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Pulmonary embolism in Bradford, UK: role of end-tidal CO_2 as a screening tool

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ABSTRACT

End-tidal CO_2 ($ETCO_2$) can represent dead space ventilation. The authors aimed to define the optimum $ETCO_2$ to conclusively exclude a pulmonary embolic event. One hundred consecutive patients with suspected pulmonary embolisms (PEs) were enrolled over 6 months in 2012. Symptoms, demographic date, Wells' score, D-dimer levels and the gold standard computed tomography pulmonary angiogram (CTPA) results were collated for analysis. $ETCO_2$ was measured within 24 hours of presentation in all 100 patients. Patient ages ranged from 18 years to 93 years. PE was diagnosed in 38% of cases. The average $ETCO_2$ in patients with a positive CTPA was 3.35 kPa (range 2.4–4.2 kPa, SD 0.50). The average $ETCO_2$ in patients without a PE was 4.41 kPa (range 1.3–6.6 kPa, SD 1.10). All patients positive for a PE obtained an $ETCO_2$ <4.3 kPa (32.3 mmHg). This point (4.3 kPa) had a sensitivity and specificity (100% and 68% respectively), with a negative predictive value of 100% and positive predictive value of 66%. $ETCO_2$ may reliably be used to screen and exclude patients with suspected PEs. If used in combination with D-dimer with clinical probability as a screening tool, CTPA will be required in only a minority of patients.

KEYWORDS: End-tidal carbon dioxide, computed tomography pulmonary angiogram, pulmonary embolism

Introduction

Pulmonary embolism (PE) is a global problem and a leading cause of cardiovascular death in the western world.[1] The diagnosis of PE remains a challenge because of the high variability in clinical presentation. Patients can present with chest pain, dyspnoea, haemoptysis, syncope and hypoxaemia.[2] Diagnosis of a PE is confirmed in <35% of patients with a clinical suspicion.[3] Despite the low relative incidence of the disease, there is a significant rise in the number of patients undergoing an unnecessary computed tomography pulmonary angiogram (CTPA) to exclude a PE.[4]

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In most centres patients with a high clinical suspicion undergo serum D-dimer assessment as a screening test.[5] Treatment is initiated in those with a positive D-dimer and continuation of treatment is determined by the outcome of the CTPA scan.[5] Measurement of serum D-dimer requires venepuncture and the results are not immediate.[5] CTPA scans are associated with high cost and exposure to radiation and nephrotoxic contrasts, a worrying concept with their current increasing use.[4,6,7] It has been proposed that the Wells' score can be used as a safe, simple and quick means of determining clinical suspicion.[8] End-tidal carbon dioxide ($ETCO_2$) is a simple bedside test with the ability to exclude a PE in patients who do not have it, while not overlooking true positive cases; unnecessary venepuncture, exposure to radiation, contrast medium and user bias will thus be avoided.

The assessment for alveolar dead space ventilation and $ETCO_2$, as surrogates for pulmonary vascular obstruction, has been proposed as a valuable screening tool for excluding PEs. PEs result in the formation of a lung compartment that is ventilated but not perfused, causing dead space ventilation.[9] Alveolar dead space prevents adequate gas exchange, yielding a low alveolar CO_2 content, which can be measured at end-expiration using a handheld capnograph at the bedside. Conditions such as angina, which have a similar clinical presentation to a PE, do not increase alveolar dead space. Pathologies that increase alveolar dead space, such as end-stage chronic pulmonary obstructive disease, can be easily differentiated from a pulmonary embolic event. The size of the alveolar dead space has been approximated by measuring the CO_2 arterial tension to end-tidal CO_2 gradient as a percentage of the ventilated but non-perfused lung.[10] $ETCO_2$ determination may be used in isolation as a simple bedside test when measurement of the exhaled gas and alveolar–arterial gradient requires arterial blood gas sampling and specialised equipment. Previous studies have shown that $ETCO_2$ is a reliable screening tool when combined with bedside prediction in excluding PE.[11] The authors hypothesise that a high $ETCO_2$ can be used in isolation as a reliable screening tool to exclude PEs in patients, avoiding the unnecessary need for a CTPA.

