Acute phase reactants in patients with coronary slow flow phenomenon

Koroner yavaş akım fenomeni olan hastalarda akut faz reaktanları

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ABSTRACT

Objective: In this study, we sought to investigate the serum levels of high sensitivity C-reactive protein (Hs-CRP), N-terminal pro-brain natriuretic peptide (NT proBNP), erythrocyte sedimentation rate, leukocyte, thyroid hormone and fibrinogen levels in patients with coronary slow flow phenomenon (CSFP).

Methods: A total of 82 patients with angiographically proven normal coronary arteries and slow coronary flow in all three coronary vessels (45 males and 37 females, mean age 59±11 years) and 34 patients with normal coronary arteries and normal coronary flow (19 males and 15 females, mean age 56±10 years) with similar risk profiles were included in this cross-sectional observational study. Coronary flow rates of all patients and control subjects were documented by Thrombolysis In Myocardial Infarction (TIMI) frame count, serum level of Hs-CRP, NT proBNP, sedimentation, leukocyte, free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH) and fibrinogen levels were measured. Statistical analysis was performed using t test for independent samples, Chi-square test and Pearson correlation analysis.

Results: Hs-CRP (0.88±0.86 vs 0.36±0.35 mg/L, p<0.001) and NT proBNP (117.83±163.2 vs 47.33±30.6 ng/ml, p<0.01) were found to be significantly higher in patients with coronary slow flow compared with normal control group. There were no significant differences regarding thyroid hormones, fibrinogen, sedimentation rate and leukocyte count between two groups. The mean TIMI frame counts were positively correlated (r=0.454, p=0.001 and r=0.554, p=0.001, respectively) with plasma Hs-CRP levels and NT-proBNP levels.

Conclusion: Hs-CRP and NT proBNP are significantly higher in patients with coronary slow flow compared with normal control group. Their increased levels are positively correlated with TIMI frame count. *(Anadolu Kardiyol Derg 2010; 10: 416-20)*

Key words: Coronary artery disease, coronary angiography, coronary slow flow, C-reactive protein, N-terminal pro-brain natriuretic peptide

ÖZET

Amaç: Çalışmamızda koroner yavaş akımlı hastalarda yüksek-duyarlı C-reaktif protein (Hs-CRP), N-terminal pro-beyin natriüretik peptit (NT-proBNP), eritrosit sedimantasyon hızı, lökosit, tiroid hormonları ve fibrinojen seviyelerini araştırmayı amaçladık.

Yöntemler: Bu enine-kesitli gözlemsel çalışmaya koroner arterleri normal olarak değerlendirilen fakat üç koroner damarında da yavaş akımı olan 82 hasta (45 erkek, 37 kadın, ortalama yaş 59±11), normal koroner arter yapısına, normal koroner akıma ve benzer koroner risk faktörlerine sahip 34 olgu (19 erkek, 15 kadın, ortalama yaş:56±10) çalışmaya dahil edildi. Hastaların ve kontrol grubunun koroner akım hızları TIMI kare sayısı yöntemi ile ölçüldü. Kan numunelerinden Hs-CRP, NT ProBNP, sedimantasyon, lökosit sayısı, tiroid hormonları ve fibrinojen seviyeleri ölçüldü. İstatistiksel analiz bağımsız örneklem t testi, Ki-kare testi ve Pearson korelasyon analizi ile yapıldı.

Bulgular: Hs-CRP (0.88±0.86'ya karşın 0.36±0.35 mg/L, p<0.001) ve NT proBNP (117.83±163.2'ye karşın 47.33±30.6 ng/ml, p<0.01) seviyeleri koroner yavaş akım grubunda kontrol grubuna göre istatistiksel açıdan anlamlı olarak yüksek bulundu. Tiroid hormonları, fibrinojen, sedimantasyon ve lökosit düzeylerine bakıldığında iki grup arasında anlamlı fark yoktu. TIMI sayısı ve plazma Hs-CRP ve NT-proBNP değerleri arasında pozitif korelasyon mevcuttu (sırası ile r=0.454, p=0.001 ve r=0.554, p=0.001).

