Platelet Volume is Increased in Patients with Slow Coronary Flow

Trombosit Hacmi Yavaş Koroner Akımlı Hastalarda Artmıştır

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Geliş Tarihi/*Received:* 03.07.2010
Kabul Tarihi/*Accepted:* 13.10.2010

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ABSTRACT Objective: Slow coronary flow (SCF) is characterized by delayed opacification of coronary vessels in a normal coronary angiogram. Although clinical and pathological features have been previously described, the underlying pathophysiology has not been fully understood. The platelet function disorders have been suggested to play a role in the pathogenesis of SCF. The aim of this study was to assess the mean platelet volume (MPV), an indicator of platelet activation in patients with SCF. **Material and Methods:** The study group consisted of 35 patients with SCF. An age and gender matched control group was composed of 35 healthy volunteers. We measured serum MPV values in patients and control subjects. **Results:** The thrombolysis in myocardial infarction (TIMI) frame count for all the epicardial coronary arteries and the mean TIMI frame count were significantly higher in the SCF group than control group. MPV was significantly higher among patients with SCF when compared with control group (8.6 ± 0.9 vs. 8.1 ± 0.5 fl respectively; p= 0.004). The only univariate predictor of SCF was MPV (p= 0.007; OR, 2.58; CI, 1.29 to 5.15). The only multivariate predictor of SCF was MPV (p= 0.01 ; OR, 2.43; CI, 1.20 to 4.87). **Conclusion:** We have shown that MPV was significantly elevated in patients with SCF compared to control subjects.

Key Words: Platelet activation; coronary circulation

ÖZET Amaç: Yavaş koroner akım (YKA) normal koroner anjiyografide koroner damarların gecikmiş boyanmasıdır. Her ne kadar klinik ve patolojik özellikleri daha önce tanımlansa da altta yatan patofizyoloji kesin olarak anlaşılamamıştır. Trombosit fonksiyon bozukluklarının YKA'nın patojenezinde rol oynadığı sanılmaktadır. Bu çalışmanın amacı YKA'lı hastalarda trombosit aktivasyonun bir göstergesi olan ortalama trombosit hacmi'ni (OTH) değerlendirmekti. **Gereç ve Yöntemler**: Çalışma grubu YKA'lı 35 hastadan oluştu. Yaş ve cinsiyet eşitlenmiş 35 sağlıklı birey kontrol grubunu oluşturdu. Hasta ve kontrol grubunda OTH değerleri ölçüldü. **Bulgular:** Bütün koroner damarların "Thrombolysis in Myocardial Infarction" (TIMI) kare sayıları ve TIMI kare sayısı ortalaması YKA' lı hastalarda kontrollere göre anlamlı derecede yüksek bulundu. OTH YKA'lı hastalarda kontrol grubundan anlamlı derecede yüksekti (8.6 ± 0.9 ve 8.1 ± 0.5 fl; sırayla; p= 0.004). YKA'nın tek ünivariyat belirteci OTH idi (p= 0.007; OR, 2.58; GA, 1.29-5.15). YKA'nın tek multivaryat belirteci OTH idi (p= 0.01; OR, 2.43; GA, 1.20-4.87). **Sonuç:** Biz bu çalışmada, YKA'lı hastalarda OTH'nin kontrol grubuyla karşılaştırıldığında anlamlı olarak artmış olduğunu gösterdik.

Anahtar Kelimeler: Trombosit aktivasyonu; koroner dolaşım

Turkiye Klinikleri J Cardiovasc Sci 2010;22(3):279-83

Slow coronary flow (SCF) is an angiographic finding characterized by slow antegrade progression of contrast agent to the distal branch of a coronary artery in the absence of obstructive coronary artery disease.[1] Several mechanisms have been proposed for the etiology of SCF, including microvascular and endothelial dysfunction, small-vessel disease, diffuse at-

herosclerosis and inflamation.[1-5] Its etiopathogenesis is not still clear. The importance of SCF phenomenon results from its association with angina pectoris, acute myocardial infarction, hypertension and sudden cardiac death.[6]

Platelets have an important role in the pathophysiology of cardiovascular diseases.[7] Mean platelet volume (MPV) is a simple and easy method of assessing platelet function.[8,9] In comparison to smaller ones, larger platelets have more granules, aggregate more rapidly with collagen, have higher thromboxane A2 level and express more glycoprotein Ib and IIb/IIIa receptors.[10-12] Therefore larger platelets have higher thrombotic potential.

