Clinical research

Presepsin (sCD14-ST): could it be a novel marker for the diagnosis of ST elevation myocardial infarction?

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Abstract

Introduction: Acute myocardial infarction (AMI) could be considered to be a state of inflammation. Many inflammatory markers have been evaluated in the AMI setting so far. Presepsin (PSP) is a novel biomarker for diagnosis and prognosis of systemic inflammation that has not been studied in the AMI setting to date. In this study, we aimed to examine serum PSP levels in patients with acute ST elevation myocardial infarction (STEMI).
Material and methods: Forty-eight patients with STEMI and fifty healthy controls without coronary artery disease, verified by coronary angiography, were included in the study. Together with routine laboratory tests needed for STEMI, plasma concentrations of PSP were measured in peripheral venous blood samples of the participants.
Results: Plasma PSP and troponin levels were significantly higher in patients with STEMI than controls (1988.89 ±3101.55 vs. 914.22 ±911.35 pg/ml, $p = 0.001$ and 3.46 ±3.39 vs. 0.08 ±0.43 ng/ml, $p = 0.001$, respectively). The cut-off value for PSP of 447 pg/ml was found to detect STEMI with 87.5% sensitivity, 44% specificity, 60% positive predictive value and 78.5% negative predictive value.
Conclusions: In this study, PSP levels were found to be significantly elevated in patients with STEMI together with high-sensitivity troponins. The PSP may be a new marker for AMI detection. Large scale studies are needed to reveal the importance of PSP in the diagnosis and prognosis of AMI.

Key words: myocardial infarction, presepsin, inflammation, atherosclerosis.

Introduction

Coronary artery disease (CAD) is still the leading cause of death worldwide [1]. The role of inflammation in the process of atherosclerosis from fatty streak formation to plaque erosion, rupture and thrombosis is well documented [1]. Inflammatory biochemical markers facilitate early and accurate diagnosis of acute myocardial infarction (AMI) and help to predict prognosis [2]. Over the past decade, the role of T-lymphocytes, monocytes, macrophages and platelets in atherosclerosis has been broadly studied [3]. C-reactive protein (CRP), interleukin-6 (IL-6),

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tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1), CD40L and P-selectin are some of the mostly studied inflammatory markers in patients with AMI [1]. Alongside these well-studied inflammatory markers, there is enthusiasm in the research of novel markers on the early detection of AMI and their prognostic importance. Monocytes, macrophages and neutrophils express a cluster of differentiation (CD) surface glycoprotein named CD14 [4]. CD14 forms a circulating soluble subtype after being activated by plasma proteases, which is named sCD14-ST, also known as presepsin (PSP) [4]. Several clinical studies have suggested that PSP is an acute phase reactant similar to CRP [5]. Although the diagnostic power, prognostic value and mortality predictive capacity of PSP are widely evaluated and accepted in sepsis, no publications about the association between PSP and atherosclerosis are available in the literature [2].

In this study, we aimed to examine plasma PSP levels in patients with acute ST elevation myocardial infarction (STEMI).

Material and methods

Study population

This observational comparative study was conducted in a tertiary referral center from August 2014 to December 2014. Forty-eight patients diagnosed with acute STEMI undergoing primary percutaneous coronary intervention within 6 h of symptom onset were included in the patient group and fifty healthy patients without coronary artery disease as verified by coronary angiography were enrolled in the control group. The diagnosis of AMI was made according to related guideline, so symptoms of myocardial ischemia and ST segment elevation ≥ 1 mm in two contiguous electrocardiographic leads or new onset of complete left bundle-branch block was defined as ST elevation myocardial infarction [6]. Patients with known CAD, estimated glomerular filtration rate (eGFR) < 60 ml/min, serious valvular disease, uncontrolled hypertension, heart failure, serious hepatic failure, acute or chronic infection, fever, muscle aches, headache, receiving antibiotics therapy, immunoproliferative disease, rheumatic disease, malignancy, osteoporosis and older than 75 years old were excluded. The study protocol was approved by the local ethics committee of the institution and written informed consent was taken from all patients for participation. The study process was rigorously conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines.

