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Increased mean platelet volume associated with extent of slow coronary flow

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Abstract

Background: *Slow coronary flow (SCF) is characterized by delayed opacification of epicardial coronary vessels. SCF can cause ischemia and sudden cardiac death. We investigated the association between presence and extent of SCF, and cardiovascular risk factors and hematologic indices.*

Methods: *In this study, 2467 patients who received coronary angiography for suspected or known ischemic heart disease were retrospectively evaluated between April 2009 and November 2010. Following the application of exclusion criteria, our study population consisted of 57 SCF patients (experimental group) and 90 patients with age- and gender-matched subjects who proved to have normal coronary angiograms (control group). Baseline hematologic indices were measured by the automated complete blood count (CBC) analysis. The groups were evaluated for cardiovascular risk factors and medications. Patients were categorized based on the angiographic findings of vessels with or without SCF. Moreover, patients with SCF were divided into subgroups relative to the extent of SCF.*

Results: *Among the 147 patients (mean age 52.7 ± 10.0, 53.7% male), mean platelet volume (MPV) ranged from 6.5 fL to 11.7 fL (median 7.9 fL, mean 8.1 ± 0.8 fL). Diabetes (OR = 3.64, 95% CI 1.15–10.43, p = 0.03), hypercholesterolemia (OR = 4.94, 95% CI 1.99–12.21, p = 0.001), smoking (OR = 3.54, 95% CI 1.43–8.72, p = 0.006), hemoglobin (OR = 1.69, 95% CI 1.22–2.36, p = 0.002), and MPV (OR = 2.52, 95% CI 1.43–4.44, p = 0.001) were found to be the independent correlates of SCF presence. Only MPV (OR = 2.13, 95% CI 1.05–4.33, p = 0.03) was identified as an independent correlate of extent of SCF.*

Conclusions: *Elevated baseline MPV value was found to be an independent predictor of the presence and extent of SCF.* (Cardiol J 2012; 19, 4: 355–362)

Key words: mean platelet volume, extent of slow coronary flow

Introduction

Slow coronary flow (SCF) phenomenon is characterized by delayed opacification of epicardial coronary vessels in the absence of stenosis and/or conditions such as coronary ectasia, coronary spasm, valvular and myocardial heart disease, acute myocardial infarction and coronary reperfusion therapy [1]. Various studies have found the incidence of SCF ranging between 1% and 7% in patients undergo-

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ing angiography [2, 3]. The reason behind varying incidence rates derives from methodological differences. The underlying mechanism responsible for SFC phenomenon is not known clearly. Nonetheless, mechanisms that are possibly involved in the SCF process are small vessel dysfunction [4], diffuse atherosclerosis [5], inflammation [6], and increased platelet aggregability [7]. It is also hypothesized that SCF may be a form of atherosclerosis involving small vessels because of its close relationship with cardiovascular risk factors and its pathogenesis overlapping with that of atherosclerosis [8]. Moreover, previous studies have shown that, similar to coronary artery disease, SCF is associated with increased cardivascular mortality as well [9].

The more the number of affected vessels rises in coronary artery disease, the lower the survival rate [10], however, there is no study on this subject in SCF patients. Elevated thrombogenicity, another factor believed to involve in the SCF pathogenesis, is known to have a relationship with increased hemoglobin (Hb) and mean platelet volume (MPV) [11, 12]. Platelet volume is a marker of platelet activation and it is measured by using MPV [13]. Previous studies have shown that high MPV levels are associated with cardiovascular risk factors [14] and were increased in acute myocardial infarction, coronary ectasia, and SCF [15–17] with a poor prognosis [18].

While there are various studies about the relationship among presence of SCF, hematologic indices and cardiovascular risk factors [8, 17], there is no study focusing on their relationship with the extent of SCF. In our study, for the first time in the literature, we aimed to investigate the relationship between the extent of SCF, and hematologic indices and cardiovascular risk factors.