In previous studies, increased platelet activation[13,14] and increased MPV[14-16] have been reported in patients with SCF. In this study, we aimed to investigate MPV values prospectively in patients with SCF.

MATERIAL AND METHODS

The study group consisted of 35 patients with SCF (19 females, 16 males, mean age 51.8 ± 8.7 years). An age and gender matched control group was composed of 35 healthy volunteers (18 females, 17 males with a mean age 51.0 ± 10.1 years). The indication for coronary angiography was either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischemia in both of the group. The control subjects were selected in a consecutive manner from the catheterized patients during the same study period and who proved to have normal coronary angiograms. Hypertension was considered to be present if the systolic pressure was >140 mmHg and/or diastolic pressure was >90 mmHg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose level >126 mg/dl or current use of a diet or medication to lower blood glucose. Patients who were smoking before hospitalization were accepted as smokers

Exclusion criteria were coronary artery disease, prior myocardial infarction, valvular heart disease, heart failure, peripheral vascular disease, coronary artery ectasia, diabetes mellitus, hypertension, renal and hepatic dysfunction, hematological disorders, history of malignancy, acute or chronic infection and stroke. None of the subjects were on antihypertensive and antiaggregation therapy including aspirin. There is only one patient using statin in patients group. The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

CORONARY ANGIOGRAPHY

Coronary angiography was routinely performed without the use of nitroglycerin. Selective coronary angiography was performed by means of the Judkins technique in multiple projections. We used iohexol (Omnipaque) as contrast agent during coronary angiography in all patients and control subjects. Coronary blood flow was measured quantitatively using the thrombolysis in myocardial infarction (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 mean TIMI frame count for each patient and control subject was calculated by adding the TIMI frame counts for LAD, CFX and RCA and then dividing the obtained value into three. Coronary angiograms and TIMI frame counting were analysed by two blinded interventional cardiologists without knowledge of the clinical status and laboratory measurements of the subjects.

BLOOD SAMPLING

Blood samples were drawn from the antecubital vein by careful vein puncture in a 21 G sterile syringe without stasis at 08.00-10.00 AM after a fasting period of 12 h. Glucose, creatinine, and lipid profiles were determined by standard methods. MPV was measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter

(Beckman Coulter) was used for whole blood counts. MPV was measured within an hour after sampling.

STATISTICAL ANALYSIS

Data were analyzed with the SPSS software version 10.0 for Windows. Continuous variables from the study groups were reported as mean ± 1 standard deviation, categorical variables as percentages. To compare continuous variables, the Student t-test or Mann-Whitney U test were used where appropriate. Categorical variables were compared with the chi-squared test. Statistical significance was defined as $p< 0.05$. Demographic characteristics, clinical and angiographic profile were evaluated in a univariate analysis, and those with $p< 0.15$ (BMI and MPV) were then entered into a Multivariate logistic regression analysis. Strength of association between variables and occurrence of SCF was represented by odds ratios (ORs) and their accompanying 95% confidence intervals (CIs).

RESULTS

Clinical and laboratory characteristics of the patients with SCF and control group are presented in Table 1. There were no statistically significant differences between the two groups with respect to age, gender, systolic and diastolic blood pressures and levels of glucose, creatinine, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, hemoglobin, white blood cell and platelet count. The TIMI frame count for all the epicardial coronary arteries and the mean TIMI frame count were significantly higher in the SCF group than control group. MPV was significantly higher among patients with SCF when compared with control group (8.6 ± 0.9 vs. 8.1 ± 0.5 fl respectively; p= 0.004). The only univariate predictor of SCF was MPV (p= 0.007; OR, 2.58; CI, 1.29 to 5.15). The only multivariate predictor of SCF was MPV (p= 0.01 ; OR, 2.43; CI, 1.20 to 4.87).