Laboratory measurements

Blood samples for PSP and other measurements were drawn as soon as the diagnosis of AMI was made in the patient group and just after randomization from the control group. All of the laboratory data including high-sensitivity cardiac troponin-T (cTn-T) and high-sensitivity CRP (hs-CRP) were documented. Blood samples for PSP measurement were obtained by vein puncture into ethylene diamine tetra acetic acid (EDTA) blood collection tubes without additives and immediately centrifuged at 2500 rpm for 10 min. The serum was collected after centrifugation and stored at –80ºC until analysis up to 6 months. The samples were thawed out once. All the assays were performed on serum according to the manufacturer's recommendations with the Pathfast immunoassay analytical system (Progen Biotechnik GmbH, Germany and Mitsubishi Chemical Medience Corporation, Japan) using plasma from EDTA tubes. cTn-T measurements were performed from the obtained plasma samples with the device of Cobas e411 (Roche High Sensitive Troponin T, Hoffman-La Roche Ltd, Basel, Switzerland) with the method of chemiluminescence.

Statistical analysis

The Number Cruncher Statistical system (NCSS) (Kaysville, Utah, USA 2007) program was used for statistical analysis. Study data were analyzed using descriptive statistical methods. Normally distributed quantitative data were analyzed by Student's t test, and non-normally distributed data were analyzed by the Mann-Whitney U test. Qualitative data were analyzed by Yates' continuity correction test. Diagnostic screening tests such as sensitivity, specificity, positive predictive value and negative predictive value and the receiver operating characteristic (ROC) curve test were used for determining PSP and cTn-T cut-off values. Spearman's rank correlation was used to test the association of PSP with other laboratory parameters. P-values (two-tailed) lower than 0.01 with a 99% confidence interval and 0.05 with a 95% confidence interval were considered as statistically significant.

Results

Baseline characteristics and laboratory findings are shown in Table I. Mean age, body mass index (BMI), smoking and history of hypertension were similar between groups. cTn-T levels were significantly higher in the STEMI group than controls, as expected (3.46 ±3.39 vs. 0.08 ±0.43 ng/ml, respectively, p = 0.001). The PSP levels were significantly higher in the STEMI group than controls (1988.89 ±3101.55 vs. 914.22 ±911.35 pg/

Table I. Demographic features and laboratory findings of STEMI and controls

Parameter		Controls (n = 50)	STEMI (n = 48)	P-value
Age [years]	Mean ± SD Min.–max. (median)	58.58 ±8.52 36–76 (59)	59.19 ±11.62 42–89 (58.5)	[a]0.873*
Gender, n (%)	Male	16 (32.0)	35 (72.9)	[b]0.001**
	Female	34 (68.0)	13 (27.1)	
BMI [kg/m²]	Mean ± SD Min.–max. (median)	28.38 ±3.27 20–36 (29)	27.33 ±3.18 21–33 (27.5)	[b]0.112*
Smoking, n (%)	No	26 (52.0)	16 (33.3)	[c]0.096*
	Yes	24 (48.0)	32 (66.7)	
Hypertension, n (%)	No	28 (56.0)	28 (58.3)	[c]0.977*
	Yes	22 (44.0)	20 (41.7)	
Diabetes, n (%)	No	40 (80.0)	37 (77.1)	[c]0.916*
	Yes	10 (20.0)	11 (22.9)	
cTn-T [ng/ml]	Mean ± SD Min.–max. (median)	0.08 ±0.43 0.002–2.98 (0.007)	3.46 ±3.39 0.006–13.80 (2.2)	[a]0.001**
Presepsin [pg/ml]	Mean ± SD Min.–max. (median)	914.22 ±911.35 111–4000 (541.5)	1988.89 ±3101.55 243–19137 (1086)	[a]0.001**
Hs-CRP [mg/l]	Mean ± SD Min.–max. (median)	5.70 ±11.90 0.04–68.70 (2.8)	4.43 ±8.22 0.09–33.66 (1.5)	[a]0.239*
Creatinine [mg/dl]	Mean ± SD Min.–max. (median)	0.78 ±0.17 0.42–1.03 (0.68)	0.87 ±0.25 0.41–1.13 (0.74)	[a]0.056**
WBC [× 10⁹/l]	Mean ± SD Min.–max. (median)	8.92 ±3.21 5.00–17.60 (8.20)	12.49 ±2.89 3.03–18.00 (12.6)	[a]0.001**

