. No strategy changed the prevalence of subsegmental PE.**

***Conclusions*: In moderate-risk patients with a positive D-dimer, the et $etCO_2/O_2$ less than 0.28 significantly increases the probability of segmental or larger PE and the $etCO_2/O_2$ greater than 0.45 predicts the absence of segmental or larger PE on MDCTPA.**

Clinical trial registered with www.clinicaltrials.gov (NCT 00368836).

Keywords: fibrin fragment D; venous thromboembolism; medical decision making; capnography; tomography, spiral computed

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Pulmonary embolism (PE) that obstructs a segmental or larger pulmonary artery increases alveolar dead space, which leads to decreased exhaled CO_2. The combination of alveolar dead space plus D-dimer has been found to accurately screen for acute pulmonary embolism. However, current methods of assessing alveolar dead space require arterial blood sampling.

What This Study Adds to the Field

This study tests the diagnostic accuracy of a purely breath-based, novel device that simultaneously measures exhaled CO_2/O_2 ratio, as a noninvasive method to assess increased alveolar dead space with segmental or larger PE. This measurement does not require arterial blood sampling. The combination of either a normal $etCO_2/O_2$ or a normal D-dimer is associated with a very low rate of segmental or larger PE.

Multidetector-row computerized tomographic pulmonary angiography (MDCTPA) has become a mainstay in diagnosis and exclusion of acute pulmonary embolism (PE). Reasons for its widespread adoption may include the perception of superior diagnostic and operational test performance compared with ventilation–perfusion lung scanning and the ability to show alternative diseases (1). However, clinical trials have not found superior outcome to MDCTPA compared with VQ scanning, and MDCTPA imparts a higher lifetime risk of cancer from radiation exposure and contrast nephropathy. The increasing resolution afforded by 64-head computed tomography (CT) equipment has produced a concomitant increase in the frequency of PE diagnosis based on an isolated subsegmental filling defect (2–7). The finding of an isolated subsegmental PE on MDCTPA in the absence of a deep venous thrombosis (DVT) confers significant diagnostic and therapeutic uncertainty. The diagnostic uncertainty arises from the low interobserver agreement between two radiologists for the interpretation of isolated subsegmental PE (6–8). The therapeutic uncertainty arises from the fact that many clinicians and authors believe that patients with isolated subsegmental PE do not benefit from anticoagulation, although no clinical trial has tested this hypothesis (5, 9). In contrast, published guidelines recommend immediate heparin anticoagulation for patients with moderate to high suspicion of segmental or larger PE and no contraindications to anticoagulation (10, 11).

Acute PE that obstructs a segmental or larger pulmonary artery increases the volume of alveolar dead space in the lung to an extent that can be measured. The alveolar dead space can be estimated by simultaneously measuring the exhaled CO_2 and arterial blood partial pressure of CO_2 (12). The alveolar dead space can significantly improve the diagnostic performance of the D-dimer as a screening tool for PE in the emergency department (ED) setting (12–15). However, the requirement

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for simultaneous, steady-state measurement of exhaled CO_2 and arterial blood CO_2 represents a technical challenge and causes pain to the patient. Accordingly, a purely breath-based test that does not require a simultaneous blood sample would have advantages. Patients with PE large enough to elevate the alveolar dead space exhale breaths that are more like ambient air—dilute in CO_2 and higher in O_2—when compared with patients who have normal pulmonary ventilation–perfusion or ventilation–perfusion mismatch caused by obstruction of the airways. Several studies have found that a low exhaled, end-tidal (et) CO_2 measurement increases, and a normal or high $etCO_2$ decreases, the probability of acute PE in symptomatic patients previously selected for PE evaluation (16, 17). Kline and Hogg reported the end-tidal ratio of CO_2/O_2 had an advantage over the $etCO_2$ alone for the detection of acute PE (18).

