Mean platelet volume is not associated with coronary slow flow: A retrospective cohort study

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Abstract

Objective: To investigate mean platelet volume (MPV) levels in patients with coronary slow flow (CSF).
Methods: 465 stable angina pectoris cases with angiographically normal coronary arteries were recruited [coronary slow flow group (n=76), control group (n=389)] in the observational retrospective cohort study. Clinical, biochemical and demographic variables including MPV were noted and coronary blood flow was assessed with TIMI frame count (TFC).
Results: Gender, smoking, height, serum creatinine, uric acid levels, hemoglobin, waist/hip ratio, systolic blood pressure but not MPV were significantly different among groups. Independent predictors of CSF were height (p=.029) and serum uric acid level (p=.045). Gender, height, weight, hip circumference, systolic blood pressure, fasting blood glucose, serum urea, creatinine, uric acid levels, hemoglobin and platelet count were associated with mean TFC whereas independent predictors of mean TIMI frame count were height (p=.010) and serum uric acid level (p=.041).
Conclusion: Height and serum uric acid level but not MPV were independent predictors of both CSF and mean TFC.
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Key words: mean platelet volume, coronary slow flow, stable angina pectoris, regression analysis

Introduction

Coronary slow flow (CSF) is an angiographic concept which is characterized by delayed opacification of the epicardial coronary arteries in the presence of a normal coronary angiogram. CSF is evaluated with precise and reproducible Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method that counts the number of cineangiographic frames from initial contrast opacification of the proximal coronary artery to opacification of distal arterial landmarks. Although the exact mechanism of CSF is still not clear, diffuse atherosclerosis, inflammatory, oxidative factors and endothelial vasomotor dysfunction have been suggested as possible responsible factors (1-3). Platelet function disorders have also been suggested to be involved in the development of CSF, as well (4, 5). Mean platelet volume (MPV) is an indicator of platelet activation and was postulated to play role in the pathophysiology of coronary artery disease (CAD) (6, 7). In previous studies, increased MPV was demonstrated in acute myocardial infarction, unstable angina pectoris, congestive heart failure, non-dipper hypertension and coronary artery ectasia (6-8).

Although based upon these putative relationships between heart diseases and MPV, a limited number of studies have been performed yet to demonstrate the association of CSF with MPV. Beyond these studies, we aimed to investigate whether MPV levels increased or not within a larger sample size of CSF patients with stable angina pectoris (SAP).

Methods

Study design

This observational retrospective cohort study was conducted at Harran University School of Medicine, Şanlıurfa, Turkey. The study protocol was reviewed and approved by the local ethics committee, in accordance with the ethical principles for human investigations, as outlined by the Second Declaration of Helsinki. Consecutively 465 patients with SAP who underwent elective coronary angiography, on suspicion of CAD, during a

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3-year period and were diagnosed as having angiographically normal (0% stenosis) coronary arteries were recruited for the study. The indications for coronary angiography were established with myocardial ischemia suggestive findings on non-invasive tests (exercise stress electrocardiography or nuclear cardiac imaging) besides the presence of typical angina pectoris. All patients were in Canadian Cardiovascular Society (CCS) class 2 or 3.

Determination of study sample size

Sample size was calculated according to the results of the first thirteen patients in each study groups, from whom we observed a difference of 5.76% in MPV with a standard deviation of 9.14% between groups. From these differences and assuming a two-tailed α value of 0.05 (sensitivity 95%) and a β value 0.20 (study power: 80%), we determined that at least 34 patients were required in each group.

To include 34 CSF cases we have reviewed angiography of 500 cases. Of these 500 cases 35 were excluded due to several reasons [extremes of heart rate (8 cases), different catheter size (6 cases), suboptimal angiographic images (6 cases) and other reasons (5 cases)]. As a result 465 cases with normal coronary arteries were included in the analysis and TIMI evaluation revealed CSF in 76 cases and normal coronary blood flow (CBF) in 389 cases.

Study population

Patients were divided into 2 groups; group 1 (n=76) consisted of patients who had SAP with CSF, and group 2 (n=389) consisted of patients who had SAP without CSF. The exclusion criteria were as follows: CAD; acute coronary syndromes on admission; history of myocardial infarction; left ventricular dysfunction, left ventricular hypertrophy; atrial fibrillation and valvular, myocardial or pericardial disease. Patients with renal dysfunction (creatinine $\geq$1.5 mg/dL); hepatic and hemolytic disorders; concomitant inflammatory diseases such as infections and autoimmune disorders, neoplastic diseases; recent major surgical procedure and/or any systemic disorders, and patients taking nitrates, diuretics and uric acid-lowering agents were also excluded from the study.

