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Bedside end tidal CO2 as a screening tool to exclude pulmonary embolism

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ABSTRACT:

Background: End tidal CO2 (ETCO2) is a surrogate for dead space ventilation that may be useful in evaluation of pulmonary embolism (PE). We aimed to define the optimal ETCO2 level to exclude PE in patients evaluated for possible thromboembolism.

Methods: 298 patients were enrolled over six months at a single academic center. ETCO2 was measured within 24 hours of contrast enhanced helical CT, lower extremity duplex or ventilation/perfusion scan. Performance characteristics were measured by comparing test results with clinical diagnosis of PE.

Results: PE was diagnosed in 39 patients (13%). Mean ETCO2 in healthy volunteers was not different from ETCO2 in patients without PE (36.3 ± 2.8, SD mmHg vs. 35.5 ±6.8 mmHg). ETCO2 in patients with PE was 30.5 ± 5.5 mmHg ($p<0.001$ versus no PE group). End tidal CO2 of ≥ 36 mmHg had optimal sensitivity and specificity (87.2 and 53.0%) with a negative predictive value of 96.6% (92.3-98.5 95% CI). This increased to 97.6% (93.2-99.2 95% CI) when combined with Wells score <4.

Conclusion: ETCO2 of ≥ 36mmHg may reliably exclude PE. Accuracy is augmented by combination with Wells score. ETCO2 should be prospectively compared to D dimer in accuracy and simplicity to exclude PE.

Introduction

Pulmonary embolism (PE) is a common concern in the evaluation of diverse clinical presentations including chest pain, dyspnea and hypoxemia[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 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 partial pressure of CO2 (ETCO2) 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 CO2 content as low as zero mmHg. As

a result, carbon dioxide content measured at end expiration, which represents admixture of all alveolar gas, drops in proportion to dead space ventilation. While there are many potential etiologies 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, gastroesophageal reflux. Dead space measurement and arterial-alveolar carbon dioxide tension gradient have been studied in the evaluation of PE [11-14], but the utility of end tidal CO2 measurement alone in diagnosis of PE is not known. ETCO2 is safe, non-invasive, inexpensive, and rapidly done 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 ETCO2 in a large cohort of patients undergoing evaluation for PE without controlling clinical care or management. We hypothesized that ETCO2 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 center study designed to investigate the potential role of ETCO2 in the diagnosis of PE. The Vanderbilt University Medical Center Institutional Review Board approved the study.

Setting and Population:

All patients ≥18 years 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 end tidal CO2 determination within 24 hours of study order placement. Exclusion criteria were inability to consent, pregnancy, known hypercarbic respiratory failure, mechanical ventilation, face mask oxygen or more than 5L/minute 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, ETCO2 was measured by a trained single tester, blinded to diagnosis (ALN), using the Nellcor NPB 75 handheld capnograph (Miallinckrodt:Nellcor, St. Louis, MO) [15]. The device is calibrated to ± 2 mmHg up to 38mmHg and ± 0.08% for every 1 mmHg over 40mmHg. 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 CO2 was measured (shown in **Figure 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.

ETCO2 for each breath and respiratory rate were measured. The capnometer was validated every two weeks at two levels of CO2 using a Medical Graphics exercise machine calibrated to zero and 5.6% CO2. Patient charts were analyzed for demographic data including comorbid conditions and thromboembolic risks, self-reported race/ethnicity (categorized 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 (ARH), 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[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 pretest probability, or positive lower extremity duplex examination with a high clinical suspicion for PE.

Validation of ETCO2 measurement in Normal Controls

To ensure accuracy and reproducibility, and to standardize the modified sensing device, and discover stability of ETCO2 measurements over time in healthy individuals, we measured ETCO2 for five breaths in 24 healthy volunteers (mean age 40.0 (12.0), 10/24 male) on three different days. Additionally, we measured ETCO2 with different FiO2 delivered by nasal cannula up to 5 lpm and found no difference (data not shown).

