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The Diagnostic Value of End-tidal Carbon Dioxide (EtCO2) and Alveolar Dead Space (AVDS) in Patients with Suspected Pulmonary Thrombo-embolism (PTE)

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ABSTRACT

Introduction: Capnography, is an easy, fast and practical method which its application in the diagnosis of Pulmonary Thromboendarterectomy (PTE) has recently been studied. This study aimed to assess the diagnostic value of end-tidal CO2 (ETCO2) and the alveolar dead space (AVDS) in the diagnosis of patients suspected to PTE who have been referred to the emergency department.

Materials and Methods: This cross-sectional study was conducted during one year in the emergency department of Ghaem Hospital on patients with suspected PTE who scored less than 4 for the Wells' criteria during the initial evaluation. After excluding other differential diagnoses, all patients underwent CT pulmonary angiography CTPA to confirm PTE. Following that, arterial blood gas sampling, ETCO2 and AVDS were requested for all the patients based on capnography. Data analysis was performed using descriptive statistical tests in SPSS software version 11.5. The sensitivity, specificity, and positive and negative predictive values of AVDS and ETCO2 were measured based on (CTPA) results.

Results: The study was performed on 78 patients (mean age of 47.08± 15.6 years, 43 males/35 females) suspected to PTE. According to the results of CTPA, 37 patients did not develop PTE while 41 patients were with PTE. There was no significant difference between the two groups in terms of age and gender (P=0.999), while a statistically significant difference was found between the mean values of ETCO2 and AVDS between the two groups (P<0.001). The best cut-off points for PTE diagnosis were 0.17 (based on AVDS, with sensitivity and specificity of 78.0% and 56.8%, respectively), and 26.5 (based on ETCO2, with sensitivity and specificity of 67.6% and 75.6%, respectively). In addition, the negative predictive values for AVDS and ETCO2 were estimated as 70.0% and 71.43%, respectively.

Conclusion: According to the results of this study, capnography could be effective to promptly rule out PTE in emergency situations. Given its negative predictive value to rule out PTE, ETCO2 is considered as the most valid criterion among capnography parameters.

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Introduction

Pulmonary thrombo-embolism (PTE) is a major medical issue and a leading cause of mortality and morbidity (1). Early detection and rapid rule-

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out of PTE in order to reduce hospitalization costs and prevent unnecessary diagnostic measures have always been a main concern of medical researchers (2, 3).

According to several studies, diagnosis of PTE has only been possible in less than 50% of the affected patients before their death (1, 3). On the other hand, various clinical manifestations of the disease may complicate the diagnosis of PTE, especially when advanced diagnostic tools are not available. Therefore, many patients might unnecessarily undergo CT pulmonary angiography (CTPA) each year in order to rule out PTE (4, 5). As of today, D-dimer testing is commonly used in medical centers for patients with highly suspected PTE (6); if the the test result is positive, the patient requires treatment, and CTPA needs to be performed immediately (6). D-dimer test is a time-consuming procedure, and the use of needles in this test for sampling may appear as unpleasant to many patients (1).

On the other hand, CTPA is a costly, invasive method which involves the risk of exposure to radiation and nephrotoxic contrast agents (1, 3, 7). Thus, continuous efforts have been made in recent years in order to find less aggressive and faster methods of PTE treatment. As a fast, practical approach, the application of capnography in the diagnosis of PTE has lately been investigated (2, 8).

Several studies have found the cut-off points for the end-tidal carbon dioxide (ETCO2) and alveolar dead space (AVDS) with high sensitivity and specificity based on capnography (2, 9). However, only 9 studies have been conducted in this regard so far, and based on the last meta-analysis on this subject, further investigation is required in order to achieve certainty about these cut-off points with a high diagnostic power in different health care settings.

No studies have been performed on this subject in the Iranian population. Therefore, the present study aimed to evaluate the diagnostic values of ETCO2 and AVDS in patients with suspected PTE admitted to the emergency department of Ghaem Hospital of Mashhad.