Methods

Patient selection

In this study, 2467 patients who received coronary angiography between April 2009 and November 2010 were retrospectively evaluated. All the patients included in our study had received coronary angiography because of chest pain or objective signs of ischemia (treadmill exercise or myocardial SPECT). One hundred and seven SCF patients were found on coronary angiograms. Fifty patients with SCF were excluded from the study for the following reason; history of coronary artery disease or sign of coronary artery disease on coronary angiograms (n = 17), coronary ectasia on coronary angiograms (n = 11) moderate to severe valvular heart disease and heart failure (n = 3), left ventricular (LV) hypertrophy (n = 2), anemia (n = 8), end-stage renal disease (ESRD) (n = 2), inflammatory diseases (n = 2), malignancy (n = 1), peripheral or cerebral artery disease (n = 2), thrombocytopenia (n=1), and thyroid gland dysfunction (n = 1). Finally, 57 patients with SCF (experimental group) were included in the study. Control group consisted of 90 patients with age- and gender-matched subjects who were selected in a consecutive manner from the catheterized patients during the same study period and who proved to have normal coronary angiograms. Control subjects selected from patients without exclusion criteria. Routinely measured laboratory and clinical parameters (e.g. diabetes mellitus [DM], hypertension [HTN], hypercholesterolemia, smoking, family history of cardiovascular disease, height and weight) of the patients were obtained from the medical records. In cases having dubious or inconsistent records, patients were contacted directly via phone.

Transthoracic echocardiography was carried out before discharge by a system V (Vingmed, GE) device using 2.5 MHz phased-array transducer. Recordings were performed while the patients were in the left lateral decubitus position. The LV ejection fraction was measured using modified Simpson's rule according to the most recent guidelines [19]. Our study was approved by the local ethics committee.

Coronary angiography

In our clinic, coronary angiography is routinely performed by Judkins method using iohexol (Omnipaque, Nycomed Ireland ltd., Cork, Ireland). During each injection, 6–10 mL contrast agent is manually delivered and nitroglycerin is not routinely applied. The coronary flow rates of all patients were measured by the Thrombolysis In Myocardial Infarction (TIMI) frame count (TFC) method with cineangiography at 25 frames per second. Since the left anterior descending (LAD) artery is usually longer than other coronary arteries, the corrected-TFC of the LAD artery was calculated by dividing TFC by 1.7. The TFC of the LAD was assessed either in right anterior oblique projection with caudal angulation or left anterior oblique projection with cranial angulation, while the assessments of the left circumferential (LCx) artery and right coronary artery (RCA) were usually performed in straight left anterior oblique projection. TFC for each coronary artery was determined from a distal marking point specific for the coronary artery of interest [20]. Coronary angiograms were assessed

independently by two invasive cardiologists who were blinded to the clinical findings.

Laboratory measurements

In our hospital the blood samples are collected from the antecubital vein by an atraumatic puncture prior to the coronary angiography and are sent to the laboratory for analysis within 1 hour after collection. Routinely venous blood is collected in a tube containing K3 EDTA for measurement of hematologic indices in all patients undergoing the coronary angiography. Hematologic indices are evaluated from complete blood count (CBC) analysis performed by a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland).

Definitions

Stable angina was defined as discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress, and relieved by rest or nitroglycerin. HTN was defined as systolic blood pressure > 140 mm Hg and/or a diastolic blood pressure > 90 mm Hg, or use of antihypertensive medications. The diagnosis of DM was based on previous history of diabetes treated with or without medical therapy. Hypercholesterolemia was described as total cholesterol ≥ 200 mg/dL. Body mass index (BMI) was calculated by dividing the weight (kg) of an individual by the square of his/her height (m). A BMI value ≥ 30 kg/m^2 was defined as obese. Current smokers were defined as having a history of smoking for a certain period within the past year. Anemia on admission was defined in accordance with the World Health Organization criteria, as having a baseline hemoglobin concentration value less than 13 mg/dL in men and less than 12 mg/dL in women. The glomerular filtration rate (GFR) was estimated by the simplified Modification of Diet in Renal Disease Equation [21]. Renal insufficiency was described as a GFR value < 60 mL/min/1.732 m^2. Patients were considered as having ESRD if they were dependent on chronic dialysis.

