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Bedside end-tidal CO_2 tension as a screening tool to exclude pulmonary embolism

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ABSTRACT: End tidal carbon dioxide tension (P_{ET,CO_2}) is a surrogate for dead space ventilation which may be useful in the evaluation of pulmonary embolism (PE). We aimed to define the optimal P_{ET,CO_2} level to exclude PE in patients evaluated for possible thromboembolism.

298 patients were enrolled over 6 months at a single academic centre. P_{ET,CO_2} was measured within 24 h of contrast-enhanced helical computed tomography, lower extremity duplex or ventilation/perfusion scan. Performance characteristics were measured by comparing test results with clinical diagnosis of PE.

PE was diagnosed in 39 (13%) patients. Mean P_{ET,CO_2} in healthy volunteers did not differ from P_{ET,CO_2} in patients without PE (36.3±2.8 *versus* 35.5±6.8 mmHg). P_{ET,CO_2} in patients with PE was 30.5±5.5 mmHg ($p<0.001$ *versus* patients without PE). A P_{ET,CO_2} of ⩾36 mmHg had optimal sensitivity and specificity (87.2 and 53.0%, respectively) with a negative predictive value of 96.6% (95% CI 92.3–98.5). This increased to 97.6% (95% CI 93.2–99.) when combined with Wells score <4.

A P_{ET,CO_2} of ⩾36 mmHg may reliably exclude PE. Accuracy is augmented by combination with Wells score. P_{ET,CO_2} should be prospectively compared to D-dimer in accuracy and simplicity to exclude PE.

KEYWORDS: End-tidal carbon dioxide, prediction model, pulmonary embolism, sensitivity, specificity, Wells score

Pulmonary embolism (PE) is a common concern in the evaluation of diverse clinical presentations including chest pain, dyspnoea and hypoxaemia [1]. Extensive diagnostic evaluation, including contrast-enhanced helical computed tomography (CT), is frequently undertaken, despite a relatively low incidence of disease [2]. In addition to the cost of these studies, the risks of contrast and radiation exposure add to the burden of evaluation [3, 4].

Diagnostic algorithms to simplify testing procedures in PE diagnosis have been explored, most combining D-dimer testing and CT angiography [5, 6]. D-dimer testing requires venipuncture and time for test performance [1, 5]. CT angiography use in PE diagnosis has increased markedly [2]. As a low percentage of CT angiograms demonstrate PE [2, 7, 8], concern has been raised regarding contrast and radiation risk [4, 9]. Clinical prediction rules, including the Wells score, have also been proposed [6, 10] which have the advantage of instantaneous results, avoidance of invasive procedures, and low risk and cost. Thus, there is a need for safer, more accurate and readily available diagnostic testing for PE.

End-tidal carbon dioxide tension (P_{ET,CO_2}) is a physiological surrogate for vascular obstruction from PE. Pulmonary thromboembolism results in dead space ventilation and, therefore, prevents meaningful gas exchange in the subtended lung unit, yielding an alveolar CO_2 content as low as 0 mmHg. As a result, CO_2 content measured at end expiration, which represents admixture of all alveolar gas, decreases in proportion to dead space ventilation. While there are many potential aetiologies of increased dead space ventilation, *e.g.* advanced chronic obstructive pulmonary disease, these diseases are usually easily identified. Increased dead space ventilation is not associated with common clinical conditions that can present similarly to PE, *e.g.* unstable angina and gastro-oesophageal reflux. Dead space measurement and arterial–alveolar CO_2 tension gradient have been

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studied in the evaluation of PE [11–14], but the utility of P_{ET,CO_2} measurement alone in the diagnosis of PE is not known. P_{ET,CO_2} is safe, noninvasive, inexpensive and rapidly performed at the bedside, whereas dead space measurement requires collection of exhaled gas and alveolar–arterial gradient requires arterial blood gas sampling.