This study was conducted to test the incremental change in posterior probability of PE produced by adding the $etCO_2/O_2$ to the high-sensitivity, quantitative D-dimer (<500 ng/ml normal) as a screening battery for patients with suspected PE. The *a priori*, explicitly defined primary efficacy aims were to measure the posterior probability of PE for the D-dimer test alone compared with the following test combinations: (*1*) the D-dimer greater than 499 ng/ml and $etCO_2/O_2$ less than 0.28, and (*2*) the D-dimer less than 500 ng/ml or an $etCO_2/O_2$ greater than 0.45. We hypothesized that the addition of $etCO_2/O_2$ to the D-dimer would significantly increase the posterior probability of PE and increase the proportion of patients who could have segmental or larger PE ruled out before MDCTPA.

Some of the results of this study have been previously reported in the form of an abstract (19) and in a published report (7).

METHODS

Study Design

This was a prospective, four-center noninterventional, Food and Drug Administration–regulated study of diagnostic accuracy of a proprietary device conducted in accordance with the guidelines set out by the Standards for Reporting of Diagnostic Accuracy criteria (20).

Study Setting and Population

Prospective enrollment occurred from EDs, wards, and intensive care units of four academic medical centers in the United States (*see* online supplement).

Because MDCTPA scans at the four sites were ordered in equal proportions from the ED as for admitted inpatients, we enrolled patients in approximately a 1:1 ratio from each location. Inclusion criteria required that an MDCTPA be ordered as standard care, and the patient had to have both one or more of 15 predefined signs or symptoms of PE and one or more of 21 predefined known risk factors for PE (*see* Table E1 in the online supplement) (7). All patients had to provide written informed consent. Patients were excluded if they could not provide follow-up or if they were incarcerated, pregnant, hemodynamically unstable, unable to breathe through their mouth, had fibrinolytic treatment within 48 hours, had PE diagnosed within the last 6 months and were on anticoagulation or had a history of noncompliance with anticoagulation for PE, or had known active tuberculosis.

Study Protocol

MDCTPA images were obtained at each site as part of standard care, and were done on 64-slice multidetector equipment with less than or equal to 2.5 mm collimation. Details of image acquisition and interpretation have been described (7).

Breath and blood collection. Breath and blood collection had to be completed within 24 hours of MDCTPA completion in accordance with standard operating procedures contained in the study binder. Breath was collected and the $etCO_2/O_2$ analyzed using the Breathscreen PE device, which used a computer algorithm to examine each breath in real time to reject breaths with an alveolar volume less than 100 ml or less than 150% of the airway dead space volume (21). Seven accepted breaths were required for per-protocol analysis. Blood was analyzed for D-dimer (VIDAS ELISA; bioMerieux, Durham, NC) using FDA-cleared devices (*see* online supplement).

MDCTPA interpretation. Images were interpreted by two independent radiologists who were blinded to each other's interpretations (7). Images were interpreted as "No PE," "Positive for acute PE," "Positive for chronic PE," "Positive for other finding," or "Indeterminate." All scans read as positive for PE were further evaluated for the percentage obstruction of the vessel(s) using the modified method of Mastora and colleagues; PE was considered subsegmental for a total percentage lung obstruction of less than 5% (22) (*see* online supplement).

Criterion standard for acute PE. For the first analysis, the criterion standard defined PE as present for any MDCTPA interpreted as positive for acute PE by either or both radiologists together with clinical decision to initiate and maintain anticoagulation. In the per protocol analysis, the criterion standard for PE(+) was the interpretation of a segmental or larger filling defect on MDCTPA(−).

Follow-up

Using previously described methods (23), we used a standardized telephone survey to participants supplemented by review of updated medical records to determine if any patients developed new PE or DVT within 45 days after enrollment.

Data Analysis

The per-protocol primary efficacy aims were to measure the change in posterior probability of PE when the $etCO_2/O_2$ was added to the D-dimer for the detection of segmental or larger PE. The test-positive comparison was ([D-dimer > 499 ng/ml] vs. [D-dimer > 499 ng/ml *and* $etCO_2/O_2 < 0.28$]) and the test-negative comparison was ([D-dimer < 500 ng/ml] vs. [D-dimer < 500 ng/ml *or* $etCO_2/O_2 > 0.45$]). We used linear and logistic regression to test D-dimer and $etCO_2/O_2$ values as independent variables for correlation with percentage pulmonary vascular obstruction and prediction of PE diagnosis, as dependent variables, respectively (*see* online supplement).