Sonuç: Hs CRP ve NT ProBNP seviyeleri normal olgulara kıyasla koroner yavaş akımlı olgularda anlamlı düzeyde yüksek bulundu. Hs CRP ve NT ProBNP artmış seviyeleri ve TIMI kare sayısı arasında pozitif korelasyon ilişkisi mevcut. *(Anadolu Kardiyol Derg 2010; 10: 416-20)*

Anahtar kelimeler: Koroner arter hastalığı, koroner yavaş akım, koroner anjiyografi, C-reaktif protein, N-terminal pro-beyin natriüretik peptit

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Accepted/Kabul Tarihi: 12.01.2009

doi:10.5152/akd.2010.139

Introduction

Coronary slow flow phenomenon (CSFP) is not a rare finding in patients undergoing routine coronary angiography. CSFP was demonstrated in 25% of patients evaluated for angina or angina-like chest pain, who had normal epicardial coronary arteries on angiography (1). Since its original description in 1972 by Tambe et al. (2), the phenomenon of slow dye progression in the coronary arteries has been a well known entity. It has been reported that coronary endothelial dysfunction play an important pathogenetic role in patients with CSFP. Previously, inflammation has been reported to be a major contributing factor to many cardiovascular events, including initiation and progression of atherosclerosis, atherosclerotic plaque development and rupture, aortic aneurysm formation, angiogenesis, ischemia/reperfusion damage and variant angina (3, 4). Diffuse atherosclerosis and endothelial vasomotor dysfunction have also been suggested as possible responsible factors for CSFP (5-8). Myocardial biopsy studies have also revealed the presence of coronary microvascular disease in patients exhibiting CSFP (9, 10). Recent study have reported that the active metabolite of the thyroid hormone (FT3) reduced in patient with CSFP (11).

In addition, a large amount of data indicated that C-reactive protein (CRP), a sensitive marker of underlying systemic inflammation, is increased among men and women at risk for future cardiovascular events, and the addition of CRP testing to standard lipid screening seems to provide an improved method to determine vascular risk (12). Vila et al. (13) demonstrated that plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) is increased in a model of systemic infection/inflammation in healthy men with normal heart function. Therefore, NT proBNP is accepted as an acute phase reactant.

Although, previously a negative correlation between CRP and slow coronary flow was found in a smaller population of patients using the less sensitive technique, there is no data regarding relationship between NT-proBNP and slow coronary flow.

The aim of this study was to investigate the serum levels of high-sensitivity C-reactive protein (Hs-CRP), NT-proBNP, erythrocyte sedimentation rate, leukocyte, thyroid hormone and fibrinogen levels in patients with coronary slow flow phenomenon.

Methods

Study population

A total of 82 patients with angiographically proven normal coronary arteries and slow coronary flow in all three coronary vessels (45 males and 37 females, mean age 59±11 years) and 34 patients with normal coronary artery and normal coronary flow (19 males and 15 females, mean age 56±10 years) were included in this cross-sectional observational study.

The exclusion criteria were the use of anti-inflammatory and anti-ischemic drugs, acute or chronic infections, valvular heart disease, thyroid disease, coronary artery ectasia, known malignancy or inflammatory-immunologic disease, hepatic or renal dysfunction, history of myocardial infarction, left ventricular dysfunction and left ventricular hypertrophy on echocardiography. Ethics committee approval and informed consent was obtained from all patients.

Diagnosis of slow coronary flow and TIMI frame count

Selective coronary angiography was performed by femoral approach using the Judkins technique in conventional projections. A nonionic contrast agent (Iohexol, Nycomed, Ireland Ltd. Cork, Ireland) was used in this study. The time elapsing from the appearance of the contrast agent until it reaches the distal end of either left anterior descending artery (LAD), circumflex artery (Cx) or the right coronary artery (RCA) in terms of cine-frame count was considered for the quantitative measurement of coronary blood flow. Coronary arteries were demonstrated in the left and right oblique planes and in cranial and caudal angles by 25 fps rate in the same catheter laboratory using standard equipments. Thrombolysis in myocardial infarction (TIMI) frame count is a quantitative, simple, objective and reproducible index of coronary flow velocity (14). Initial frame count is defined as the frame in which concentrated dye occupies the full width of proximal coronary artery lumen, touching both borders of the lumen, and forward motion down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal end. Distal end was defined as distal bifurcation for the LAD and the Cx and first branch of posterolateral artery for RCA. The final count was then subtracted from the initial count and the exact TIMI frame count was calculated for the given artery. LAD coronary artery is usually longer than the other major coronary arteries (15), the TIMI frame count for this vessel is often higher. To obtain corrected TIMI frame count for LAD coronary artery, TIMI frame count was divided by 1.7 (14).