As a proof of concept study, we measured P_{ET,CO_2} in a large cohort of patients undergoing evaluation for PE without controlling clinical care or management. We hypothesised that P_{ET,CO_2} would be reduced in patients with PE and that a normal measurement would have a high negative predictive value to exclude PE.

METHODS

Study design

This was a prospective, single centre study designed to investigate the potential role of P_{ET,CO_2} in the diagnosis of PE. The Vanderbilt University Medical Center Institutional Review Board (Nashville, TN, USA) approved the study.

Setting and population

All patients aged $\geqslant$18 yrs of age who were seen in the Emergency Department or inpatient wards at an academic university hospital from October 2007 to April 2008 were screened electronically for a computer order for contrasted chest helical CT, ventilation/perfusion lung scan, pulmonary angiogram or lower extremity duplex evaluation. Patients meeting screening criteria were approached for consent to undergo P_{ET,CO_2} determination within 24 h of study order placement. Exclusion criteria were inability to consent, pregnancy, known hypercarbic respiratory failure, mechanical ventilation, face mask oxygen or >5 L·min^{-1} nasal cannula oxygen, or known neuromuscular disease. Patients who presented for evaluation more than once could be enrolled multiple times (n=5, two studies each).

Measurements

After informed consent, P_{ET,CO_2} was measured by a trained single tester, blinded to diagnosis (A.L. Newman), using the Nellcor NPB 75 handheld capnograph (Mallinckrodt:Nellcor, St Louis, MO, USA) [15]. The device is calibrated to $\pm$2 mmHg up to 38 mmHg and $\pm$0.08% for every 1 mmHg over 40 mmHg. We modified the apparatus by inserting the uptake cannula into a plastic tube that, when placed in the mouth, allowed patients to tidally breathe while CO_2 was measured (fig. 1). Patients were instructed to breathe normally and were tested for five breaths in either a supine or seated position. Nostrils were not clipped shut. P_{ET,CO_2} for each breath and respiratory rate were measured. The capnometer was validated every 2 weeks at two levels of CO_2 using a Medical Graphics exercise machine (Medical Graphics Corporation, St Paul, MN, USA) calibrated to zero and 5.6% CO_2. Patient charts were analysed for: demographic data including comorbid conditions and thromboembolic risks; self-reported race/ethnicity (categorised into Hispanic, African–American, Caucasian or other); results of serum chemistries; blood counts; ventilation/perfusion lung scan; CT (Brilliance CT 64 Channel; Phillips, Amsterdam, The Netherlands); pulmonary angiography; and venous duplex exams. Wells score [6] was assigned by a single physician (A.R. Hemnes), blinded from final diagnosis, from data obtained at the time that diagnostic tests were ordered. Plasma D-dimer testing (STA LIATEST; Diagnostica Stago, Parsippany, NJ, USA) [16] was performed at the discretion of the treating physician. Patients with D-dimer testing alone for PE were not included in this study because of the risk of false positive D-dimer tests.

Criteria for diagnosis of PE

PE was defined by published consensus criteria [1] including positive contrast-enhanced CT, intermediate- or high-probability ventilation/perfusion lung scan (as described in PIOPED I [17]) combined with high pre-test probability, or positive lower extremity duplex examination with a high clinical suspicion for PE.

Validation of P_{ET,CO_2} measurement in normal controls

To ensure accuracy and reproducibility, and to standardise the modified sensing device and discover stability of P_{ET,CO_2} measurements over time in healthy individuals, we measured P_{ET,CO_2} for five breaths in 24 healthy volunteers (age mean $\pm$ SD 40.0 $\pm$ 12.0; 10 males) on 3 different days. In addition, we measured P_{ET,CO_2} with different inspiratory oxygen fraction delivered by nasal cannula up to 5 L·min^{-1} and found no difference (data not shown).

