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Koroner yavaş akım olan hastalarda pentraksin-3 düzeyi artmıştır

Increased pentraxin-3 level in patients with slow coronary flow

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Özet

Amaç: Koroner yavaş akım (YKA), anjiyografisinde normal koroner arterlere sahip olup opak maddenin koronerlerin distaline geç ulaşması ile karakterizedir. YKA'ın inflamasyon ve yüksek duyarlıklı C reaktif protein (hs-CRP) gibi inflamatuvar belirteçler ile ilişkisi bilinmektedir. Pentraksin-3 (PTX-3), yeni bir akut faz reaktanı olup CRP gibi pentraksin ailesinin bir üyesidir. Biz bu çalışmada YKA hastalarında PTX-3 düzeyini araştırdık.

Yöntem: Çalışmaya YKA saptanan 25 hasta ve koroner arter hastalığı (KAH) olan 26 hasta alındı. Yavaş koroner akım ve KAH tanısı koroner anjiyografi ile konuldu. Kardiyoloji polikliniğine başvurmuş iskemik bulguların gözlenmediği 24 sağlıklı birey kontrol grubu olarak alındı. Tüm grubun PTX-3 ve hs-CRP çalışıldı.

Bulgular: KYA grubundaki hastaların PTX-3 ve hs-CRP seviyesi kontrol grubuna göre daha yüksekti(sırasıyla 0.52 ± 0.2 ng/ml ve 0.20 ±0.08 ng/ml, p< 0.001; 1.1±0.4 mg/dl ve 0.6±0.5 mg/dl, p< 0.001). Ancak KYA grubu ile KAH grubu arasında serum PTX-3 ile hs-CRP seviyesinde fark bulunmadı (sırasıyla 0.52 ± 0.2 ng/ml ve 0.58 ± 0.18 ng/ml, p: 0.24; 1.1 ± 0.4 mg/dl ve 1.1 ± 0.6 mg/dl; p: 0.32). Korelasyon analizi sonucu serum PTX-3 ve hs-CRP seviyeleri birbirleriyle ilişkili bulundu. (Rho=0.34, p: 0.003).

Sonuç: PTX-3, yeni bir inflamatuvar marker olup YKA olan hastalarda yükselmiştir ve bu hastalarda inflamatuvar durumu yansıtmada bir belirteçtir.

Anahtar Kelimeler: Koroner yavaş akım, hs-CRP, inflamasyon, Pentraksin-3.

Abstract

Objective: Slow coronary flow (SCF) is defined as late opacification in the epicardial coronary artery without significant stenosis on the coronary angiographic images. The association between SCF and inflammation and inflammatory markers such as high sensitivity-C reactive protein (hs-CRP) is well known. Pentraxin-3 (PTX-3), a new acute phase reactant, is a member of pentraxine family like hs-CRP. We investigated the association between PTX-3 and hs-CRP in patients with SCF.

Method: The study included 25 patients with SCF and 26 patients with coronary artery disease (CAD) whose diagnoses were made by coronary angiography. The control group consisted of 24 healthy subjects admitted cardiology outpatient clinic without any sign of ischemia. From the all study population PTX-3 and hs-CRP levels were measured.

Results: The SCF group had significantly increased PTX-3 and hs-CRP levels than the control group (0.52 ± 0.2 ng/ml vs 0.20 ±0.08 ng/ml, p< 0.001; 1.1±0.4 mg/dl vs 0.6±0.5 mg/dl, p< 0.001, respectively). However there were no differences in levels of PTX-3 and hs-CRP between the SCF and the CAD groups (0.52 ± 0.2 ng/ml vs 0.58 ± 0.18 ng/ml, p: 0.24; 1.1 ± 0.4 mg/dl vs 1.1 ± 0.6 mg/dl; p: 0.32, respectively). Correlation analysis revealed a positive correlation between serum PTX-3 levels and hs-CRP levels (r=0.34, p: 0.003).

Conclusion: PTX-3, a novel inflammatory marker, is elevated in patients with SCF and may be reflecting the inflammatory status in patients with SCF.

Keywords: Slow coronary flow, Pentraxin-3, hs-CRP.