Materials and methods

This prospective study was performed at the Bradford Teaching Hospital, Bradford, in the UK. The aim of the study was to investigate the role of $ETCO_2$ as a screening tool in the diagnosis of a PE. Inpatients and patients admitted to the acute medical

assessment unit (AMAU) who were suspected of having a PE were enrolled over a 6-month period in 2012. Clinical suspicion was based on a high Wells' score or a positive plasma D-dimer. In patients in whom the clinician had a high suspicion of a PE a CTPA scan was requested without D-dimer determination. In others a CTPA was requested only if the D-dimer was positive. The radiology department was contacted on a daily basis to find patients for whom a CTPA scan had been requested. The CTPA scan results were taken as the gold standard in diagnosing a PE. Only those patients for whom a CTPA scan had been requested were approached for consent to undergo $ETCO_2$ determination. Levels of $ETCO_2$ were obtained within 24 hours of onset of symptoms. Exclusion criteria included: non-invasive ventilation, pregnancy, inability to consent, known type 2 respiratory failure, oxygen therapy >4 l/min and neuromuscular disorders. Some 142 patients were initially screened, 25 of whom were excluded because their $ETCO_2$ levels were obtained 24 hours post-symptom onset and 17 individuals did not consent. No patient was enrolled multiple times. Demographic data was collected from the medical notes, and all patients had a detailed medical history taken, including smoking status and co-morbidities. The Wells' score was obtained from the medical notes, as calculated by the admitting doctor. If a plasma D-dimer test was requested by the patient's physician the results were recorded. This study in no way interfered with the management of the authors' patient group.

After obtaining informed consent, the $ETCO_2$ was measured by a trained tester (Riaz) who was blinded to the diagnosis. A Nellcor N85 handheld capnograph/pulse oximeter was the device used to record the $ETCO_2$ values. The capnograph was calibrated every 4 weeks at two levels of CO_2 by the medical physics department (Bradford Royal Infirmary) calibrated to zero and 5.6% of CO_2. The plastic tubing which has an uptake mouth cannula was placed in the patient's mouth, allowing tidal breathing while the $ETCO_2$ was measured. The nostrils were not clipped shut. Patients were instructed to breath normally for 10 seconds. This was repeated three times and an average $ETCO_2$ value was recorded. No adverse events were noted when obtaining $ETCO_2$ values. Most of the CTPA scans took placed within 48 hours of admission, and the results were noted.

Data was analysed using logistic regression models with PE status, as confirmed by a CTPA scan, with the outcome measure and individual test scores as the predictors. Receiver operator analysis was then performed, for each test individually, and a classification table produced for a range of thresholds for both $ETCO_2$ and D-dimer. Receiver operating curves (ROCs) with area under the curve (AUC) were used to determine the optimal $ETCO_2$ to discriminate between patients with and those without a PE. *P* values of ≤0.05 were considered statistically significant. All analyses were conducted using Stata 12 (StataCorp.2011 Stata release 12, statistical software, College Station, TX, USA).

Results

A total of 100 patients (56 females and 44 males) were included in the study. The patient ages ranged from 18 years to 93 years; 100 were included in the final analysis, and 38 patients (38%) were diagnosed with a PE on CTPA scanning. No patient was enrolled twice and 59 patients were enrolled from the AMAU with 23 PEs, and 41 were inpatients with 15 PEs. Table 1 shows the age, sex, smoking status and medical co-morbidities in the two groups.

Table 1. Comparison of demographics, smoking status and co-morbidities between patients with pulmonary embolism and those without.

	All (n)	PE (n)	No PE (n)
Number of patients	100	38	62
Average age (years)	59.31	62.66	57.26
Males	44	21	23
Females	56	17	39
Smoking			
> Past	33	15	18
> Current	17	7	10
> Never	50	16	34
Co-morbidities			
> Multiple co-morbidities	28	14	14
> Cardiovascular disease	15	8	7
> Chronic lung disease	20	11	9
> Diabetes	5	3	2
> Hypertension	24	11	13
> Cancer	14	12	2
> Obesity	26	15	11
> None	50	24	26
> Other	11	6	5

PE = pulmonary embolism.
Data represents numbers (n).