Statistical Analysis:

Based on our hospital's experience and previous work [8, 18], we assumed a 15% positive rate of diagnostic tests for patients undergoing PE evaluation. Given this diagnostic rate and a standard deviation of 2.8 mmHg in ETCO2 measurements in normal volunteers, a sample size calculation determined that 300 patients would be required to detect a difference in ETCO2 of 1.3 mmHg between groups with 80% power at an alpha level of 0.05. This sample size would allow detection of a difference of 9% in sensitivity compared to the Wells score <4[6]. Continuous variables are reported as mean (standard deviation) and analyzed using Student's t-test or Wilcoxon Rank Sum testing. Categorical variables are reported as percentages and were analyzed using Fisher's Exact test. Receiver Operating Characteristic (ROC) curves with area under the curve (AUC) were used for determining the optimal ETCO2 to discriminate between patients with and without PE. All p-values are two-tailed and values ≤ 0.05 were considered significant. Data analyses were done using both R version 2.7.1 and SPSS (Version 15.0; Chicago, IL, USA).

Results

Study Patients

A total of 335 patients were screened and approached for entry into the trial. Twenty patients did not consent. Of the 315 patients in whom ETCO2 was measured, 17 patients were excluded after enrollment (two were found to be pregnant and 15 did not have any imaging studies) (**Figure 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, two positive lower extremity duplex examination with high clinical suspicion). Five patients were enrolled twice. One hundred eighty 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, gender, ethnicity, smoking status or presence or absence of medical comorbidities in the two groups. The group with PE was significantly enriched for the presence of one or more risk factors for venous thromboembolic disease than the no PE group ($p<0.001$). 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 vs. No PE groups, **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 of 39 patients with PE had a Wells score ≤ 2.0. Fourteen percent of CTs in the emergency department were positive for PE and 17% of CTs ordered as an inpatient were positive for PE. 97/298 patients had serum D dimer measured, of these 47 were negative (0 PEs) and 48 positive (4 PEs).

Validation of ETCO2 and consistency of ETCO2 method in healthy volunteers

In normal volunteers, mean ETCO2 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 ETCO2s in an individual over the three separate days. Age and gender did not affect ETCO2.

ETCO2 in Patients

There was no significant difference in ETCO2 between normal controls and the no PE group (36.3 ±2.8 vs. 35.5 ± 6.8 mmHg respectively, p=0.56, **Figure 3**).

The group with PE had a significantly lower ETCO2 (30.5 ± 5.5 mmHg vs. healthy volunteers, p<0.001), which was also significant compared with the no PE group (P<0.001). Mean ETCO2 was not different in the two D dimer groups (35.3 ± 5.9 mmHg D dimer positive vs. 36.1 ± 5.2 in D dimer negative groups, p=0.35). There were no adverse events related to ETCO2 measurement.

Sensitivity and Specificity of ETCO2 in the diagnosis of PE

A ROC curve demonstrating the ability of ETCO2 to discriminate between patients with and without PE and the corresponding sensitivities and specificities are shown in **Figure 3** (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 4**).

When patients with ETCO2 ≥ 36 mmHg but < 44 mmHg (2.78 SD above normal) were analyzed, there was an increase in negative predictive value to 97.6% (95% CI 93.2-99.2). We found a negative predictive value for Wells score < 4 of 93.8% (95% CI 89.9-96.2) in this population. In combining the Wells score < 4 with the ETCO2 ≥ 36 mmHg without restriction on maximum ETCO2, 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 ETCO2 has a high negative predictive value in excluding PE and that the ETCO2 in combination with the Wells Score improves negative predictive value to a very high level of accuracy.

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 speed of decision-making.

Dead space fraction (Vd/Vt), measured by comparing total exhaled partial pressure CO2 (PCO2) with arterial partial pressure CO2 (PaCO2), has previously been shown to be abnormal in PE and Vd/Vt in combination with D-dimer testing is effective at ruling out PE [11-13, 21]. However, the requirement of specialized equipment and an arterial puncture limit its widespread adaptation. ETCO2, 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 ETCO2 to determine optimal sensitivity and specificity of this test. Using a cut off of ≥ 36mmHg, 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 an ETCO2 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 ETCO2 measurement similarly numerically improved our testing characteristics without adding further confusion about patient exclusions. Importantly, we did find that at the lower levels of ETCO2, there was a substantial increase in specificity for PE. This improved specificity at lower ETCO2 levels is a marked contrast with D dimer, with results that are either positive or negative.