Introduction

Slow coronary flow (SCF) is characterized by deceleration of filling and emptying time of contrast medium without any obstructive lesion in epicardial coronary artery (1). When examined with Thrombolysis in Myocardial Infarction (TIMI) frame count method (2), coronary blood flow was seen to be increased numerically compared to normal individuals (3). Many opinions were suggested addressing SCF mechanism and those were reserve abnormality at microvascular level, diffuse atherosclerosis, microvascular dysfunction, and endothelial dysfunction (4-6). Atherosclerosis is considered as an inflammatory process involving leukocytes and inflammatory markers (7). It was shown that acute phase reactants, such as C-reactive protein (CRP) and interleukin-6 (IL-6) also increased in SCF (8).

Pentraxin-3 (PTX-3) is a novel acute phase reactant similar to CRP in structure and function (9). This biomarker of inflammation, which was shown to increase in metabolic syndrome, stabil angina pectoris, unstable angina pectoris and acute myocardial infarction was demonstrated to be associated with

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cardiovascular poor prognosis after acute coronary syndrome (10-12). It is known that there is a chronic inflammation in all forms caused by atherosclerosis. The present study was designed to investigate the serum levels of PTX-3 in patients with SCF.

Material and Method

The study included 25 patients (16 men, mean age 42.1±2.8 years) with SCF and 26 patients (18 men, mean age 41.7±3.4 years) with CAD whose diagnoses were made by coronary angiography. Diagnosis of SCF was based on TIMI frame count and the presence of normal coronary arteries without luminal irregularities. Coronary artery stenosis was considered significant in the presence of a luminal diameter narrowing of >50% in any of major coronary arteries or their primary branches with normal coronary flow. The control group consisted of 24 healthy subjects admitted cardiology outpatient clinic without any sign of ischemia. Patients with acute coronary syndrome, history of previous myocardial infarction, coronary artery bypass grafting (CABG) or percoutenous coronary intervention (PCI), secondary hypertension (HT), renal failure, hepatic failure, chronic obstructive lung disease and/or manifest heart disease, such as cardiac failure (left ventricular ejection fraction <50%), atrial fibrillation, and moderate to severe cardiac valve disease were excluded from the study. Similarly, patients with infection, acute stress, chronic systemic inflammatory disease, and those who had been receiving medications affecting the number of leukocytes were excluded, as well. All the participants included in the study were informed about the study, and their oral and written consents on participating voluntarily were obtained. Our study was approved by the local ethics committee.

Table-1. Baseline clinical and laboratory characteristics of patient groups

Variables	SCF group (n=25)	CAD group (n=26)	Control group (n:24)	p value
Age (years)	42.1±2.8	41.7±3.4	42.2±3.2	0.47
Sex, male (%)	16 (64%)	18 (69%)	14 (58%)	0.72
BMI (kg/m^2)	25.2±4.5	25.6±3.3	25.1±5.4	0.89
Smoking (%)	14 (56%)	15 (57.6%)	15 (62.5%)	0.89
Ejection Fraction (%)	61.4±3.1	60.2±2.4	62.3±3.1	0.38
Glucose (mg/dL)	89.4±14.2	88.8±14.8	86.5±17.1	0.33
HDL-C (mg/dL)	34,4±9	33±8.7	35±9	0.69
LDL-C (mg/dL)	116.7±30.5	126.6±32.7	112.5±33.9	0.41
TG (mg/dL)	171±87	154±82	147±61	0.65
Creatinine	0.92±0.27	0.90±0.23	0.93±0.23	0.83
TSH	1.5±0.2	1.37±1.28	1.32±0.38	0.58
Pentraxine-3 (ng/ml)	0,52±0,2	0,58±0,18	0,20±0,08	**<0.001**
hs-CRP (mg/dl)	1,1±0.4	1,1±0.6	0.6±0.5	**<0.001**
Hemoglobin (g/dL)	13.2±1.1	12.9±0.96	13.3±1.26	0.56
WBC,x10^3 mg/dl	8.67±2	8.08±1.73	8.53±2.8	0.604

CSF: coronary slow flow, CAD: coronary artery disease, BMI: body mass index, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, TG: triglyceride, TSH: thyroid stimulating hormone, WBC: White blood cell

Sample collection

After history was obtained and physical examination was completed, blood samples were obtained from the patients on the day of coronary angiography. Serum glucose, urea, creatinine, total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglyceride, and high sensitive-CRP (hs-CRP) levels were

investigated. Enzyme-linked immunosorbent assay (ELISA) kit (Immage hs-CRP EIA kit, Beckman Coulter Inc., USA) was used for serum hs-CRP measurement. Serum PTX-3 level was investigated using specific ELISA kit (Human PTX-3/TSG-14 Immunoassay, DPTX30, R&D Systems Inc., MN, USA). Left ventricular systolic functions were assessed with transthoracic echocardiography (TTE), and ejection fraction (EF, %) was calculated with Simpson method.

