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Serum copeptin level may not play an important role in acute pulmonary embolism.

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Abstract

Objective: To evaluate serum copeptin levels in acute pulmonary embolism (APE) patients and healthy controls and to determine the role of the serum copeptin level in the diagnosis and severity of APE.
Methods: This prospective, case-control study was conducted in the Department of Chest Diseases. Fifty patients newly diagnosed with pulmonary embolism and 39 healthy individuals were enrolled. The diagnosis of APE was confirmed by computed tomography angiography. Copeptin levels were evaluated in both groups. All APE patients were evaluated with echocardiography to identify right ventricular dysfunction and to measure the pulmonary artery systolic pressure (PASP). Patients with APE were classified according to the risk of early mortality. The correlation between early mortality risk and PASP and copeptin levels was evaluated in patients with APE.
Results: There was no significant difference between the APE and control groups in age or gender (both, p>0.05), and serum copeptin levels were similar between the two groups (p=0.309). The relationship between serum copeptin levels and early mortality risk and PASP in the APE group was also evaluated. There was no correlation between early mortality risk and serum copeptin levels and PASP.
Conclusion: The serum copeptin level, which is an important prognostic marker for cardiovascular diseases, may not be a suitable biomarker for APE.

Keywords: Acute pulmonary thromboembolism, Copeptin, Biomarker.

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Introduction

Venous thromboembolism (VTE) is an important health problem that causes 10 million cases every year [1]. VTE is the third leading vascular disease after acute myocardial infarction (AMI) and stroke and is associated with substantial morbidity and mortality [1,2]. Acute pulmonary embolism (APE) is a life-threatening clinical condition of VTE [3]. APE can cause right ventricular (RV) dysfunction, and myocardial damage is associated with an increase in biomarkers such as brain natriuretic peptide (BNP), N-terminal (NT)-proBNP, and plasma troponin [3,4].

Copeptin is a novel biomarker that has been discussed in recent years. It is the C-terminal fragment of vasopressin and is a 39-amino-acid-long peptide [5-7]. Vasopressin plays a key role in cardiovascular balance [8]. It is secreted from the hypothalamus when plasma osmolality changes due to stress and hypotension [8,9]. However, it has a short half-life and is unstable in plasma, meaning it is rapidly cleared from plasma. Therefore, the measurement of vasopressin levels presents a challenge [8,10-13]. Copeptin is secreted in equimolar amounts with vasopressin and can be used instead of vasopressin [8,11,12]. It is a stable peptide in circulation and can therefore be measured easily [5,10]. It is thought that copeptin is an acute stress marker in stroke, severe sepsis, and cardiovascular diseases [14]. There are several studies in the literature showing the relationship between PE and copeptin levels [4,8,15,16].

The aim of this study was to compare serum copeptin levels in APE and healthy controls, and to determine the role of serum copeptin levels in the diagnosis and severity of APE.

Material and Method

This prospective, case-control study was conducted in the Department of Chest Diseases between October 2015 and March 2016. The study was approved by the local Ethics Committee (approval no. 26379996/199) and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Fifty patients newly diagnosed with acute pulmonary embolism and 39 healthy individuals were enrolled. The diagnosis of APE was confirmed by computed tomography angiography (CTA). Patients younger than 18 years and pregnant women were excluded from the study. Copeptin levels were evaluated in both groups. Patients with APE were classified according to the risk of early mortality. All APE patients underwent evaluation with echocardiography (ECHO) for RV dysfunction and for measurement of pulmonary artery systolic pressure (PASP). Also, Troponin T were analysed in APE patients. The correlation between early mortality risk and PASP and copeptin levels was evaluated in patients with APE.

Laboratory tests

Blood samples were collected from subjects within a maximum of 6 h after the diagnosis of APE was confirmed with CTA to evaluate the acute phase. The collected samples were centrifuged at 1,600 g for 15 min and the serum was separated and stored at -80°C until analysis. The serum copeptin levels were measured using an autoanalyzer (Hangzhou Eastbiopharm Co., Ltd, China) with a commercial kit that utilized an enzymatic colorimetric method.

