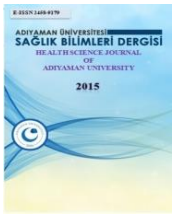
Adıyaman Üni. Sağlık Bilimleri Derg, 2019; 5(2);1528-1539

ADIYAMAN ÜNİVERSİTESİ SAĞLIK BİLİMLERİ DERGİSİ
E-ISSN 2458-9179
dergipark.gov.tr/adiyamansaglik



Araştırma/Research

The Relationship Between Procalcitonin Levels and Coronary Slow Flow

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Abstract

Objective: Coronary slow flow phenomenon is associated with angina pectoris and acute coronary syndromes. Procalcitonin levels are correlated with the extent of atherosclerosis in patients with coronary artery disease. We aimed to evaluate the relationship between procalcitonin and coronary slow flow phenomenon.

Material and Method: The present study included 50 patients with coronary slow flow and 42 healthy subjects. The coronary slow flow phenomenon is defined as delayed coronary opacification in the absence of obstructive coronary artery disease. Coronary slow flow is evaluated with Thrombolysis in Myocardial Infarction frame count method. The Procalcitonin was calculated from the blood to analyze.

Results: The C-reactive protein was significantly higher in the coronary slow flow group than the control group. There was a positive and significant correlation between the Mean Thrombolysis in Myocardial Infarction frame count and C-reactive protein levels. There were no correlations between the C-reactive protein and procalcitonin levels (r= -0.134, p= 0.204).

Conclusion: Serum procalcitonin level was not associated with coronary slow flow. We have shown the relationship between serum procalcitonin and C-reactive protein and coronary slow flow.

Key Words: coronary slow flow,procalcitonin, C-reactive protein.

YazışmadanSorumluYazar

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GelişTarihi:	**21.05.2019**
Kabul Tarihi:	**19.06.2019**

Prokalsitonin Düzeyleri ile Koroner Yavaş Akım Arasındaki İlişki

ÖZET

Amaç: Koroner yavaş akım fenomeni anjina pektoris ve akut koroner sendrom ile ilişkilidir. Prokalsitonin seviyeleri koroner arter hastalığı olan hastalarda aterosklerozun yaygınlığı ile ilişkilidir. Bu çalışmada prokalsitonin ve koroner yavaş akım fenomeni arasındaki ilişkinin değerlendirilmesini amaçladık.

Yöntem: Çalışmaya koroner yavaş akımı olan 50 hasta ve 42 sağlıklı birey alındı. Koroner yavaş akım fenomeni, obstrüktif koroner arter hastalığı yokluğunda gecikmiş koroner opasifikasyon olarak tanımlanmaktadır. Koroner yavaş akım, Tromboliz Miyokard İnfarktüsü frame sayma yöntemi ile değerlendirildi. Prokalsitonin değerleri kandan analiz edildi.

Bulgular: C-reaktif protein koroner yavaş akım grubunda control grubundan anlamlı derecede yüksekti. Ortalama Tromboliz Miyokard İnfarktüsü frame sayısı ile C-reaktif protein düzeyleri arasında pozitif ve anlamlı bir korelasyon vardı. C-reaktif protein ve prokalsitonin düzeyleri arasında korelasyon yoktu ($r = -0.134$, $p = 0.204$).

Sonuç: Serum prokalsitonin düzeyi koroner yavaş akım ile ilişkili değildi. Bu çalışmada **prokalsitonin ve** serum C-reaktif protein ve koroner yavaş akım arasındaki ilişkiyi gösterdik.

AnahtarKelimeler: koroner yavaş akım, prokalsitonin, C-reaktif protein.

INTRODUCTION

The coronary slow flow (CSF) phenomenon is defined as delayed coronary opacification in the absence of obstructive coronary artery disease (1). The CSF is evaluated with Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method that counts the number of cine-angiographic frames from initial contrast opacification of the proximal coronary artery to opacification of distal arterial landmarks. The underlying mechanism responsible for CSF phenomenon is not known clearly. Endothelial dysfunction and diffuse atherosclerosis have been suggested for etiology of CSF (2,3). CSF is associated with angina pectoris, acute coronary syndromes, life-threatening arrhythmias, and sudden cardiac death (4,5). A significant relationship has also been reported between inflammatory markers and coronary flow rate (6).