Materials and Methods

This cross-sectional study aimed to investigate the validity of the diagnostic power of capnography to rule out PTE. The study was conducted from April 2014 to September 2014 in the emergency department of Ghaem Hospital of Mashhad, Iran.

The subjects were selected by purposive sampling and consisted of patients with symptoms such as sudden shortness of breath or chest pain referred to the emergency department of the hospital by the internists.

In a study by Chopin et al. (8), the sample size consisted of 78 patients, determined by a confidence interval of 99% and 95% power. In the current study, the inclusion criteria were as follows: 1) sudden shortness of breath; 2) sudden chest pain and 3) scores less than 4 for the Wells' Criteria.

The exclusion criteria of this study were as follows: 1)pregnancy; 2)renalfailure; 3)yocardial infarction; 4)treatment with anticoagulant agents; 5) intubation and 6) negative D-dimer test result.

The variables of this study included demographic data (age and gender), capnometry variables (ETCO2 and AVDS), and arterial blood gas for measuring the partial pressure of carbon dioxide (PaCO2).

Initially, 5 ml of venous blood was taken from the brachial veins of all the patients in order to rule out the possibility of cardiovascular problems via troponin I measurement, and to examine D-dimer levels. Afterwards, 0.5 ml of arterial blood was prepared for performing radial arterial gasometry.

While performing the arterial gasometry, side-stream capnography was measured and recorded by an internal resident for all the patients in the emergency ward using a capnometer (Comdek®, MD-660P, Taiwan) and a standard nasal probe. Considering the standard slope of the capnogram curve, the levels of ETCO2 and AVDS ventilation (PaCo2-PetCo2/PaCo2) were also evaluated.

In order to confirm PTE with the gold standard diagnosis, all the patients underwent CTPA. The sensitivity, specificity, and the positive and negative predictive values of AVDS and ETCO2 were evaluated based on the CTPA results.

This trial was performed in accordance with the Declaration of Helsinki (DoH) and was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Statistical Analysis

Data analysis was performed using SPSS V.11.5 for Windows (SSPS Inc., Chicago, IL, USA), expressed in mean ± Standard Deviation, and a P value of <0.05 was considered as significant. In addition, T-test was used for the quantitative variables, and in case the variables were not normal, we used the Mann-Whitney test. For qualitative variables, we used Chi-square test, and Fisher's exact test was also used when necessary. Moreover, the receiver operating characteristic (ROC) curve was used to determine the cut-off points, and Medcalc software V.15.0 was applied for the calculation of diagnostic sensitivity, specificity, and the positive and negative predictive values of AVDS and ETCO2.

Results

During the one-year period of this study, 118 patients referred to the emergency department with sudden shortness of breath or chest pain who also scored less than 4 for the Wells' Criteria during the initial evaluation. In total, 100 patients who met the inclusion criteria were enrolled in this study, out of which 22 patients were excluded due to pregnancy (N=2), renal failure (N=3), treatment with anticoagulant agents (N=3), and myocardial infarction (N=14).

Eventually, the study was conducted on 78 patients (43 male, mean age: 47.0±15.6 years). After performing CTPA, 41 patients were diagnosed with PTE while 37 were found to be without PTE. There were no significant differences between the two study groups in terms of age and gender (Table 1). Furthermore, the mean PaCO2 was calculated as 33.3± 6.9 mmHg, and the two groups showed no significant difference in terms of PaCO2 levels at the time of admission (P=0.393) (Table 1).

The mean ETCO2 and AVDS in the studied patients were 25.8±5.9 mmHg and 0.21±0.2 mmHg, respectively. The results of T-test were also indicative of statistically significant differences between the two study groups (with PTE and without PTE) in terms of the mean values of ETCO2 and AVDS (P<0.05) (Table 1).

According to the ROC curve, the best cut-off point for PTE based on AVDS was calculated as much as 0.17 mmHg (Figure 1). Additionally, the sensitivity and specificity values of this point in the differentiation of PTE were estimated as 78.0% and 56.8%, respectively.