RESULTS

Figure 1 shows the flow diagram of patients starting with those subjects screened for inclusion to the point of final outcome with respect to PE diagnosis. A total of 547 patients signed a consent form and 495 had complete data. Exclusions included 9 patients for whom a blood specimen could not be obtained, 7 other patients for whom seven accepted breaths could not be obtained, and 11 other patients with missing blood and breath samples. All 495 patients with complete data had both the D-dimer assay performed and the $etCO_2/O_2$ measurement performed. Breaths were collected in an average of 45 ± 14 seconds and $etCO_2/O_2$ data are based on an average of 10.5 ± 2.6 breaths. General demographic characteristics and clinical characteristics of patients are shown in Table 1.

The criterion standard for acute PE was found in 89 MDCTA scans (either reader interpreted acute PE); chronic PE was found in 4 others in the absence of any findings suggestive of acute PE. Twenty-nine of 89 (32.5%) MDCTPA scans demonstrated acute PE that was subsegmental. The mean pulmonary vascular obstruction was 19.7 ± 23.6% for the 89 scans with acute PE interpretations and 6.8 ± 5.0% for the four scans with chronic PE (*see* online supplement).

Compared with those without PE, patients with PE(+) had significantly higher mean D-dimer (3,566 ± 4,103 ng/ml [PE(+)] vs. 1,468 ± 2,141 ng/ml [PE(−)]) and significantly lower $etCO_2/O_2$ values (0.32 ± 0.08 vs. 0.35 ± 0.09). First-order regression analyses of the raw D-dimer and $etCO_2/O_2$ values