Coronary angiograph and analysis of TIMI frame count

All the images were evaluated by an interventional cardiologist. Coronary angiography was performed by the femoral approach using the standard Judkins technique. Coronary arteries on the left and right oblique planes, and cranial and caudal angles were demonstrated. As the contrast medium iopromid 370/100 ml (ultravist-Schering AG, Berlin;Germany) was used in all the patients. The coronary slow flow diagnosis was made using the TIMI frame count method (2). Frame count extended from the origin of the coronary artery to its most distal segments. As the frame in which the coronary artery ostium was completely filled with contrast selected as the outset frame. The distal reference points were the terminal bifurcations of the left anterior descending (LAD) and circumflex (Cx) arteries, and the first side-branch of the posterolateral artery and the right coronary artery (RCA). The final frame was selected as the frame in which the branch terminating distally had contact with the contrast matter. For further evaluation, corrected TIMI frame count was calculated for the LAD artery by dividing TIMI frame count of the LAD by a factor of 1.7. TIMI frame counts for the LAD and Cx arteries were assessed in the right anterior oblique projection with caudal angulation and for RCA in the left anterior oblique projection with cranial angulation. The cutoff values for TIMI frame count were taken from a previous study (for LAD: 36.2±2.6 ; for Cx:22.2±4.1; for RCA: 20.4±3.0) (2). Any TIMI frame count above these levels was considered coronary slow flow.

Statistical analysis

Statistical evaluation was performed by Statistical Package for the Social Sciences (SPSS) Version 17.0 (SPSS Inc, Chicago, IL, USA). Continuous variables were given as mean ± standard deviation (SD) and categorical variables as number (percentage). The difference between continuous variables distributing normally were analyzed with Student's t test or one-way analysis of variance (ANOVA) test, whereas the difference between continuous variables not distributing normally with Kruskal-Wallis test. Categorical variables were compared with Chi-square test. Spearman's test was used for correlation analysis. Each p value <0.05 was considered significant.

Results

The study population divided into three groups as follows: "Coronary artery disease (CAD)" group (n=26), "SCF" group (n=25), and control group (n=24). There were no differences between the groups for age, gender, body mass index (BMI), smoking, ejection fraction and levels of glucose, creatinine, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), white blood cell. General characteristics of the groups were shown in Table 1.

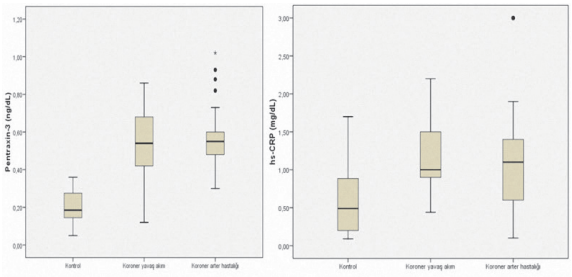

Figure 1. Pentraxin-3 and hs-CRP levels of patients according to groups.

Pentraxin-3 levels of the patients in CAD (0.58±0.18 ng/m vs 0.20±0.08 ng/m, p<0.001) and SCF (0.52±0.2 ng/ml vs 0.20±0.08 ng/ml, p<0.001) groups were higher than the control group. However, there was no significant difference between PTX-3 levels of CAD and SCF groups (0.58±0.18 ng/ml vs 0.52±0.20 ng/ml, p:0.24). Similarly, hs-CRP levels in CAD

and SCF groups were similar (1.1±0.6 mg/dl vs 1.1±0.4 mg/dL, p:0.32), whereas hs-CRP levels of both groups were higher compared to the control group (for CAD and control groups, 1.10±0.6 mg/dl vs 0.6±0.5 mg/dl, p<0.001; for SCF and control groups, 1.1±0.4 mg/dl vs 0.6±0.5 mg/dl, p<0.001). Correlation analysis revealed that serum PTX-3 and hs-CRP levels were associated (Rho=0.34, p=0.003).

Table-2. TIMI frame count measurements of the study population

Groups	CSF group (n: 25)	CAD group (n: 26)	p
LADc	44±4	24±4	<0.001
Cx	47±5	28±4	<0.001
RCA	49±4	21±3	<0.001

CSF: coronary slow flow, CAD: coronary artery disease, LAD: left anterior descending artery, Cx: Circumflex artery, RCA: right coronary artery /c: Corrected TFC was given for the LAD artery.