Baseline definitions and measurements

Baseline demographic and clinical variables such as age, gender, height, weight, waist circumference, hip circumference, heart rate, systolic and diastolic blood pressure, personal history of hypertension, and diabetes mellitus and family history of coronary heart disease, and current use of medications were gathered from institutional records. Body mass index was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2).

Evaluation of coronary blood flow

All participants underwent selective coronary angiography with the Judkins technique using the Philips Angioscop Xray (Integris HM3000, Philips Medical Systems, Best, The Netherlands). Two observers blinded to the clinical details of the individual participants independently quantified the coronary flow using the TFC as previously described (9). The TFC in the left anterior descending coronary artery (LAD) and left circumflex artery (LCx) was assessed in a right anterior oblique projection with caudal angulation, and the right coronary artery (RCA) was assessed in a left anterior oblique projection with cranial angulation. The number of cineangiographic frames, recorded at 25 frames/s, required for the leading edge of the column of radiographic contrast to reach a predetermined distal landmark was determined. The first frame was defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and indicates forward motion down the artery. The final frame counted was that in which the contrast first reaches the distal predefined landmark branch without the necessity for full opacification. These landmarks were as follows (9). The distal bifurcation of the LAD (i.e. the mustache, pitchfork or whale's tail) for LAD, the distal branch of the lateral left ventricular wall artery with the longest total distance from the coronary ostium for the LCx, and the first branch of the posterolateral artery for the RCA. If one of these landmarks was not visualized properly, another well visualized landmark close to these landmarks was chosen. Study participants with a TFC greater than two standard deviations from the normal published range for any one of the three vessels (>40.6 frames for LAD, >29.8 frames for LCx and >27.3 frames for RCA) were accepted as having CSF (9). Accordingly, 76 participants were grouped as the SAP with CSF group and 389 participants as the SAP without CSF in our study. As the normal frame counts for the LAD are 1.7 times the mean for the LCx and the RCA, the LAD frame counts were corrected by dividing by 1.7 to derive the corrected TFC (9). The mean TFC for each participant was calculated by adding the TFCs for the corrected LAD, LCx and RCA and then dividing the sum by three. The inter and intra assay CVs were respectively 7% and 3%.

Biochemical variables

Biochemical variables (assessed on index admission) such as fasting glucose, triglyceride (TG), total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol and uric acid, white blood cell and platelet count, hemoglobin level, mean corpuscular hemoglobin, mean corpuscular volume and MPV were also gathered from institutional records.

Commercially-available assay kits (Abbott®, Abbott Park, North Chicago, Illinois, USA) with an auto-analyzer (Abbott®, Abbott Park, North Chicago, Illinois, USA) is used for biochemical analysis. In our institutions, MPV is measured in blood samples collected in EDTA tubes, which are analyzed by Abbott Cell-Dyne 4000 cell counter (Abbott®, Abbott Park, North Chicago, Illinois, USA). The normal value range for MPV in our laboratory was 6.8-10.8 fL.

Timing of MPV measurement must be within 120 minutes after venipuncture to avoid MPV increase caused by EDTA. Our study is in a retrospective design. So it is unlikely to say an absolute timing

for MPV measurement. However, in our clinic, analyzing of blood samples takes about one hour after venopuncture for the complete blood count. Namely, although this is a retrospective study, we may say that measurement of MPV values ended up within one hour after blood sampling in nearly all patients. In addition, we suggest that our patients should leave eating, drinking and smoking 6-h before angiography procedure. So, we think that optimal conditions were present for MPV measurement in our patients.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 11.5 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentages. Comparisons of categorical and continuous variables between the two groups were performed using the chi-square test and independent samples t-test, respectively. To determine independent predictors of CSF, multiple logistic regression analysis was performed by including the parameters, which were significantly different between the CSF and control groups. Odds ratio (OR), 95% confidence interval (CI) values and their significance from multiple logistic regression analysis were reported. The correlation between mean TFC

Table 1. Baseline clinical and laboratory characteristics of normal coronary flow and slow coronary slow flow (CSF) groups

