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Diagnostic accuracy of noninvasive end-tidal carbon dioxide measurement in emergency department patients with suspected pulmonary embolism84-90

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Background/aim: Pulmonary embolism (PE) is a frequent health problem representing a diagnostic challenge with high mortality and morbidity rates. The aim of this study was to investigate the value of end-tidal carbon dioxide ($ETCO_2$) and alveolar dead space fraction (ADSF) in the diagnosis of PE.

Materials and methods: $ETCO_2$ levels of patients with suspected PE were measured with a noninvasive mainstream sensor. ADSF of patients was calculated and $PaCO_2$ levels were also obtained. ROC curve analysis was used to determine diagnostic values of $ETCO_2$ and ADSF for PE.

Results: The study included 159 patients. The mean values for $ETCO_2$ and ADSF were 16.27 (95% CI, 14.52–18.03) and 0.48 (95% CI, 0.43–0.539) in the PE group and 21.57 (95% CI, 20.52–22.639) and 0.35 (95% CI, 0.32–0.38) in the non-PE group. The area under the curve (AUC) and the cut-off point for $ETCO_2$ were found as 0.751 and ≤19, with 83.8% sensitivity and 61.5% specificity. AUC and cut-off point for ADSF were found as 0.738 and >0.443, with 67.57% sensitivity and 73.77% specificity.

Conclusion: The diagnostic value of calculated ADSF and noninvasive bedside $ETCO_2$ for PE was found to be low.

Key words: Pulmonary embolism, end-tidal carbon dioxide, alveolar dead space fraction, emergency department

1. Introduction

Pulmonary embolism (PE) is a frequently seen health problem representing a diagnostic challenge with high mortality and morbidity rates (1). Because of variations in its symptoms and clinical findings, difficulties and delays can be experienced in the diagnosis of PE. This is one of the important reasons for higher mortality and morbidity. In postmortem studies, higher rates of PE among all-cause mortality demonstrate the seriousness of this condition (2). Although mortality rates change, nearly 100,000 deaths are associated with PE in the United States every year (3). Therefore, early diagnosis and treatment of PE is life-saving (4). Since pulmonary angiography, which is accepted as a gold standard, is an invasive, expensive, and hardly applicable method, it has limited use in the emergency department (ED). Due to difficulty in the application of ventilation/perfusion (V/Q) scanning in the ED, which yields results after a considerable time, computed tomography (CT) angiography especially has become an increasingly preferred imaging method in the last decade (5–7). However, use of CT has certain disadvantages, such as radiation exposure, use of contrast agents, and logistic difficulties.

Monitorization of end-tidal carbon dioxide ($ETCO_2$) is a measurement method of carbon dioxide (CO_2) in exhaled air. This method was first used as a clinical method in the 1970s by Smallhout and Kalenda (8). Recently, utilization of the $ETCO_2$ measurement method in ED includes confirmation of endotracheal intubation, monitorization of quality of cardiopulmonary resuscitation and ventilation in unconscious patients, and evaluation of pulmonary diseases (9–12). Alveolar CO_2 exchange is impaired in the area affected by vascular occlusion, which induces PE, with a resultant increase in alveolar dead space (13). Nunn described a method for the calculation of the alveolar dead space, which is termed as alveolar dead space fraction (ADSF) (14). Since the volume of the previous alveolar dead space is not usually known, and dead space may increase as a result of chronic bronchitis, myocardial infarction, pulmonary hypertension, and

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shock, the accuracy of this method is not obvious. It has been reported that ADSF can be used for the diagnosis of PE (15–18).

The aim of the present study was to investigate the accuracy of $ETCO_2$, which can be measured by bedside noninvasive mainstream capnometer, and ADSF in the diagnosis of PE.

2. Materials and methods

2.1. Study design

The study was performed at the ED of a university hospital with an annual census of 30,000 between 1 November 2010 and 31 October 2011. Approval was obtained by the ethics committee (2010/37). Written consent of all patients was also acquired.

2.2. Inclusion criteria

Adult patients who presented to the ED with nontraumatic complaints suggesting PE were included in the study. These complaints included shortness of breath, chest pain, and unexplained syncope starting within the previous 48 h. Consent to participate was obtained.

2.3. Exclusion criteria

Pregnant women and patients with contrast allergy, renal failure, or other alternative diagnoses (acute coronary syndrome, chronic obstructive pulmonary disease, pneumonia) or those lost to follow-up and individuals who refused to participate were excluded from the study.

