The relationship between inflammation and slow coronary flow: increased red cell distribution width and serum uric acid levels

Enflamasyon ve yavaş koroner akım ilişkisi: Kırmızı kan hücrelerinin dağılım genişliğinde ve serum ürik asit düzeylerinde artış

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ABSTRACT

Objectives: The underlying mechanism of slow coronary flow (SCF) has yet to be elucidated. Increased red cell distribution width (RDW) and uric acid level may be indicative of an underlying inflammatory state. We aimed to investigate RDW and serum uric acid levels in patients with normal coronary arteries and SCF without stenosis.

Study design: The study included 46 consecutive patients (25 males, 21 females; mean age 54±11 years) with angiographically normal coronary arteries but having SCF in all three coronary arteries. The control group consisted of 40 patients (18 males, 22 females; mean age 54±9 years) with angiographically normal coronary arteries without SCF. In both groups, RDW and serum uric acid levels were measured and compared.

Results: In the SCF group, TIMI frame counts measured in the left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery were significantly higher compared to the control group ($p<0.05$). Patients with SCF exhibited significantly higher RDW (13.4±1.6% *vs.* 12.6±1.2%, p=0.01) and serum uric acid levels (5.3±1.6 mg/dl *vs.* 4.7±1.3 mg/dl, p=0.01) compared to controls. In logistic regression analysis, uric acid [Exp(B)=1.612, 95% CI 0.206-5.35, p=0.021] and RDW [Exp(B)=1.496, 95% CI 0.403-4.72, p=0.030] were found as independent predictors of SCF.

Conclusion: Our findings show that patients with SCF have significantly increased RDW and serum uric acid levels. This may help throw more light on the pathophysiological basis of SCF.

ÖZET

Amaç: Yavaş koroner akımın (YKA) nedenleri tam olarak anlaşılamamıştır. Kırmızı kan hücrelerinin dağılım genişliğinde (KHDG) artma ve yüksek ürik asit düzeyi enflamasyon için belirteç olabilir. Bu çalışmada, koroner anjiyografide koroner damarlarda daralma olmaksızın YKA bulunan hastalarda KHDG ve serum ürik asit düzeyleri araştırıldı.

Çalışma planı: Çalışmaya, koroner anjiyografide koroner arterleri normal bulunmasına karşın, üç ana koroner arterde de YKA saptanan ardışık 46 hasta (25 erkek 21 kadın; ort. yaş 54±11) ile kontrol grubu olarak, koroner arterleri normal bulunan ve YKA olmayan 40 hasta (18 erkek, 22 kadın; ort. yaş 54±9) alındı. İki grupta KHDG ve serum ürik asit düzeyleri ölçülerek karşılaştırıldı.

Bulgular: Yavaş koroner akım grubunda sol ön inen arter, sirkumfleks arter ve sağ koroner arterde ölçülen TIMI kare sayıları kontrol grubuna göre anlamlı yükseklik gösterdi ($p<0.05$). Ortalama KHDG ve serum ürik asit düzeyi YKA grubunda kontrol grubuna göre anlamlı derecede daha yüksek bulundu (sırasıyla, %13.4±1.6 ve %12.6±1.2, p=0.01; 5.3±1.6 mg/dl ve 4.7±1.3 mg/dl, p=0.01). Lojistik regresyon analizinde, ürik asit [Exp(B)=1.612, %95 GA 0.206-5.35, p=0.021] ve KHDG [Exp(B)=1.496, %95 GA 0.403-4.72, p=0.030] YKA için bağımsız öngördürücüler idi.

Sonuç: Bulgularımız YKA'lı hastalarda KHDG ve serum ürik asit düzeyinin anlamlı derecede yükseldiğini göstermiştir. Bu bulgu YKA'nın patofizyolojik temelini anlamamıza yardımcı olabilir.

Received: March 8, 2011 *Accepted:* July 10, 2011

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Slow coronary flow is defined as late opacification in the epicardial coronary arteries without significant stenosis based on the coronary angiographic images.[1,2] On selective coronary angiography, the frequency of SCF is approximately 1%.[3] The underlying mechanism of SCF is not fully understood. Potential causes include small vessel disease, diffuse atherosclerosis, platelet dysfunction, microvascular dysfunction, and vasomotor dysfunction.[1,4,5] Atherosclerosis is a complex process in which inflammation plays a major role in conjunction with other factors observed both at the onset and during progression of the disease.[6,7] Recent studies investigating the role of inflammation in the etiology of SCF have demonstrated a significant relationship between inflammatory markers and coronary flow rate assessed by the TIMI (Thrombolysis in Myocardial Infarction) frame count method.[8-10]

