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Original Article CARDIOLOGY

Serum fibrinopeptide A is increased in patients with acute coronary syndrome

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ABSTRACT

OBJECTIVE: Acute coronary syndrome (ACS) is one of the leading causes of mortality, globally. Atherosclerosis is an underlying factor in ACS process and coagulative cascade is activated secondary to atherosclerotic plaque rupture. Fibrinopeptide A (FPA) takes an active role in thrombus formation and is an indicator of coagulative process. We aimed to evaluate serum FPA level in patients with ACS.

METHODS: Patients diagnosed with ACS and chronic coronary syndrome (CCS), with non-obstructive coronary artery disease as a control group, were included in the study. Blood samples and demographic data of all patients were obtained at admission. Obtained data were compared between ACS and control groups.

RESULTS: The study consisted of 107 patients with ACS and 69 patients with CCS. ACS group was older ($p<0.001$) with male preponderance ($p<0.001$), more likely to had hypertension ($p<0.001$), and had a higher smoking rate ($p<0.001$). Serum FPA level was highest in the ST elevated myocardial infarction group ($p<0.001$). FPA>3.38 ng/mL predicted ACS with 89.7% sensitivity and 78% specificity (AUC: 0.825, 95% CI 0.745–0.905; $p<0.001$).

CONCLUSION: Serum FPA may be used for the differential diagnosis of ACS. In addition, patients with increased FPA may be considered to be given more aggressive antithrombotic medication.

Keywords: Acute coronary syndrome; atherothrombosis; fibrinopeptide A.

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Acute coronary syndrome (ACS) is the leading cause of morbidity and death worldwide, despite novel treatment modalities. Acute ischemic cardiovascular event occurs as a result of atherosclerotic plaque rupture. Subsequently, thrombus formation launches in the torn area, and partially or completely blocks the coronary blood flow. The underlying atherothrombotic process is a complex and includes multifactorial pathways. Determination the important role of thrombosis in the pathogenesis of ACS has increased the interest in hemostatic factors [1]. Prevention of ischemic cardiovascular diseases (CVD) with antiplatelet, anticoagulant, and fibrinolytic treatments has, further, increased the thrombotic process's value [2]. However, in the chronic coronary syndrome (CCS) development course, thrombus formation is not foreground. Therefore, these patients are treated with less aggressive treatment modalities.

The hypercoagulative state is evaluated by measuring the hemostatic factors showing the increased prothrombotic process. It is plausible to detect the coagulation factors as part of the continuous coagulation/fibrinolysis

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balance. Indeed, increased amount of these factors is indicative of hypercoagulable state. Fibrinogen and its' destruction product, Fibrinopeptide A (FPA), are triggering factors involved in the coagulation cascade [3]. Thus, the measurement of plasma levels of these activation markers was shown to be an indicator of adverse events related to ACS. It was aimed in this study to evaluate FPA levels in ACS and CCS patients.

MATERIALS AND METHODS

Study Population

This prospective observational study was conducted between January 2015 and April 2017 with patients that were diagnosed with ACS and CCS. ACS diagnoses was created according to the following criteria: Patients with ≥1 mm ST-elevation in consecutive leads related to one of the major coronary arteries' tertiaries on electrocardiography were accepted ST-elevated myocardial infarction (STEMI) and delivered to angiography laboratory, immediately. In addition, those with ischemic symptoms (typical chest discomfort, shortness of breath, etc.) and ischemic ST-segment depression, or T-wave inversion were taken blood sample for cardiac biomarkers. Elevation in Troponin I/T or creatine kinase myocardial bant (CK/MB) levels was considered to be non-STEMI (NSTEMI) and if these cardiac biomarkers were in normal range, patients were accepted as unstable angina pectoris (USAP) [4]. Patients incompatible with above-mentioned criteria and have stable ischemic symptoms without elevated cardiac biomarkers were considered to be the CCS. Patients were demonstrated not to have coronary obstructive stenosis and were considered to be the control group [5]. The study was performed in accordance with the principles stated in the Declaration of Helsinki. The Kanuni Training and Research Hospital Clinical Research Ethics Committee approved the study with 2015/51 number and February 24, 2016 date.

