Mean platelet volume in patients with slow coronary flow and its relationship with clinical presentation

Yavaş koroner akıma sahip hastalarda ortalama trombosit hacmi ve bunun klinik prezantasyonla ilişkisi

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Objectives: We investigated mean platelet volume (MPV) in patients with slow coronary flow (SCF) and its possible relationship with clinical presentation.

Study design: The study included 50 patients with SCF and otherwise normal coronary arteries and 22 patients (control group) with normal coronary arteries. In the SCF group, there were 26 patients with stable angina pectoris (SAP), and 24 patients with unstable angina pectoris (USAP). Coronary blood flow was measured using the TIMI frame count. To determine MPV, blood samples with K3 EDTA were processed after one hour of venipuncture. The relationship between MPV and SCF was sought.

Results: The mean TIMI frame count was markedly increased in patients with SCF compared to controls (p<0.0001). No significant differences existed between the groups with regard to white blood cell and platelet counts. Patients with SCF had significantly higher MPV values compared to controls (9.4±2.3 fl *vs* 8.1±2.0 fl, p=0.014). In subgroup analysis, MPV was significantly increased only in patients presenting with USAP, compared to patients with SAP (p=0.044) and controls (p=0.002). There was a positive correlation between the mean TIMI frame count and MPV in patients with SCF (r=0.32, p=0.01). In multivariate analysis, MPV was the only independent predictor of SCF (p=0.006, odds ratio=1.305, 95% CI=0.985-1.730).

Conclusion: Our findings show that MPV is increased in patients with SCF, and SCF patients presenting with USAP exhibit significantly increased MPV values, suggesting an altered platelet reactivity and aggregation which may require effective anti-platelet therapy in this patient subgroup.

Key words: Angina, unstable; blood flow velocity/physiology; coronary circulation/physiology; coronary disease; platelet activation; platelet count.

Amaç: Çalışmamızda yavaş koroner akımlı (YKA) hastalarda ortalama trombosit hacmi (OTH) ve bunun klinik prezantasyonla ilişkisi araştırıldı.

Çalışma planı: Çalışmada YKA saptanan, koroner arterleri normal 50 hasta ve normal koroner anatomiye sahip 22 hasta (kontrol grubu) incelendi. Yavaş koroner akım grubunda 26 hastada kararlı angina, 24 hastada kararsız angina vardı. Koroner kan akımı TIMI kare sayısından hesaplandı. Ortalama trombosit hacmini belirlemek için, K3 EDTA'lı kan örnekleri kan alımından bir saat sonra çalışıldı. Ortalama trombosit hacmi ile YKA arasındaki ilişki araştırıldı.

Bulgular: TIMI kare sayısı ortalaması YKA'lı hastalarda kontrollere göre anlamlı derecede yüksek bulundu (p<0.0001). Beyaz küre ve trombosit sayılarında gruplar arasında anlamlı fark saptanmadı. Ancak, OTH değerleri YKA grubunda anlamlı derecede daha yüksekti (9.4±2.3 fl ve 8.1±2.0 fl, p=0.014). Altgrup analizinde, OTH'nin sadece kararsız anginalı hasta grubunda, kararlı anginalı hastalardan (p=0.044) ve kontrollerden (p=0.002) anlamlı derecede yüksek olduğu görüldü. Yavaş koroner akımlı hastalarda ortalama TIMI kare sayısı ile OTH arasında pozitif ilişki saptandı (r=0.32, p=0.01). Çokdeğişkenli regresyon analizinde, OTH YKA'nın tek bağımsız öngördürücüsü idi (p=0.006, odds oranı=1.305, %95 güvenlik aralığı=0.985-1.730).

Sonuç: Bulgularımız, YKA'lı hastalarda OTH'nin artış gösterdiğini ve kararsız angina tablosuna, trombosit reaktivitesi ve agregasyonunda önemli değişiklikleri yansıtan anlamlı derecede yüksek OTH değerlerinin eşlik etmesi nedeniyle, bu hasta grubunda etkili anti-trombosit tedavi gerekebileceğini göstermektedir.

Anahtar sözcükler: Angina, kararsız; kan akım hızı/fizyoloji; koroner dolaşım/fizyoloji; koroner hastalık; trombosit aktivasyonu; trombosit sayısı.