SCF was defined as a corrected TFC greater than two standart deviations from the normal range (40.8 frames for LAD, 29.8 frames for LCx, and 27.3 frames for RCA), while normal coronary flow was described as a corrected TFC within two standart deviations of normal range reported for the related vessel [20]. Patients with SFC were categorized as non-extensive (1 vessel, Group 1) and extensive (> 1 vessels, Group 2) SCF cases relative to the number of vessels affected by the slow flow. Mean TFC for each subject was calculated by dividing the total of corrected LAD, LCx and RCA values by three.

Statistical analysis

Continuous variables are expressed as mean ± ± SD. Categorical variables are expressed as percentages. To compare parametric continuous variables, Student's *t* test were used; to compare nonparametric continuous variables, Mann-Whitney U were used. Chi-square test was used to compare the categorical variables. Multivariate logistic regression analysis was used to identify the independent predictors of presence and extent of coronary slow flow. All variables showing significance values < 0.1 in univariate analysis (DM, hypercholesterolemia, current smoker, family history of cardiovascular disease, obesity, Hb, MPV, and medications) were included in the model. Association between variables was tested using Spearman's or Pearson's correlation coefficient, when appropriate. Two-tailed p values < 0.05 were considered as statistically significance. All statistical studies were carried out with the SPSS program (version 15.0, SPSS, Chicago, Illinois, USA).

Results

Among the 147 patients (mean age 52.7 ± 10.0, 53.7% male), MPV ranged from 6.5 fL to 11.7 fL (median 7.9 fL, mean 8.1 ± 0.8 fL). The baseline characteristics of angiographic normal vessels or those with angiographic SCF, are summarized in Table 1. In patients with SCF, DM, hypercholesterolemia, and smoking were more common, and they also exhibited significantly higher Hb (Fig. 1A) and MPV (Fig. 1B) values. When SCF patients and controls were compared with regard to TFC (regarding both mean and individual values), SCF patients demonstrated significantly higher TFC findings compared with the control group (p < 0.001).

Moreover, SCF was determined to affect RCA the most (64.9%), followed by LAD (57.9%) and LCx (38.6%). SCF was observed to have a tendency to affect a single vessel (49.1%) or two vessels (40.4%); whereas three-vessel involvement was less common (10.5%).

Statistically significant variables of univariate analysis were included in the multivariate logistic regression analysis. DM (OR = 3.64, 95% CI 1.15–10.43, p = 0.03), hypercholesterolemia (OR = 4.94, 95% CI 1.99–12.21, p = 0.001), smoking (OR = 3.54, 95% CI 1.43–8.72, p = 0.002), Hb (OR = 1.69, 95% CI 1.22–2.36, p = 0.002), and MPV (OR = 2.52, 95%

Table 1. Baseline characteristics of angiographic normaly and slow coronary flow patients.