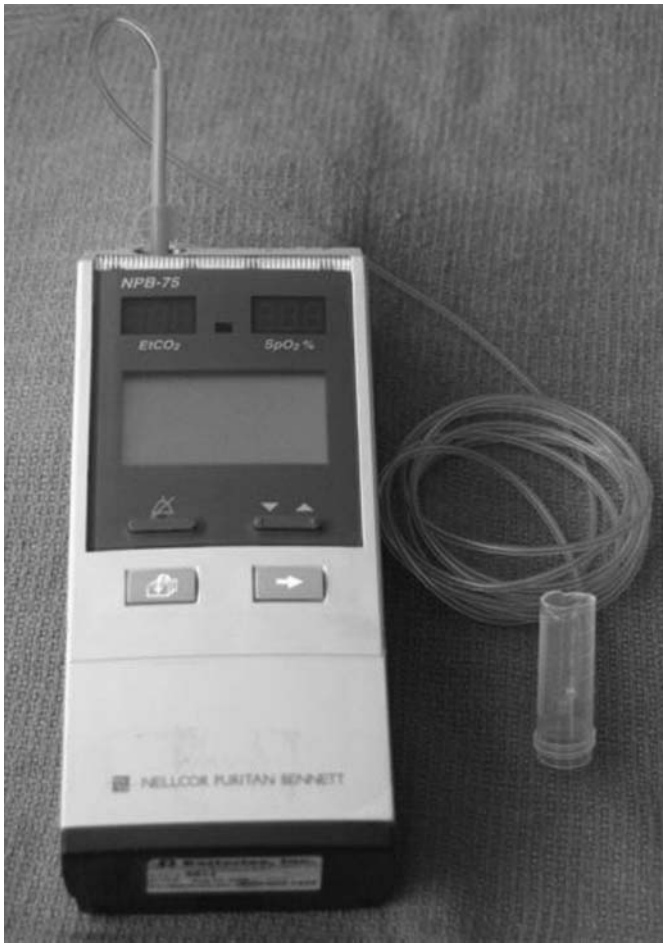

FIGURE 1. A modified sensor for detection of end-tidal carbon dioxide tension. The modified sensor is 5 cm long with a diameter of 1 cm.