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Platelets play a crucial role in the pathogenesis of atherosclerotic complications by contributing to thrombus formation or plaque rupture.[1] Larger platelets are hemostatically more active and are a risk factor for developing coronary thrombosis, leading to unstable coronary syndromes.[2-5] Platelet volume is a marker of platelet activation and function, and is measured using mean platelet volume (MPV).[6]

Slow coronary flow (SCF) is a well-recognized clinical entity, characterized by delayed opacification of coronary arteries in the presence of a normal coronary angiogram.[7,8] Albeit not frequent, clinical presentation with acute coronary syndromes could be seen in angiographic series.[9] We investigated the clinical value of MPV in SCF and its possible relation to clinical presentation.

PATIENTS AND METHODS

Study population. Among 3,475 consecutive patients who underwent their first diagnostic coronary angiography for the evaluation of angina in our center between June 2005 and January 2006, 50 patients with SCF and otherwise normal coronary arteries were selected for the study group, and 22 patients with normal coronary arteries were selected for the control group (group I). Patients with SCF were further divided into two groups depending on the presence of stable or unstable angina pectoris. Thus group II included 26 patients with stable angina pectoris (SAP), and group III included 24 patients with unstable angina pectoris (USAP). The patients were then prospectively evaluated to determine the relationship between MPV and SCF.

The subjects were defined as hypertensive if their blood pressure was ≥140/90 mmHg or if they were receiving any antihypertensive medication. Diabetes mellitus was defined as the presence of a history of antidiabetic medication usage or fasting glucose level above 126 mg/dl. Smoking status was classified as smokers or those who never smoked. All examinations were performed by investigators who had no information about the clinical status of the patients. Informed consent was obtained from all participants and the study protocol was approved by the ethical committee of our hospital.

In all groups, coronary arteriography was performed since most of the subjects were suffering from angina and angina-like symptoms (shortness of breath, palpitation, etc.) and their symptoms could not be adequately clarified with noninvasive tests. The criteria for unstable angina included symptoms of angina at rest, new-onset exertional angina, or recent acceleration of angina.[10]

Exclusion criteria were known coronary artery disease, coronary plaque in coronary angiography, peripheral artery disease, left ventricular systolic dysfunction, malignancy, renal and hepatic insufficiency, chronic inflammatory disease, thyroid gland dysfunction, pregnancy, septicemia, cerebrovascular accident, and thrombocytopenia.

Thrombolysis in Myocardial Infarction (TIMI) frame count and definition of slow coronary flow. Coronary arteriography was performed with a femoral approach using the Judkins catheters and iopromide (Ultravist-370, Schering AG, Berlin, Germany) as the contrast agent (cine angiographic equipment: Philips Integris H 3000, Holland; cine frame: 30 fps). The angiograms were recorded on a compact disc in DICOM format. Coronary blood flow was measured quantitatively using the TIMI frame count which was derived from the number of cine-frames recorded from the first entrance of contrast to its arrival at the distal end of either the left anterior descending artery (LAD), circumflex artery (Cx), or right coronary artery (RCA). The last frames used for the LAD, Cx, and RCA were those in which the dye first entered the mustache segment, distal bifurcation segment, and first branch of the posterolateral artery, respectively. The TIMI frame count of the LAD artery was corrected by dividing the final count by 1.7. The cut-off values were defined according to the TIMI frame count method of Gibson et al.[11] (36±2.6 for LAD, 22.2±4.1 for Cx, and 20.4±3.0 for RCA). TIMI frame counts were evaluated by an experienced observer blinded to the clinical status of the patients.

Blood samples and analysis. Blood samples were collected from the patients after a 12-hr overnight fasting. All routine biochemical tests were carried out on an autoanalyser (Roche Diagnostic Modular Systems). Plasma glucose concentrations were determined by an enzymatic glucose oxidase method (Roche Diagnostics, Ontario, Canada). For the analysis of MPV, blood samples with K3 EDTA were analyzed after one hour of venipuncture by the Sysmex XT-2000i analyzer (Sysmex, Kobe, Japan).