In our study group, 166 subjects had an ETCO2 >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 4.0 or higher. Thus, in our study, 146/298 (49%) of subjects would have been spared further evaluation for PE using these criteria. Three of 39 PEs would be missed in our study using these criteria. All three of these patients were discovered to have hypoventilation after further evaluation during the hospitalization (morbid obesity, chronic narcotic use and interstitial lung disease).

The importance of sparing these diagnostic procedures is not trivial. In our cohort, 226 patients (76%) 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 approximately 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 six-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 $1739 [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, ETCO2 was similar in the normal controls and the group without PE, suggesting that physiologically the group without PE was similar to normals. Too few patients had PEs in the group with D dimer data to allow a meaningful direct comparison with ETCO2. While our CT positivity rate for PE was lower than some prior published reports[7, 8, 26], it is similar to other publications in the literature and

may represent local practice patterns[21, 27]. The ETCO2 would likely be abnormal in conditions affecting metabolic activity or carbon dioxide 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 totaling fewer than 10 patients. Thyroid disease at its extremes may affect ETCO2 results, but this is often not known at initial evaluation, thus we did not exclude these patients. ETCO2 cannot distinguish between type of pulmonary arterial obstruction such as acute PE, chronic thromboembolic disease or tumor emboli. No CT angiograms showed changes typical for chronic thromboembolic pulmonary hypertension.

We have shown that a cheap, simple, readily available, non-invasive test of ETCO2 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 ETCO2 with D dimer in the evaluation of PE and in sparing costly and potentially risky radiation exposure.

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Figure Legends

Figure 1. ETCO2 sensor. Photo of modified sensor for ETCO2 detection. The modified sensor is 5 cm long with a diameter of 1 cm.

Figure 1

Figure 2. Study flow diagram.

Figure 2

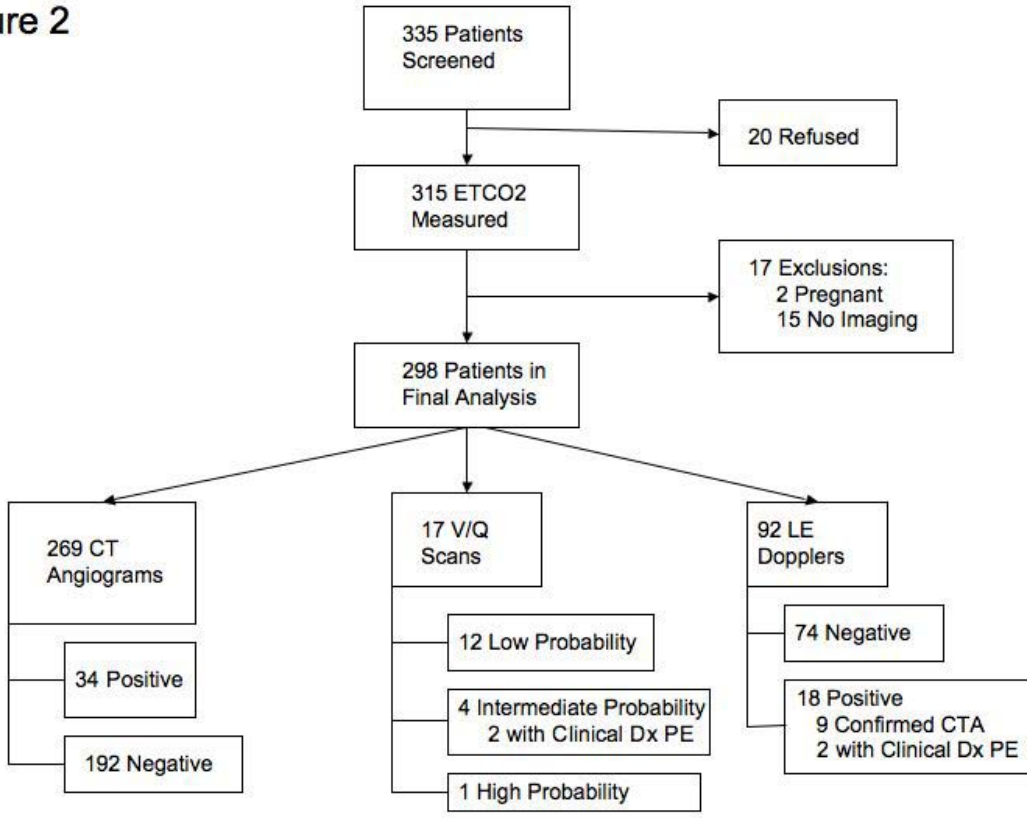
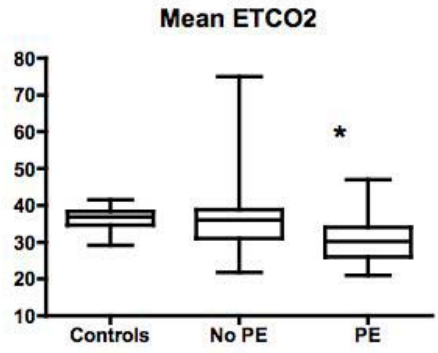
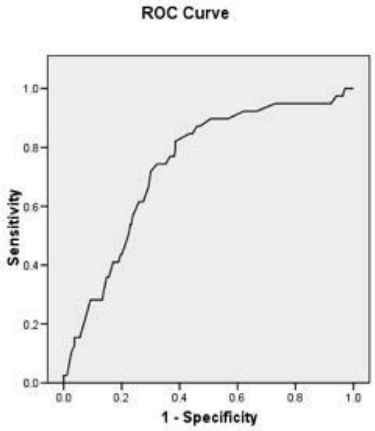