It was noted that the average age of those who had a PE was 62.7 years compared with 57.3 years among the non-PE group. Of the males recruited 48% experienced a pulmonary embolic event compared with 30% of the females; 41% of past smokers and 45% of current smokers had a PE compared with 32% with no smoking history. There was no difference in the presence or absence of medical co-morbidities in the two groups. A significant proportion of patients with a PE had multiple co-morbidities (50%) compared with the non-PE group (23%); 58% of obese and 86% of cancer patients had a PE.

The mean Wells' score was 2.93 (range 0–9) in the PE group and 2.7 (range 0–10.5) in the non-PE group. Figure 1a demonstrates that the AUC for Wells' score is 0.52.

Of the 100 patients 64 had their plasma D-dimer levels measured. Serum D-dimer in this centre was positive if ≥275 µg/l and is measured via the use of monoclonal antibodies coupled to latex beads. All patients with a PE had a positive D-dimer. Of patients who did not have a PE 78% had a positive D-dimer result. Mean D-dimer in the PE-positive and -negative groups was 1,855 µg/l (range 289–6,899 µg/l) and 912 µg/l (range 65–11,919 µg/l) respectively. An ROC curve and the corresponding sensitivities and specificities are shown in Fig 1b and Table 2, respectively. The AUC is 0.82. As seen in Table 2 the D-dimer, at 275 µg/l, is 100% sensitive