Coronary angiography results

Mean corrected TIMI frame counts were 44±4 for left anterior descending coronary artery (LAD), 47±5 for circumflex coronary artery (Cx), and 49±4 for right coronary artery (RCA). Mean TIMI frame counts of CAD group were 24±4 for LAD, 28±4 for Cx, and 21±3 for RCA (Table 2). (All p values were <0.001.)

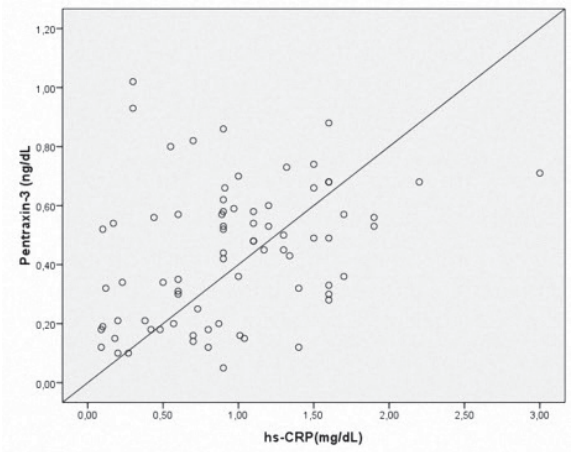

Figure 2. Correlation plots for PTX-3 and hs-CRP

Discussion

Our study results demonstrated that serum PTX-3, a novel promising inflammatory marker, levels were increased in patients with CSF which might propose the inflammation in the pathogenesis of the CSF.

Slow coronary flow (SCF) is a clinical feature characterized by deceleration of filling and emptying time of contrast medium administered during coronary angiography in where epicardial coronary arteries are normal (1). Although many factors are considered, the pathophysiology is yet to be clarified completely. Currently, microvascular reserve abnormality and circular impairment are mostly dwelled on mechanisms (4). There are studies showing that the cause of impaired circulation at microvascular level was related to endothelial dysfunction and diffuse atherosclerosis (5-6). Development of atherosclerosis is a chronic, complex process in which various factors play a role. Recent studies emphasized that inflammation played an active role in the process, and acknowledged that there was a chronic, systemic inflammation (9). Inflammatory cytokines and growth factors produce inflammatory and proliferative response on the vessel wall and cause microvascular destruction (13). Such endothelial dysfunction at microvascular level leads atherothrombosis or angina (14-15). Demonstration of diffuse atherosclerosis and elevation of acute phase reactants, such as CRP, are significant findings in understanding the etiopathogenesis of SCF (16-17). In the present study, while hs-CRP level in SCF group was found to increase significantly compared to the control group, there was no difference between CAD and SCF groups.

Pentraxin is an acute phase reactant that is a quite stable protein in discoid shape structurally composed of cyclic pentamers, and has subgroups as short and long pentraxins. C-reactive protein is the most known member of short pentraxin family, and is a marker accepted as an acute phase reactant in indicating subclinical inflammation. Pentraxin-3 belongs to long pentraxin family, and has different features from CRP not only structurally, but also with different secretion site. While CRP is secreted from hepatocytes, PTX-3 is secreted from macrophages, dendritic

cells, neutrophils, fibroblasts, and vascular endothelial cells at the inflammation site (18). Pentraxin-3 is considered to be secreted locally in the main region where inflammation occurs (19). Furthermore, it is detected that PTX-3 is also produced at atherosclerotic plaque. Demonstration of correlated increase of PTX-3 secreted from neutrophils and platelet aggregation in acute coronary syndrome (20) may be one reason of increased platelet aggregation shown in patients with SCF (21). Level of PTX-3 was shown to increase in acute atherothrombosis in CAD, and was accepted as a predictor of mortality (20). In the present study, it was found that PTX-3 levels were significantly higher in CAD and SCF groups compared to the control group.

Limitations

The major limitation of the present study is the low number of patients included. Additional inflammatory markers such as IL-6, TNF-alpha, etc. would give more detailed data. Due to no long term follow up of these patients, there is no prognostic data in terms of future cardiovascular events which may be considered as another limitation. TIMI frame count might be influenced by heart rate, nitrate usage and coronary catheter size. However, we excluded the patients who were on nitrates and the all the patients were catheterized with a constant catheter size.

Conclusion

PTX-3, a novel inflammatory marker, is elevated in patients with SCF and may be reflecting the inflammatory status in patients with SCF.

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