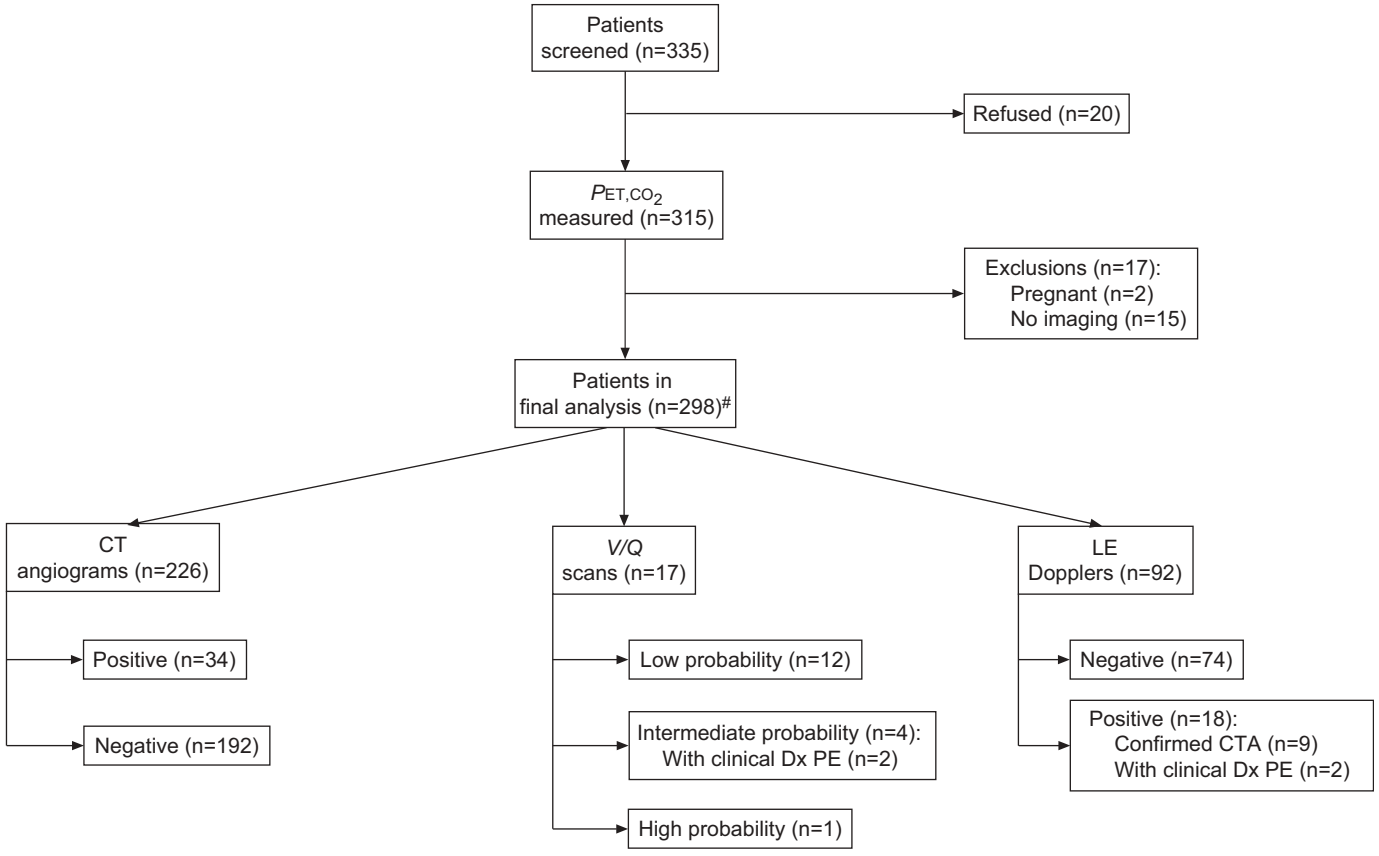

FIGURE 2. Flow-diagram of the study. P_{ET,CO_2}: end-tidal carbon dioxide tension; CT: computed tomography; V/Q: ventilation/perfusion scan; PE: pulmonary embolism; Dx: duplex; LE: lower extremity; CTA: computed tomography angiogram. #: multiple studies were performed in some patients.

Statistical analysis

Based on our hospital's experience and previous studies [8, 18], we assumed a 15% positive rate of diagnostic tests for patients undergoing PE evaluation. Given this diagnostic rate and a SD of 2.8 mmHg in P_{ET,CO_2} measurements in normal volunteers, a sample size calculation determined that 300 patients would be required to detect a difference in P_{ET,CO_2} of 1.3 mmHg between groups with 80% power at an α-level of 0.05. This sample size would allow detection of a difference of 9% in sensitivity compared with a Wells score <4 [6]. Continuous variables are presented as mean$\pm$SD and analysed using an unpaired t-test or Wilcoxon Rank Sum testing. Categorical variables are reported as percentages and were analysed using Fisher's exact test. Receiver operating characteristic (ROC) curves with area under the curve (AUC) were used for determining the optimal P_{ET,CO_2} to discriminate between patients with and without PE. All p-values are two-tailed and values $\leqslant$0.05 were considered significant. Data analyses were performed using both R version 2.7.1 and SPSS (Version 15.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Study patients

A total of 335 patients were screened and approached for entry into the trial. 20 patients did not consent. Of the 315 patients in whom P_{ET,CO_2} was measured, 17 patients were excluded after enrolment (two were found to be pregnant and 15 did not have any imaging studies) (fig. 2). Of the remaining 298 patients included in the final analysis, 39 were diagnosed with PE: 34 positive helical CT; three intermediate- or high-probability ventilation/perfusion scans with high clinical suspicion; and two positive lower extremity duplex examinations with high clinical suspicion. Five patients were enrolled twice. 180 patients were enrolled from the Emergency Department with 21 PEs, and 118 were inpatients with 18 PEs.