Figure 3. Top. ETCO2 in normal volunteers, patients without PE and patients with PE. Mean ETCO2 ± SD in healthy volunteers, patients without PE (no PE) and patients with PE (PE). * $p<0.001$ vs. healthy volunteers and no PE group. **Below. ETCO2 performance characteristics PE diagnosis.** On the left is the receiver operator characteristics curve for ETCO2 in the diagnosis of PE and the corresponding sensitivities and specificities to a given ETCO2 measurement are shown on the right.

Figure 3





Mean ETCO2, 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

Tables

Table 1. Demographics

	All (n=298)	No PE (n=259)	PE (n=39)	p Value
Age (yrs)	**52.1 ± 17.2**	**51.0 ± 17.1**	**59.5 ± 16.1**	**0.004**
Gender (% female)	**53**	**54**	**46**	**0.36**
Race (%, n=294)				
White	**72**	**72**	**77**	
African-American	**25**	**25**	**23**	
Other	**3**	**3**	**0**	
Smoking (%, n=290)				
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**	
Immobilized	**3**	**2**	**8**	
Previous DVT/PE	**8**	**7**	**13**	
Multiple	**8**	**4**	**33**	
Other	**1**	**0**	**5**	

Data are presented as mean ± SD unless otherwise stated, n=298 unless otherwise stated, p values are for No PE vs. PE groups.

Table 2. Presenting Features of Study Enrollees

	All (n=298)	No PE (n=259)	PE (n=39)	p Value
Indication for PE evaluation (%)				
Chest pain	**35**	**37**	**23**	**0.01**
Hypoxemia	**1**	**0**	**5**	
Dyspnea	**25**	**24**	**31**	
Hemoptysis	**0**	**0**	**3**	
Fever	**6**	**6**	**5**	
Chest pain and dyspnea	**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 mean ± SD unless otherwise stated, n=298 unless otherwise stated, p values are for No PE vs. PE groups

Table 3. ETCO2 in normal individuals over 5 separate days

Age (yrs)	**40.0 ± 12.0**	
Female no.	**14**	
Smoking no.		
Never	**20**	
Past	**4**	
Current	**0**	
ETCO2 by breath (Day 1)		
(mmHg)	**36.7 ± 3.0**	**p=0.21**
Breath 1	**36.3 ± 2.9**	
Breath 2	**36.7 ± 3.0**	
Breath 3	**37.1 ± 3.5**	
Breath 4	**37.3 ± 3.6**	
Breath 5		
ETCO2 by day (mmHg)		
Day 1	**36.6 ± 3.0**	**p=0.25**
Day 2	**36.6 ± 3.8**	
Day 3	**35.6 ± 3.6**	
Overall mean ETCO2 (mmHg)	**36.4 ± 2.8**	

Data are presented as mean ± SD, n=24

Table 4. Test performance characteristics

	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Positive Predictive Value (%, 95% CI)	Negative Predictive Value (%, 95% CI)
ETCO2 <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)**
ETCO2 <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)**
ETCO2 <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)**