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Göğüs Ağrısı Olan Hastalarda Kararsız Anjina Pektorisi Ayırt Etmede End-Tidal CO2'nin Tanısal Rolü

The Diagnostic Role Of End-Tidal CO2 To Distinguish Unstable Angina Pectoris In Patients With Chest Pain

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Özet: Amaç: Akut koroner sendrom (AKS) türlerinden biri olan kararsız angina pektoris (UAP), kalp dışı göğüs ağrısından (non-CCP) ayırt edilmesi zordur, bu nedenle doğru tanı için çeşitli stratejiler uygulanır. Bu çalışma, kardiyovasküler öyküsü olmayan göğüs ağrısı ile acil servise (AS) başvuran hastalarda non-invaziv olarak ölçülen end-tidal CO2'nin (ETCO2) UAP'yi saptayıp saptayamayacağını incelemeyi amaçlamaktadır. **Yöntemler:** Bu araştırma prospektif gözlemsel bir çalışma olarak yürütülmüştür. Bireyler, dahil etme ve hariç tutma kriterlerine göre iki gruba ayrıldı: CCP olmayan 75 hasta ve 75 UAP. Teşhis değeri kesimini tanımlamak için alıcı işletim özelliklerinin (ROC) analizlerinden yararlanılmıştır. Tek değişkenli regresyon analizi kullanılarak, UAP tahmini için ETCO2'nin olasılık oranı (%95 CI ile) hesaplandı. **Bulgular:** ETCO2 seviyeleri UAP grubunda CCP olmayan grupla karşılaştırıldığında önemli ölçüde daha düşüktü (p<0.001). ROC eğrisinin analizi, %78 duyarlılık ve %89 özgüllükle (EAA:0.81, p <0.001) azalmış bir ETCO2 <35'in UAP'yi öngördüğünü ortaya koydu. Ayrıca negatif prediktif değer %71.6, pozitif prediktif değer ise %79.4 olarak bulundu. UAP'li hastaların ETCO2 <35'e sahip olma olasılığı ÇKP olmayan hastalara göre 8.84 kat daha fazlaydı. **Sonuç:** UAP, göğüs ağrısı olan hastalarda non-invaziv bir parametre olarak ölçülen ETCO2 ile CCP olmayandan ayırt edilebilir.

Anahtar Kelimeler: Akut koroner sendrom, kalp dışı göğüs ağrısı, kararsız anjina, koroner bakım ünitesi, soluk sonu karbondioksit.

Abstract: **Objective:** Unstable angina pectoris (UAP), one of the acute coronary syndrome (ACS) types, is difficult to identify from non-cardiac chest pain (non-CCP), hence various strategies are applied for accurate diagnosis. This study aims to examine whether non-invasively measured end-tidal CO2 (ETCO2) can detect UAP in patients admitted to the emergency department (ED) with chest pain in the lack of a cardiovascular history. **Methods:** This research was conducted as a prospective observational study. The individuals were separated into two groups based on the inclusion and exclusion criteria: 75 patients with non-CCP and 75 UAP. Analyses of receiver operating characteristics (ROC) were utilized to define the diagnostic value cutoff. Using univariate regression analysis, the odds ratio of ETCO2 (with 95%CI) was computed for UAP prediction. **Results:** ETCO2 levels were substantially lower in the UAP group compared to the non-CCP group (p<0.001). Analysis of the ROC curve revealed that a decreased ETCO2 <35 predicted UAP with 78% sensitivity and 89% specificity (AUC:0.81, p <0.001). In addition, the negative predictive value was 71.6%, and the positive predictive value was 79.4%. Patients with UAP were 8.84 times more likely to have ETCO2 <35 than patients with non-CCP. **Conclusion:** UAP may be differentiated from non-CCP by ETCO2 measured as a non-invasive parameter in patients with chest pain.

Keywords: Acute coronary syndrome, non-cardiac chest pain, unstable angina, coronary care unit, end-tidal carbon dioxide.