Red cell distribution width, a measurement of variability and size of erythrocytes, is easily measured during routine complete blood counts.[11] Increased RDW have been reported to be associated with negative clinical outcomes in patients with heart failure, previous myocardial infarction, and stable coronary artery disease, independent of hemoglobin values.[12,13] The association of RDW with adverse outcomes in cardiovascular diseases has not been fully elucidated. Inflammation may induce changes in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW.[14] A strong correlation of RDW with inflammatory markers, C-reactive protein and sedimentation rate has also been observed.[15] Increased RDW may arise from an underlying inflammatory state that is associated with adverse outcomes.[16] Serum uric acid is one of independent risk factors for cardiovascular diseases.[17] Hyperuricemia is closely associated with inflammatory process. Inflammatory cytokines activate xanthine oxidase enzyme in epithelial cells, resulting in elevated serum uric acid levels.[18] Hyperuricemia with elevated CRP and interleukin-6 have been detected simultaneously in several inflammatory diseases.[19,20] Myocardial ischemia and hypoxia can induce hyperuricemia.[18]

In the present study, we aimed to investigate RDW and serum uric acid levels in patients with normal coronary arteries and SCF without stenosis.

PATIENTS AND METHODS

Study population

The study included 46 consecutive patients (25 males, 21 females; mean age 54±11 years) with angiographically normal coronary arteries but having SCF in all three coronary arteries. The control group consisted of 40 consecutive patients (18 males, 22 females; mean age 54±9 years) with angiographically normal coronary arteries without SCF. Normal coronary arteries were defined as coronary arteries without any obstructive or non-obstructive lesion in the left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery. Coronary angiograms were analyzed by cardiologists blinded to the patients' data. Patients with a history of coronary artery disease, heart failure, uncontrolled hypertension, and systemic disorders were excluded from the study. Approval was obtained from the local ethics committee and informed consent was obtained from all the participants.

Abbreviations:

CAD *Coronary artery disease*
CRP *C-reactive protein*
RDW *Red cell distribution width*
SCF *Slow coronary flow*
TFC *TIMI frame count*

Coronary angiography

Coronary angiography was performed using the Judkins technique. Coronary arteries were visualized in the left and right oblique planes with cranial and caudal angles at a speed of 30 frames per second. An injection of 5-8 ml contrast medium was given manually at each position. Coronary blood flow was quantified by two independent cardiologists who were blinded to the clinical data. Coronary flow rates of all subjects were determined by the TFC method. The TFC for each coronary artery was determined at a distal marking point specific for the coronary artery of interest.[21] Diagnosis of SCF was made as described previously.[22]

Laboratory measurements

Blood samples were drawn from an antecubital vein before coronary angiography after a 12-hour overnight fasting and were collected in K3 EDTA tubes. Hematologic parameters were measured on an automatic blood counter. Serum uric acid levels were measured using an enzymatic colorimetric test on a Roche/Hitachi analyzer.

Statistical analysis

All statistical analyses were performed using the SPSS (for Windows version 15) software package. Categorical variables were presented as counts and percentages and compared using the Pearson's chi-square test and Fisher's exact test. The Kolmogorov-Smirnov test was used to evaluate whether the variables were distributed normally. Continuous variables were presented as mean ± standard deviation or as median and 25th and

Table 1. Demographic and clinical characteristics of the study groups

	Slow coronary flow (n=46)			Control group (n=40)			
	n	%	Mean±SD/ Median (Q_1-Q_3)	n	%	Mean±SD/ Median (Q_1-Q_3)	*p*
Age (years)			54±11			54±9	0.99
Sex							0.39
Male	25	54.4		18	45.0		
Female	21	45.7		22	55.0		
Systolic blood pressure (mmHg)			126±19			127±24	0.89
Diastolic blood pressure (mmHg)			80 (70-90)			80 (70-90)	0.45
Body mass index (kg/m^2)			30.3±4.1			29.4±4.5	0.34
Hypertension	25	54.4		18	45.0		0.39
Diabetes mellitus	6	13.0		8	20.0		0.38
Family history	9	19.6		5	12.5		0.38
Smoking	9	19.6		9	22.5		0.74
Fasting serum glucose (mg/dl)			96 (86-111)			100 (91-114)	0.26
Total cholesterol (mg/dl)			204±41			203±39	0.95
HDL cholesterol (mg/dl)			44±12			44±11	0.92
LDL cholesterol (mg/dl)			123±30			129±31	0.36
Triglycerides (mg/dl)			152 (99-209)			121 (94-189)	0.57
Vitamin B_{12} (pg/ml)			264±121			275±121	0.75
Folic acid (ng/ml)			7.8±2.2			7.9±2.9	0.88
White blood cell count (10^3/mm^3)			6.5±1.7			6.8±1.9	0.52
Hemoglobin (g/dl)			14.0±1.4			13.6±1.5	0.15
Mean corpuscular volume (fl)			89±7			90±7	0.38
Red cell distribution width (%)			13.4±1.6			12.6±1.2	**0.01**
Uric acid (mg/dl)			5.3±1.6			4.7±1.3	**0.01**
Platelet count (10^3/mm^3)			224±56			229±54	0.69
Anemia[#]	10	21.7		11	27.5		0.54
Medications							
Angiotensin-converting enzyme inhibitor/ Angiotensin II receptor blocker	16	34.8		10	25.0		0.32
Beta-blocker	14	30.4		10	25.0		0.58
Calcium antagonists	5	10.9		4	10.0		1.00
Nitrates	6	13.0		4	10.0		0.75
Statins	13	28.3		6	15.0		0.14
TIMI frame counts							
Left anterior descending coronary artery			54 (42-70)			34 (33-37)	**<0.01**
Left circumflex coronary artery			29 (22-37)			22 (20-23)	**<0.01**
Right coronary artery			27 (25-34)			20 (19-22)	**<0.01**

[#]According to World Health Organization (WHO) definition.