[a]Mann-Whitney U Test, [b]Student t test, [c]Yates continuity correction test, *$p < 0.05$, **$p < 0.01$; SD – standard deviation, cTn-T – cardiac troponin T, BMI – body mass index, CVA – cerebrovascular accident, WBC – white blood cells.

ml, respectively, $p = 0.001$, Figure 1). White blood cells count was higher in patients with STEMI than controls (8.92 ±3.21 × 10³ vs. 12.49 ±2.89 × 10³, respectively, $p = 0.001$). Diagnostic screening tests and ROC curve analysis for determining cut-off for cTn-T and PSP are presented in Table II. The cut-off value for cTn-T was 0.017 ng/ml to detect STEMI with 97.9% sensitivity, 92.0% specificity, 92.1% positive predictive value and 97.8% negative predictive value, and the cutoff value for PSP was 447 pg/ml to detect STEMI with 87.5% sensitivity, 44% specificity, 60% positive predictive value and 78.5% negative predictive value. The diagnostic value of PSP levels (AUC = 0.69) to diag-
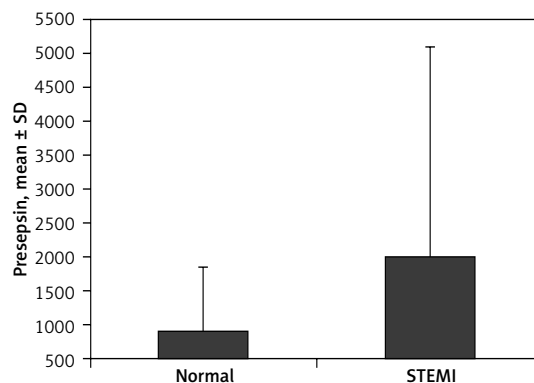
Figure 1. Presepsin values between STEMI and controls

Table II. Diagnostic screening tests and ROC curve analysis for troponin and presepsin

Parameter	Diagnostic scan					ROC curve		P-value
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC	Confidence interval 95%	
cTn-T	≥ 0.017	97.92	92.00	92.16	97.87	0.973	0.940–1.000	0.001
Presepsin	≥ 447	87.50	44.00	60.00	78.57	0.692	0.587–0.797	0.001

ROC – receiver operating characteristic, AUC – area under the curve, cTn-T – cardiac troponin T.

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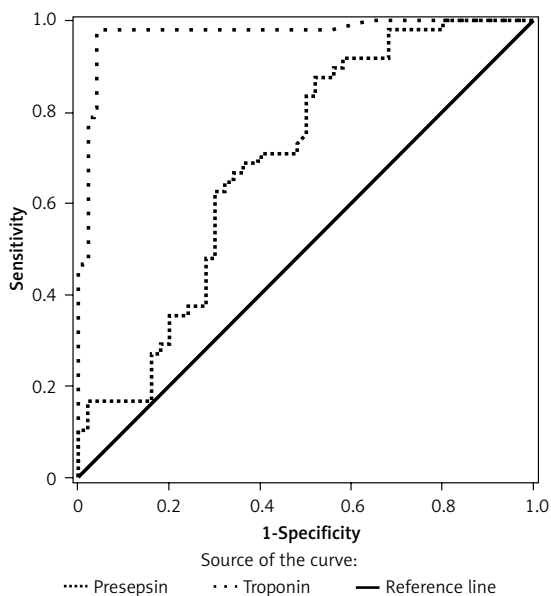