Statistical analysis. All statistical data were processed using the SPSS (11.5 for Windows) software. Data were expressed as mean ± standard deviation (SD). Student t-test, one-way ANOVA- and chi-square test were used to compare the variables. Correlations between the mean TIMI frame count and other parameters were analyzed. The multivariate model

Table 1. Clinical and biochemical characteristics of the three groups

	Group I (n=22)			Group II (n=26)			Group III (n=24)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			48±7			51±12			52±10	0.358
Sex										0.212
Female	3	13.6		3	11.5		4	28.6		
Male	19	86.4		23	88.5		20	83.3		
Hypertension	9	40.9		10	38.5		9	37.5		0.677
Diabetes	4	18.2		4	15.4		3	12.5		0.989
Smokers	7	31.8		10	38.5		10	41.7		0.141
Body mass index (kg/m^2)			27.9±3.3			27.3±3.3			28.1±4.8	0.151
Blood pressure (mmHg)										
Systolic			125.5±21.9			125.8±26.4			125.6±26.1	0.997
Diastolic			73.8±11.9			75.8±12.5			76.6±16.2	0.792
Mean TIMI frame count			23.8±8.5			42.8±18.3			44.0±13.6	<0.0001
Biochemical parameters										
Fasting plasma glucose (mg/dl)			98.1±15.6			100.5±24.4			103.0±37.5	0.859
Total cholesterol (mg/dl)			190.6±53.6			183.9±38.8			171.3±27.0	0.279
Triglyceride (mg/dl)			116.8±53.6			141.9±58.5			96.3±35.8	0.231
HDL-cholesterol (mg/dl)			49.0±12.0			44.0±7.3			52.2±13.3	0.112
LDL-cholesterol (mg/dl)			117.2±26.1			114.1±34.6			99.8±26.1	0.219
White blood cell count (x10^3/mm^3)			8.0±2.1			8.2±2.6			8.9±2.8	0.447
Platelet count (x10^3/mm^3)			23.0±0.6			21.8±0.6			26.1±0.7	0.07
Mean platelet volume (fl)			8.1±2.0			8.8±2.3			10.1±2.1	0.007

Gdoup I: Control group; Group II: Patients with stable angina pectoris; Group III: Patients with unstable angina pectoris; TIMI: Thrombolysis in Myocardial Infarction.

included SCF as the dependent variable and a simple linear regression analysis was made for independent variables. Odds ratios and 95% confidence intervals were also calculated. A P value of less than 0.05 was considered significant.

RESULTS

The two SCF groups did not differ significantly from the control group with regard to the frequency of hypertension, diabetes, smoking, and body mass index values. Characteristics of the three groups are summarized in Table 1.

Corrected TIMI frame counts were higher in both SCF groups (group II and III) compared to controls, being 42.94±14.42 and 45.25±22.62 *vs* 26.62±14.29 for LAD (p=0.007), 44.41±18.97 and 48.42±17.71 *vs* 20.35±6.50 for Cx (p<0.0001), and 38.86±17.20 and 40.71±20.95 *vs* 18.54±8.06 for RCA (p<0.0001), respectively. The mean TIMI frame count was markedly increased in patients with SCF compared to controls (p<0.0001) (Table 1). Twenty-four patients had SCF in three vessels, 15 patients in two vessels, and 11 patients in one vessel.

There were no significant differences between the three groups with regard to lipid profile, fasting glucose levels, white blood cell and platelet counts. However, MPV was found to be significantly higher in patients with SCF (9.4±2.3 fl *vs* 8.1±2.0 fl, p=0.014). In subgroup analysis, MPV was not significantly different in patients with SAP compared to controls (p=0.195), but patients with USAP had significantly increased MPV compared to group II (p=0.044) and group I (p=0.002) (Table 1).

There was a positive correlation between the mean TIMI frame count and MPV in patients with SCF (r=0.32, p=0.01; Fig. 1). The univariate relationships of MPV with other parameters are summarized in

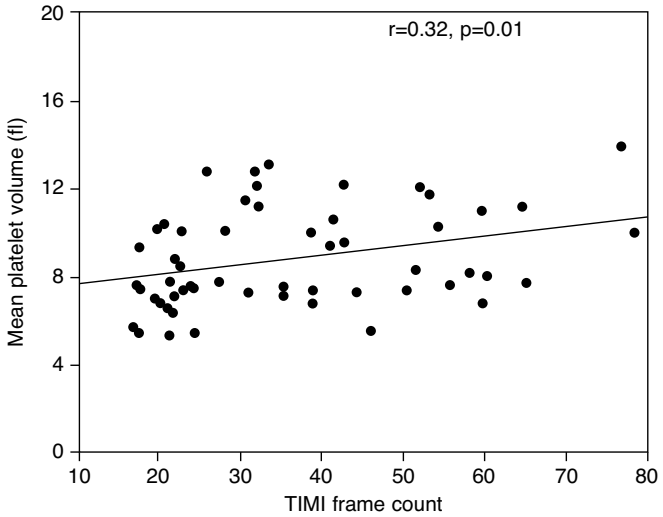

Figure 1. Correlation between the mean TIMI frame count and mean platelet volume.