TABLE 1: Comparison of the clinical and laboratory characteristics of the slow coronary flow (SCF) and the control groups.

	SCF (n= 35)	Control (n= 35)	P value
Age (years)	51.8 ± 8.7	51.0 ± 10.1	0.06
Sex (M/F)	16/19	17/18	0.75
Smoking (%)	6(17%)	7(20%)	0.75
BMI (kg/m^2)	27.7 ± 3.1	26.6 ± 2.7	0.13
SBP (mmHg)	121.6 ± 7.3	120.8 ± 10.6	0.71
DBP (mmHg)	75.8 ± 8.2	75.7 ± 9.8	0.96
Heart rate (beats/min)	73.5 ± 3.8	72.2 ± 4.3	0.17
Glucase (mg/dl)	97.2 ± 8.0	93.3 ± 11.8	0.11
Creatinin (mg/dl)	0.91 ± 0.15	0.87 ± 0.17	0.36
Total cholesterol (mg/dl)	190.1 ± 29.2	187.9 ± 48.3	0.82
Triglycerides (mg/dl)	139.7 ± 56.4	121.4 ± 52.7	0.16
LDL-cholesterol (mg/dl)	111.0 ± 27.0	112.2 ± 36.7	0.87
HDL-cholesterol (mg/dl)	49.3 ± 14.3	49.9 ± 12.9	0.85
Hemoglobin (g/dl)	14.2 ± 1.3	14.3 ± 1.3	0.75
WBC (×103 mg/dl)	7.5 ± 2.1	7.7 ± 1.9	0.72
Platelet count (×109)	259.6 ± 59.1	263.2 ± 94.3	0.84
MPV (fl)	8.6 ± 0.9	8.1 ± 0.5	0.004
TIMI frame count			
LADc	33.0 ± 8.1	16.0 ± 4.5	< 0.001
Cx	27.9 ± 10.4	17.8 ± 7.3	0.006
RCA	20.7 ± 4.9	15.3 ± 6.2	0.006
Mean	27.6 ± 6.1	16.2 ± 5.1	< 0.001

M/F: male to female, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL-cholesterol: low density lipoprotein cholesterol, HDL-cholesterol: high density lipoprotein cholesterol, WBC: white blood cells, MPV: mean platelet volume. TIMI: Thrombolysis in Myocardial Infarction, c: Corrected TIMI frame count, P value is for comparison between control and study population.

DISCUSSION

In this study, we found that MPV was significantly higher in patients with SCF compared to control subjects. Several mechanisms have been proposed for the etiology of SCF, including occlusion of small vessels, increased microvascular resistance, and diffuse atherosclerosis.[1-4] However, the exact underlying pathophysiological mechanisms as well as the clinical importance of this angiographic phenomenon are not fully understood at present.

In previous studies, the platelet function disorders have been suggested to play a role in the pathogenesis of SCF.[13,14] Gokce et al. found that the ratio of platelet aggregability was significantly higher in the patients with SCF than that in the control subjects, suggesting that platelet function disorder may play a role in the pathogenesis in

SCF.[13] Celik et al found that MPV and sP-selectin levels of the patients with SCF were significantly higher compared to those of the subjects with normal coronary flow.[14] Increased MPV have been reported in patients with SCF also in some other studies.[15,16]

The determination of platelet size, usually via quantification of MPV is a simple and easy method of accurately assessing platelet function. Platelets are heterogeneous in size, density, and reactivity. Metabolically and enzymatically larger platelets are more active than smaller platelets.[9] Elevation of MPV values has been shown in acute coronary syndromes and acute myocardial infarction.[17-19] The increased MPV has been reported in a number of patient groups with known coronary artery disease risk factors, such as smoking,[20] diabetes mellitus,[21] obesity,[22] hypertension,[23] and increased cholesterol[24] when compared with healthy controls. The difference of our study from previous studies is that we excluded the patients with hypertension and diabetes mellitus. Because of this exclusion our sample size was small. There was also no significant difference between SCF and control groups with respect to body mass index, the percentages of smoking and levels of cholesterol in the present study. So we concluded that MPV values increased in patients with SCF regardless of these factors.