Consequently, those patients with an AVDS above 0.17 mmHg were identified as affected by PTE with the reported sensitivity and specificity. On the other hand, the best PTE cut-off point was 26.5 mmHg based on the ETCO2 variable (Figure 2). The sensitivity and specificity values of this point in the differentiation of PTE were estimated as 67.6% and 75.6%, respectively. Therefore, those patients with an ETCO2 below 26.5 mmHg were identified as affected by PTE with the reported sensitivity and specificity (Table 2).

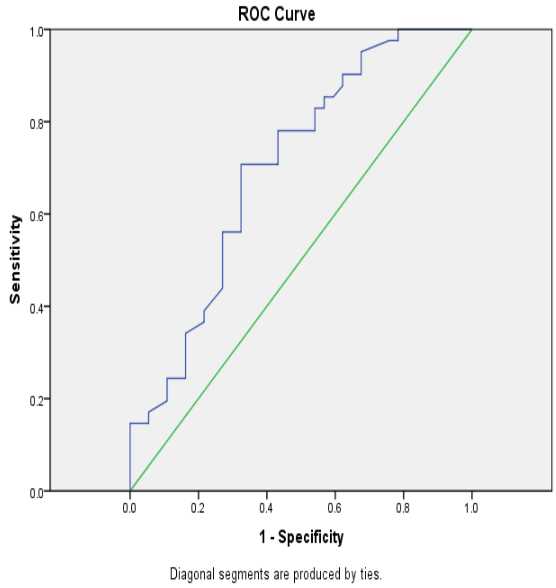

Figure 1. Alveolar dead space ROC curve

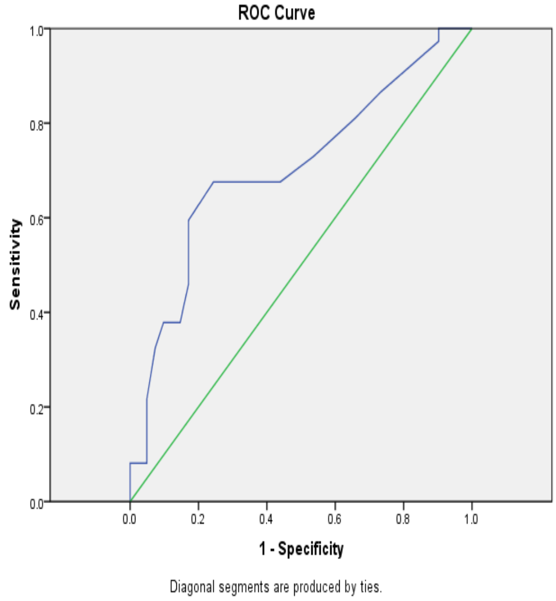

Figure 2. End-tidal carbon dioxide ROC curve

Table 1. Mean basic and diagnostic variables between two study groups (with and without pulmonary thrombo-embolism (PTE)

Disease group Variable (unit)	With PTE (N=37)	Without PTE (N=41)	P-value
Gender, male/ female	18/23	17/20	0.999
Age, year (Mean±SD)	48.0+16.7	47.4±13.7	0.999
PaCO2, mmHg, (Mean±SD)	6.4±34.68	6.6±33.4	0.393
ETCO2, mmHg	5.2±23.8	5.8±28.0	0.001
Alveolar dead space, mmHg, ($\overline{X} \pm SD$)	0.171±0.295	0.217±0.133	0.001

Table 2. Results of ROC curves for variables of end-tidal carbon dioxide and alveolar dead space

Variable	Alveolar dead space		End-tidal carbon dioxide	
Index	Value	Confidence interval of 95%	Value	Confidence interval of 95%
Area under the ROC curve (P-value)	0.702 (0.002)	0.819-0.585	0.704 (0.002)	0.823-0.586
Best cut-off point	0.17		26.5	
Sensitivity	78.0%	%89.4-%62.3	67.6%	%89.4-%62.3
Specificity	56.8%	%72.9-%39.5	75.6%	%72.9-%39.5
Positive likelihood ratio (PLR)	1.80	2.70-1.21	2.33	3.83-1.42
Negative likelihood ratio (NLR)	0.39	0.74-0.20	0.36	0.65-0.20
Positive predictive value (PPV)	66.67%	%79.6-%51.6	72.09%	%79.6-%51.6
Negative predictive value (NPV)	70.00%	%85.2-%50.6	71.43%	%85.2-%50.6