TIMI frame count in the LAD and Cx arteries were assessed in the right anterior oblique projection with caudal angulation and RCA in left anterior oblique projection with cranial angulation. Two cardiologists performed TIMI frame counting; in case of a disagreement, the frames were referred to a third cardiologist. Due to different durations required for normal visualization of coronary arteries, the corrected cutoff values were 36.28±2.6 frames for LAD, 22.28±4.1 frames for Cx, and 20.48±3 frames for RCA, as has been reported earlier in the literature (14, 15) . Any values in excess of these thresholds were considered as CSFP.

Blood sampling

Peripheral blood samples of both patients with coronary slow flow and control subjects were collected after a 12- hour overnight fasting. Plasma was obtained by centrifugation of 3000 rpm for 15 minute. Concentration of NT-proBNP were carried out on Roche modular Analytic E170 immunoassay analyzers by the agency of Elecsys NT-proBNP kit (Roche diagnostics, Mannheim,

Germany). The lower limit was accepted 5 pg/ml, and the upper limit was accepted 100 pg/ml. Plasma CRP concentrations were determined by turbidimetric method (UniCel® DxC 800 Synchron® Clinical System, Beckman Coulter, Inc., Brea, CA, USA). Leukocytes were measured Beckman Coulter Gens hematological analyzer (Beckman Coulter, Inc., Brea, CA, USA). Rate of erythrocyte sedimentation was determined by Alifax apparatus. Fibrinogen was measured by Sta Compact analyzer (Diagnostica Stago, Albio, France). FT3, thyroxine (fT4), thyroid stimulating hormone (TSH) were measured by an electrochemiluminescence method (Roche Modular Analytics E170 Elecsys module immunoassay analyzers equipment, Roche Diagnostics, Mannheim, Germany). The reference levels of thyroid hormones were taken as 2-4.9 pg/ml for fT 3, 0.82-1.63 ng/dl for fT 4 and 0.4-4 IU/ml for TSH.

Statistical analyses

All statistical analyses were performed using SPSS version 11.5 statistical pack software (SPSS Inc., Chicago, IL, USA). Data were expressed as proportions or mean value±SD. Unpaired t test was used for evaluation of continuous variables in the two groups and Fisher's exact test for proportions when appropriate. Our data showed a normal distribution of values for each group. Chi-square analysis and unpaired t test for independent samples were used to compare variables between groups. The correlations between plasma levels of Hs-CRP, NT-proBNP and mean TIMI frame count were assessed by the Pearson correlation test. The p values lower than 0.05 were considered statistically significant.

Results

There were no significant differences between the two groups regarding gender, age, hypertension and diabetes (Table 1). Smoking rate was significantly higher in the coronary slow flow group compared to the normal flow group ($p<0.001$).

Hs-CRP and NT ProBNP were found to be significantly higher in patients with coronary slow flow compared with normal flow group ($p<0.001$ and $p< 0.01$, respectively). There were no significant differences regarding thyroid hormones between the slow flow and normal flow groups ($p>0.05$ for all). There were no significant differences regarding levels of conventional markers of inflammation (leukocyte count, erythrocyte sedimentation rate and fibrinogen level) between the two groups ($p>0.05$ for all).

TIMI frame counts for all three major epicardial coronary arteries of patients with CSFP were significantly higher compared to the control subjects ($p<0.05$, Table 1). The mean TIMI frame counts were also significantly higher in patients with CSFP than in normal subjects.

The mean TIMI frame counts were positively correlated ($r=0.454$, $p=0.001$ and $r=0.554$, $p=0.001$, respectively) with plasma Hs-CRP levels (Fig. 1) and NT-proBNP levels (Fig. 2).