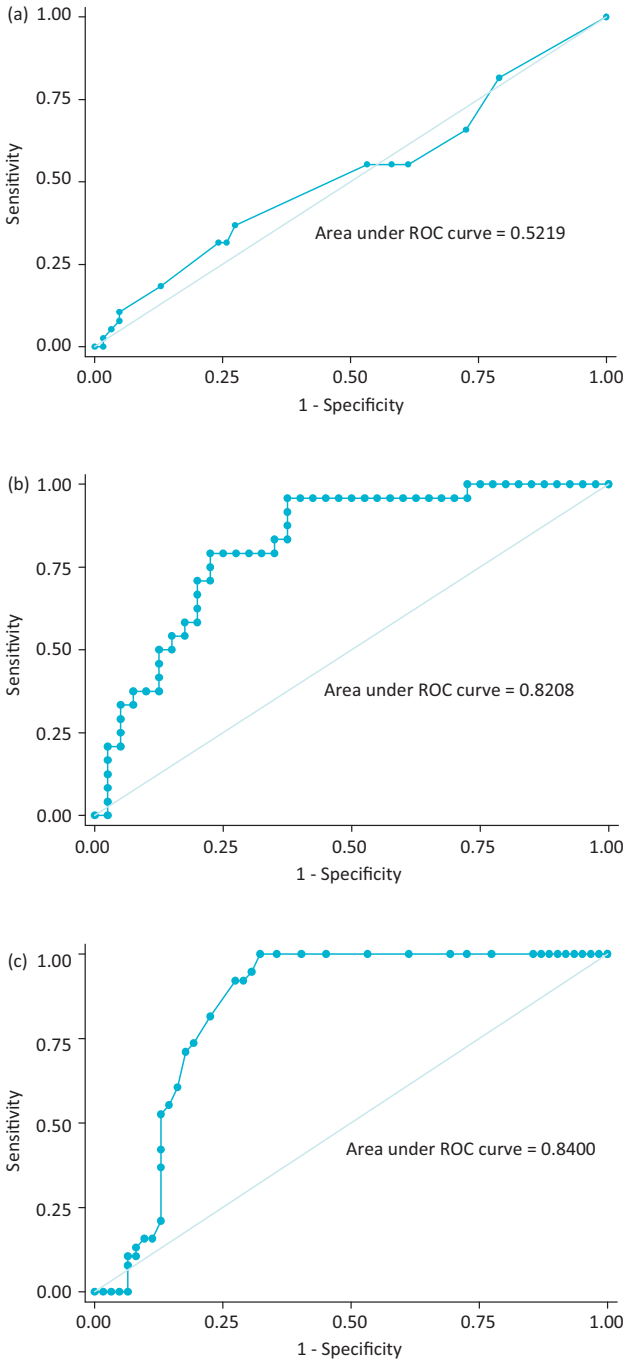

Fig 1. Receiver operator curves for (a) Wells' score, (b) D-dimer and (c) $ETCO_2$. Plot of the true-positive rate against the false-positive rate for the different possible cut-off points for these diagnostic tests. The area under the curve for Wells' score, D-dimer and $ETCO_2$ is 0.52, 0.82 and 0.84 respectively. $ETCO_2$ = end-tidal carbon dioxide. ROC = receiver operating curve.

with a 100% negative predictive value (NPV), but only 20% specificity. Specificity increases with an increasing D-dimer, with a compromise in sensitivity and NPV. At 450 µg/l there is a high combination of sensitivity (96%) and specificity (53%) with an NPV of 95%.

There was no significant difference noted among the three 10-second breathing intervals for the $ETCO_2$ readings. The average $ETCO_2$ in patients with a positive CTPA was 3.35 kPa (25.1 mmHg; range 2.4–4.2 kPa, standard deviation [SD] 0.50). The average $ETCO_2$ in patients without a PE was 4.41 kPa (33.1 mmHg; range 1.3–6.6 kPa, SD 1.10). The ROC curve demonstrating the ability of $ETCO_2$ to discriminate between patients with and those without PE, and the corresponding sensitivities and specificities, are shown in Table 3 and Fig 1c (AUC 0.84). All patients negative for a PE obtained an $ETCO_2$ >4.3 kPa (32.3 mmHg). This point had a sensitivity and specificity of 100% and 68%, respectively, with an NPV of 100% and a positive predictive value (PPV) of 66% (Table 3).Table 3 shows that 4.3 kPa is the lowest point where the sensitivity and NPV become 100%, and yet a high specificity is maintained. No patient with a PE had an $ETCO_2$ >4.2 kPa (31.5 mmHg). This is demonstrated clearly in Fig 2. Combination of a positive D-dimer (≥275 µg/l), and an $ETCO_2$ <4.3 kPa when determining a positive PE result, obtained a sensitivity value of 85%, specificity of 64%, and PPV and NPV of 60% and 87%, respectively. Three patients negative for a PE obtained an $ETCO_2$ reading <2.3 kPa (Fig 2). All three had a positive D-dimer. The $ETCO_2$ ROC curve inverts initially below the 45° diagonal due to these results (Fig 1C).

Discussion

Our study has demonstrated that $ETCO_2$ is a quick, safe, reliable and non-invasive bedside test in excluding PEs. This study shows that, of the 38 patients who had a PE, no patient obtained an $ETCO_2$ value ≥4.3 kPa (32.3 mmHg) (Fig 2).

In a similar larger study of 298 patients, Hemnes *et al* undertook $ETCO_2$ determination within 24 hours of diagnostic imaging.[11] Their results, with a cut-off of 36 mmHg, achieved sensitivities of 87%, specificity of 53%, with a 97% NPV. The results of the current study, with a much lower cut-off (32.3 mmHg), demonstrate sensitivity, specificity and NPVs of 100%, 68% and 100%, respectively (Table 3). This study has a lower cut-off with a higher NPV, which may have been the consequence of a smaller study group and determination of $ETCO_2$ within 24 hours of symptom onset. Studies have shown that prolonged heparin administration reduces the clinical effectiveness of screening tests for PE because the proportion of false-negative results is increased.[12] Delay in $ETCO_2$ determination could mean a longer course of treatment, and hence a potential reduction in alveolar dead space ventilation and clot burden.[10]

The assessment of alveolar dead space ventilation and expired CO_2 acts as a surrogate for pulmonary vascular obstruction. This model has been proposed as vital in the exclusion of pulmonary embolic events.[9] The three-compartment lung model can be used to demonstrate this phenomenon: an ideal compartment that is both ventilated and perfused, a shunt compartment that is only perfused and the alveolar dead space that is only ventilated.[9] The size of the alveolar dead space can be estimated by $ETCO_2$ determination.