Variables	Slow flow (n = 57)	Normal flow (n = 90)	P
Age [years]	53.7 ± 10.7	51.9 ± 9.5	0.18
Male sex	32 (56.1%)	47 (52.2%)	0.64
Diabetes mellitus	17 (29.8)	8 (8.9%)	0.001
Hypertension	23 (40.4%)	30 (33.3%)	0.38
Hypercholesterolemia	28 (49.1%)	17 (18.9%)	< 0.001
Current smokers	25 (43.9%)	22 (24.4%)	0.01
Family history	11 (19.3%)	25 (27.8%)	0.24
BMI ≥ 30 kg/m^2	13 (22.8%)	11 (12.2%)	0.09
GFR< 60 mL/mn/1.73 m^2	3 (5.3%)	7 (7.8%)	0.55
Aspirin use	13 (22.8%)	28 (31.1%)	0.27
Beta-blocker use	8 (14%)	13 (14.4%)	0.94
ACE inhibitor use	12 (21.1%)	21 (23.3%)	0.74
Statin use	9 (15.8%)	12 (13.3%)	0.67
Diuretic use	10 (17.5%)	10 (11.1%)	0.26
Nitrates	6 (10.5%)	12 (13.3%)	0.61
Calcium canal blokers	9 (15.8%)	12 (13.5%)	0.69
LVEF [%]	61.4 ± 5.7	60.2 ± 8.7	0.42
Hemoglobine [g/dL]	15.0 ± 1.3	14.2 ± 1.2	0.001
MCV [fL]	88.2 ± 4.9	87.9 ± 3.4	0.70
WBC [10^3/μL]	7.5 ± 2.4	7.7 ± 1.7	0.17
Platelet [mm^3]	245.7 ± 58.1	232.9 ± 36.3	0.20
MPV [fL]	8.4 ± 1.0	7.9 ± 0.6	0.002
RDW [%]	13.9 ± 1.5	13.7 ± 0.6	0.80
Hemodynamic data on coronary angiography:			
SBP [mm Hg]	126.1 ± 12.8	129.9 ± 14.7	0.21
DBP [mm Hg]	76.5 ± 8.9	79.2 ± 10.7	0.15
Heart rate [bpm]	77.9 ± 14.2	79.1 ± 11.9	0.51
TIMI frame count:			
LAD (corrected)	37.8 ± 12.1	27.2 ± 4.3	< 0.001
LCx	28.7 ± 9.0	21.0 ± 3.9	< 0.001
RCA	32.7 ± 9.8	21.1 ± 3.8	< 0.001
Mean	33.1 ± 6.3	23.1 ± 2.7	< 0.001
Distribution of slow flow:			
LAD	33 (57.9%)		
LCx	22 (38.6%)		
RCA	37 (64.9%)		
Number of slow flow vessels:			
One vessel	28 (49.1%)		
Two vessels	23 (40.4%)		
Three vessels	6 (10.5%)		

Results are expressed as mean ± SD and percentage; ACE — angiotensin converting enzyme; BMI — body mass index; DBP — diastolic blood pressure; GFR — glomerular filtration rate, LAD — left anterior descending artery; LCx — left circumflex artery; LVEF — left ventricular ejection fraction; MCV — mean corpuscular volume; MPV — mean platelet volume; RCA — right coronary artery; RDW — red cell distribution width; SBP — systolic blood pressure; TIMI — Thrombolysis In Myocardial Infarction; WBC — white blood cell

CI 1.43–4.44, p = 0.001) were the independent correlates of SCF presence (Table 2). The extensive and non-extensive SCF cases (Group 1 and 2) are compared in Table 3. Group 2 had higher rates for DM and family history of cardiovascular disease, as well as significantly increased MPV (Fig. 1C). In the multiple logistic regression analysis, only MPV (OR = 2.13, 95% CI 1.05–4.33, p = 0.03) was found to be the independent correlate of extent of SCF. Moreover, MPV was found to show a moderate cor-