Inflammation may play a role in the initiation and progression of atherosclerosis (7,8). Procalcitonin (PCT) is a calcitonin precursor that was defined as an inflammatory biomarker in patients with sepsis and infection (9). Also, procalcitonin has a higher sensitivity and specificity than acute phase proteins such as C-reactive protein in systemic inflammation (10). Increased levels of PCT are correlated with interleukin (IL)-6 and C-reactive protein (CRP) in patients with AMI (11). PCT levels, also, were found to correlate with the extent of atherosclerosis in patients with CAD and associated with an adverse clinical outcome, including mortality (12). The role of serum PCT has not been investigated in patients with CSF. Our aim in this study was to evaluate the relationship between PCT levels and CSF.

MATERIAL METHOD

From February 2019 to May 2019, a totally of 92 consecutive patients with stable angina pectoris (50 patients with CSF, 42 patients with the normal coronary flow), which underwent CAG in our institution, were enrolled into the study. Coronary angiography was performed using standard techniques (Siemens Axiom Artis zee 2011; Siemens Healthcare, Erlangen, Germany). Angiographic images were obtained in standard views using right and left, cranial, and caudal angulations. All angiograms were recorded at 25 frames/s. Iopromide, as a contrast agent (Ultravist-370, Bayer Schering Pharma, Germany), was used in all subjects. All study participants were referred for coronary angiography as outpatients due to the presence of typical angina or symptoms considered to represent angina equivalence. Normal coronaries were defined as coronary arteries without any obstructive or non-obstructive lesions in any coronary artery. Coronary flow was defined by Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method.

Coronary flow rates of all subjects were determined by the TFC method, as described by Gibson et al.(13). TFC was evaluated for each coronary vessel by two trained cardiologists, blind to the patient's clinical information. The first frame was considered to be that at which > 70 % lumen opacification with the ante-grade filling was noted. The final frames were determined when contrast opacification reached a certain distal landmark in each vessel. The distal bifurcation was used ("whale's tail") for the left anterior descending artery (LAD). The most distal bifurcation of the obtuse marginal branch was used as the distal landmark for the left circumflex artery (LCx). The first branch of the posterolateral segment was used for the right coronary

artery (RCA). LAD is usually longer than the other major coronary arteries, and TFC for the LAD coronary artery was divided by 1.7 to obtain corrected TFC (13). The mean TFC for each patient and control participant was calculated by dividing the sum of the TFCs of LAD, LCx, and RCA by 3.

Blood samples are collected from the antecubital vein by an atraumatic puncture and are sent to the laboratory for analysis after an overnight fast of at least 8 hours. Common blood counting parameters stored in citrate based anti-coagulated tubes were measured by Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc, Mervue, Galway, Ireland) within 5 minutes of sampling. Routine complete blood count and biochemical parameters including total cholesterol, triglyceride, low-density lipoprotein-cholesterol (LDL) and high-density lipoprotein cholesterol (HDL), fasting blood glucose, creatinine, and levels of **CRP** were determined by the hospital biochemistry laboratory. The blood drawn at the time of cardiac catheterization for the analysis of PCT levels was centrifuged for 20 min after being protected at room temperature for 30 min. VIDAS® BRAHMS PCT® assay (BioMerieux Inc., Marcy l'Etoile, France) was used for detection of PCT serum levels with a functional detection limit of 0.05 ng/mL.

We obtained demographic information, cardiovascular history, and risk factors for CAD from medical records and treatment received during the in-hospital period. Weight and height of the patients were measured, and Body-mass index (BMI) was calculated as body weight divided by the square of the height. Heart rate, systolic, and diastolic blood pressure of patients were recorded at the same time of coronary angiography. Clinical information included data on systemic hypertension (HTN), diabetes mellitus, dyslipidemia, smoking, and previous history of CAD. Diabetes was based on a fasting blood sugar level ≥126 mg/dL or use of an anti-diabetes medication. Hypertension was reported for systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or use of antihypertensive agents. Smoking included active or previous (>10 pack-years) tobacco use. A 12-lead electrocardiography (ECG) was recorded, and transthoracic echocardiography study was performed with a 3.5-MHz transducer to all patients (Vivid 3; GE Medical System, Horten, Norway). The left ventricular ejection fraction (LVEF) was measured according to the Simpson's method. The study protocol was approved by the local ethics committee of the Adıyaman University Training and Research Hospital, and each patient provided written, informed consent.