75th percentile values. The independent two-sample t-test or Mann-Whitney U-test were used for comparison of continuous variables. Logistic regression analysis was performed to determine the role of variables for the development of SCF. A *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

There were no differences between the patients with and without SCF with regard to gender and age (p>0.05). The risk factors for CAD were similar between the two groups (Table 1). In the SCF group, TFCs measured in the left anterior descending artery, circumflex artery, and right coronary artery were significantly higher compared to the control group. Patients with SCF exhibited significantly higher RDW (13.4±1.6% *vs*. 12.6±1.2%, p=0.01) and serum uric acid levels (5.3±1.6 mg/dl *vs*. 4.7±1.3 mg/dl, p=0.01) compared to controls. The other hematologic and biochemical parameters were similar in the two groups. In logistic regression analysis, uric acid [Exp(B)=1.612, 95% CI 0.206-5.35, p=0.021] and RDW [Exp(B)=1.496, 95% CI 0.403-4.72, p=0.030] were found as independent predictors of SCF.

DISCUSSION

Red cell distribution width shows variability in the size of circulating erythrocytes and is routinely measured by automated hematology analyzers as part of a complete blood count.[10] We demonstrated increased RDW and serum uric acid levels in SCF patients compared to controls.

The underlying mechanism of late opacification in the epicardial coronary arteries without stenosis observed in SCF has yet to be elucidated. The histopathological characteristics are similar to those of coronary atherosclerosis and microvascular dysfunction. Free radical damage may be responsible for the pathological findings associated with coronary atherosclerosis and microvascular dysfunction.[1,4,23,24] Several studies have reported significantly increased intima media thickness of the carotid artery, a known marker of subclinical atherosclerosis in patients with SCF.[25,26] Atherosclerosis is a composite syndrome resulting from several factors.[27] Recently, mechanism-oriented studies on atherosclerosis have focused on inflammation.[28] Cardiovascular diseases have an established relationship with the inflammatory marker CRP.[15] Fukata et al.[29] showed that a chronic inflammatory state may correlate with increased mortality in patients with CAD. Parameters of inflammation in patients with SCF have been investigated and found to be increased compared to controls.[9,10,30] Li et al.[30] reported increased plasma concentrations of CRP and interleukin-6 and positive correlations with TFC in patients with SCF compared with normal coronary flow subjects. Increase in RDW is observed with nutritional deficiencies (iron, vitamin B_{12}, and folate deficiency), suggesting that these conditions may be associated with inflammation.[29] Inflammatory cytokines may cause increased heterogeneity of erythrocyte maturation and impairment.[29] Lippi et al.[15] demonstrated a graded association of RDW with high-sensitivity CRP and erythrocyte sedimentation rate, independent of other factors. The sympathetic system and renin-angiotensin system stimulate the release of erythropoietin which may in turn increase RDW. As a result, both chronic inflammation and neurohumoral activation can act together causing increased RDW that may further contribute to the atherosclerotic process.[28] Increased RDW was found to be independently and strongly associated with death and coronary events in patients with myocardial infarction[31] and heart failure.[32] In a study of healthy individuals, increased RDW was found as a powerful independent risk for future cardiovascular disease.[33] Uyarel et al.[34] demonstrated that higher admission RDW levels in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction were associated with increased risk for in-hospital and long-term cardiovascular mortality. Hyperuricemia may be caused by many inflammatory risk factors and it can further induce acute and chronic inflammation due to its co-product of superoxide.[18] Elevated serum uric acid levels have been shown to be related to carotid atherosclerosis, peripheral vascular disease, and CAD.[35-37] Yıldız et al.[17] reported that serum uric acid levels were higher in patients with SCF compared to controls. In this study, we consistently found high serum uric acid levels in patients with SCF.

In conclusion, we found that RDW and serum uric acid levels were higher in SCF patients than controls. These results may be important to understand the pathophysiological basis of SCF, but further studies with a greater sample size are needed to confirm our hypothesis.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Biological markers; blood flow velocity; coronary circulation; erythrocyte indices; inflammation; uric acid.

Anahtar sözcükler: Biyolojik belirteç; kan akım hızı; koroner dolaşım; eritrosit indeksi; enflamasyon; ürik asit.