Although the pathophysiologic mechanisms for increased platelet activation in patients with SCF remains to be largely unknown, the abnormal slow flow pattern in a coronary artery might lead to thrombus formation and, hence, distal embolization or myocardial infarction. In a previous study, we have shown that, MPV was significantly higher in patients with coronary artery ectasia when compared with control subjects.[25] In this previous study, we thought the similar mechanism.

Increased platelet aggregability and MPV was also found in patients with cardiac syndrome X in which exercise induced myocardial ischemia and angina could be seen without obstructive coronary artery disease like SCF.[26,27] The results of these studies support our findings.

There can be an association between platelet function and coronary endothelial dysfunction or impaired coronary flow.

Inflammation has also been suggested to be involved in the pathophysiology of SCF. Turhan et al. performed a study, evaluating 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 in patients with SCF, but with angiographically proven normal coronary arteries. They showed that serum ICAM-1, VCAM-1, and E-selectin concentrations of patients with SCF were found to be significantly higher than those of control subjects with normal coronary flow suggesting the presence of a more severe and extensive chronic inflammation in the coronary circulation in these patients.[5] In an other study, Li et al showed that plasma levels of inflammatory factors, CRP and IL-6 in patients with SCF were found to be significantly higher than those of control subjects.[28]

Platelet size is regulated at the level of the megakaryocyte. It has been shown that inflammatory cytokines such as interleukin-3 or interleukin-6 influence megakaryocyte ploidy and can lead to the production of more reactive and larger platelets.[29] Therefore, IL-6, a major inflammatory cytokine which increased in patients with SCF can cause an increase in MPV values by stimulating the megakaryocyte ploidy. As a result, inflammatory process in patients with SCF might be cause of increased MPV.

MPV increases over time in EDTA-anticoagulated samples,[30] and this increase was shown to be proportional with the time period between sample collection and laboratory analysis. Therefore, whole blood count including MPV was determined in less than one hour.

Recently, MPV has been an interesting topic in cardiovascular research. It is a simple laboratory measurement which can be measured in almost all laboratories and it can guide us to identify high risk patients with SCF.

There are some limitations of this study that should be concerned. The small number of patients was the limitation of the study. We excluded the factors like hypertension and diabetes mellitus that could affect MPV. Because of that our sample size was small. Another limitation of this study is that analysis was based on a simple baseline determination that may not reflect the patient status over long periods.

CONCLUSION

In this study, we found that MPV, an indicator of platelet aggregation, was significantly higher in patients with SCF when compared with control group. Further prospective studies are needed to establish the pathophysiological and clinical significance of increased MPV and to investigate the effect of anti-platelet agents in patients with SCF.