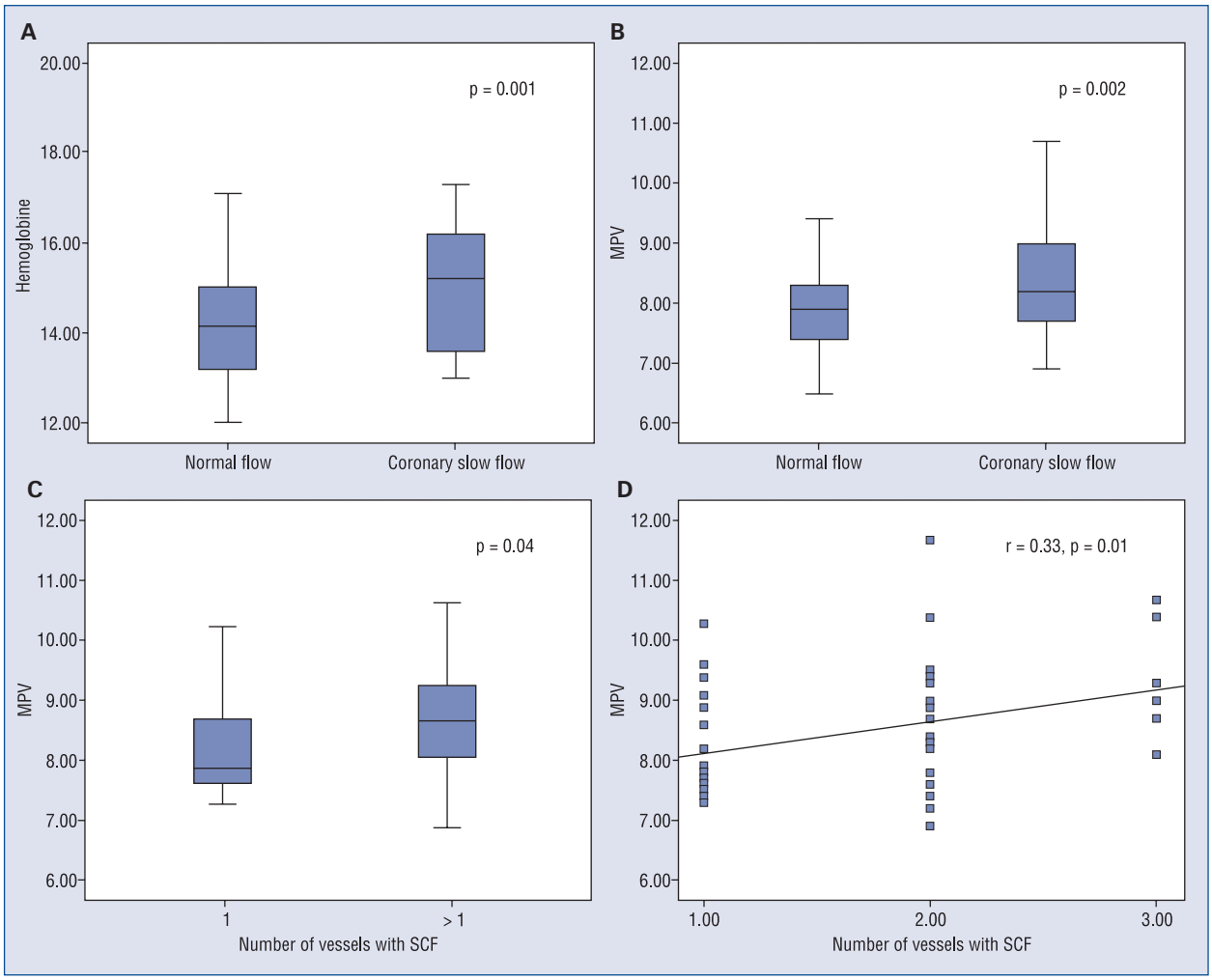

Figure 1. A, B. Hemoglobin and mean platelet volume (MPV) values of patients with and without slow coronary flow (SCF); **C.** The relationship of MPV with extensive and non-extensive SCF; **D.** The relationship between MPV and the number of vessels with SCF.

Table 2. Independant predictors of slow coronary flow in multivariate logistic regression analysis.

Variables	Univariate OR (95% CI)	P	Mulivariate OR (95% CI)	P
Diabetes mellitus	4.35 (1.73–10.94)	0.001	3.64 (1.15–10.43)	0.03
Hypercholesterolemia	4.14 (1.97–8.69)	< 0.001	4.94 (1.99–12.21)	0.001
Current smoker	2.41 (1.18–4.91)	0.01	3.54 (1.43–8.72)	0.006
BMI ≥ 30 kg/m^2	2.12 (0.87–5.13)	0.09	1.69 (1.22–2.36)	0.18
Hemoglobine [g/dL]	1.57 (1.19–2.07)	0.001	1.69 (1.22–2.36)	0.002
MPV [fL]	2.32 (1.44–3.72)	< 0.001	2.52 (1.43–4.44)	0.001

BMI — body mass index; MPV — mean platelet volume; OR — odds ratio; CI — confidence interval

relation with the number of vessels affected by SCF ($r = 0.33$, $p = 0.01$, Fig. 1D) and TFC values (mean TFC: $r = 0.43$, $p < 0.001$; LAD TFC: $r = 0.27$, $p = 0.001$; LCx TFC: $r = 0.33$, $p < 0.001$; RCA TFC: $r = 0.31$, $p < 0.001$, Figs. 2A–D).

Discussion

This is the first study to evaluate the relationship between the extent of SCF, and cardiovascular risk factors and hematologic indices. We found

Table 3. Baseline characteristics with and without extent of slow coronary flow.