2.4. Outcome parameters

All patients were monitored and vital signs and clinical data were recorded. Blood samples were drawn from patients and sent to the central laboratory for the analysis of D-dimer and arterial blood gas (ABG). D-Dimer was analyzed using the macro-ELISA method (STA-LIATEST, Asnières-sur-Seine, France) and a cut-off value of 0.5 μg/mL, determined by the manufacturing firm, was used. ABG analysis was performed using an ABL-700 radiometer device. $ETCO_2$ was measured noninvasively in all patients with a mainstream sensor (TG-921T3 Nihon Kohden, Tokyo, Japan). For each patient, ADSF was calculated using the formula ADSF = $(PaCO_2 - PETCO_2) / PaCO_2$.

The Wells scoring system was used to evaluate the probability of clinical PE. The patients were divided into 4 groups based on D-dimer test results for imaging decisions:

1. High probability of clinical PE regardless of the D-dimer test results (Wells score of >6).

2. D-Dimer-positive patients with a low (Wells score <2) or moderate (Wells score 2–6) probability of PE.

3. D-Dimer-negative patients with a moderate probability of PE (Wells score 2–6).

4. D-Dimer-negative patients with a low probability of PE (Wells score <2).

In the patients of groups 1, 2 and 3, multislice thoracic CT angiography (Toshiba Aqullion 64, Tokyo, Japan) was performed. Group 4 did not undergo CT angiography, but patients were reached by phone to enquire about sudden death or development of PE.

Study subjects were assigned as either PE (study group) or non-PE (control group) at the end of the follow-up period. Demographic, clinical, and laboratory features of the groups were compared. Diagnostic values of $ETCO_2$ and ADSF were investigated for PE.

2.5. Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software 13.1.0 (MedCalc Software, Ostend, Belgium). Normality of distribution of data was analyzed using the one-sample Kolmogorov–Smirnov test. Quantitative variables in demographic and clinical features were expressed as percentages (%), and continuous variables with mean and 95% confidence interval (CI). In the comparison of variables in both groups, t-test and chi-square tests were used for independent samples. ROC curves were drawn to analyze the diagnostic value of $ETCO_2$ and ADSF, and $P < 0.05$ was considered statistically significant.

3. Results

A total of 189 patients were eligible for the study. Thirty patients were excluded from the study and the analysis was performed with 159 patients (Figure 1). Prevalence of PE was 23.3% (37/159 patients). The study population consisted of 85 (53.5%) female and 74 (46.5%) male patients with a mean age of 58.68 years (95% CI: 56.25–61.11). The most frequent complaints at presentation were shortness of breath (n = 133; 83.6%) and palpitations (n = 80; 50.3%). Fifty-five patients (34.6%) had pulmonary malignancies. Six patients (16.2%) from the PE group (one patient in the intensive care unit, five patients in wards) and 9 patients (7.4%) from the non-PE group (one in the intensive care unit, eight in wards) suffered in-hospital mortality. Mean values of vital signs of the patients were as follows: SBP, 135.55 mmHg (95% CI: 131.06–140.04); DBP, 82.23 mmHg (95% CI: 79.15–85.30); pulse rate, 108.82 bpm (95% CI: 105.05–112.58); respiratory rate, 31.45/min (95% CI: 30.10–32.80). The demographic and clinical features of the groups are presented in Table 1.

In patients with PE, mean $ETCO_2$ was 16.27 mmHg (95% CI: 14.52–18.03), while mean ADSF was found to be 0.48 (95% CI: 0.43–0.53). 0.53. The corresponding values of the non-PE group for $ETCO_2$ and ADSF were 21.57 mmHg (95% CI: 20.52–22.63) and 0.35 (95% CI: 0.32–0.38), respectively. Higher D-dimer levels were identified in patients with PE (Table 2).

ROC curves of $ETCO_2$ and ADSF levels were drawn for the diagnosis of PE. For $ETCO_2$, the area under the