Statistical Analyze

Data were analyzed with SPSS software version 20.0 for Windows (SPSS Inc, Chicago, Illinois). The Kolmogorov-Smirnov test was used to verify that continuous variables were normally distributed. Normally distributed variables were expressed as mean ± standard deviation (SD). The categorical variables are presented as percentages. Differences between two groups were evaluated with Student's unpaired t-test for parameters with a normal distribution. The frequencies of nominal variables were compared using Fisher's exact test or chi-square test. The Pearson test was used for correlation analysis. Statistical significance was defined as $P < .05$

RESULTS

The demographic and clinical data of the study population are presented in **Table 1**. No difference was found in the demographic characteristics between the groups regarding age and gender. In the electrocardiographic analyze, the heart rate was similar between the groups. There was no significant difference between the groups regarding ejection fraction, body mass index, and glomerular filtration rate. The beta blocker and calcium channel blocker usage are higher in the normal coronary flow group. Biochemical parameters were similar between the groups regarding glucose, creatine, total cholesterol, triglyceride, and high-density lipoprotein, whereas the CRP, **Aspartate trans aminase (AST), Alanine trans aminase (ALT)**, low-density lipoprotein, white blood cell, and hemoglobin were significantly higher in the CSF group. Against the PCT was similar, the CRP was significantly higher because of inflammatory status in the CSF group than the control group ($p<0.01$). **Table-2** shows the significant differences in the TFC between the groups. There was a positive and significant correlation between the Mean-TFC and CRP, AST, and ALT **(Table-3)**. The correlation between the PCT and Mean-TFC was insignificant ($r= -0.100$, $p=0.927$). **Figure-1** presents the correlation between CRP and Mean-TFC in the groups. There was no correlations between the CRP and PCT ($r= -0.134$, $p= 0.204$) **(Figure-2**).

Table.1 The demographic and clinical data of the study population.

	Coronary Slow Flow n=50	Normal Coronary Flow n=42	p
Age (years)	53.86±9.85	49.11±10.33	0.51
Male %(n)	52(26)	41(18)	0.38
BMI (kg/m2)	25.52±2.38	25.44±2.68	0.88
Hypertension (%)n	26(13)	31(13)	0.59
Diabetes mellitus (%)n	24(12)	12(5)	0.13
Smoking (%)n	30(15)	31(13)	0.92
Ejection Fraction (%)	56.80±3.75	57.26±3.70	0.55
Systolic BP (mm Hg)	122.20±12.30	122.02±12.45	0.94
Diastolic BP (mm Hg)	76.50±8.28	76.67±8.09	0.92
Heart rate (bpm)	77.50±12.46	82.02±13.57	0.09
ASA (%)n	26(13)	28(12)	0.78
Beta blocker (%)n	12(6)	28(12)	**0.04**
ACE inhibitor/ARB (%)n	8(4)	28(12)	0.10
CCB (%)n	4(2)	19(8)	**0.02**
Statin (%)n	16(8)	9(4)	0.35
OAD (%)n	12(6)	12(5)	0.98
PCT (ng/ml)	0.15±0.07	0.15±0.18	0.86
CRP (mg/L)	0.82±0.51	0.42±0.38	**<0.01**
Serum glucose (mg/dl)	107.96±34.29	106.10±27.25	0.77
Creatinine (mg/dl)	0.77±0.17	0.73±0.14	0.16
Aspartatetransaminase (U/l)	37.74±12.68	18.74±5.89	**<0.01**
Alaninetransaminase (U/l)	39.14±14.46	19.10±12.45	**<0.01**
Albumin (g/dL)	4.04±4.04	4.06±0.33	0.83
Total cholesterol (mg/dl)	192.74±38.79	190.14±47.66	0.77
Triglyceride (mg/dl)	202.98±85.85	172.45±84.48	0.09
High density lipoprotein (mg/dl)	40.62±12.59	44.71±12.61	0.12
Lowdensity lipoprotein (mg/dl)	120.92±26.99	104.21±23.97	**<0.01**
White bloodcell count (103/mm3)	8.16±1.89	7.24±2.03	**<0.01**
Hemoglobin (g/dL)	14.12±1.55	13.29±1.76	**0.01**
Hematocrit (%)	43.62±4.44	41.86±4.19	0.05
Platelet count (103/mm3)	250.18±59.69	231.07±63.26	0.14
Lymphocyte (103/mm3)	2.51±0.77	2.41±0.83	0.57
Neutrophyle (103/mm3)	4.87±1.94	4.30±1.16	0.10
Glomerularfiltration rate (ml/min/1.73m2)	57.82±14.19	59.10±13.76	0.66

BMI, Body Mass Index; ACE, Angiotensin ConvertingEnzyme; ARB,Angiotensin Recepto rBlockers; CCB, Calcium Channel Blockers; OAD, Oral Antidiabetic Drug; PCT, procalcitonin; CRP, C-reactive protein.