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries-a new angiographic finding. Am Heart J 1972;84(1): 66-71.
2. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation 1986;74(5):964-72.
3. Sezgin AT, Sigirci A, Barutcu I, Topal E, Sezgin N, Ozdemir R, et al. Vascular endothelial function in patients with slow coronary flow. Coron Artery Dis 2003;14(2):155-61.
4. Pekdemir H, Cin VG, Cicek D, Camsari A, Akkus N, Döven O, et al. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. Acta Cardiol 2004;59 (2):127-133.
5. Turhan H, Saydam GS, Erbay AR, Ayaz S, Yasar AS, Aksoy Y, et al. Increased plasma soluble adhesion molecules; ICAM-1, VCAM-1, and E-selectin levels in patients with slow coronary flow. Int J Cardiol 2006;108(2):224-30.
6. Fragasso G, Chierchia SL, Arioli F, Carandente O, Gerosa S, Carlino M, et al. Coronary slow-flow causing transient myocardial hypoperfusion in patients with cardiac syndrome X: long-term clinical and functional prognosis. Int J Cardiol 2009;137(2):137-44.
7. Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictors of vascular risk: is there a practical index of platelet activity? Clin Appl Thromb Hemost 2003;9(3):177-90.
8. Park Y, Schoene N, Haris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets 2002;13(5-6):301-6.
9. Boos CJ, Lip GY. Assessment of mean platelet volume in coronary artery disease - what does it mean? Thromb Res 2007;120(1):11-3.
10. Martin JF, Trowbridge EA, Salmon GL, Plumb J. The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. Thromb Res 1983;32(5):443-60.
11. Jakubowski JA, Thompson CB, Vaillancourt R, Valeri CR, Deykin D. Arachidonic acid metabolism by platelets of differing size. Br J Haematol 1983;53(3):503-11.
12. Giles H, Smith REA, Martin JF. Platelet glycoprotein IIb-IIIa and size are increased in acute myocardial infarction. Eur J Clin Invest 1994;24(1):69-72.
13. Gokce M, Kaplan S, Tekelioglu Y, Erdogan T, Kucukosmanoglu M. Platelet function disorder in patients with coronary slow flow. Clin Cardiol 2005;28(3):145-8.
14. Celik T, Yuksel UC, Bugan B, Iyisoy A, Celik M, Demirkol S, et al. Increased platelet activation in patients with slow coronary flow. J Thromb Thrombolysis 2010;29(3):310-5.
15. Sen N, Basar N, Maden O, Ozcan F, Ozlu MF, Gungor O, et al. Increased mean platelet volume in patients with slow coronary flow. Platelets 2009;20(1):23-8.
16. Nurkalem Z, Alper AT, Orhan AL, Zencirci AE, Sari I, Erer B, et al. Mean platelet volume in patients with slow coronary flow and its relationship with clinical presentation. Turk Kardiyol Dern Ars 2008;36(6):363-7.
17. Jagroop IA, Mikhailidis DP. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol 2003; 120(1):169-70.
18. Varol E, Icli A, Ozaydin M, Erdogan D, Arslan A. Mean platelet volume is elevated in patients with myocardial infarction with normal coronary arteries, as in patients with myocardial infarction with obstructive coronary artery disease. Scand J Clin Lab Invest 2009;69(5):570-4.
19. Yilmaz MB, Cihan G, Guray Y, Guray U, Kisacik HL, Sasmaz H, et al. Role of mean platelet volume in triagging acute coronary syndromes. J Thromb Thrombolysis 2008;26 (1):49-54.
20. Kario K, Matsuo T, Nakao K. Cigarette smoking increases the mean platelet volume in elderly patients with risk factors for atheros- clerosis. Clin Lab Haematol 1992;14(4):281-7.
21. Papanas N, Symeonidis G, Maltezos E, Mavridis G, Karavageli E, Vosnakidis T, et al. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets 2004;15(8):475-8.
22. Coban E, Ozdogan M, Yazicioglu G, Akcit F. The mean platelet volume in patients with obesity. Int J Clin Pract 2005;59(8):981-2.
23. Nadar S, Blann AD, Lip GY. Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipine-based antihypertensive therapy. Ann Med 2004;36(7):552-7.
24. Pathansali R, Smith N, Bath P. Altered megakaryocyte-platelet haemostatic axis in hypercholesterolaemia. Platelets 2001;12(5):292-7.
25. Varol E, Akcay S, Ozaydin M, Erdogan D, Dogan A. Mean platelet volume in patients with coronary artery ectasia. Blood Coagul Fibrinolysis 2009;20(5):321-4.
26. Cay S, Biyikoglu F, Cihan G, Korkmaz S. Mean platelet volume in the patients with cardiac syndrome X. J Thromb Thrombolysis 2005;20 (3):175-8.
27. Lanza GA, Andreotti F, Sestito A, Sciahbasi A, Crea F, Maseri A. Platelet aggregability in cardiac syndrome X. Eur Heart J 2001;22(20): 1924-30.
28. Li JJ, Qin XW, Li ZC, Zeng HS, Gao Z, Xu B, et al. Increased plasma C-reactive protein and interleukin-6 concentrations in patients with slow coronary flow. Clin Chim Acta 2007;385(1-2):43-7.
29. Debili N, Masse JM, Katz A, Guichard J, Breton-Gorius J, Vainchenker W. Effects of the recombinant hematopoietic growth factors interleukin-3, interleukin-6, stem cell factor, and leukemia inhibitory factor on the megakaryocytic differentiation of CD34s cells. Blood 1993;82(1):84-95.
30. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis 1996;7(2):157-61.