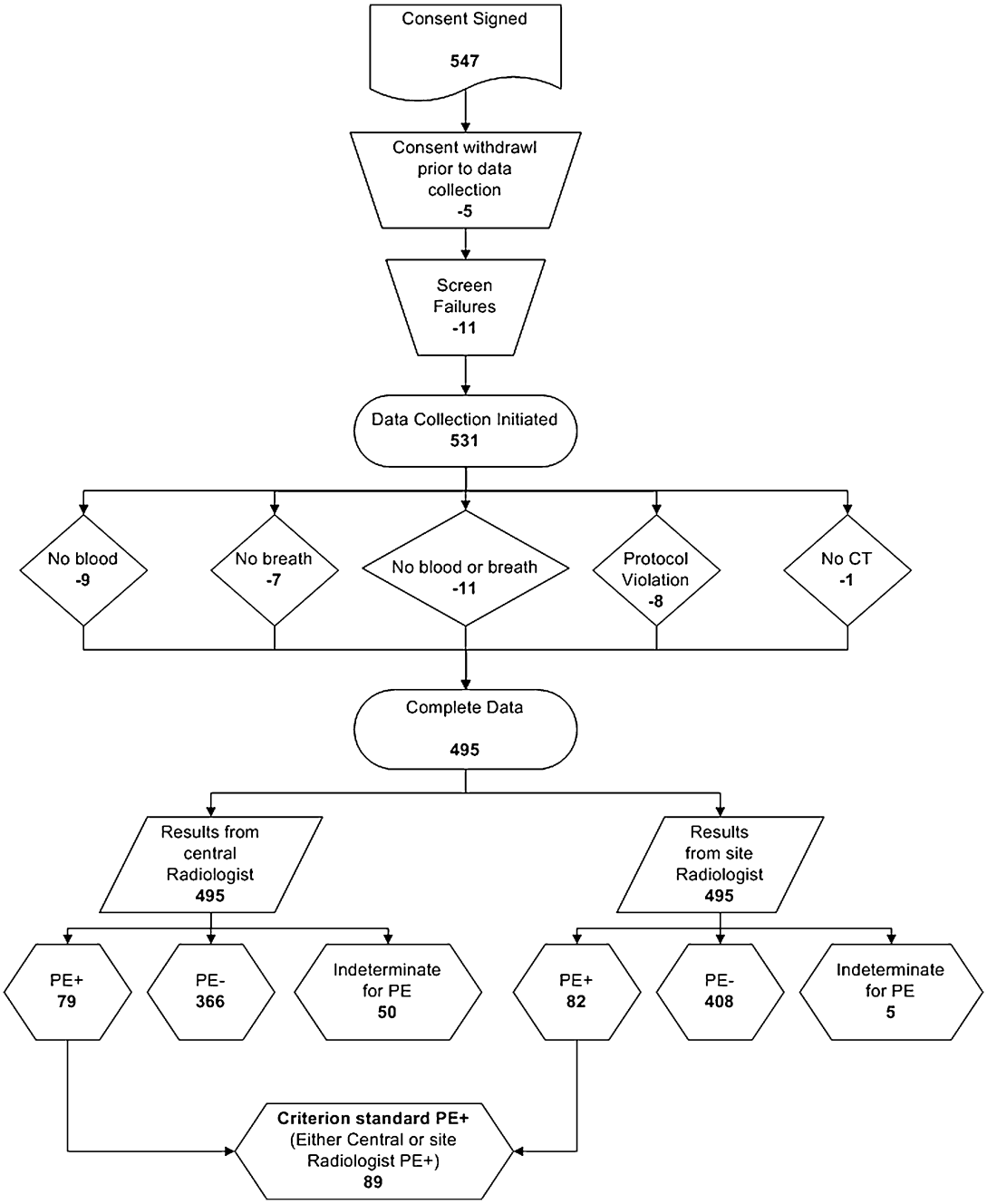

Figure 1. Flow diagram showing the number of patients screened, enrolled, and reasons for exclusions. CT = computed tomography; PE = pulmonary embolism.

versus percentage pulmonary vascular obstruction demonstrated Pearson correlation coefficient (R^2) equal to 0.11 for D-dimer and 0.20 for $etCO_2/O_2$ (*see* online supplement). Transformation of the D-dimer value into its natural logarithm yielded $R^2 = 0.14$. Multivariate logistic regression analysis containing D-dimer, $etCO_2/O_2$, pulse rate, % Sa_{O_2}, thrombophilia, age greater than 49 years, bed confinement more than 72 hours, recent surgery, active malignancy, estrogen use, and prior venous thromboembolism found only the D-dimer and $etCO_2/O_2$ to have significant predictive value ($P < 0.05$ for the coefficient) (*see* online supplement)

Detection of Any Acute PE

Table 2 shows the diagnostic indexes and posterior probabilities of PE that would have been produced by the D-dimer, $etCO_2/O_2$ alone, and the combinations of these tests using the first criterion standard. This table considers all 89 PE(+) scans as criterion positive, including 29 MDCTPA scans with subsegmental-sized filling defects. The D-dimer was positive in 367 (74%) of the cohort, including 85 patients with PE, leading to a posterior probability of PE of 23.2% (95% confidence interval [CI], 18.9–27.8%) for a positive D-dimer. The D-dimer was negative in 128/495 (26%; 95% CI, 18.3–25.0%), including four patients with PE, leading to a posterior probability of 3.1% (95% CI, 0.9–7.8%). These four had isolated subsegmental PE. The addition of the $etCO_2/O_2$ to the D-dimer increased the posterior probability of PE with a positive test result, and expanded the proportion of the cohort with a negative test result. First, from the 367 patients with a positive D-dimer, 95 also had an $etCO_2/O_2$ less than 0.28, including 33 who had PE, leading to a posterior probability of 33/95 or 34.7% (95% CI for the difference, 34.7−23.2 = 11.5%, 1.6–22.4%). Second, when

TABLE 1. CLINICAL FEATURES OF THE PATIENT POPULATION AT THE TIME OF ENROLLMENT

Feature	N	%
General characteristics		
Age, mean, median (range), yr	495	54, 55 (18–94)
Female	311	63
Hispanic or Latino ethnicity	22	4
White	342	69
Black or African American	145	29
American Indian or Alaskan native	4	0.8
Native Hawaiian or native Pacific Islander	2	0.4
Asian	2	0.4
Enrolled in the ED	238	48
Enrolled as an inpatient	257	52
Signs and symptoms of PE		
New-onset dyspnea	293	59
Pulse ⩾ 90 beats/min	289	58
Substernal chest pain	207	42
Cough	206	42
Respiratory rate > 20 breaths/min	197	40
Pulse oxygenation < 95%	185	37
Increased chronic dyspnea	77	16
Risk factors for PE		
Age > 49 yr	335	68
Body mass index > 36 kg/m^2	125	25
Bed rest or hospitalization > 48 h	83	17
Previous surgery within 4 wk	76	15
Active malignancy	68	14
Estrogen use	50	10
Indwelling deep venous catheter	47	9
Patient history of PE or DVT		
PE > 6 mo on current treatment	14	3
DVT on current treatment	29	6
PE or DVT on no current treatment	51	10