	SAP with CSF (n=76)	SAP without SCF (n=389)	*P** Value	OR	95% CI	*P*# Value
Age, year	51.80±12.10	53.00±10.80	.350			
Gender [Female], n (%)	35.50	60.40	<.001	2.00	.627-6.385	.241
Hypertension, n (%)	44.00	45.20	.899			
Diabetes mellitus, n (%)	14.50	15.20	1.0			
Smoking, n (%)	47.40	30.30	.005	.47	.211-1.058	.068
Height, m	1.68±0.11	1.63±0.11	<.001	165	1.67-16321	.029
Weight, kg	73.60±14.80	70.10±14.2	.057			
BMI, kg/m^2	26.20±5.70	26.40±5.10	.845			
Waist circumference, m	0.93±0.13	0.94±0.11	.702			
Hip circumference, m	0.90±0.13	0.88±0.11	.139			
Waist/hip ratio	1.04±0.08	1.07±0.08	.008	.084	.001-6.634	.267
SBP, mm Hg	126.1±24.5	134.3±26.9	.021	.986	.97-1.001	.071
DBP, mm Hg	74.80±13.70	77.60±13.10	.115			
Heart rate, bpm	76.40±12.40	79.20±11.90	.075			
Fasting blood glucose, mg/dL	114.9±57.4	112.2±47.2	.672			
Total cholesterol, mg/dL	186.9±54.0	190.5±45.7	.537			
Triglyceride, mg/dL	186.5±126.5	175.8±135.6	.532			
HDL cholesterol, mg/dL	38.10±9.50	40.00±11.00	.185			
LDL cholesterol, mg/dL	114.3±40.0	118.1±38.8	.482			
Urea, mg/dL	38.70±15.50	35.00±14.30	.045			
Creatinine, mg/dL	0.95±0.24	0.86±0.20	<.001	5.711	.631-51.7	.121
Uric acid, mg/dL	5.28±1.60	4.60±1.54	.001	1.327	1.006-1.749	.045
WBC count, x10^6/L	8482±1941	8000±2226	.079			
Hemoglobin, g/dL	14.20±1.60	13.80±1.60	.016	1.078	.809-1.437	.609
MCH, pg/cell	30.40±2.50	29.70±2.60	.043	1.036	.821-1.306	.767
MCV, fL	86.00±5.30	84.30±5.90	.036	1.019	.914-1.137	.733
Platelet count, x10^9/L	274.8±73.3	275.7±69.3	.916			
MPV, fL	8.73±1.27	8.76±1.43	.881			

All measurable values were given with mean±standard deviation; categorical variables were given with percentage.
*P** Value = Comparison of baseline clinical and laboratory characteristics between normal coronary flow and coronary slow flow (SCF) groups
P# Value= Multiple logistic regression analysis for the parameters which were significantly different between the CSF and control groups.
A two-sided P value < .05 was considered statistically significant.
BMI - body mass index; DBP - diastolic blood pressure; HDL - high density lipoprotein; LDL - low density lipoprotein; MCH - mean corpuscular hemoglobin; MCV - mean corpuscular volume; MPV - mean platelets volume; SAP - stable angina pectoris; SBP - systolic blood pressure; WBC - white blood cell

and clinical laboratory parameters was assessed by the Pearson's correlation test. Multiple linear regression analysis was performed to identify the independently associated parameters of mean TFC by including the parameters that were correlated with mean TFC in bivariate analysis. Standardized [beta]-regression coefficients and their significance from multiple linear regression analysis were reported. A two-sided p value < .05 was considered statistically significant.

Table 2. Relationship between mean TIMI frame count (TFC) and clinical and laboratory parameters

	r	*P** Value	Beta	*P*# Value
Age, year	0.015	.750		
Gender [Female], n (%)	0.245	<.001	-0.009	.914
Hypertension, n (%)	0.024	.597		
Diabetes mellitus, n (%)	0.014	.763		
Smoking, n (%)	0.083	.073		
Height, m	0.257	<.001	0.210	.010
Weight, kg	0.172	<.001	0.093	.265
BMI, kg/m^2	0.015	.763		
Waist circumference, m	0.064	.215		
Hip circumference, m	0.132	.011	-0.003	.966
Waist/hip ratio	-0.095	.069		
SBP, mm Hg	-0.111	.020	-0.106	.077
DBP, mm Hg	-0.059	.214		
Heart rate, bpm	-0.113	.019	-0.033	.577
Fasting blood glucose, mg/dL	0.100	.038	0.131	.027
Total cholesterol, mg/dL	-0.024	.610		
Triglyceride, mg/dL	0.039	.412		
HDL cholesterol, mg/dL	-0.011	.821		
LDL cholesterol, mg/dL	-0.071	.154		
Urea, mg/dL	0.106	.024	-0.028	.687
Creatinine, mg/dL	0.218	<.001	0.110	.133
Uric acid, mg/dL	0.228	<.001	0.150	.041
WBC, x10^6/L	0.072	.120		
Hemoglobin, g/dL	0.211	<.001	0.082	.239
MCH, pg/cell	0.093	.064		
MCV, fL	0.070	.158		
Platelet, x10^9/L	-0.121	.010	-0.050	.407
MPV, fL	-0.017	.8713		