Table-2. Angiographic TIMI Frame Count (TFC) of the coronary arteries in the groups.

	Coronary Slow Flow (n=50)	Normal Coronary Flow (n=42)	p
LAD-TFC	44,28±7,16	15,93±3,47	<**0.01**
CX-TFC	24,84±7,44	12,36±3,08	<**0.01**
RCA-TFC	20,86±4,35	10,79±2,78	<**0.01**
MEAN TFC	75,28±12,18	27,08±5,89	<**0.01**
cLAD-TFC	29,99±4,75	13,02±2,69	<**0.01**
Total-TFC	89,98±14,25	39,07±8,08	<**0.01**

LAD, Left Anterior DescendingArtery; CX, Circum flexArtery; RCA, Right Coronary Artery; cLAD, corrected Left Anterior Descending Artery.

Table-3. The correlation between Mean TFC and PCT, CRP, AST, ALT, GFR and BMI.

	r	p
PCT (ng/ml)	–0.100	0.927
CRP (mg/L)	0.413	**0.001**
AST	0.735	**0.001**
ALT (U/l)	0.605	**0.001**
GFR (ml/min/1.73m2)	–0.410	0.695
BMI (kg/m2)	0.035	0.741

TFC, TIMI Frame Count; PCT, procalcitonin; CRP, C-Reactive Protein; AST, Aspartate Transaminase; ALT, Alanine Transaminase; GFR, Glomerular Filtration Rate; BMI, Body Mass Index.

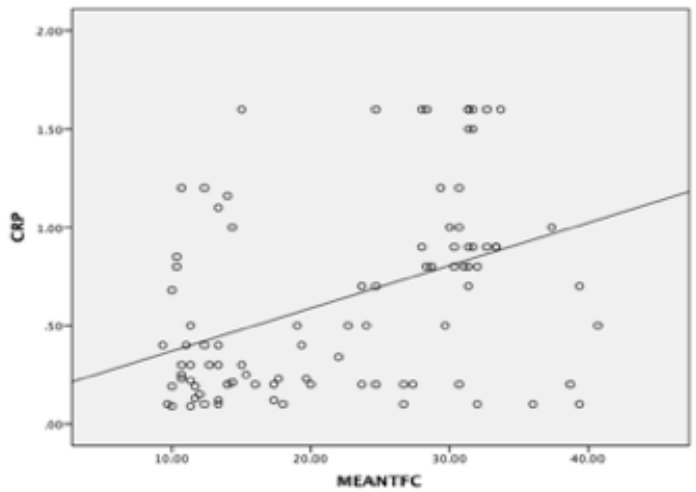

Figure-1. The correlations between the CRP (C-Reactive Protein) and Mean-TFC (TIMI Frame Count).

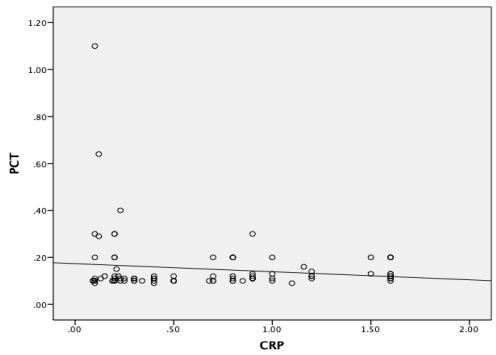

Figure-2. There was no correlations between the CRP (C-Reactive Protein) and PCT (Procalcitonin) (r= -0.134, p= 0.204).

DISCUSSION

This study demonstrated two major findings in patients with CSF. First, the CRP levels were significantly higher in the CSF group. Second, there was no significant correlation between concentration PCT and CRP levels.