Exclusion Criteria

Pulmonary embolism, any type of malignancy and history of radiotherapy or chemotherapy, history of coronary artery disease (CAD), cardiac surgery with any indication, congenital heart disease, endocrine disorders, collagenous vascular disease, acute or chronic renal failure, end-stage liver disease, active inflammatory disease, history of cerebrovascular disease, moderate-to-severe valvular heart disease, myocarditis, and cardiomyopathies were determined as exclusion criteria.

Highlight key points

- ACS includes the atherothrombotic process. Estimating the thrombotic burden in the coronary arteries would provide to be given more appropriate treatment.
- FPA is one of the key components of the coagulation cascade and, thus, plays a pivotal role in ACS development.
- Determining a high level of serum FPA level implies a higher thrombotic burden in ACS and even in all CAD groups. More aggressive antithrombotic treatment might be thinking in these patient groups.
- In addition, FPA level may be used for differential diagnosis of ACS.

Demographical and Laboratory Data

Clinical characteristics including detailed medical history and physical examination were obtained from each patient by experienced cardiologists. All data were stored in the database of our institution. Routine biochemistry including blood urea nitrogen, creatinine, glucose, complete blood count, CK-MB, troponin I, and C-reactive protein (CRP) was measured at admission. The FPA concentration (Boehringer, Mannheim) was measured by sandwich enzyme-linked immunosorbent assay method from centrifuged blood samples. Peak CK-MB and peak troponin-I levels were monitored with blood samples taken at 8-h intervals in the coronary care unit.

Systolic and diastolic arterial pressure, previous history of CAD, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), and smoking status were evaluated [6]. HT was defined by considering the following parameters: (i) patients who were diagnosed with HT with the international diagnostic code and/or (ii) patients who were taking one or more of the following medications: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and diuretics treatments for at least 6 months. DM was diagnosed according to at least one of the following criteria: (1) History of DM and taking any anti-diabetic medication; (2) randomly measured blood glucose value of 200 mg/dL or higher; (3) blood glucose level of 126 mg/dL or above after at least 8 h of fasting; and (4) A1c value of 6.5% or higher. Smoking was defined as a regular smoker if occurred at least one cigarette a day in the past month. Family history presence of CAD was defined as the development of atherosclerotic CVD or death from CVD in a first-degree relative (i.e., parent or sibling) before age 55 for males or 65 for females. The presence of HL was defined according to age and sex-adjusted percentiles

from the National Health and Nutrition Examination Survey III data [7]. The height and weight data of the patients were recorded, and body mass index was calculated according to the weight/height(cm)^2 formula.

Transthoracic Echocardiographic Evaluation

Two-dimensional M-mode transthoracic echocardiography was performed for all patients by the EPIQ 7°C ultrasound system (Philips, Best, The Netherlands) before coronary intervention. Left ventricular (LV) dimensions, and septal and posterior wall thicknesses obtained at the parasternal long-axis image M-mode echocardiography and LV ejection fraction was calculated according to the modified Simpson's method [8].

Selective Coronary Angiography

Primary PCI was performed immediately after admission to all patients presented with STEMI at the angiography laboratory. Patients diagnosed with USAP and NSTEMI underwent PCI by the Judkins method urgently or as soon as possible from the femoral, brachial, or radial artery according to the current guidelines. Multiple views were obtained with visualization of the left anterior descending and left circumflex coronary artery in at least four views, and the right coronary artery in at least two views. Coronary stenting directly, or followed by balloon angioplasty, was performed where eligible [9–11]. After the procedure, patients were followed in the intensive coronary unit until stabilization is achieved. All obtained data, coronary angiography views, and results were recorded in the database of ours institute. Patients diagnosed with CCS were hospitalized and underwent coronary angiogram following days of hospitalization. Syntax score was calculated based on the www.syntaxscore.com website tool to quantify the severity and complexity of CAD [12]. In addition, Gensini score was also calculated to evaluate coronary lesion characteristics [13].

Statistical Analysis

SPSS software package (Version 23.0, SPSS, Inc., Chicago, IL) was employed to analyze the obtained data. $P<0.05$ was considered to have statistical significance. A 5% type-I error level was used to infer statistical significance. The normality assumption of data was assessed by the visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test). Levene's test was used to check the homogeneity of variances. While the mean±standard deviation scheme was used to represent the continuous variables, the percentages were used to present the categorical variables. The Chi-square or Fisher's exact test was employed for the purpose of comparing the categorical groups. While the two-tailed Student t-test and one-way ANOVA analysis (for more than two groups) were used for normally distributed parameters, Mann–Whitney U-test and Kruskal–Wallis analysis (for more than two groups) were performed for the non-normally distributed continuous variables. Pearson and Spearman correlation analysis were used to assess the relationship between FPA level and obtained parameters.