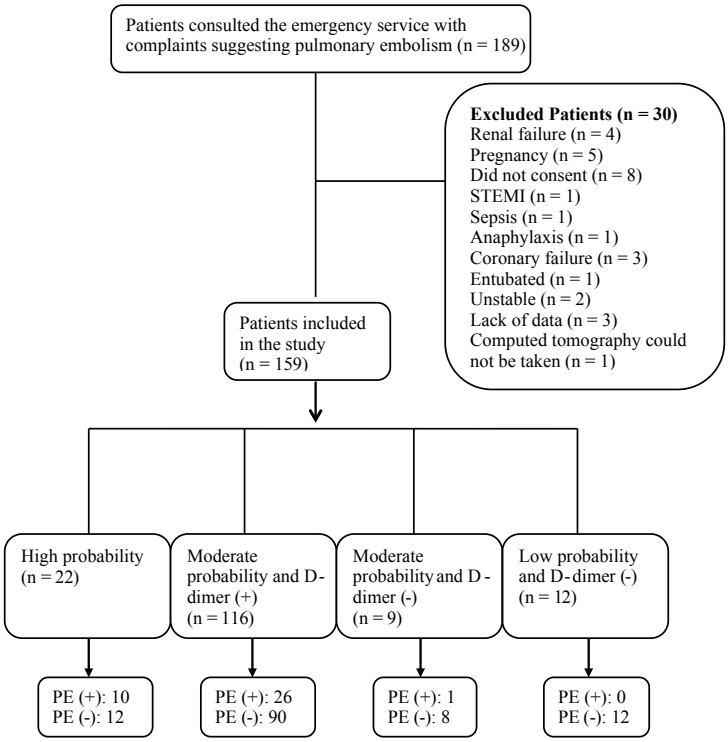

Figure 1. Selection of patients for the study group.

Table 1. Demographic and clinical features of the study groups.

	PE (+)	PE (–)	P-value
Demographic features			
Number of patients, n (%)	37 (23.3%)	122 (76.6%)	0.128
Age, mean, years	62.08	57.65	0.786
Female sex, n (%)	21 (56.75%)	64 (52.46%)	0.117
Exitus, n (%)	6 (16.21%)	9 (7.37%)	<0.001
Admission to hospital, n (%)	27 (75.00%)	48 (39.66%)	1.000
Symptoms, n (%)			
Dyspnea	30 (81.08%)	103 (84.42%)	0.819
Palpitation	23 (62.16%)	57 (46.72%)	0.145
Chest pain	19 (51.35%)	60 (49.18%)	0.965
Loss of consciousness	17 (45.94%)	37 (30.32%)	0.119
Syncope	4 (10.81%)	13 (10.65%)	1.000
Hemoptysis	3 (8.10%)	13 (10.65%)	0.765
Comorbidities, n (%)			
Malignancy	11 (29.72%)	44 (36.06%)	0.608
Previous deep vein thrombosis/PE	10 (27.02%)	14 (11.47%)	0.040
Surgical intervention in the past month	14 (37.83%)	35 (28.68%)	0.394
Probability of clinical PE (Wells scoring system), n (%)			
High probability	10 (27.02%)	12 (9.83%)	
Moderate probability	25 67.56%)	63 (51.63%)	<0.001
Low probability	2 (5.40%)	47 (38.52%)	1.000
Clinical features, n (%)			
SBP, mmHg	134.38	135.90	0.778
DBP, mmHg	82.11	82.26	0.967
Pulse, /min	118.22	105.97	0.006
Respiratory rate, /min	32.24	31.21	0.526

PE: Pulmonary embolism; SBP: systolic blood pressure; DBP: diastolic blood pressure; CI: confidence interval.

Table 2. D-Dimer, $ETCO_2$, and ADSF values according to the study groups.

Variable	PE (+)	PE (–)	P-value
D-dimer, µg/mL	9.13 (6.63–13.63)	3.96 (2.98–4.94)	<0.001
$ETCO_2$, mmHg	16.27 (14.52–18.03)	21.57 (20.52–22.63)	<0.001
ADSF	0.48 (0.43–0.53)	0.35 (0.32–0.38)	<0.001

PE: Pulmonary embolism; $ETCO_2$: end-tidal carbon dioxide; ADSF: alveolar dead space fraction.

ROC curve (AUC) was found to be 0.751 (95% CI: 0.663–0.838). The Youden index J value for $ETCO_2$ of ≤19 (95% CI: 12–19) was calculated as 0.45 (95% CI: 0.282–0.577). For this value, sensitivity of 83.8% (95% CI: 68–93.8) and specificity of 61.5% (95% CI: 52.2–70.1) were determined (Figure 2). For ADSF, the AUC was found to be 0.738 (95% CI: 0.651–0.824). The Youden index J value for >0.443 (95% CI: 0.288–0.480) was calculated as 0.413 (95% CI: 0.255–0.535). For this value, sensitivity and specificity were found to be 67.57% (95% CI: 50.2–82) and 73.77% (95% CI: 65–81.3), respectively (Figure 3). Diagnostic performances of various cut-off values of $ETCO_2$ and ADSF are shown in Table 3.

4. Discussion

This study revealed low diagnostic values of $ETCO_2$ as measured by bedside noninvasive mainstream capnometer and calculated ADSF for PE in ED patients with suspected PE.

In similar studies, prevalence of PE was reported as 15%p40% (17–20). Prevalence of PE in this study was similar to that of other studies.