Table 1. Baseline clinical, laboratory and angiogarphic characteristics of study groups

Variables	Patients with CSFP	Normal	p*
Number of patients	82	34	-
Age, years	59±11	56±10	NS
Gender, female/male	45/37	19/15	NS
Cardiac risk factors, n (%)			
Hypertension	27(32)	12(35)	NS
Diabetes mellitus	9 (11)	5(14)	NS
Cigarette smoking	53(64)	13(38)	0.001
Typical angina	54(65)	18(52)	NS
Positive exercise test, n (%)	49(59)	11(33)	0.01
Hs-CRP, mg/L	0.88±0.86	0.36±0.35	0.001
NT-pro BNP, ng/ml	117.8±163	47.3±30	0.01
Leukocyte count, x 10^9/L	6.47±4.52	7.22±4.94	NS
Sedimentation, mm/h	13.63±9.25	11.22±8.83	NS
Fibrinogen, mg/dl	304±45	294±44	NS
Free T3, pq/ml	3.3±5.4	3.4±5.6	NS
Free T4, ng/dl	1.2±1.8	1.0±1.6	NS
TSH, uIU/ ml	4.3±7.5	3.9±6.5	NS
TIMI frame count, frame/s			
Left anterior descending artery	45±18	36±14	0.01
Left circumflex artery	43±19	35±17	0.03
Right coronary artery	40±18	33±15	0.04
Mean TIMI frame count, frame/s	41.8±17.0	34.6±16.0	0.001

Data are presented as mean±SD and proportions/percentages
*unpaired t test for independent samples and Chi-square test
BNP - brain natriuretic peptide, hs-CRP - high sensitive C-reactive protein, CSFP - coronary slow flow, NS - not significant, T3 - tri-iodothyronine, T4 - thyroxine, TSH - thyroid stimulating hormone

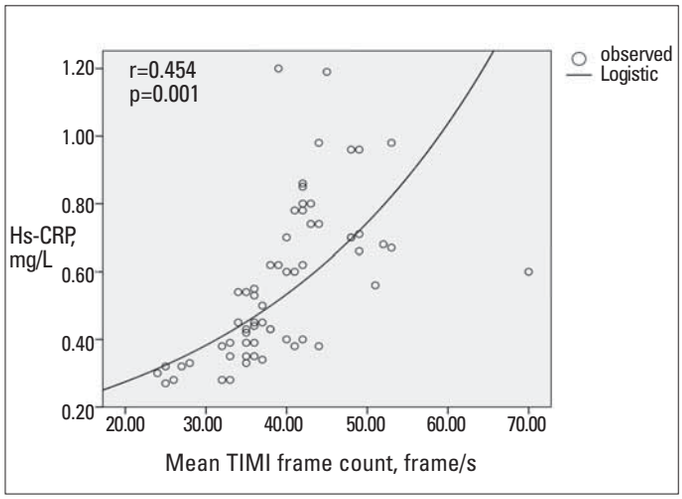

Figure 1. Correlation analysis between mean TIMI frame count and high-sensitive C-reactive protein (Hs-CRP)
Pearson correlation analysis

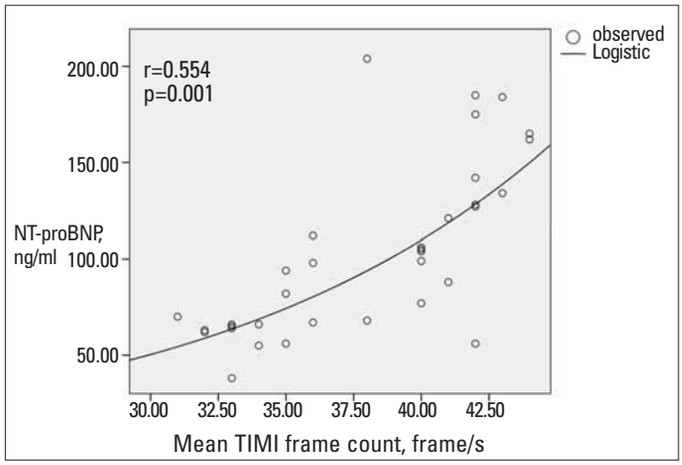

Figure 2. Correlation analysis between mean TIMI frame count and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels
Pearson correlation analysis

Discussion

Main finding of the present study was the increased the levels of Hs-CRP and NT-proBNP in patients with CSFP when compared to normal subjects. Moreover, a strong relationship was established between Hs-CRP and mean TIMI frame count.