RESULTS

A total of 176 patients were included in the study. The mean age was 63.5±13.2 years and 61 (34.7%) of them were female. The mean value of FPA was 5.18±4.02 mg/dL (Table 1). Patients were separated into three groups according to the diagnosis: Group I, NSTEMI; Group II, STEMI; and Group III, CCS.

Patients in Group I were older (69.8±11.5 vs. 63.4±12.4 vs. 57.5±12.6, respectively, $p<0.001$) and more likely to be male ($p<0.021$), while HT rate was higher (86.6% vs. 80.0% vs. 31.9%, respectively, $p<0.001$) in Group I, DM (22.4% vs. 25.0% vs. 4.3%, respectively, $p=0.039$) and smoking (32.8% vs. 52.5% vs. 7.2%, respectively, $p<0.001$) rates were higher in group II. In addition, FPA level (5.57±3.7 vs. 7.2±3.47 vs. 3.62±4.05 mg/dl, respectively, $p<0.001$), admission troponin (0.56 [0.13–3.46] vs. 4.48 [1–16.72], respectively, $p<0.001$), peak troponin (2.27 [0.33–9.4] vs. 15 [4.8–43.8], respectively, $p<0.001$), white blood cell (8.89±2.80 vs. 10.10±3.06 vs. 7.04±1.96 mg/dl, respectively, $p<0.001$), neutrophil-to-lymphocyte ratio (NLR) (2.86 [1.8–5.1] vs. 4.43 [2.3–7.5] vs. 1.82 [1.3–2.4], respectively, $p<0.001$), admission CK-MB (5.3 [2.4–14.5] vs. 21.9 [4.8–47.1], respectively, $p<0.001$), and peak CK-MB (15.5 [5.1–66.3] vs. 54.2 [25.7–115.5], respectively, <0.001) levels were highest in group II (Fig. 1), whereas serum creatinine level (1 [0.8–1.2] vs. 0.85 [0.73–1] vs. 0.7 [0.6–0.81], respectively, $p=0.009$) was highest in group I (Table 2).

Among echocardiographic findings, LVEF was highest in group III (49.76±11.88 vs. 51.56±10.52 vs. 58.80±7.97, respectively, $p<0.001$). Syntax and Gensini scores were similar between groups (Table 2).

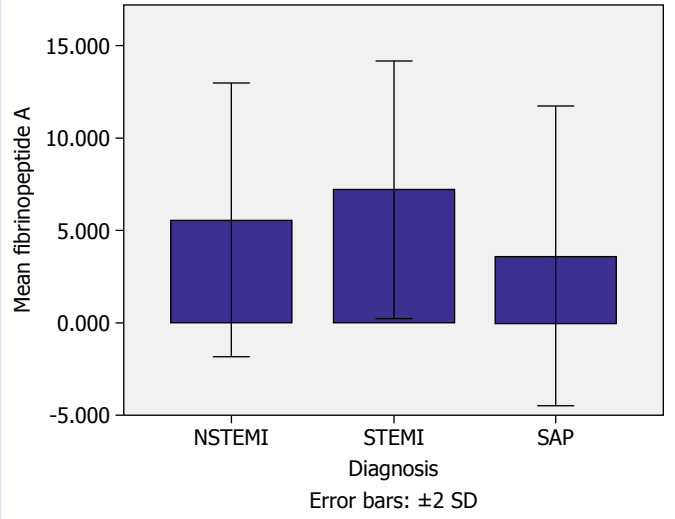

Figure 1. Fibrinopeptide A levels in coronary artery disease groups.