In 170 ambulatory patients, Kline *et al* obtained 100% sensitivity and 65% specificity in excluding PEs with a combination of alveolar dead space fraction (*VD*/*VT*) and a negative D-dimer.[13] In a larger study (246 patients) Roger *et al* obtained a sensitivity of 80% and a specificity of 70%, with

VD/*VT*, in excluding PEs.[14] The combination of the *VD*/*VT* fraction with a D-dimer improved sensitivity to 98%.[14] The current study obtained the same sensitivity at 100% and 68% specificity with $ETCO_2$ determination alone (Table 3), without requiring specialised equipment or arterial puncture. All the patients with a negative D-dimer and $ETCO_2$ ≥4.3 kPa (32.3 mmHg) were negative for a PE (100% sensitivity and 100% NPV).

It was noted that in larger studies the prevalence of PEs was lower when compared with this study at 38%.[15,16] A study with 1,177 patients had a prevalence of 17%.[8] Perrier *et al*, using a cut-off value of 500 µg/l for D-dimer, obtained sensitivities of 99.5% and specificity of 41% (NPV 99%).[15] The current authors obtained similar values using 450 µg/l, with marginally lower sensitivity (96%) but much better specificity (53%). These results also correspond to similar studies with varying classification values depending on the threshold chosen for a positive D-dimer.[16] Likewise, as D-dimer values increase, sensitivity is compromised with a rise in specificity (see Table 2). The threshold used for D-dimer by the authors' centre obtained 100% sensitivity but only 20% specificity. A retrospective study of 220 patients showed that only 4.2% of patients with an elevated D-dimer value were diagnosed with a PE.[17] Tests ordered based on the elevated D-dimer were billed for >$US200,000.[17] In the current study 38% of patients with a positive D-dimer had a PE and 41 participants had an $ETCO_2$ ≥4.3 kPa (32.3 mmHg); 41 patients would not have undergone further testing if this threshold was used as the sole criterion for ruling out PEs.

A 4.3-kPa (32.3-mmHg) cut-off for $ETCO_2$ has much higher specificity (68%) than plasma D-dimer with the same sensitivity value (100%). Determination of plasma D-dimer requires venous access and results are not immediate. Heparin administration can also reduce the usefulness of D-dimer results because the rate of false positives is increased.[12] If both tests are combined in excluding PEs, sensitivity remains high but specificity values fall dramatically.[15,16] It is therefore noted that $ETCO_2$ in isolation has better screening potential compared with D-dimer.

Wells' score, as a screening tool in this study, did not exhibit conclusive results. Other studies show that Wells' score has a moderate-to-substantial risk stratification ability when diagnosing PEs.[8] Hemnes *et al* also demonstrated that a Wells' score <4, when combined with an $ETCO_2$ >36 mmHg, increased NPV from 96.6% to 97.6%.[11]

It is established that increasing age, multiple co-morbidities and male sex increase the probability of a pulmonary embolic event.[18,19] This may be related in part to increasing activation of blood coagulation, fibrinolysis and inflammation, possibly related to the increasing inflammatory burden of both atherosclerotic and non-vascular disease. These increases also

Table 2. D-dimer classification table over a range of cut-off thresholds: 65 values of D-dimer in total.

D-dimer (µg/l)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
200	100	10	40	100
275	100	20	43	100
300	100	28	45	100
400	96	48	52	95
450	96	53	55	95
500	83	63	57	86
1,000	58	83	67	77

NPV = negative predictive value; PPV = positive predictive value.
Positive D-dimer at 275 µg/l = 100% sensitive with 100% NPV but only 20% specificity. Specificity increases with an increasing D-dimer with a compromise in sensitivity and NPV.

Table 3. End-tidal carbon dioxide ($ETCO_2$) classification table over a range of cut-off thresholds.

$ETCO_2$ (kPa)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
1	0	100	0	62
2	0	95	0	61
3	16	89	46	63
4	92	71	66	94
4.3*	**100**	**68**	**66**	**100**
5	100	23	44	100
6	100	8	40	100

$ETCO_2$ = End-tidal carbon dioxide
*4.3 kPa used as threshold. Patients with values >4.2 kPa do not have a pulmonary embolism.