Definition of abbreviations: DVT = deep venous thrombosis; ED = emergency department; PE = pulmonary embolism.

the 40 (8.1% of the cohort) patients who had a positive D-dimer but had an $etCO_2/O_2$ greater than 0.45 were also considered test negative in addition to the 128 patients with a negative D-dimer (D-dimer < 500 ng/ml or $etCO_2/O_2 > 0.45$), the proportion of patients with a negative combined test result was significantly increased to 168/495 or 34.0% (95% CI for difference of 8.1%, 5.8–10.8%), and six of these 168 patients had PE, all six of which were isolated subsegmental PE, resulting in a posterior probability for any PE equal to 6/168 or 3.8% (95% CI, 1.3–7.6%). Further details of these six patients include a D-dimer greater than 500 in three and an $etCO_2/O_2$ greater than 0.45 in three; risk factors for PE of estrogen use (2), prior history of PE (1), and active malignancy (1); one patient with COPD; and none with DVT found on ultrasound.

Detection of Segmental or Larger PE

Table 3 shows the results of the per protocol analysis that restricts the criterion standard for PE(+) to the 60 (12.1%) patients with MDCTPA scans that demonstrated segmental or larger filling defects. For the detection of segmental or larger PE, the addition of the $etCO_2/O_2$ to the D-dimer increased both the posterior probability of PE with a positive test result and the proportion of the cohort with a negative test result. Of the 367 patients with a positive D-dimer, 60 had segmental or larger PE, leading to a posterior probability of 16.3% (95% CI, 12.7–20.5%). Among the 95 with both a positive D-dimer and an $etCO_2/O_2$ less than 0.28, 27/95 (28.4%) had segmental or larger PE, leading to a significantly increased posterior probability compared with the prevalence of segmental or larger PE in the entire cohort (95% CI for difference of 12.1%, 3.0–22.5%). None of the 128 patients with a negative D-dimer and none of the 53 patients with an $etCO_2/O_2$ greater than 0.45 had a segmental or larger PE. Forty patients (8% of cohort) had D-dimer greater than 499 ng/ml but had $etCO_2/O_2$ greater than 0.45. Thus, the incremental value of the $etCO_2/O_2$ added to the D-dimer in terms of the number needed to test to prevent one MDCTPA was 12.3. In total, 168 patients had either the D-dimer less than 500 ng/ml or the $etCO_2/O_2$ greater than 0.45, and none of these had segmental or larger PE. Thus, the posterior probability of segmental or larger PE in patients with the negative combined test(−) result (D-dimer < 500 ng/ml or $etCO_2/O_2 > 0.45$) was 0/168 (95% CI, 0–2.2%).

Detection of Subsegmental and Chronic PE

The baseline frequency of isolated subsegmental PE discovered on MDCTPA was 29/495 (5.8%). Had clinicians only ordered MDCTPA scanning for patients with a positive D-dimer, then the frequency of isolated subsegmental PE would have been 25/367 or 6.8%, and had they only ordered MDCTPA for patients with a positive D-dimer and an $etCO_2/O_2$ less than 0.45, this frequency would have been 23/327 (7.0%). Among the four patients with chronic PE and no evidence of acute PE, the D-dimer was normal in one (350 ng/ml), and all four patients had an $etCO_2/O_2$ less than 0.45.