Figure 2. ROC curve analysis of presepsin and troponin

Table III. Univariate correlations of presepsin with laboratory parameters

Parameter		Normal	STEMI
cTn-T	r	0.061	0.133
	p	0.673	0.368
Creatinine	r	0.046	0.157
	p	0.750	0.286
WBC	r	0.043	0.180
	p	0.768	0.221
Hs-CRP	r	0.124	0.144
	p	0.493	0.557

r – Spearman's correlation coefficient, p – p-value, cTn-T – cardiac troponin T, WBC – white blood cells, hs-CRP – high sensitivity C-reactive protein, STEMI – ST elevation myocardial infarction.

nose STEMI was statistically lower than troponin (AUC = 0.97, $p < 0.001$) (Figure 2). The PSP levels were not correlated with cTn-T, creatinine, hsCRP or WBC (Table III).

Discussion

The present study suggested that plasma PSP levels are significantly higher in STEMI patients compared to controls, and the cut-off value of PSP to detect STEMI is 447 pg/ml, and it has 87.5% sensitivity, 44% specificity, 60% positive predictive value and 78.5% negative predictive value. However, the diagnostic power of PSP to diagnose STEMI was found to be statistically lower than that of cTn-T. Acute inflammation due to diminished oxygen supply to the myocardium and related myocyte necrosis during AMI are mostly controlled by monocytes and macrophages [2, 7, 8]. Also, neutrophils play a crucial role in myocardial reperfusion injury and positive remodeling of the myocardial tissue after AMI, and this process is also mediated in part by monocytes and macrophages [8, 9]. Although WBC count, hsCRP, polymorphonuclear leukocytes and interleukin-6 (IL-6) have been widely investigated for this purpose and have shown promising results, they are influenced by many different factors and the results are still controversial [1, 7, 9–11]. In this context, PSP may be a promising biomarker in scientific research of AMI pathogenesis and may reflect vascular inflammation during AMI [2]. The PSP was first found in 2004 [12]. Previous studies demonstrated the diagnostic capacity of PSP with high sensitivity and specificity for the diagnosis of diseases accompanied by systemic inflammation such as sepsis [4, 13]. Our study is the first to evaluate serum PSP levels in the AMI setting. Furthermore, we also assessed other well-known inflammatory biomarkers related to atherosclerosis such as WBC count and serum hs-CRP levels. Although hs-CRP levels were similar among groups, WBC count was significantly higher in STEMI patients compared to controls. Similarly, previous reports have demonstrated increased levels of WBC count in AMI patients [9, 14]. In spite of the fact that how PSP is produced in the body is not well known, it normally exists for a certain amount in the plasma of healthy subjects and increases in response to inflammation [13, 15]. The present study revealed a median value of PSP concentration of 541 pg/ml, ranging between 111 and 4000 pg/ml in the plasma of healthy subjects. Previous studies have demonstrated different plasma PSP concentrations and cut-off levels for both healthy subjects and various patient groups [15]. Chenevier-Gobeaux *et al.* compared PSP concentrations in patients admitted to the emergency room without acute infection or acute disorders and healthy volunteers, and found a median PSP value of 202 pg/ml in healthy volunteers, whereas the median PSP concentration was 750 pg/ml in the patient population, and they also reported that presepsin concentrations increase with age and kidney dysfunction [16]. Endo *et al.* suggested 600 pg/ml as the cut-off value for bacterial and non-bacterial infectious diseases [17]. Shozushima *et al.* obtained a median PSP level of 294 pg/ml in the plasma of healthy subjects and determined 415 pg/ml as the cut-off value for inflammatory diseases with 0.80 sensitivity and 0.81 specificity [18]. The cut-off value of PSP to diagnose STEMI was 447 pg/ml with 0.87 sensitivity and 0.44 specificity in the present study. The wide range of PSP levels among studies may be due to the selection bias of the subjects [12, 15]. Accordingly, plasma PSP