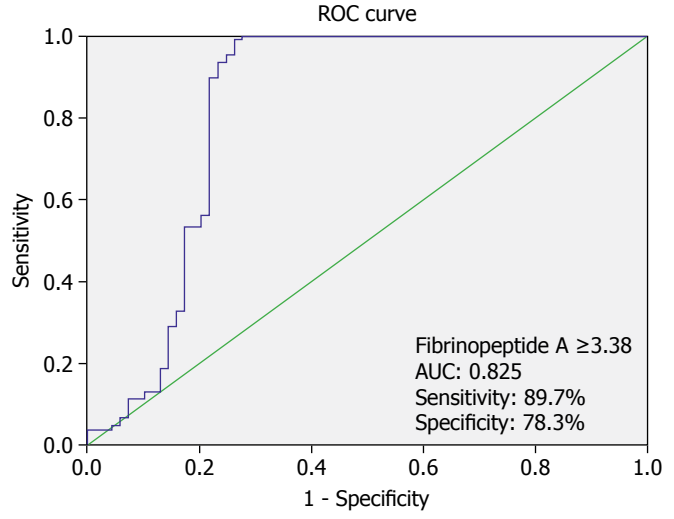

Figure 2. ROC curve analysis of fibrinopeptide A level in determining acute coronary syndrome.

While FPA was positively correlated with troponin level, CK-MB level, SYNTAX score, Gensini score, neutrophil count, and NLR; there was a negative correlation with LVEF (Table 3).

The receiver operating curve analysis was performed to demonstrate the sensitivity and specificity of each FPA levels for predicting ACS. FPA>3.38 ng/mL predicted ACS with 89.7% sensitivity and 78% specificity and the area under curve (AUC) was found to be 0.825 (95% CI 0.745–0.905; p<0.001) (Fig. 2).

DISCUSSION

In the present study, we found that serum FPA level was increased in patients with ACS. The novelty of our study was based on the thrombus burden that was evaluated by serum FPA level firstly in patients with ACS by comparing with the control group.

The main process in ACS occurrence is atherosclerosis, chronic plaque formation, rupture of this plaque, subsequently thrombus composition, and occlusion of this region. This process occurs through complex pathways including inflammation, thrombus, and coronary spasm. Thrombus formation has a central role in both the acute and chronic phases of this process [14, 15]. Thus, markers that signalizing the atherothrombotic activity would illuminate diagnosis, decision-making, risk classification, and choosing treatment options. Until now, troponin and CK-MB markers were used in clinical practice to differentiate cardiac patients from non-cardiac causes. However, these markers have limitations such as non-specificity to cardiac damage, causing a delay in diagnosis, and provoking bleeding risk due to the unnecessary given antiplatelet agents [16].

The FPA is a peptide derived from the alpha chain during the transforming of fibrinogen to fibrin monomers through the thrombin. FPA is a coagulation trig-

Table 1. Baseline characteristics of the study population

Variable	All participants (n=176)
Age (year) (mean±SD)	63.56±13.27
Gender (female) (%)	34.7
Hypertension (yes) (%)	63.6
Diabetes mellitus (yes) (%)	15.9
Hyperlipidemia (yes) (%)	34.6
Smoking (yes) (%)	27.3
Pain duration (hours) (mean±SD)	10.72±9.44
Fibrinopeptide A (mg/dL) (mean±SD)	5.18±4.02
Admission troponin (ng/uL) (mean±SD)	7.52±29.23
Peak troponin (ng/uL) (mean±SD)	18.46±31.34
Admission CK-MB (ng/uL) (mean±SD)	67.66±637.21
Peak CK-MB (ng/uL) (mean±SD)	34.96±65.00
Gensini score (mean±SD)	26.53±32.36
Syntax score (mean±SD)	9.28±10.53
LVEF (mean±SD)	53.73±10.94

CK-MB: Creatinine kinase; LVEF: Left ventricular ejection fraction; SD: Standard deviation.

Table 2. The patients' characteristics according to coronary artery disease types