Table 2. Univariate relationships between mean platelet volume and other parameters

	r	*p*
Age	0.01	0.91
Body mass index	0.11	0.09
Diabetes	0.07	0.61
Smoking	0.04	0.77
Hypertension	0.08	0.24
Platelet count	0.06	0.66
White blood cells	-0.06	0.59
Fasting plasma glucose	-0.01	0.93
Total cholesterol	-0.04	0.78
Triglyceride	0.09	0.27
HDL-cholesterol	-0.07	0.59
LDL-cholesterol	-0.10	0.34
Slow coronary flow	**0.30**	**0.01**
TIMI frame count	**0.32**	**0.01**
Unstable angina	**0.37**	**0.001**

Table 2. In multivariate analysis including age, sex, hypertension, clinical presentation, body mass index, glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, white blood cell and platelet counts, and MPV, it was found that MPV was the only independent predictor of SCF (p=0.006, odds ratio=1.305, 95% CI=0.985-1.730).

DISCUSSION

The present study showed that MPV was significantly higher in patients with SCF presenting with USAP, compared to patients with SAP and controls. It is known that platelets having dense granules are more active biochemically, functionally, and metabolically and are a risk factor for developing coronary thrombosis, leading to myocardial infarction.[12-15] In previous studies, increased MPV was demonstrated in acute myocardial infarction,[15] unstable angina pectoris,[6] congestive heart failure,[16] and coronary artery ectasia.[17] In acute coronary syndromes, platelet activation plays a considerable role.[5,15] Larger platelets secrete high levels of prothrombogenic thromboxane A2, serotonin, beta-thromboglobulin, and procoagulant membrane proteins like P-selectin and glycoprotein IIIa.[1,15] In addition, they are less sensitive to inhibitory effects of prostacyclin on aggregation and secretion than small platelets are.[17] In our study, no statistical difference was found between patients with SAP and controls with respect to MPV, supporting previous studies.[5,15]

Mean platelet volume varies with time in EDTA-anticoagulated samples.[18] EDTA-induced changes in platelet shape result in a progressive increase in MPV with impedance technology. Therefore, we analyzed the sample after one hour to allow stabilization of platelet shape and to lessen the disadvantage of EDTA in all the groups.

Slow coronary flow is a coronary microvascular disorder characterized by the delayed passage of contrast in the absence of an obstructive coronary disease. The exact pathophysiologic mechanisms of SCF phenomenon remain uncertain. Small vessel dysfunction has been implicated in the pathogenesis of SCF phenomenon since its first description.[7,8] In addition, platelet function disorders have also been suggested to be involved in the development of SCF.[19-21] The abnormal slow flow pattern in a coronary artery might lead to thrombus formation and, hence, distal embolization or myocardial infarction. In a study analyzing platelet aggregability with ristocetin, collagen, and adenosine diphosphate, it was shown that platelet aggregability was increased in patients with SCF compared with controls.[20] Increased platelet aggregability was also found in patients with cardiac syndrome X.[20,21] The results of these studies support our findings. However, both studies did not analyze clinical presentations in patient subgroups. Our study was the first to investigate the relationship between clinical presentation and MPV in SCF patients. In our study, MPV was increased in SCF patients compared with the control group. In addition, a positive correlation was found between TIMI frame count and MPV. In subgroup analysis, MPV was significantly increased only in SCF patients presenting with USAP, and increase in MPV in SCF patients presenting with SAP was not significant compared to controls.

In conclusion, our findings show that MPV is increased in patients with SCF, compared to controls having normal coronary angiograms. Furthermore, SCF patients presenting with USAP exhibit significantly increased MPV values, making clinical presentation to be a principal factor for increased MPV, and suggesting an altered platelet reactivity and aggregation which may require effective anti-platelet therapy in this patient subgroup. On the other hand, sufficient data was not obtained to justify the need for anti-platelet therapy in SCF patients presenting with SAP. Further prospective studies are required to establish the clinical significance of increased MPV and to investigate the role of anti-platelet agents in SCF.

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