*P**=Bivariate analysis
P#=Multiple linear regression analysis to identify the independent predictors of mean TFC by including the parameters that were correlated with mean TFC in bivariate analysis.
A two-sided *P* value <.05 was considered statistically significant.
BMI - body mass index; DBP - diastolic blood pressure; HDL - high density lipoprotein; LDL - low density lipoprotein; MCH - mean corpuscular hemoglobin; MCV - mean corpuscular volume; MPV - mean platelets volume; SBP - systolic blood pressure; WBC - white blood cell

Results

Mean TFC was 23.6±3.6 in CSF group whereas 15.7±2.6 in normal coronary flow group. Biochemical and demographic characteristics of all patients were presented on Table 1. There were no statistical differences in age, history of hypertension, and diabetes mellitus among groups (p>.05 for all). Compared to group 2, group 1 had not significantly different MPV levels (p>.05) (Table 1). Male gender and smoking was more frequent among CSF group, height, serum creatinine and uric acid levels and hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume were significantly increased in CSF group compared to controls whereas waist/hip ratio and systolic blood pressure were significantly decreased in CSF group compared to controls (p<.05 for all). Logistic regression analysis revealed that the only independent predictors of CSF were height (p=.029) and serum uric acid level (p=.045) (Table 1).

On bivariate correlation analysis, gender, height, weight, hip circumference, systolic blood pressure, fasting blood glucose, serum urea, creatinine and uric acid levels, hemoglobin level and platelet count were associated with mean TFC (p<.05 for all) whereas height (Beta=0.210, p=.010) and serum uric acid level (Beta=0.150, p=.041) were independently associated with mean TFC (Table 2).

Discussion

The present study demonstrated that the MPV level is not associated with CSF in patients with SAP.

Platelet function disorders, early phases of diffuse atherosclerosis, inflammation, and imbalance of vessel active substance, impaired diastolic function as well as reduced endothelium-mediated dilation have been suggested to be involved in the development of CSF (1 0-13). MPV, an indicator of platelet activation, has an important role in the pathophysiology of cardiovascular diseases and it has been demonstrated that they are involved in the development of CSF (14-16). It is known that platelets having dense granules are biochemically, functionally, and metabolically more active and are risk factor for developing coronary thrombosis, leading to myocardial infarction. In comparison to smaller ones, larger platelets are associated with other markers of platelet activity, including increased platelet aggregation, increased thromboxane synthesis and beta-thromboglobulin release, and increased expression of adhesion molecules (17, 18). Elevations of MPV values have also been shown in patients with CAD, insulin resistance such as metabolic syndrome, obesity, impaired fasting glucose, diabetes mellitus, hypertension, stroke, hypercholesterolemia, and smoking suggesting a common mechanism by which these factors may increase the risk of cardiovascular disease (15, 19-22).

The general hypothesis that the pathogenesis of CSF is related to an increased MPV levels. Indeed, some studies have provided the evidence of increased MPV levels in CSF (Table 3). Şen et al. (23) have compared 84 CSF patients with 88 CAD and

Table 3. Previously published studies to demonstrate the association between MPV and SCF