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INTRODUCTION

The number of individuals presenting to health institutions with symptoms of chest pain increases daily. This patient population accounts for around 5 to 20% of emergency department (ED) admissions (Kargoli et al., 2020). The etiology of chest pain in patients covers a wide spectrum. Although 50% of the applicants were diagnosed with musculoskeletal disease and 12% with acute coronary syndrome, 17% were not diagnosed with any disease (Wertli et a., 2019).

Chest pain that is not diagnosed directly or after exclusion is considered non-cardiac chest pain (non-CCP). On the other hand, the number of acute coronary syndrome (ACS) patients who are undiagnosed or misdiagnosed is rising day by day (Writing Committee, Kontos et al., 2022). Correct diagnosis of these patients is of vital importance for patients. Numerous strategies have been developed to establish an accurate diagnosis, and there will always be a need for new strategies (Ford et al., 2021).

Unstable angina pectoris (UAP) is challenging to diagnose despite using many cardiac biomarkers and risk-scoring algorithms at first admission (Tilea et al., 2021). Several biomarkers such as troponin have been used (Collet et al., 2021). Currently, there is no UAP-specific cardiac biomarker that makes a true diagnosis.

End-tidal carbon dioxide (ETCO2) from breathed air is measured as CO2 from cell metabolism disperses across the alveolar membrane of the lungs (Ghorbani et al., 2018). Alterations in ETCO2 levels are diagnostic indicators of metabolic, circulatory, and ventilation abnormalities (Finet et al., 2021). ETCO2 is a reflection of the pulmonary blood flow and cardiac output (Long et al., 2017). ETCO2 indirectly indicates coronary perfusion pressure since the venous system transports CO2 to the right ventricle before it pumps to the lungs (Paiva et al., 2018). We hypothesized that ETCO2 may be utilized to diagnose UAP due to its correlation with coronary perfusion pressure.

The purpose of this research was to examine whether ETCO2 could be utilized to differentiate between non-CCP and UAP in individuals presenting with chest pain to the hospital.

MATERIALS AND METHODS

Study design and settings

This study was carried out as a prospective observational study between January 2020 and July 2022 at the Mardin Artuklu University, Mardin Training and Research Hospital, a tertiary hospital. The study was approved by the Ethics Committee of the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (No: 2023-325, Date: 27th January 2023). Informed consent was obtained from the patients. It conforms to the Declaration of Helsinki's ethical criteria for human testing (2013).

Sample size

A priori power analysis was conducted to distinguish unstable angina pectoris in patients with chest pain by ETCO2, where a differential of 0.50 standard deviations was judged clinically significant between-group means (Norman et al., 2003), the required sample size was determined as 75 in each group, with a lower power of 0.80 and the highest error of 0.05.

Selection of participants

Patients over the age of 18 who were hospitalized with chest pain in the emergency department (ED) were included in the study. Patients with preexisting coronary artery disease, and diagnosed with STEMI or NSTEMI after serial ECG and hs-cTnT were excluded from the study. Furthermore, patients with pulmonary disease, neuromuscular disease, diabetes mellitus, pregnancy, undergoing oxygen therapy (>4L/min), hyperthermia, or bicarbonate were excluded since they impacted the ETCO2 values.

Study protocol

The patients admitted with chest pain simultaneously underwent ETCO2 measurement and were monitored for vital signs at ED. Serial

ECG was performed and hs-cTnT was measured at least twice. After instructing the patients to breathe normally, they underwent a five-breath test. The average ETCO2 value measurement period was accepted. ETCO2 was obtained using a mainstream capnometer (Masimo EMMATM, Danderyd, Sweden). Vital signs, mean ETCO2 value, and laboratory values were recorded. Patients with persistent chest pain underwent coronary angiography to determine whether their chest pain was cardiac in origin. Stenosis of 70% or more was deemed severe, and stenosis of 50 to 69% was deemed moderate (Cury et al., 2022). Patients with undocumented ischemia and angiographically intermediate stenoses were evaluated by using FFR according to guidelines recommendations (Lawton et al., 2022). Coronary angiographies were evaluated by two separate experts who were blind to the study. A significant agreement was found between the cardiologists (κ=0.921). Following the assessment, individuals were separated into two groups: those with UAP and those with non-CCP. Figure 1 shows a flow diagram of the patients.