Variable	NSTEMI(I) n=67 Mean±SD/IQR	STEMI(II) n=40 Mean±SD/IQR	SAP(III) n=69 Mean±SD/IQR	F/t/z/X2	Post hoc	p
Age (year)	69.88±11.49	63.43±12.39	57.51±12.67	17.56[a]	I>II>III	<0.001
Gender (female) (%)	20.9	25.0	53.6	18.21[b]	III>I=II	<0.001
Hypertension (%)	86.6	80.0	31.9	49.91[b]	I=II>III	<0.001
Diabetes mellitus (%)	22.4	25.0	4.3	11.46[b]	I=II>III	0.003
Hyperlipidemia (yes) (%)	29.9	37.5	37.7	1.105[b]	I=II=III	0.576
Smoking (%)	32.8	52.5	7.2	27.83[b]	II>I>III	<0.001
Pain duration (hours)	13.26±10.63	6.47±4.62	–	-4.558[c]	I>II	<0.001
Fibrinopeptide A (mg/dl)	5.57±3.70	7.20±3.47	3.62±4.05	68.35[a]	II>I>III	<0.001
Admission troponin (ng/uL)	0.56 (0.13–3.46)	4.48 (1–16.72)	–	-3.863[e]	II>I	<0.001
Peak troponin (ng/uL)	2.27 (0.33–9.4)	15 (4.8–43.8)	–	3.756[e]	II>I	<0.001
Admission CKMB (ng/uL)	5.3 (2.4–14.5)	21.9 (4.8–47.1)	–	-2.840[e]	II>I	<0.001
Peak CKMB (ng/uL)	15.5 (5.1–66.3)	54.2 (25.7–115.5)	–	-3.296[e]	II>I	<0.001
Gensini score	42.25±32.17	53.43±25.52	–	1.781[c]	I=II	0.078
Syntax score	15.26±9.37	18.12±7.82	–	1.537[c]	I=II	0.128
Serum creatine (mg/dL)	1 (0.8–1.2)	0.85 (0.73–1)	0.7 (0.6–0.81)	9.461[d]	I=II>III	0.009
Max. creatine	1.35 (1.07–1.9)	1.13 (1–1.34)	0.81 (0.74–1.1)	48.50[d]	I>II>III	<0.001
Total cholesterol	195.55±40.23	197.73±44.44	199.96±45.61	0.175[a]	I=II=III	0.839
LDL-C (mg/dl)	134.63±35.17	140.08±44.28	123.75±35.58	2.739[a]	I=II=III	0.067
HDL-C (mg/dl)	41.39±10.70	42.93±9.02	44.80±9.18	2.081[a]	I=II=III	0.128
Triglyceride (mg/dl)	148.75±95.03	120.43±71.57	178.51±101.06	16.55[d]	III>I=II	<0.001
LVEF	49.76±11.88	51.56±10.52	58.80±7.97	14.44[a]	III>I=II	<0.001
LVEDD	50.63±5.15	49.43±4.26	48.29±4.42	4.233[a]	I>III, II=III	0.016
LVESD	34.66±6.82	32.50±5.15	31.36±5.11	5.530[a]	I>III, II=III	0.005
Glucose (mg/dl)	116 (99–144)	124 (98–162)	96 (88–116)	10.42[d]	II>I>III	<0.001
IVS	11 (10–13)	12 (11–13)	10 (10–12)	11.52[d]	I=II>III	0.004
PW	11.01±1.44	10.80±1.30	10.42±1.23	3.461[a]	I>III, II=III	0.034
Platelet /mm^3	230.44±55.27	208.50±57.34	225.84±61.37	1.860[a]	I=II=III	0.159
MPV	8.45±0.93	8.65±0.89	8.47±0.90	0.675[a]	I=II=III	0.511
WBC (10^3/µl)	8.89±2.80	10.10±3.06	7.04±1.96	19.43[a]	II>I>III	<0.001
NLR	2.86 (1.8–5.1)	4.43 (2.3–7.5)	82 (1.3–2.4)	38.15[d]	II>I>III	<0.001
PLR	118 (91–156)	108 (83–155)	105 (83–131)	4.806[d]	I=II=III	0.157

STEMI: ST-elevated myocardial infarction; NSTEMI: Non-STEMI; a: One-Way ANOVA; b: Pearson Chi-square; c: Student t-test; d: Kruskal–Wallis test; e: Mann–Whitney U-test; SD: Standard deviation; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-diastolic diameter; IVS: Interventricular septum; PW: Posterior Wall; MPV: Mean platelet volume; WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

gering factor and indicates thrombin activation, thus, is a hypercoagulable state marker. Factor Xa cannot produce adequate thrombin for thrombus formation when the FPA level is not high enough. With this respect, FPA acts as an activator of the coagulation cascade [17]. In addition, serum FPA level is a sensitive indicator of thrombus formation, plasminogen activator inhibitor activity, and decreased fibrinolysis in ACS patients. Besides, FPA is associated with acute inflammation which is an instigator factor for the atherosclerotic process: triggers the releases of inflammatory markers such as CRP, IL-1β, and IL-6 from vascular smooth muscle cells. Increased FPA level causes a higher inflammatory response which results in aggravation of atherosclerosis [18].