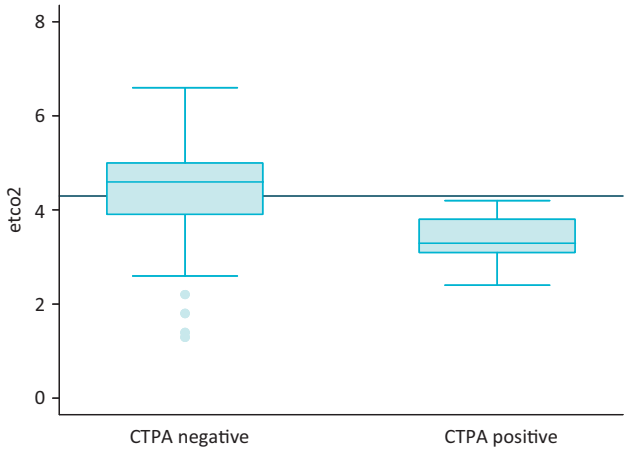

Fig 2. Box diagram comparing CTPA-positive and CTPA-negative results for $ETCO_2$ (kPa). Line represents threshold of 4.3 kPa (32.3 mmHg). This figure shows that no patient with a $ETCO_2$ >4.2 kPa had a pulmonary embolism. CTPA = computed tomography pulmonary angiogram; $ETCO_2$ = end-tidal carbon dioxide.

have implications for diagnosis of suspected acute venous thromboembolism (D-dimer).[18] There has been a clear link already established between smoking and increasing risk of a PE.[20] Our data shows that 58% of patients who experienced a PE had a smoking history, compared with 45% in the non-PE group. The mean $ETCO_2$ in the non-PE group is lower (33.1 mmHg) compared with the findings of Hemnes *et al* (36.3 mmHg).[11] In the current study a much larger proportion of patients in the non-PE group had chronic lung diseases (15%) compared with the patients of Hemnes *et al* (2.7%). Exacerbation of such conditions can increase the respiratory rate, and so can reduce the $ETCO_2$.

The incidence of PEs, based on 37,892 Pennsylvanian residents, increased by 0.004%, whereas there was a 21.6% increase in patients undergoing CTPA scans for the same 4-year period.[4] Patients are exposed to high levels of radiation despite the low prevalence.[6,7] This may be due to the increasing role of defensive medicine and partially due to physicians underestimating the radiation dose associated with a CT scan.[6,7] In a study, 91% of emergency physicians and 53% of radiologists did not believe that CT scans increased the lifetime risk of cancer.[6] Contrast material administered during a CTPA scan increases the risk of nephrotoxicty by 9% in those patients who have diabetes or pre-existing renal insufficiency.[21] In the current study 8% of patients who had a CTPA had diabetes and 5% had renal impairment.

This study included a combination of inpatients and AMAU patients to capture the complete population perceived to be at risk of a PE. Determination of $ETCO_2$ within 24 hours of symptom onset may be the reason that a lower threshold of $ETCO_2$ was obtained in excluding PEs when compared with previous studies.[11] $ETCO_2$ can be abnormal in certain conditions.[1] Patients who were on non-invasive ventilation or oxygen therapy >4 l/min, were pregnant, or had known type 2 respiratory failures and neuromuscular disorders were all excluded. In retrospect, recruitment of a control group would have allowed the authors to capture the $ETCO_2$ trend among the normal population. This, coupled with a larger sample size, would have allowed better comparison with previous studies. It would have also been beneficial if the individual determining the $ETCO_2$ for each patient calculated the Wells' score. All these measures would have allowed better comparison of these three screening tools in isolation and in combination.

Conclusion

This study highlights that $ETCO_2$ is a quick, safe, reliable and non-invasive bedside test that can be used to screen and exclude patients with suspected PEs. If used in combination with D-dimer, with clinical probability as a screening tool, CTPA will be required in only a minority of patients. Further larger studies are needed to compare $ETCO_2$ with D-dimer and Wells' score in the screening of PEs. ■

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