Hemnes et al. reported that the mean $ETCO_2$ values they obtained using microstream capnograph were comparable in patients with or without PE at 36.3 mmHg and 35.5 mmHg, respectively (21). In cases with $ETCO_2$ values of ≥36, sensitivity, specificity, and NPV values were reported as 87.2%, 53%, and 96.6%, respectively. In our study, the mean $ETCO_2$ levels of patients with or without PE differed. In addition, $ETCO_2$ values were lower, and a cut-off value of 19 mmHg was determined. We think that this discrepancy arose from characteristics of the patient population and measurement methods.

In studies that investigated the diagnostic value of ADSF for PE, measurements were performed using volumetric capnograph, sidestream, and mainstream adaptors. In those studies, the cut-off value for ADSF ranged between 0.15 and 0.40 with rates of sensitivity and

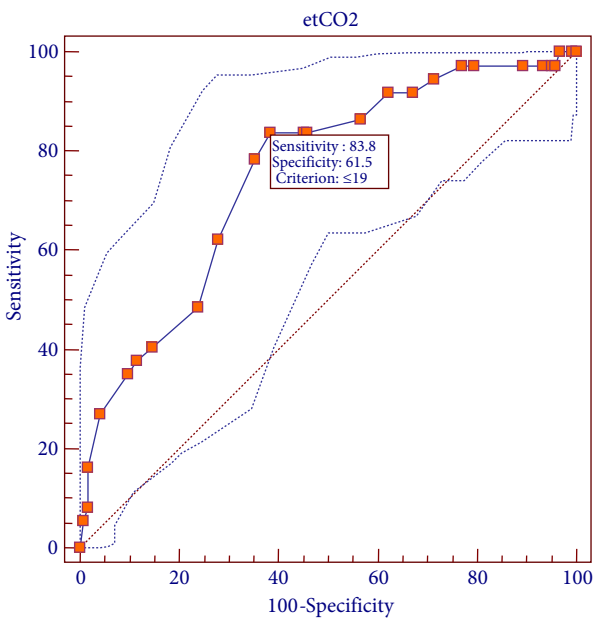

Figure 2. Sensitivity and specificity for $ETCO_2$ of ≤19.

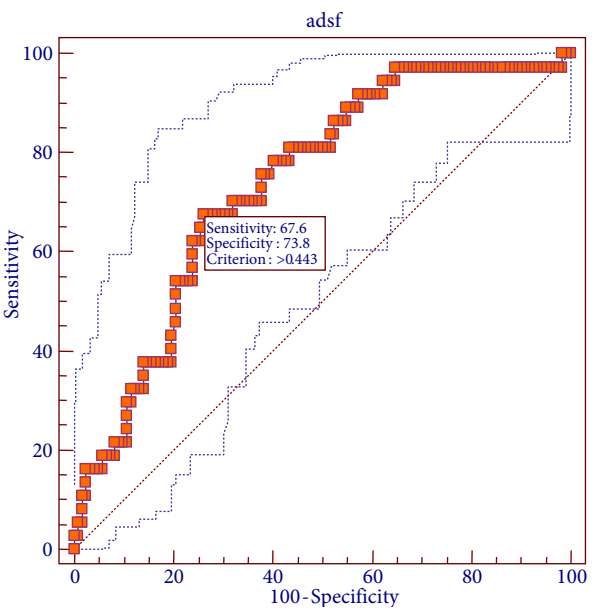

Figure 3. Sensitivity and specificity for ADSF > 0.443.

Table 3. Diagnostic values of various $ETCO_2$ and ADSF values.

Criteria	Sensitivity	Specificity	PPV	NPV	+LR	–LR
$ETCO_2 \leq 11$	16.22	98.36	75	79.5	9.89	0.85
$ETCO_2 \leq 19$	83.78	61.48	39.7	92.6	2.17	0.26
$ETCO_2 \leq 31$	97.3	4.1	23.5	83.3	1.01	0.66
ADSF > 0.04	97.3	1.64	23.1	66.7	0.99	1.65
ADSF > 0.15	97.3	5.74	23.8	87.5	1.03	0.47
ADSF > 0.20	97.3	10.66	24.8	92.9	1.09	0.25
ADSF > 0.44	67.57	73.77	43.9	88.2	2.58	0.44
ADSF > 0.68	5.41	99.18	66.7	77.6	6.59	0.95

$ETCO_2$: End-tidal carbon dioxide; ADSF: alveolar dead space fraction; PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio; –LR: negative likelihood ratio.