Demographic characteristics of the group as a whole and the sub-categories of those with and without PE are shown in table 1. There was no difference in age, sex, ethnicity, smoking status or presence or absence of medical comorbidities in the two groups. There were more patients with one or more risk factors for venous thromboembolic disease in the group with PE compared with the group without PE ($p<0.001$). The group without PE had a range of diagnoses from no cause identified (n=44, 17%), pulmonary disease such as COPD, asthma or lung cancer (n=84, 32%) and cardiac disease (n=48, 19%) to musculoskeletal disease, neuromuscular disease and deep venous thrombosis without PE which made up the remainder.

Clinical presentation

Patients with PE were less likely than those without PE to undergo chest CT imaging for chest pain alone ($p=0.01$ PE *versus* No PE) (table 2); however there were no significant differences in the other indications for chest imaging between the two groups. The mean Wells score was 4.3 ± 2.5 in the group with PE and 1.7 ± 1.9 ($p<0.001$) in the no PE group. Five

TABLE 1 Demographic characteristics of the study population

	All	No PE	PE	p-value#
Subjects n	298	259	39	
Age yrs	52.1±17.2	51.0±17.1	59.5±16.1	0.004
Females	53	54	46	0.36
Race¶				
White	72	72	77	
African–American	25	25	23	
Other	3	3	0	
Smoking+				
Never	53	53	54	0.39
Current	32	33	24	
Past	15	14	22	
Comorbidities				
None	33	33	31	0.17
Diabetes	3	2	10	
Hypertension	25	25	23	
Diabetes+hypertension	13	14	8	
Cancer	13	12	15	
Chronic lung disease	6	7	3	
Other	7	7	10	
PE risk factors				
None	62	68	18	<0.001
Post-operative	4	4	5	
Cancer	13	12	18	
Post-partum	1	1	0	
Immobilised	3	2	8	
Previous DVT/PE	8	7	13	
Multiple	8	4	33	
Other	1	0	5	

Data are presented as mean±SD or %, unless otherwise stated. PE: pulmonary embolism; DVT: deep vein thrombosis. #: no PE *versus* PE; ¶: n=294; +: n=290.

TABLE 2 Presenting features of subjects enrolled in the study

	All	No PE	PE	p-value
Subjects n	298	259	39	
Indication for PE evaluation				
Chest pain	35	37	23	0.01
Hypoxemia	1	0	5	
Dyspnoea	25	24	31	
Haemoptysis	0	0	3	
Fever	6	6	5	
Chest pain and dyspnoea	9	8	15	
Limb swelling/pain	4	4	3	
Miscellaneous	20	21	15	
Wells score	2.0±2.1	1.7±1.9	4.3±2.5	<0.001
Heart rate bpm	86.2±17.1	86.0±17.1	87.8±15.0	0.42
Systolic blood pressure mmHg	125.3±20.7	126.3±21.0	118.7±17.0	0.02
Diastolic blood pressure mmHg	72.2±14.5	72.5±15.0	70.4±10.5	0.37
Respiratory rate bpm	17.2±6.2	17.0±6.3	18.6±5.6	0.09
Oxygen saturation %	96.6±2.6	96.6±2.6	96.4±2.3	0.39
Supplemental oxygen	26	24	44	0.01

Data are presented as % or mean±SD, unless otherwise stated. PE: pulmonary embolism. #: no PE *versus* PE.

out of 39 patients with PE had a Wells score of ⩽2.0. In the Emergency Department, 14% of the CTs were positive for PE and 17% were ordered as an inpatient was positive for PE. 97 out of 298 patients had serum D-dimer measured, of these 47 were negative (0 PEs) and 48 positive (4 PEs).