Table 3. Correlation coefficients (r-value) between Fibrinopeptide A and other clinical parameters

Variables	Fibrinopeptide A	Adm. troponin	Peak troponin	Adm. CK-MB	Peak CK-MB	Syntax score	Gensini score	LVEF	WBC	NLR	PLR
Fibrinopeptide A	1										
Adm. troponin	0.539	1									
Peak troponin	0.561	0.899	1								
Adm. CK-MB	0.549	0.938	0.912	1							
Peak CK-MB	0.555	0.884	0.961	0.930	1						
Syntax score	0.507	0.831	0.865	0.822	0.839	1					
Gensini score	0.520	0.840	0.874	0.846	0.862	0.965	1				
LVEF	-0.266	-0.387	-0.425	-0.370	-0.387	-0.468	-0.493	1			
WBC	0.234	0.489	0.486	0.484	0.486	0.461	0.481	-0.243	1		
NLR	0.353	0.509	0.490	0.516	0.526	0.490	0.495	-0.311	0.505	1	
PLR	0.187	0.202	0.203	0.237	0.265	0.175	0.155	-0.126	0.014	0.651	1

Adm: Admission; CK-MB: Creatinine kinase; LVEF: Left ventricular ejection fraction; LVEF: Left ventricular ejection fraction; WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Moreover, FPA expresses the lesion burden and is the precursor of complicated and thrombogenic atherosclerotic lesions. Indeed, the previous studies demonstrated that there is a relationship between CAD extensity and FPA level [19]. Therefore, it was speculated that the higher amount of FPA in ACS compared to CCS is an indicator of unstable atherothrombogenic plaque formation [20, 21]. Wilensky et al. [22] demonstrated the relationship between FPA level and grade 3 and 4 intracoronary thrombus in patients with USAP. Although there was no evidence of thrombus formation with coronary angiography, some trials postulated that increased FPA was related to temporary thrombus activation. The present study was consistent with the previous studies that found that FPA is an indicator of unstable atherosclerotic plaque presence.

On the other hand, it was shown that the hypercoagulative process remains after ACS. Despite the FPA level returns to normal range back after the early phase, the increased level during the acute event is predictive of the increased coagulative activity in the later periods [23]. In addition, FPA level was shown to be associated with adverse events including ventricular fibrillation and heart failure, after myocardial infarction [20]. Thus, FPA was recommended to be used as a risk assessment tool [24]. However, heart failure development is not fully understood, the hypercoagulative process is thought to contribute to larger infarct size and microcirculatory thrombosis. The improved outcome was ensured by reducing the thrombotic burden in MI patients [21]. And also, neurohumoral activation triggered by emotional and physical stress is thought to create both heart failure and FPA release [25]. Although the heart failure rate was low in our patients, LVEF was lower in patients with ACS than CCS. However, this result is expected when these patient groups were compared, but we think FPA level would be useful for the prediction of heart failure and even arrhythmia so.

Limitations

This study was conducted with relatively few patients. Angiographic evaluation of thrombus grade could be added in the analysis. Lesion analysis such as intravascular ultrasonography and fractional flow reserve did not perform.

Conclusion

Increased serum FPA level indicates the active intracoronary thrombus burden in CAD. Serum FPA level may be used for differential diagnosis of ACS and CCS, as well as estimation of ACS intensity. In addition, risk assessment for future adverse events could be useful with serum FPA levels. Moreover, in patients with increased FPA levels, more aggressive antithrombotic treatment may be planned.

Ethics Committee Approval: The Kanuni Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 24.02.2016, number: 2015/51).

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Authorship Contributions: Concept – ASY, AU; Design – FK, AU, OFC; Supervision – FK, AU; Materials – ASY; Data collection and/or processing – ASY, FK; Analysis and/or interpretation – AU, FK, OFC; Literature review – ASY, AU; Writing – ASY, FK, AU; Critical review – FK, OFC.

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