specificity varying between 68.5% and 100% and between 20% and 81.5%, respectively. Sanchez et al. measured levels of $ETCO_2$ in 270 suspected PE patients using a CO_2 flow sensor mounted on a rubber mouthpiece resembling that of a snorkel and reported rates of sensitivity and specificity for ADSF of <0.15 as 68.5% and 81.5%, respectively (17). Kline et al. reported rates of sensitivity and specificity for ADSF, with 0.2 set as the cut-off, of 88.5% and 66% in 170 ICU patients with suspected PE (19). Rodger et al. determined an ADSF cut-off value of 0.15, which derived from $ETCO_2$ measurements performed using a mainstream adaptor in a volumetric capnograph. In that study, rates of sensitivity, specificity, and negative predictive value of this cut-off value were 92.6%, 29%, and 95.1%, respectively (22). Burki et al. investigated the value of physiological dead space in the diagnosis of PE and determined the ADSF cut-off value as 0.40, with 100% sensitivity and 55% specificity (23). Yoon et al. reported rates of sensitivity, specificity, and false negativity when $ETCO_2$ was measured with the sidestream method. The calculated ADSF value was ≥0.2, with 100%, 65%, and 0%, respectively (15). Verschuren et al. expressed sensitivity and specificity of $ETCO_2$ measured by the sidestream method and calculated ADSF (<0.15) as 96% and 26% for the exclusion of PE (24). Hogg et al. determined 0.32 as the cut-off value of ADSF, calculated with $ETCO_2$ value and measured by mainstream method with sensitivity and specificity rates of 95.3% and 20%, respectively (16). In another multicenter study conducted by Kline et al., sensitivity and specificity of the analysis based only on ADSF were found to be 67.2% and 76.3%, respectively (25).

The performance of capnography in PE diagnosis was reported with a sensitivity of 0.8, specificity of 0.49, –LR of 0.32, +LR of 2.4, and diagnostic odds ratio of 10.4. This suggested the potential use of $ETCO_2$ in patients with suspected PE who have low clinical probability with high D-dimer levels (20).

In 49 (19.9%) of 246 patients who were examined in the Department of Nuclear Medicine with suspected PE, diagnosis of PE was confirmed, whereas in 34 (13.8%) patients diagnosis could not be established. Rates of sensitivity and specificity of the cut-off value of ADSF (<0.15) for the exclusion of PE diagnosis were reported as 79.5% and 70.3%, respectively (18). The study used mainstream adaptors for the measurement of $ETCO_2$ in the first cohort of patients' sidestream and in the last cohort. Mean ADSF was found to be 0.27 and 0.11 in patients with or without established diagnosis of PE, respectively. However, in our study, mean ADSF values were calculated as 0.48 and 0.35 in groups of patients with or without PE, respectively.

Our calculated ADSF value is above the cut-off value generally accepted in the literature. However, its sensitivity and specificity are similar to those accepted in the literature. Use of different measurement techniques and diverse outcomes with the same technique have been reported. We suggest that the most important factors responsible for this difference are related to variability in patient inclusion and measurement methods. In many other studies, the sidestream technique has been used more frequently for the measurement of $ETCO_2$. However, in our study, the measurements were performed using the mainstream technique. In the sidestream measurement technique, CO_2 that accumulates in the air sampling catheter may artificially increase the $ETCO_2$ value measured by capnometer. In the mainstream measurement technique, real-time measurements are performed within the airway, which avoids the mixture

of the air sample with other gases in the surrounding atmosphere. However, mainstream measurement values may be lower than sidestream measurement values (26). The outcomes might be affected by the difference between measurement techniques. Besides, as stated by Eriksson et al., in the presence of underlying pulmonary disease, the number of false results may increase (27).

Since this study was conducted at a single center, the results are not generalizable. No power analysis was performed before the initiation of the study for the estimation of the sample size; thus, the study was performed on eligible patients over a 1-year period. In addition, a relatively higher number of patients with malignancies among the study participants might affect the outcomes. In this study, the cut-off value of D-dimer (0.5 ng/mL) recommended by the manufacturer was accepted as a positive value so as to determine the patients who would undergo CT. However, the mean D-dimer value of patients without PE (3.96 ng/mL) was much higher than the threshold value. Therefore, many patients might have undergone unnecessary CT examinations. Moreover, since baseline alveolar dead volume is not known, the presence of other abnormalities, which increases alveolar dead space, can lead to inappropriate interpretations.

This study yielded a low diagnostic value of calculated ADSF and noninvasive bedside $ETCO_2$ for PE in the ED. This finding differs from the outcomes of several other studies. We think that taking the method of measurement into consideration and evaluating this measurement together with pretest clinical probability will be more useful. Further studies are needed on this subject.

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