Validation of P_{ET,CO_2} and consistency of P_{ET,CO_2} method in healthy volunteers

In normal volunteers, mean P_{ET,CO_2} was 36.3±2.8 mmHg (95% CI 35.1–37.4) (table 3). There were no significant differences among the five measured breaths each day or among the mean P_{ET,CO_2} in an individual over the 3 separate days. Age and sex did not affect P_{ET,CO_2}.

P_{ET,CO_2} in patients

There was no significant difference in P_{ET,CO_2} between normal controls and the no PE group (36.3±2.8 *versus* 35.5±6.8 mmHg, respectively, p=0.56) (fig 3). The group with PE had a significantly lower P_{ET,CO_2} (30.5±5.5 mmHg *versus* healthy volunteers, p<0.001), which was also significant compared with the no PE group (p<0.001). Mean P_{ET,CO_2} was not different in the two D-dimer groups (35.3±5.9 mmHg *versus* 36.1±5.2 in D-dimer positive and negative groups, respectively, p=0.35). There were no adverse events related to P_{ET,CO_2} measurement.

Sensitivity and specificity of P_{ET,CO_2} in the diagnosis of PE

A ROC curve demonstrating the ability of P_{ET,CO_2} to discriminate between patients with and without PE and the corresponding sensitivities and specificities are shown in figure 3 and table 4 (AUC 0.739). In order to avoid the most unnecessary procedures in the diagnosis of PE while maintaining optimal sensitivity for diagnosis, we chose a cut-off of 36 mmHg for further analysis of the characteristics of this test. At this cut-off, the negative predictive value was 96.6% (95% CI 92.3–98.5) (table 5).

When patients with P_{ET,CO_2} ⩾36 mmHg but <44 mmHg (2.78SD above normal) were analysed, there was an increase in negative predictive value to 97.6% (95% CI 93.2–99.2). We found a negative predictive value for a Wells score <4 of 93.8% (95% CI 89.9–96.2) in this population. In combining the Wells score <4 with the P_{ET,CO_2} ⩾36 mmHg without restriction on maximum P_{ET,CO_2}, the negative predictive value again rose to 97.6% (95% CI 93.2–99.2).

CONCLUSIONS AND DISCUSSION

In this preliminary study we show that a safe, simple, inexpensive, bedside test for P_{ET,CO_2} has a high negative predictive value in excluding PE and that the P_{ET,CO_2} in combination with the Wells score improves negative predictive value to a very high level of accuracy.

TABLE 3 End-tidal carbon dioxide tension (P_{ET,CO_2}) in normal individuals over 5 separate days

	P_{ET,CO_2}	p-value
Subjects	24	
Age yrs	40.0±12.0	
Female	14	
Smoking		
Never	20	
Past	4	
Current	0	
P_{ET,CO_2} by breath# mmHg		
Breath 1	36.7±3.0	0.21
Breath 2	36.3±2.9	
Breath 3	36.7±3.0	
Breath 4	37.1±3.5	
Breath 5	37.3±3.6	
P_{ET,CO_2} by day mmHg		
Day 1	36.6±3.0	0.25
Day 2	36.6±3.8	
Day 3	35.6±3.6	
Overall mean P_{ET,CO_2} mmHg	36.4±2.8	

Data are presented as mean±SD or n, unless otherwise stated. #: day 1.

The D-dimer has been studied extensively in the exclusion of PE and its value in exclusion of low-risk patients for further diagnostic evaluation is well established [1]. Despite a high negative predictive value in low-risk patients [19], D-dimer has a highly variable sensitivity [20] and its interpretation can be confusing with multiple commercially available tests and cut-off values [19]. Most importantly, D-dimer testing requires venipuncture and time for transport, measurement and reporting which may increase total healthcare expenditure. A more rapidly available test would enhance the speed of decision-making.