Previous studies on relationship of acute phase reactants and slow coronary flow have reported controversial results (16, 17). Our findings on the presence of relation between Hs-CRP and TIMI frame count, may have emerged from the contribution Hs-CRP as inflammation marker to the atherosclerotic process and related coronary flow pattern (18). Slevin et al. (19) have shown the importance of CRP within the angiogenic microvessels from diseased tissues. Yazıcı et al. (17) have suggested that microvascular abnormalities have resulted in coronary slow flow. Plasma concentration of interleukin-6 and CRP levels were found to be increased in patient with slow coronary flow. Pekdemir et al. (18) found that the levels of CRP and TIMI frame count had no significant relationship in patients with CSFP. In this study, we assessed the levels of Hs-CRP, which is highly specific compared to CRP. In contrast to Yazıcı et al. (17) findings, the relationship between Hs-CRP and TIMI frame count were found to be correlated significantly in this study.

In some of the patients, coronary angiography already showed normal or near normal epicardial arteries with delayed opacification of the distal vasculature at rest (16). The normal coronary system consists of large epicardial vessels that normally offers little intrinsic resistance to coronary blood flow and small intramyocardial vessels (microcirculation) that, because of their small diameters and well-developed media, are the major source of coronary vascular resistance (17) Although the mechanisms of CSFP remain uncertain, occlusive disease of small coronary arteries has been suggested as the etiology (18). Based on this hypothesis, CSFP may be a form of early phase of atherosclerosis in some patients (18). Moreover, coronary microvascular endothelial dysfunction has been implicated in slow coronary flow (2). Recently, the association between slow coronary flow and impaired endothelium-dependent vasorelaxation has been demonstrated (10). Sezgin et al. (10) have also demonstrated that there is significant relationship between TIMI frame counts for major epicardial coronary arteries and endothelium-dependent vasodilatation in the brachial artery.

Inflammation has been reported to be a major contributing factor many cardiovascular event, and demonstrated to be associated with different clinical settings of coronary artery disease. The potential role of chronic inflammation has become increasingly recognized in cardiovascular diseases (6, 11, 20). Besides, endothelial activation and inflammation have been reported to be important precursors of initiation and progression of atherosclerosis (6, 21, 22). During the last few years, inflammation mechanism has also been suggested to be involved in CSFP. Turhan et al. (23) performed a study to evaluate plasma soluble adhesion molecules; intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin as possible indicators of endothelial activation or inflammation. The results of this study showed that serum ICAM-1, VCAM-1 and E-selectin concentrations of patients with CSFP were found to be significantly higher than those of control subjects with normal coronary flow. Li et al. (16) demonstrated that increased inflammatory markers including CRP and interleukin-6 (IL-6) were found in patients with CSFP.

We also demonstrated a relationship between pro-BNP and mean TIMI frame count in patients with CSFP. The relationship between CSFP and pro-BNP was not assessed previously. Baykan et al. (24) evaluated diastolic function by tissue Doppler technique and found a positive correlation with mean TIMI frame count in patients with CSFP. In our study, the relationship a positive correlation between proBNP and TIMI frame count was determined in patients with CSFP supporting the results of Baykan et al. (24).

Significantly high levels of Hs-CRP and NT-proBNP found in this study might be suggestive of a low-grade chronic inflammation involved in the pathogenesis of CSFP.

Regarding thyroid functions, Harun et al. (25) found that the levels of FT3 were reduced in patients with CSFP. In our study, we found that the FT3 level was reduced although insignificantly. The levels of FT4 and TSH did not differ significantly compared to the control group. Hypothyroid state can stimulate the atherosclerotic process and related coronary flow pattern. Previously both subclinical and overt hypothyroidism states have been found to be associated with coronary artery disease (25). Thyroid hormonal state has an important role in the development of endothelial dysfunction, which is suggested to be the underlying mechanism of CSFP.

Study limitations

The overall sample size of this study is small. Further studies with larger samples are required to validate our findings.

Conclusion

Our study demonstrated that patients with CSFP have increased levels of Hs-CRP and NT - proBNP compared to sub-

ject with normal coronary flow. The increased levels of Hs-CRP and NT - proBNP are positively correlated with TIMI frame count. This might suggest the role of inflammation in patients with CSFP.

Conflict of interest: None declared.

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