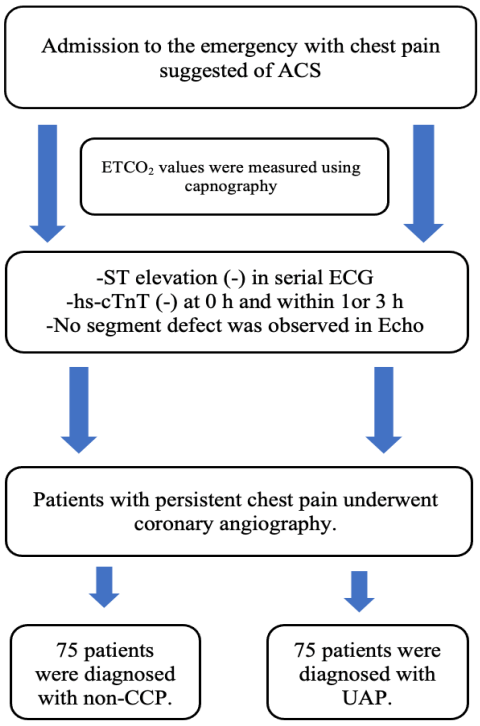

Figure 1: Study flow diagram

Statistics

The IBM SPSS 24.0 package software was applied for the analysis. The initial continuous variables are presented as mean ± standard deviation or median (interquartile range). Frequencies and percentages were used to represent categorical variables. The chi-Square test was used to compare nominal variables between groups. Student's t-test was conducted to determine potential differences between groups for continuous variables. Furthermore, the cut-off in diagnostic value measurements was determined using Receiver Operating Characteristic (ROC) analysis. Using univariate and binary logistic regression analysis, the odds ratio of ETCO2 (with 95%CI) was computed for UAP prediction. The level of statistical significance for the data was set at $p<0.05$.

RESULTS

A total of 150 patients, 75 patients with non-CCP and 75 patients with UAP were enrolled in the research. The mean age of the research population was 61.2±11.3 years, with 34 females (22.7%) and, 116 males (77.3%). The patient's clinical characteristics and laboratory parameters were shown in Tables 1 and 2 respectively.

Table 1: Clinical characteristics of the groups

Parameters	Total *N=150*	Uap *N=75*	Non-Cardiac Chest-Pain *N=75*	*P*-Value
Age (Years)	61.2±11.3	60.1±10.5	62.2±12.6	0.46
Gender, Female, N (%)	34 (22.7)	14 (18.6)	20 (26.6)	0.25
Systolic Blood Pressure (Mmhg)	143.8±16.4	142.2±15.6	144.2±18.4	0.75
Diastolic Blood Pressure (Mmhg)	90.5±12.6	90.3±12.6	91.1±12.2	0.78
Respiratory Rate (Pulse/Min)	14.8±2.1	14.8±2.4	14.8±1.8	0.82
Heart Rate (Beats/Min)	84.2±18.2	83.1±19.1	85.2±18.3	0.67
Spo_2 (%)	96.9±1.2	96.8±1.6	97.1±1.5	0.91
$Etco_2$ (Mmhg)	36.1±2.5	34.2±2.6	38.1±2.5	<0.001
Fever (°C)	36.5±0.2	36.4±0.2	36.6±0.3	0.93
Dl, N (%)	22 (14.6)	12 (16)	10 (13.3)	0.82
Htn, N (%)	28 (18.6)	16 (21.3)	12 (16)	0.59
Lvef (%)	62.7±2.5	62.2±2.8	63.1±2.1	0.71
Smoking, N (%)	38 (25.3)	17 (22.6)	21 (28)	0.52

Data are expressed as mean SD, number (percentage), or median (interquartile range) as appropriate. SpO_2: Oxygen saturation, $ETCO_2$: End-tidal carbon dioxide, DL: dyslipidemia, HTN: Hypertension, LVEF: Left ventricular ejection fraction.