Dead space fraction (V_D/V_T), measured by comparing total exhaled CO_2 tension with arterial CO_2 tension, has previously been shown to be abnormal in PE and V_D/V_T in combination with D-dimer testing is effective at ruling out PE [11–13, 21]. However, the requirement of specialised equipment and an arterial puncture limit its widespread adaptation. P_{ET,CO_2}, measured only with the handheld capnograph already in use at many hospitals, is a surrogate for dead space measurement.

We examined various cut-off levels of P_{ET,CO_2} to determine optimal sensitivity and specificity of this test. Using a cut off of $\geqslant$36 mmHg, we were able to achieve a negative predictive value of 96.6%, which is similar to that reported with D-dimer testing [19]. There was a small improvement after excluding patients with a P_{ET,CO_2} significantly outside of the range of normal, but we felt this would confuse clinical decision-making without a concomitantly large improvement in test characteristics. The addition of the Wells score <4 to the P_{ET,CO_2} measurement, similarly, numerically improved our testing characteristics without adding further confusion about patient exclusions. Importantly, we did find that at the lower levels of P_{ET,CO_2}, there was a substantial increase in specificity for PE. This improved specificity at lower P_{ET,CO_2} levels is a marked contrast with D-dimer, with results that are either positive or negative.

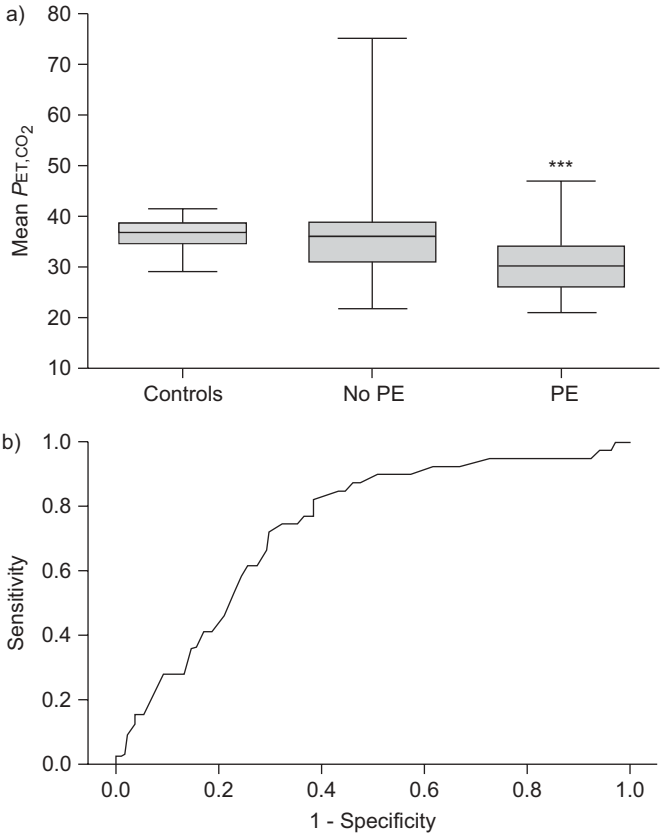

FIGURE 3. a) Mean end-tidal carbon dioxide tension (P_{ET,CO_2}) in controls, patients without pulmonary embolism (PE) and patients with PE. ***: p<0.001 *versus* healthy volunteers and patients without PE. b) The receiver operator characteristics curve for P_{ET,CO_2} in the diagnosis of PE.

In our study group, 166 subjects had a P_{ET,CO_2} of >36 mmHg and would not have undergone further testing if that were used as the sole criterion for ruling out PE. Of these 166 subjects, 20 had a Wells score of $\geqslant$4.0. Thus, in our study, 146 (49%) out of 298 subjects would have been spared further evaluation for PE using these criteria. Three out of 39 PEs

TABLE 4 Sensitivity and specificity to a given measurement of end-tidal carbon dioxide tension (P_{ET,CO_2})