PLR (Positive Likelihood Ratio), NLR (Negative Likelihood Ratio), PPV (Positive Predictive Value), NPV (Negative Predictive Value)

Discussion

The present study aimed to evaluate the diagnostic values of AVDS and ETCO2 in patients with suspected PTE, a leading cause of high mortality with a complicated diagnosis (10). Despite the fact that the ventilation of lung parenchyma is rather normal in case of PTE, it is likely to affect the perfusion (11).

AVDS may increase in PE, which could decrease the concentration of carbon dioxide in the expired air. Moreover, since ETCO2 and AVDS are both functional changes in CO2, it is presumed that capnometer could be applied for the diagnosis, or at least the rule-out of PTE (4, 11). According to our findings, AVDS and ETCO2 are considered as fast, safe, and non-invasive approaches to rule out PE.

According to the literature, six studies have used AVDS, along with positive D-dimer, to rule out PE (2), and the found AVDS cut-off points in these studies range between 0.09 and 0.33 mmHg (1-3, 7). The findings of the present study is compatible to the results of the studies conducted by Sanchez and Rodger with a cut-off point of 0.17 mmHg (12, 13). Furthermore, the obtained sensitivity and specificity of AVDS capnometry were reported to be 78% and 56.8%, respectively, which are similar to the average percentage reported by other studies (1-3, 7, 12, 13).

Similar to our research, a study by Kurt was conducted on a small sample size, and the examination of 58 patients with suspected PTE indicated the sensitivity and specificity of AVDS to be 70% and 61%, respectively (4). In addition, in a study by Yoon et al. performed on 102 patients, the sensitivity and specificity of capnometry were reported to be 100% and 38%, respectively (5).

In a meta-analysis recently published, the sensitivity and specificity of AVDS in the diagnosis of PTE were reported to be 71-73% and 61-76%, respectively, based on the combined use of positive and negative D-dimer testing (2). However, the range of AVDS sensitivity and specificity have been reported to be about 66-100% and 20-92%, respectively by a number of other studies (1-3, 6, 7, 12-15). It appears that the differences in the selected cut-off points by different researchers have resulted in diverse ranges of the reported sensitivity and specificity. Accordingly, high sensitivity could be achieved by increasing the numerical value of AVDS to 0.32, along with a 20% specificity (2).

Furthermore, differences in the studied sample sizes (varying between 45-308 patients) might be another cause of the incompatibilities in the reported sensitivity, specificity and numerical values of the AVDS cut-off points in different studies (2, 6, 14, 15).

On the other hand, the time of capnometry in various studies could also explain the incompatibilities in the obtained values (1, 3). In some studies, heparin therapy was commenced on PTE patients before performing capnometry, while several studies have indicated that heparin administration might reduce the effectiveness of PTE diagnostic tests due to the increased false-negative results, which, in fact, are one of the major limitations of D-dimer testing (1, 3). According to a number of studies, lack of a quick result and the low specificity of D-dimer are also among the notable limitations of this method, which is only able to definitely rule out PTE in approximately 30% of the cases (2, 3, 7, 16).

On the other hand, D-dimer test is associated with high hospitalization costs due to the need for laboratory materials, whereas capnometry is a device without any laboratory requirements.

As previously mentioned, AVDS and other variables related to capnometry (e.g, ETCO2) are associated with PTE and pulmonary perfusion abnormalities; however, the numerical value of this correlation has not yet been precisely determined. Nevertheless, the numerical values, as reported by the positive and negative predictive values, as well as the positive and negative likelihood ratio of capnometry, have achieved more certainty on the applicability of CO2-related variables, especially AVDS, which was investigated in the current study (2).

In the present study, the positive predictive value (PPV) was reported to be 66.7% and the negative predictive value (NPV) was reported to be 70%. It is presumed that increasing the sample size of the study is likely to result in higher levels of predictive values. However, given the association of PPV and NPV with the prevalence of the disease in the study population, and since the prevalence of PE is different in various studies, the likelihood ratio was used for comparison in our study since it is not affected by the disease prevalence.