Troponin T levels were measured by commercially available electrochemiluminescence immunoassay kits (Roche Diagnostic, Mannheim, Germany) using the Roche Cobas e601 analyzer (Roche).

The ECHO examination was performed at rest, with the patient placed in the left lateral decubitus position, and the examinations were carried out using a 2.5-3.5 MHz transducer along with a Philips cardiovascular ultrasound system (IE33 Echocardiography System; Philips Medical Systems, Eindhoven, The Netherlands) by an experienced cardiologist who was blinded to the clinical data. M-mode ECHO and quantitative analysis were conducted using parasternal long axis images according to data provided by the American Society of Echocardiography. The left ventricular end-diastolic diameter, left ventricular end-systolic diameter and left atrium diameter, and interventricular septum and posterior wall thicknesses were obtained using M-mode ECHO tracings under the guidance of 2D imaging. The left ventricular ejection fraction was calculated according to the biplane modified Simpson's method. Echocardiograms were analysed to measure PASP, tricuspid regurgitation according to vena contracta width, conventional indices of RV function, and RV diameter. All ECHO data were recorded.

Statistical analysis

The IBM SPSS Statistics for Windows software (ver. 20.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The normal distribution of data was evaluated with the Kolmogorov-Smirnov test. Variables were compared using the mean and standard deviation. The χ^2 test was used to evaluate categorical variables. Student's t-test was used to identify differences between group means for continuous variables, and a p-value ≤ 0.05 was taken to indicate significance. The Mann-Whitney U-test was used for serum copeptin levels to determine whether there was any difference between the groups' means. Correlation analysis was performed to assess the association between copeptin levels and PASP and early mortality risk.

Results

This study enrolled 50 patients with APE and 39 healthy controls. There was no significant difference between the APE and control groups in age or gender (both, $p>0.05$). The demographic data and serum copeptin levels of the two groups are summarized in Table 1. In APE groups copeptin levels 7.58 ± 8.61 (1.97-29.98) ng/ml and in control groups copeptin levels 8.36 ± 9.55 (1.73-30.92 ng/ml). Serum copeptin levels were similar between the two groups ($p=0.309$). The relationship between serum copeptin levels and early mortality risk and PASP in the APE group was also examined. There was no correlation between serum copeptin levels and early mortality risk and PASP (Table 2).

Table 1. *Demographic characteristics and laboratory parameters of APE patients and healthy controls.*

Variables	APE patients (n=50)	Controls (n=39)	p-value
Gender, n (%)			
Female	26 (52)	18 (46.2)	0.671
Male	24 (48)	21 (53.8)	
Age (y)	65.42 ± 17.32	60.48 ± 6.18	0.067
BMI (kg/m^2)	25.60 ± 2.07	25.04 ± 1.71	0.17
Smoking status (%)			
Smoker	10 (20)	15 (38.5)	0.062
Non-smoker	40 (80)	24 (61.5)	
Early mortality risk, n (%)			
Mild	21 (42)		
Moderate	11 (22)		
Severe	18 (36)		
DVT, n (%)	19 (38)		
Risk factors, %			
Immobilization	10 (22)		
Surgery (in the last 4 w)	10 (22)		

Malignancy	9 (20)		
Varicose vein	5 (11.1)		
Unknown	5 (11.1)		
Long trip	4 (8.9)		
Recurrent PE	2 (4.4)		
Copeptin (ng/ml)	7.58 ± 8.61	8.36 ± 9.55	0.309
Troponin T (pg/ml)	43.23 ± 39.59		
PASP (mmHg)	38.59 ± 26.91		

PE: Pulmonary Embolism; BMI: Body Mass Index; DVT: Deep Vein Thrombosis; PASP: Pulmonary Artery Systolic Pressure; P ≤ 0.05 was taken to indicate significance.

Table 2. *Correlations between copeptin levels and early mortality risk and PASP.*

Variables	**Copeptin (ng/ml)**	
	r	**p-value**
Mortality risk of APE	0.149	0.302
Low risk		
Moderate risk		
High risk		
PASP (mmHg)	-0.205	0.182

APE: Acute Pulmonary Embolism; PASP: Pulmonary Artery Systolic Pressure.