concentrations are known to increase in cases of renal insufficiency and in patients over 70 years [16, 19]. Therefore we excluded patients with renal insufficiency and those over 75 years old, and serum creatinine levels and mean age were similar between groups in our study. Moreover, substantial heterogeneity due to measuring PSP by different instruments has been demonstrated by a meta-analysis [12]. We measured PSP levels with the chemiluminescent enzyme immunoassay method, which is the method used most frequently in other studies. Early detection and timely treatment of AMI are of great importance to prevent complications [20]. Traditionally used troponin levels allow diagnosis of STEMI with sufficient sensitivity and specificity [20]. The results obtained in the present study are consistent with earlier reports, and cTn-T showed 97.9% sensitivity and 92% specificity for the diagnosis of STEMI, but the diagnostic value of PSP levels to diagnose STEMI was lower than cTn-T (AUC = 0.69 vs. AUC = 97, $p = 0.001$). However, in our opinion, PSP cut-off values may still allow one to recognize or exclude patients with and without AMI as accurately as the traditional cardiac marker, troponin, with 87% clinical sensitivity and 78.5% negative predictive values [15]. The PSP measurement takes only 21 min with the chemiluminescent enzyme immunoassay method, which may allow STEMI to be diagnosed as fast as troponin [13]. Studies also evaluated PSP for risk prediction in severe inflammatory diseases and found it convenient [13]. Behnes *et al.* assessed PSP in sepsis and septic shock groups, and observed higher PSP concentrations in patients who died on the first day than survivors and a decline in PSP levels by the 7th day in survivors, and PSP levels were correlated with sepsis scoring systems [21]. Moreover, PSP was better than procalcitonin for the prediction of prognosis in their study [21]. Liu *et al.* observed an increase in PSP levels among patients with sepsis, severe sepsis, the septic shock group and the death group, and diagnostic sensitivity of PSP was 82% for severe sepsis and 86% for septic shock. In predicting the risk of death, PSP was superior to IL-6, CRP and procalcitonin [22]. Olad *et al.* evaluated PSP levels in patients with chemotherapy-induced neutropenia and concluded that PSP levels are well correlated with the severity of infections in this group of patients [23]. Behnes *et al.* not only demonstrated the diagnostic capacity of PSP in recognizing the severity of sepsis, but also revealed the prognostic power of PSP, assessed during the first week of intensive care treatment, in predicting 30 days and 6 months all-cause mortality in patients with severe sepsis and septic shock [21]. They also reported significant correlations with PSP and some of the sepsis scoring systems such as APACHE II (Acute Physiology and Chronic Health Evaluation II)

and SOFA (Sepsis-related Organ Failure Assessment score) [21]. All of the above studies suggest that higher PSP levels are associated with adverse outcomes and subsequent mortality in patients with severe inflammation. According to the present study, PSP levels in patients with STEMI are not correlated with WBC count or serum hs-CRP levels. Similarly, Olad *et al.* also observed that PSP levels were independent from WBC count in their study conducted on patients with chemotherapy-induced severe neutropenia [23].

The present study has some limitations. The main limitations of our study were its single-centered basis and relatively small patient population size. Biomarker follow-up during AMI is of fundamental clinical importance. We were able to measure PSP once, so we may have missed the biological intra-individual variation of PSP in the AMI setting. Besides the above limitations, according to our knowledge, the strength of the present study comes is that it is the first in terms of evaluating serum PSP levels in AMI patients. Future comprehensive studies with large patient population groups may provide more precise results.

In conclusion, in this study, PSP levels were found to be significantly elevated in patients with STEMI together with high-sensitivity troponins. The results of this preliminary study suggest that PSP may be a promising new biomarker for AMI detection. Large scale and comprehensive studies are needed to reveal the importance of PSP in the diagnosis and the prediction of prognosis of AMI.

Conflict of interest

The authors declare no conflict of interest.

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