In the present study, the positive likelihood ratio (LHR+) and the negative likelihood ratio (LHR-) were reported to be 1.80 and 0.39, respectively while in other studies, LHR+ and LHR- were reported to be 2.8-11.58 and 0.06-0.50, respectively (2-5, 9, 12-14, 17-24). However, the LHR+ in the current study is not equal to that of other studies, and the low LHR- in our study is indicative of the effectiveness of capnometry to rule out PE. In a meta-analysis recently published, the value of LHR- was reported to be 0.39, which is equal to the findings of the present study (2).

Regarding the diagnostic value of AVDS, our findings suggest that capnography is able to reduce the amount of invasive interventions, such as CT angiography.

Another prominent result of the current study was finding a reliable cut-off point for PTE diagnosis based on ETCO2 changes. Accordingly, an ETCO2 equal to 26.5 mmHg could be a cut-off point to rule out PTE with a sensitivity and specificity of approximately 70%. In a similar study published in 2014, Riaz et al. investigated 100 patients with suspected PTE and reported a cut-off point of 32.3 mmHg with a sensitivity of 100% and a specificity of 68% (1). In addition, their findings indicated that by reducing the numerical value of the obtained cut-off point, the sensitivity of ETCO2 would decrease and the specificity would increase (1).

One of the strengths of the present study is the comparison of the mean values of ETCO2 between both study groups (with and without PTE). In the study by Riaz et al., the mean value of ETCO2 was significantly lower in subjects with positive PTE CT angiography results compared to the subjects without PTE. Similarly, our results indicated that the mean value of ETCO2 of the PTE group was lower by 4.5 units compared to that of the patients without PTE. In another similar study with a larger sample size consisting of 289 patients, Hemnes et al. measured ETCO2 within 24 hours of PTE diagnosis via CT scan (21). The results revealed that a cut-off point of 36 mmHg with 87% sensitivity, 53% specificity and an NPV of 97% could act as a powerful diagnostic tool to rule out PTE (21). Evidently, the cut-off point found in the present study is noticeably lower than the values obtained by other studies; furthermore, the NPV of this cut-off point was reported to be 70%, which is comparatively lower than that of the other studies conducted on this subject (2).

These incompatibilities in the obtained values could be due to factors such as the sample size of the study and the time of ETCO2 measurement depending on the onset of PTE symptoms. At any rate, a significant difference could be observed in the ETCO2 between the patients with and without PTE.

On the other hand, the large area under the cut-off point curve, as well as the significance of the given cut-off point, suggest that sensitivity, specificity and predictive values could be improved by increasing the sample size in further investigations. Since the current study is the first conducted on an Iranian population, the obtained results could pave the way for further investigation in this regard.

In recent years, several non-invasive tests have been evaluated in order to reduce the need for invasive tests for PTE diagnosis. For instance, although D-dimer testing is a widely accepted method in many health care centers, the low specificity of the test, especially in case of the elderly patients, pregnant women, patients with cancer and hospitalized patients, requires further efforts to modify newer, more efficient tests.

On the other hand, despite the fact that desirable results have been reported on capnometry so far, no particular studies have been conducted on cases where the D-dimer test acts with low specificity. Therefore, designing a prospective study on the diagnostic power of capnometry in cases of the elderly patients, pregnant women and patients with cancer could be beneficial for decision-makings on how to use capnometer in different medical settings in the future.

One of the limitations of the current study was the small sample size due to time constraints. Moreover, this was a single-central study, and in order to achieve the desired diagnostic value for capnometry, it is recommended that multicentral studies be conducted on this subject with a larger sample size.

Conclusion

According to the results of this study, capnometry could be an effective approach to quickly rule out PTE in emergency cases. Furthermore, based on the NPV, ETCO2 is considered to be the most valuable criterion among capnometry parameters to rule out PTE .

Conflict of Interest

The authors declare no conflict of interest

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