Discussion

In the present study, unlike previous studies, patients with APE and healthy controls were found to have similar copeptin levels, and there was no correlation between early mortality risk and PASP and serum copeptin levels.

APE is a potentially fatal disease that is life-threatening. Early diagnosis is important for prognosis. In patients with APE, the fast and accurate diagnosis of RV dysfunction is crucial for the correct identification of patients in this high-risk group [3,8,17]. RV failure indicates a high risk of early death. APE can be divided into three groups according to early mortality risk: low, intermediate, and high [3,8]. RV pressure overload is associated with increased myocardial stretch, which leads to the release of BNP or NT-proBNP [3]. Some biomarkers, such as D-dimer, BNP, and troponin, are used in the diagnosis and risk stratification of APE [13,15,18]. Copeptin is a biomarker along with pro-hormone arginine vasopressin [14] and is used as a prognostic marker in cardiovascular diseases [7,11,19,20]. Secretion of copeptin stimulates neurohormonal stress [5,19]. Several studies have examined the association of PE and serum copeptin levels. Hellenkamp et al. evaluated the prognostic value of copeptin in normotensive PE. Patients with an adverse 30 d outcome had higher copeptin levels than patients with a favorable course [8]. Wyzgal et al. showed that copeptin was a prognostic marker of the severity of APE [17]. Kalkan et al. evaluated patients admitted as emergencies due to acute chest pain and/or dyspnea who underwent pulmonary CTA. The patients diagnosed with APE had higher copeptin levels than the remaining individuals with a normal pulmonary CTA result [15]. Vuilleumier et al. undertook a comparison of cardiac and non-cardiac biomarkers for risk stratification in elderly patients with non-massive PE. They found that copeptin was an independent predictor of APE-related mortality [4].

In the present study, copeptin was not associated with APE after diagnosis, and the copeptin levels were similar in both groups. Also, the range of copeptin levels was found a wide range in two groups. This result is different from those of other studies. We believe that APE is related to stress associated with today's living conditions. Stress is defined as any condition that causes the body to deviate from homeostatic balance. Many chronic psychological stressors contribute to the development of psychiatric and cardiometabolic diseases. Activation of the sympathetic nervous system of the stressors, known as the hypothalamic-pituitary-adrenal (HPA) axis, leads to an increase in the concentration of adrenal stress hormones such as the corticotropin-releasing hormone vasopressin [10,21]. Serum copeptin levels are elevated in stress conditions that cause HPA activation. Urwyler et al. evaluated the copeptin levels of 25 students before and after their exams. They found that copeptin levels immediately prior to a written examination were higher compared with after its conclusion [22]. Siegenthaler showed that copeptin levels, in tandem with cortisol levels, increased upon psychological stress in healthy volunteers [23]. Spanakis et al. found that cortisol and copeptin showed a similar release with standardized psychological mental stress tests in men [21]. Copeptin is a sensitive stress marker [14]. We consider, therefore, that copeptin levels are increased in all conditions where stress is present.

The present study had certain limitations because it was a single-center study and had restricted population. Control group was smaller than the APE group. Also, we found that serum copeptin levels a wide range in two groups. Nevertheless healthy controls had slightly higher copeptin levels than APE group but there were not significant differences in two groups. In this study the mean ages in two groups were 60 y and over. In this age group, even if the control group consists of healthy individuals, they may have a precursor condition for any disease. Recently, researchers have been investigated between relationship copeptin levels and many diseases and conditions. Currently, we know, copeptine is a stress marker but we don't know what exactly caused the increase or decrease of copeptin levels.

As conclusion, it is known that stress is an important risk factor in AMI [24], and copeptin has been identified as a prognostic marker in AMI. On the other hand, APE is an important health problem that may result in venous stasis, hypercoagulation, and endothelial damage [25]. Copeptin may not, therefore, be a suitable biomarker for PE that arises due to organic vascular injury. In future, comprehensive multicenter studies are needed to investigate the relationship between acute pulmonary embolism and copeptin levels.

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