Mean P_{ET,CO_2}, positive if <x	Sensitivity %	Specificity %
26	15.4	94.4
28	30.8	86.3
30	43.6	80.0
32	61.5	72.6
34	74.4	64.8
36	87.2	53.0
38	92.3	33.3
40	94.9	19.6

TABLE 5 Test performance characteristics

	Sensitivity	Specificity	PPV	NPV
P_{ET,CO_2} <36 All Comers	87.2 (73.3–94.4)	53.0 (47.0–58.8)	21.1 (15.5–28.1)	96.6 (92.3–98.5)
P_{ET,CO_2} <36 excluding >44	91.9 (78.7–97.2)	49.0 (42.8–55.2)	21.1 (15.5–28.1)	97.6 (93.2–99.2)
Wells Score ⩾4	61.5 (45.9–75.1)	83.3 (78.4–87.3)	34.8 (24.6–46.6)	93.8 (89.9–96.2)
P_{ET,CO_2} <36 All Comers + Wells Score ⩾4	92.3 (79.7–97.3)	45.2 (39.4–51.1)	19.6 (14.5–25.9)	97.6 (93.2–99.2)

Data are presented as % (95% CI). PPV: positive predictive value; NPV: negative predictive value. P_{ET,CO_2}: end-tidal carbon dioxide tension.

would have been missed in our study using these criteria. All three of these patients were discovered to have hypoventilation after further evaluation during the hospitalisation (morbid obesity, chronic narcotic use and interstitial lung disease).

The importance of sparing these diagnostic procedures is not trivial. In our cohort, 226 (76%) patients underwent diagnostic CT scanning. The long-term risks of exposure to radiation from chest CT scanning are a concern [4, 9, 22, 23]. The typical contrast-enhanced chest CT for PE evaluation delivers ~20 mSv of radiation [4, 24]. This dose from a single CT approaches the 40 mSv widely thought of as a dangerous limit from historical data [4, 22, 24]. In our study alone, five people were enrolled twice in our 6-month study. While there is debate about the ''safe limit'' of radiation exposure, the American College of Radiology has called for controlling unnecessary radiation exposure [23]. The monetary savings from preventing unnecessary CT studies is also potentially substantial. At a cost per study of $1,739 [25], patients in our study underwent a total of 226 contrast-enhanced helical chest CTs, 120 of which could potentially be spared saving $208,680.

Our study included both inpatients and patients in the Emergency Department to capture the complete population perceived to be at risk for PE. Because patients who underwent only D-dimer testing were not included, we may have increased the pre-test probability for PE in our cohort. Despite this potential bias, P_{ET,CO_2} was similar in the controls and the group without PE, suggesting that, physiologically, the group without PE was similar to controls. Too few patients had PEs in the group with D-dimer data to allow a meaningful direct comparison with P_{ET,CO_2}. While our CT positivity rate for PE was lower than some previously published reports [7, 8, 26], it is similar to other publications in the literature and may represent local practice patterns [21, 27]. The P_{ET,CO_2} would likely be abnormal in conditions affecting metabolic activity or CO_2 excretion such as pregnancy, end-stage chronic obstructive lung disease or advanced neuromuscular disease. Therefore, we excluded patients known to have these conditions from participation, totalling <10 patients. Thyroid disease at its extremes may affect P_{ET,CO_2} results, but this is often not known at initial evaluation, thus, we did not exclude these patients. P_{ET,CO_2} cannot distinguish between type of pulmonary arterial obstruction such as acute PE, chronic thromboembolic disease or tumour emboli. No CT angiograms showed changes typical for chronic thromboembolic pulmonary hypertension.

We have shown that a cheap, simple, readily available, noninvasive test of P_{ET,CO_2} combined with a bedside prediction tool may be useful to exclude PE in patients without pregnancy or advanced lung or neuromuscular disease. Further study is needed to directly compare P_{ET,CO_2} with D-dimer in the evaluation of PE and in sparing costly and potentially risky radiation exposure.

STATEMENT OF INTEREST

None declared.

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