Table 2: Hematological and biochemical parameters of patients

Parameters	Total *N=150*	Uap *N=75*	Non-Cardiac Chest-Pain *N=75*	*P*-Value
WBC count ($\times 10^3/\mu L$)	9.7±3.0	9.9±2.7	9.5±3.2	0.51
Hemoglobin (g/dL)	12.2±1.7	12.0±1.8	12.2±1.6	0.59
Platelet count ($\times 10^3/\mu L$)	262.5±62.7	261.1±62.3	263.1±63.1	0.89
Sodium (meq/L)	138.5 ± 2.7	138.3 ± 2.9	138.6 ± 2.5	0.61
Potassium (meq/L)	4.2±0.4	4.2±0.3	4.2±0.4	0.68
Glucose (mg/dL)	92.7±7.7	93.7±8.6	91.6±6.7	0.75
Creatinine (mg/dL)	0.9±0.4	0.9±0.2	1.1±0.3	0.78
AST (U/L)	28.9±20.5	29.7±19.2	28.1±21.7	0.82
ALT (U/L)	21.8±16.3	22.1±19.6	21.6±12.3	0.88
LDL (mg/dl)	132.5±17.5	133.5±17.8	131.5±17.2	0.56
HDL (mg/dl)	46.6±13.7	47.0±13.6	46.2±13.8	0.84
TSH (µIU/mL)	65.7±4.3	65.5±4.2	65.8±4.5	0.91

Data are expressed as mean ± SD and median [interquartile range] as appropriate. WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Aspartate aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TSH: Thyroid-stimulating hormone.

There is no statistically significant between the groups regarding dyslipidemia (p=0.59), hypertension (p=0.82), smoking (p=0.52), and LVEF (p=0.71). There were no substantial differences across the groups including age, gender, vital signs (fever, blood pressure, SpO2, heart, and respiratory rates), laboratory parameters (white blood cell, fasting plasma glucose, platelet, sodium, potassium, creatinine, aspartate or alanine aminotransferase, low or high-density lipoprotein, and thyroid stimulating hormone) (p>0.05). ETCO2 levels were substantially lower in the UAP group compared with the non-CCP (p<0.001). Analysis of the ROC curve revealed that a decreased ETCO2 <35 predicted UAP with 78% sensitivity and 89% specificity (AUC:0.81, p <0.001, Figure 2).

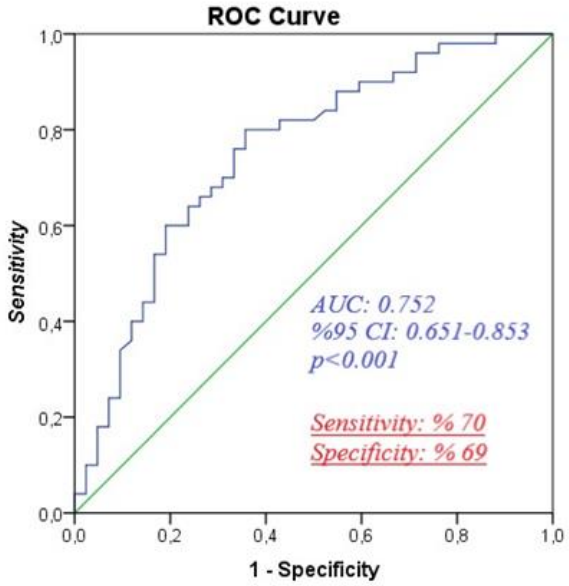

Figure 2: ROC curve of end-tidal CO2 for the diagnosis of UAP

In addition, the negative predictive value was 71.6%, and the positive predictive value was 79.4%. In univariate binary logistic regression, patients with UAP were 8.84 times more likely to have ETCO2 <35 than patients with non-cardiac chest pain [OR (95%CI), 9.84 (3.9-21.8), p<0.001].