Detection of Subsegmental PE with DVT

Of the 29 patients with subsegmental PE, 20 underwent venous ultrasonography of the legs (one included the arms as well) and

TABLE 2. DIAGNOSTIC INDEXES FOR D-DIMER AND END-TIDAL RATIO OF CARBON DIOXIDE TO OXYGEN FOR ANY PULMONARY EMBOLISM POSITIVE

Test Result	Test Interpretation	Number with Result		Sensitivity	Specificity	Likelihood Ratio		Posterior Probability of PE	
		PE(+)	PE(−)			(+)	(−)	Test (+)	Test (−)
D-dimer > 499 ng/ml	(+)	85	282	95.5	30.5	1.37		23.2%	3.1%
D-dimer < 500 ng/ml	(−)	4	124				0.15		
95% CI				88.8–98.9	26.1–35.3	1.26–1.49	0.06–0.36	18.9–27.8%	0–7.8%
$etCO_2/O_2 < 0.28$*	(+)	33	93	94.3	35.4	1.46		26.2%	3.8%
$etCO_2/O_2 > 0.45$*	(−)	2	51				0.16		
95% CI				80.8–99.3	27.6–43.8	1.23–1.70	0.04–0.54	18.8–34.8	0.5–13.0%
D-dimer > 499 and $etCO_2/O_2 < 0.28$	(+)	33	62	84.6	72.3	3.06		34.7%	3.6%
D-dimer < 500 or $etCO_2/O_2 > 0.45$	(−)	6	162				0.21		
95% CI				69.5–94.1	66.0–78.1	2.35–3.91	0.10–0.41	25.3–45.2%	1.3–7.6%

Definition of abbreviations: CI = confidence interval; $etCO_2/O_2$ = end-tidal ratio of carbon dioxide to oxygen; PE = pulmonary embolism.
* n = 316 had an $etCO_2/O_2$ of 0.28 to < 0.45, of whom 54 were PE+ and 262 were PE−.

TABLE 3. DIAGNOSTIC INDEXES FOR THE D-DIMER AND END-TIDAL RATIO OF CARBON DIOXIDE TO OXYGEN FOR SEGMENTAL OR LARGER PULMONARY EMBOLISM

Test Result	Test Interpretation	Number with Result		Sensitivity	Specificity	Likelihood Ratio		Posterior Probability of PE	
		PE(+)	PE(−)			(+)	(−)	Test (+)	Test (−)
D-dimer > 499 ng/ml	(+)	60	307	100	29.4	1.42	0	16.3%	0.0%
D-dimer < 500 ng/ml	(−)	0	128						
95% CI				94.0–100	25.2–34.0	1.30–1.50	0–0.21	12.7–20.5%	0–2.8%
$etCO_2/O_2 < 0.28$*	(+)	27	99	100	34.9	1.54	0	21.4%	0.0%
$etCO_2/O_2 > 0.45$*	(−)	0	53						
95% CI				87.2–100	27.3–43.0	1.28–1.72	0–0.36	14.6–29.6%	0–6.7%
D-dimer > 499 and $etCO_2/O_2 < 0.28$	(+)	27	68	100	71.2	3.47	0	28.4%	0.0%
D-dimer < 500 or $etCO_2/O_2 > 0.45$	(−)	0	168						
95% CI				87.2–100	65.0–76.9	2.75–4.21	0–0.18	19.6–38.6%	0–2.2%

For definition of abbreviations see Table 2.

* n = 316 had an $etCO_2/O_2$ of 0.28 to < 0.45, of whom 33 had segmental or larger PE and 283 had no PE or subsegmental PE.

9 others underwent CT venography within 10 days of enrollment. Six patients had venous noncompressibility consistent with DVT in the following veins: one in a brachial vein distal to an indwelling catheter, two with isolated calf veins, and two with isolated popliteal veins; one had both chronic femoral and calf vein findings. All six of the patients with a positive ultrasound had both a D-dimer greater than 499 ng/ml and an $etCO_2/O_2$ less than 0.45.

PE and DVT on Follow-up

Within 45 days, eight patients who did not have any PE diagnosis at enrollment had imaging performed as part of standard care that suggested new PE (n = 2) or DVT (n = 6) (Table 4). Three of these patients were prescribed anticoagulation at enrollment, but their compliance with treatment was not studied. Two of the 8 patients were prescribed new anticoagulation because of the imaging results.