Publication	Group	Sample Size	MPV (FL)	*P* Value	Comment
Nurkalem et al, 2008 (25)	USAP with SCF	24	10.10±2.10	.007	MPV is increased in SCF cases presented with USAP but not in SCF cases presented with SAP
	SAP with SCF	26	8.80±2.30		
	Controls	22	8.10±2.00		
Şen et al, 2009 (23)	SCF	84	10.50±1.65	.012	MPV is increased in SCF cases comparable with CAD patients
	CAD	88	10.43±1.55		
	Controls	80	8.30±1.32		
Çelik et al, 2010 (24)	SCF	50	8.20±0.70	<.001	MPV is increased in SCF cases compared to control cases
	Controls	50	7.20±0.60		
Elsherbiny et al, 2012 (5)	IR SCF	32	8.25±0.48	<.01	MPV is increased in SCF cases compared to control cases and coexistence of insulin resistance further increased MPV
	IS SCF	28	7.55±0.25		
	Controls	20	7.17±0.52	<.001β	
Işık et al, 2012 (26)	SCF	57	8.4±1.0	.002	MPV is increased in SCF cases compared to control cases with stable angina and ischemia on non-invasive tests
	Controls	90	7.9±0.6		
Current study	SAP with SCF	76	8.73±1.27	.881	MPV in SCF cases is comparable with control cases in the study population of stable angina
	SAP without SCF	389	8.76±1.43		

USAP - unstable angina pectoris; SAP - stable angina pectoris; SCF - slow coronary flow; IR - insulin resistance; IS - insulin sensitive; MPV - mean platelets volume
α P value for SCF with IR vs. SCF with IS is <.01
β P value for SCF vs. controls is <.001

80 healthy controls and reported that MPV is increased in CSF cases comparable with CAD patients. As an affirming finding, Çelik et al. (24) have compared 50 CSF patients with 50 healthy subjects and found that MPV is increased in CSF cases compared to control cases. Additionally, Elsherbiny et al. (5) have evaluated 32 CSF patients with insulin resistance, 28 CSF patients with insulin sensitive and 20 healthy controls, and reported that MPV is increased in CSF cases compared to control cases and coexistence of insulin resistance further increased MPV. In literature, only one study which Nurkalem et al. (25) evaluated the association between CSF patients with angina pectoris and MPV values. In this study, the authors have evaluated 24 CSF patients with unstable angina pectoris (USAP), 26 CSF patients with SAP and 22 healthy subjects, and reported that MPV value is increased in CSF cases presented with USAP but not in CSF cases presented with SAP compared to healthy individuals. Işık et al. (26) have compared 57 CSF patients with 90 healthy subjects in a retrospective study and found that MPV is increased in CSF cases compared to control cases. In our study, we evaluated 76 SAP patients with CSF and 389 SAP patients without CSF, and found no statistically significant differences in MPV values between among two groups. Results of the present study suggest, in contrary with the previous reports (5, 23-26), that elevated values of MPV may not play a role in pathogenesis of CSF in patients with SAP.

Multiple etiopathogenic mechanisms underlying CSF might be the basis of negative findings in the present study as several inflammatory, oxidative markers would play role in the development of CSF. Increased serum uric acid (27), circulating soluble CD40 (28), resistin (29), asymmetric dimethylarginine, homocysteine levels (30), besides decreased serum paraoxonase activity (2), serum adiponectin (31), and nitric oxide (30), levels was reported to be associated with the presence of CSF. Ahead of inflammatory and oxidative stress markers, markers of blood viscosity were also reported to be related with CSF (32).

Beyond the absence of association of MPV and the coronary blood flow in our study, we have found independent association of coronary blood flow and serum uric acid level supporting previous reports (27) and height. Height is a novel anthropometric marker of CSF, which is first to be reported and increased total coronary artery length in tall subjects might be the mechanism of the link between length and coronary blood flow in our study.

Study limitations

Certain limitations of the present study should be considered. First of all the study was planned as retrospective. Angiographic diagnosis of normal coronary arteries is still a debate in current cardiovascular era as contrast angiograms might underestimate the presence of atherosclerotic plaque; however we could not perform more definitive diagnostic tools. Another potential source of bias in our study was confounders of TFC such as heart rate, nitrate use and the coronary catheter size (33) although we have used same coronary catheter size and participants given nitrates and participants with extremes of heart rate were excluded from our study. As another limitation

study population continued taking previously prescribed medications at the time of angiography in both groups; however two groups did not differ with regard to medications including antiplatelet drugs (none of the patients were under anticoagulant therapy, data not shown). We also should underline the fact that we had single measurement of MPV, which limits the reliability and usefulness of this assay.

Conclusion

In spite of the retrospective study design, the present study revealed -in the largest ever reported cohort- that height and serum uric acid levels are independent predictors of CSF despite the absence of association between MPV and presence of CSF contrary to previously reported studies.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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