PCT is known to be elevated in systemic inflammation, particularly if associated with bacterial infections. Inflammation with following monocytic activation is essential for PCT production(14). PCT is a chemoattractant, and it is initially produced in adherent monocytes, and it plays an essential role during monocyte adhesion and migration. PCT is a novel biomarker of inflammation in cardiovascular diseases (15,16). In patients with atherosclerosis, ischemia, and inflammatory processes lead to the production of PCT. A recent study showed that elevated PCT concentration is associated with a worse prognosis in CAD (12). Erren et al. showed that increased PCT correlated with the degree of atherosclerosis in patients with coronary artery and peripheral arterial disease (17). In addition, Sinning et al. evaluated the relationship between PCT and cardiovascular mortality in CAD (18). They found that increased PCT was related to cardiovascular mortality, and the concentration of PCT increased relative to the number of affected coronary arteries. Also, they reported that PCT was not superior to CRP to predict outcome in CAD. In the present study, we found that PCT concentration was similar between CSF patients and healthy subjects. PCT concentration is associated with no-reflow after primary percutaneous coronary intervention in ST-elevation myocardial infarction (STEMI) patients (19). Kurtul et al. showed that there was a positive correlation between PCT

and SYNTAX score in patients with stable CAD (20). In addition, they found that PCT and high sensitive CRP (Hs-CRP) levels positively associated with atherosclerosis in the CAD.

A study by Haverkate et al. showed that serum CRP levels in patients with unstable angina pectoris (UAP) and acute myocardial infarction (AMI) were higher than the levels in patients with stable angina pectoris (8). Also, Şentürk et al. found that there was no relationship between the extent of CAD and the levels of serum CRP in patients with the acute coronary syndrome (ACS) (21). However, in another study, it is indicated that there was a relationship between serum CRP levels and CAD (22). Ilhan et al. showed that there was a strong correlation between the levels of CRP and PCT in patients with ACS(16). In our study, we found that there was no correlation between the CRP levels and concentration of PCT in patients with CSF. Ilhan et al. evaluated the PCT and CRP levels for the assessment of inflammation related to atherosclerosis in patients with ACS (16). Inflammation plays an essential role in the development of atherosclerosis, and they found that concentration PCT and CRP levels were significantly increased in patients with ACS compared to the patients with stable angina. Also, in the same study, it is revealed that there was a strong correlation between the levels of PCT and CRP. Measurement of CRP levels may provide information relating to the severity of the cardiovascular disease (23). Murat et al. studied the relationship between PCT levels and no-reflow in patients with STEMI (19). They found that increased PCT levels were an independent predictor for no-reflow (NR) in patients with STEMI. Kafkas et al. suggested that PCT might be considered as a novel and a sensitive myocardial marker in patients with AMI (11).

The pathophysiology of CSF remains incompletely understood, but one of the most possibilities are endothelial dysfunction and relationship to atherosclerosis. Previous studies demonstrated myofibril disorganization, cellular edema, microvascular thickening with luminal narrowing, and fibromuscular hyperplasia in patients with CSF (24, 25). There is a close relationship between endothelial dysfunction and inflammatory parameters (26). A study by Xia et al. showed that elevated platelet count, serum uric acid, and Hs-CRP levels are independent predictors for CSF (27). In addition, Selcuk et al. found that patients with chronic obstructive pulmonary disease and CSF had elevated levels of Hs-CRP (28). A previous study showed that inflammatory parameters display an increase in patients with CSF (29). Çetin et al. found that serum albumin and Hs-CRP were significant predictors of CSF, and serum albumin was a better biomarker than Hs-CRP to predict CSF (30). They, also found that Hs-CRP levels were

significantly higher in patients with CSF than in healthy controls and correlated with the TFC. Similarly, we found the same findings in patients with CSF. The CRP levels were significantly higher in the CSF group, and it is correlated with the mean TFC. There was no study investigating the relation between PCT levels and CSF previously. In our study, we showed that PCT levels were similar in CSF patients and normal coronary flow subjects.

Limitations

This present study has some limitations. This was a single-center study and based on a relatively small group of patients. Coronary blush grade and extent of coronary thrombus parameters were not analyzed in the coronary angiography. Lack of other established inflammatory markers, such as interleukin-6 and tumor necrosis factor-α, is another limitation of the study. The multi-center prospective and randomized studies are needed to confirm our findings.

Conclusion

In conclusion, Serum PCT level was not associated with CSF. We have described the relationship between serum CRP and CSF, and this finding suggests that CRP might reflect the inflammatory process in the vascular system.

Disclosure Statement: All authors have no declarations of interest to report.

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