DISCUSSION

This study tested the hypothesis that when compared with the D-dimer alone, the combination of D-dimer plus $etCO_2/O_2$ could produce clinically important improvements as a screening strategy for segmental or larger PE before MDCTPA in a moderate risk population. The main finding was that the test-positive combination (D-dimer > 499 ng/ml and $etCO_2/O_2 < 0.28$) produced a posterior probability of any PE equal to 34.7% and a posterior probability of segmental or larger PE equal to 28.4%, representing a significant increase over the posterior probability of PE observed with a positive D-dimer alone in either case. The second main finding was that no patient with a D-dimer less than 500 ng/ml and no patient with an $etCO_2/O_2$ greater than 0.45 had a segmental or larger PE. The test-negative combination (D-dimer < 500 ng/ml or $etCO_2/O_2 > 0.45$) occurred in 168 patients (34% of the cohort). The $etCO_2/O_2$ was test negative in 40 patients who had a positive D-dimer and no segmental PE, equating to an absolute 8% increase in the proportion of patients with a negative test compared with a negative D-dimer alone. This suggests that when added to the D-dimer, the $etCO_2/O_2$ could potentially obviate approximately 1 in 12 MDCTPA scans performed with the clinical question of whether or not the patient has segmental or larger PE. None of the 168 patients with a negative combined result had a segmental or larger PE. Multivariate logistic regression containing the independent variables D-dimer, $etCO_2$, and 10 known strong clinical risk factors for PE (including active cancer, recent surgery, and prior venous thromboembolism) revealed that both the D-dimer and the $etCO_2/O_2$ had significant independent predictive value for predicting any PE on MDCTPA. These findings confirm that both the D-dimer and $etCO_2/O_2$ predict the presence of a filling defect interpreted as PE on MDCTPA independently of standard clinical factors obtained at the bedside. First-order regression analysis demonstrated that the $etCO_2/O_2$ had a higher Pearson correlation coefficient ($R^2 = 0.20$) than did the D-dimer ($R^2 = 0.08$). These findings suggest that the $etCO_2/O_2$ may be a better predictor of the filling defect size on MDCTPA than the D-dimer.

The clinically oriented interpretations of these data are that approximately one-third of MDCTPAs in this moderate- to high-risk population could be avoided by the negative test

TABLE 4. NEW VENOUS THROMBOEMBOLIC EVENTS WITHIN 45 DAYS AFTER ENROLLMENT

Site	Enrollment Findings CTPA Readings	Findings on Follow-up						
		D-Dimer	$etCO_2/O_2$	Anticoagulation Prescribed	Days Post Enrollment	CTPA/CTV	Venous Ultrasound	New Anticoagulation
Northwestern	Neg/neg	818	0.266	Yes	9	Acute PE	Negative	NA
Carolinas	Neg/neg	502	0.418	Yes	34	Chronic PE	Not done	NA
Northwestern	Neg/neg	518	0.261	Yes	30	Not done	Jugular and subclavian thrombosis	NA
Wake Forest	Neg/indeterminate	1,071	0.369	No	50	DVT	Not done	Yes
Carolinas	Neg/neg	3,723	0.365	No	8	Negative	Proximal leg	Yes
Northwestern	Neg/neg	298	0.396	No	16	Not done	Chronic IJ	No
Northwestern	Neg/neg	2,429	0.212	No	18	Not done	Axillary, cephalic	Yes
Wake Forest	Neg/neg	286	0.258	No	7	Not done	Brachial vein	No

Definition of abbreviations: CTPA = computerized tomographic pulmonary angiography; CTV = computerized tomographic venography; DVT = deep venous thrombosis; $etCO_2/O_2$ = end-tidal ratio of carbon dioxide to oxygen; IJ = intrajugular; NA = not applicable (already anticoagulated); Neg = negative; PE = pulmonary embolism.