DISCUSSION

The results of the study showed that ETCO2 with an optimum cut-off value of 35 was a strong predictor for differentiating UAP from those non-CCP. The ETCO2 may be useful for diagnosing UAP in patients with chest pain without documented ischemia.

ACS includes a broad array of clinics, ranging from UAP to STEMI. This syndrome may continue pain-free without complications or may result in sudden death (Roffi et al., 2016). If there is persistent ST elevation on the ECG, it is classified as STEMI; otherwise, it is classified as ACS without ST elevation. NSTEMI is identified when a cardiac biomarker in the blood rises as a result of myocardial necrosis (Ibanez et al., 2018). On the other hand, since individuals with UAP have myocardial ischemia but no cell damage at minimal exertion or rest, there is no rise in the levels of cardiac biomarkers (Roos et al., 2021). Due to the challenges in distinguishing the diagnosis of NSTEMI from UAP, cardiac biomarkers such as hs-cTn, copeptin, and myosin-binding c protein have been developed currently (Kaier et al., 2017). Despite this, and even though several algorithms have been established, there is no consensus about the diagnosis of UAP.

ETCO2 is often used to identify the response to therapy in acute respiratory distress and to decide on mechanical ventilation, to check ventilation adequacy in sedated patients, to offer prognostic signs in patients with septic shock, to detect metabolic acidosis in patients with diabetes and gastroenteritis, to monitor trauma patients, and to assess the efficacy of resuscitation during cardiac arrest (Sousa et al., 2022; Long et al., 2022; İnan et al., 2022; Tremont et al., 2022; Mueller et al., 2022).

ETCO2 reflects accurately pulmonary blood flow and cardiac output in the absence of metabolic and ventilation disorders (Mossing et al., 2015). In myocardial ischemia, reduced ETCO2 signifies impaired tissue perfusion or oxygenation (Smit et al., 2020). The association between decreased coronary blood flow and myocardial oxygen utilization is linear. The heart's aerobic metabolic product, CO2, similarly declines as oxygen consumption decreases (Crystal et al., 2015). In

addition, since the increase in respiratory rate causes hypocapnia in UAP patients, carbon dioxide in exhaled air may reduce (Cornwell et al., 2021). These result in a low ETCO2 measurement. In some studies, an ETCO2 value of less than 10 mmHg during the 20th minute of resuscitation was regarded as the termination criterion (Javaudin et al., 2020). Dong et al. showed that an increased risk of postoperative mortality in individuals who had general anesthesia with an ETCO2 value of less than 35 (Dong et al., 2022). Parr et al. observed a greater percentage of functional independence in stroke patients who received successful thrombectomy under general anesthesia when ETCO2 levels surpassed 35 (Parr et al., 2022). On the other hand, Kwong et al. found no correlation between ETCO2 value and VF termination for successful defibrillation (Kwong et al., 2021). In parallel with other studies, we found that an ETCO2 value of <35 provides sufficient discriminatory power between UAP and non-CCP.

Limitations

According to the exclusion criteria, the sample size of our research was small. No patient mortality was observed in the hospital. After discharge, patients were not followed up properly.

CONCLUSION

Our study showed that ETCO2, a non-invasive biomarker, may be used to diagnose UAP-induced chest pain. Patients with an ETCO2 <35 were observed to be 8.84 times more likely to develop UAP compared to patients with an equal or more than 35 of ETCO2. With its clinical use, the rate of not being diagnosed or misdiagnosed will decrease in patients with UAP who apply to the hospital, particularly the ED without a cardiovascular disease history.

Conflict of interest

None.

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