combination defined by a D-dimer less than 500 ng/ml or an $etCO_2/O_2$ greater than 0.45. Alternatively, the presence of a D-dimer greater than 499 ng/ml and an $etCO_2/O_2$ less than 0.28, together with a moderate to high clinical suspicion for PE, could be interpreted as sufficient evidence to initiate anticoagulation before imaging results, assuming the patient had no contraindications. The clinical importance of these data depends in part on the clinician's perception of the clinical significance of the isolated subsegmental PE, which is known to vary considerably among clinicians (5). Published guidelines either imply that isolated subsegmental PE does not warrant anticoagulation, or remain silent on the issue, perhaps because of the lack of any outcomes data (10, 11, 24, 25). We found that 29/89 (32.5%) of patients with an MDCTPA interpreted as having acute PE by either radiologist as having a total filling defect less than 5%, suggesting smaller than segmental PE (*see* online supplement). Our frequency of isolated subsegmental PE is higher than was reported by Brunot and colleagues in 2005, who found 9 of 75 (12%) patients with PE observed on MDCTPA had isolated subsegmental PE (6).

This work adds to published data showing that the addition of the $etCO_2/O_2$ to pretest probability can produce very good diagnostic accuracy in a lower-risk ED population (18). In addition, the $etCO_2/O_2$ may represent a novel method to monitor patients at high risk for PE who are about to engage in surgery, chemotherapy, or other stressors that predispose to PE. Kline and Hogg found that the relative preoperative to postoperative change in $etCO_2/O_2$ was $1.6 \pm 20\%$, whereas the relative change in D-dimer was $234 \pm 292\%$ for patients undergoing surgery believed to be high risk for VTE (26).

We believe this study design was rigorous in several unique respects. The sample was multicenter. The enrollment methods were highly planned in advance (*see* clinicaltrials.gov). We designed the study to enroll a representative sample of patients undergoing MDCTPA in current practice. Although the majority of published studies of screening strategies for PE enrolled only outpatients, we included an equal balance of inpatients and ED patients. We submit that the primary effect of including inpatients was to reduce the test specificity of both the D-dimer and $etCO_2/O_2$, because inpatients may be more likely to have elevated D-dimer concentrations and abnormal pulmonary function than ambulatory patients. The inclusion criteria were designed to produce a population that was at moderate risk for PE. In addition to the requirement of an MDCTPA ordered as standard care, we restricted enrollment to those patients with explicitly documented signs or symptoms and at least one known risk factor for PE. This resulted in a significantly higher prevalence of any-size PE (18%; 95% CI, 15–22%) than the 8% prevalence we recently found in a large, multicenter sample of ED patients who enrolled on the basis of any test ordered for PE (27). Recognizing the potential confounding effect of a very low prevalence of PE was a major reason for restricting the inclusion criteria to yield at least a moderate-risk population.

Limitations include the fact that this study only tests the hypothetical contribution of the $etCO_2/O_2$ and does not test its real-time use as a diagnostic instrument. In particular, a validation study must be performed to test if anticoagulation can be safely withheld in patients with an $etCO_2/O_2$ greater than 0.45. An important limitation to the potential diagnostic usefulness of the $etCO_2/O_2$ ratio is that the majority of measurements, 316 (64%), were in an intermediate range (0.28 to < 0.45) and therefore may not be helpful to decision making. The optimal management of subsegmental PE also remains uncertain. Although we collected data required for various pretest probability scoring systems, including the Wells criteria, we elected to not include them. We collected pretest probability data after the decision was made to order MDCTPA—a decision often made by a clinical team. We submit that pretest probability data need to be collected from the individual most responsible for ordering the MDCTPA. However, in 40% of enrolled patients, the research team was unable to determine the individual clinician willing to take primary responsibility for ordering the MDCTPA. Although we did perform detailed follow-up of all patients out to 45 days, we did not include recurrent venous thrombotic events in the criterion standard in this analysis.

In summary, this study found that the addition of an $etCO_2/O_2$ less than 0.28 to a positive D-dimer significantly increases the probability of a filling defect consistent with a segmental or larger PE observed on MDCTPA, and that patients with either a negative D-dimer or an $etCO_2/O_2$ greater than 0.45 had a very low probability of segmental or larger PE on MDCTPA. We conclude that the combined testing strategy of the D-dimer plus the etCO2 produces clinically important advantages as a screening step before MDCTPA compared with the D-dimer alone.

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