Variables	Group 1 (n = 28)	Group 2 (n = 29)	P
Age [years]	52.4 ± 9.4	55.1 ± 11.9	0.27
Male sex	14 (50%)	18 (62.1%)	0.35
Diabetes mellitus	4 (14.3%)	13 (44.8%)	0.01
Hypertension	12 (42.9%)	11 (37.9%)	0.70
Hypercholesterolemia	16 (57.1%)	12 (41.4%)	0.23
Current smoker	13 (46.4%)	12 (41.4%)	0.70
Family history	2 (7.1%)	9 (31%)	0.02
BMI ≥ 30 kg/m^2	5 (17.9%)	8 (27.6%)	0.38
GFR < 60 mL/mn/1.73 m^2	1 (3.6%)	2 (6.9%)	0.57
Aspirin use	5 (17.9%)	8 (27.6%)	0.38
Beta-blocker use	2 (7.1%)	6 (20.7%)	0.14
ACE inhibitor use	8 (28.6%)	4 (13.8%)	0.17
Statin use	6 (21.4%)	3 (10.3%)	0.25
Diuretic use	5 (17.9%)	5 (17.2%)	0.95
Nitrates	4 (14.3%)	2 (6.9%)	0.36
Calsium canal blokers	7 (25%)	2 (6.9%)	0.06
LVEF [%]	61.4 ± 6.1	61.3 ± 5.3	0.71
Hemoglobine [g/dL]	15.2 ± 1.1	14.7 ± 1.4	0.22
MCV [fL]	88.4 ± 5.1	88.0 ± 4.7	0.86
WBC [10^3/μL]	7.5 ± 2.9	7.5 ± 1.9	0.50
Platelet [mm^3]	258.7 ± 59.2	233.2 ± 55.2	0.19
MPV [fL]	8.1 ± 0.8	8.7 ± 1.1	0.04
RDW [%]	13.7 ± 1.4	14.2 ± 1.7	0.23
Hemodynamic data on coronary angiography:			
SBP [mm Hg]	124.1 ± 13.3	128.0 ± 12.4	0.29
DBP [mm Hg]	76.1 ± 8.9	76.9 ± 9.2	0.71
Heart rate [bpm]	77.1 ± 15.1	78.7 ± 13.5	0.59
Mean TIMI frame count	28.3 ± 2.7	37.7 ± 5.2	< 0.001

Results are expressed as mean ± SD and percentage; Group 1 — non-extensive SCF; Group 2 — extensive SCF; rest abbreviations as in Table 3

that increased baseline MPV values were independently associated with the presence and extent of SCF. Moreover, in our study, we observed that increased Hb was independently associated with the presence of SCF.

Although the pathophysiology of SCF is not completely clear, based on its histopathologic characteristics (e.g. degeneration of the endothelial cells with narrowing of the vascular lumina) [22], accompanying atherosclerosis [5], close relationship with inflammatory parameters (e.g. CRP) [6], and increased platelet aggregability [7], it is hypothesized that SCF may be a form of atherosclerosis involving small vessels. Similarly, recent IVUS (Intravascular ultrasound) and fractional flow reserve studies have shown early diffuse atherosclerosis and increased epicardial resistance in vessels with SCF [5].

Endothelial dysfunction is the most plausible mechanism in terms of SCF pathogenesis [22]. There is a close relationship between the endothelial dysfunction, and inflammatory parameters and cardiovascular risk factors (e.g. smoking, hypercholesterolemia) [23]. In this study, we did not evaluate the inflammatory parameters, however, previous studies have already shown that inflammatory parameters exhibit an increase in patients with SCF [6]. Therefore, our findings were in agreement with the previous studies in terms of showing an independent relationship between the presence of SCF and cardiovascular risk factors (e.g. DM, hypercholesterolemia and smoking) which are known to be closely associated with inflammation and endothelial dysfunction [2, 8]. It is known that raised inflammatory parameters damage endothelial glycocalyx, the luminal surface protecting endothelium, and lead to endothelial dysfunction [24].

Platelets assume a critical role in the regulation of blood flow and thrombogenic events [25].

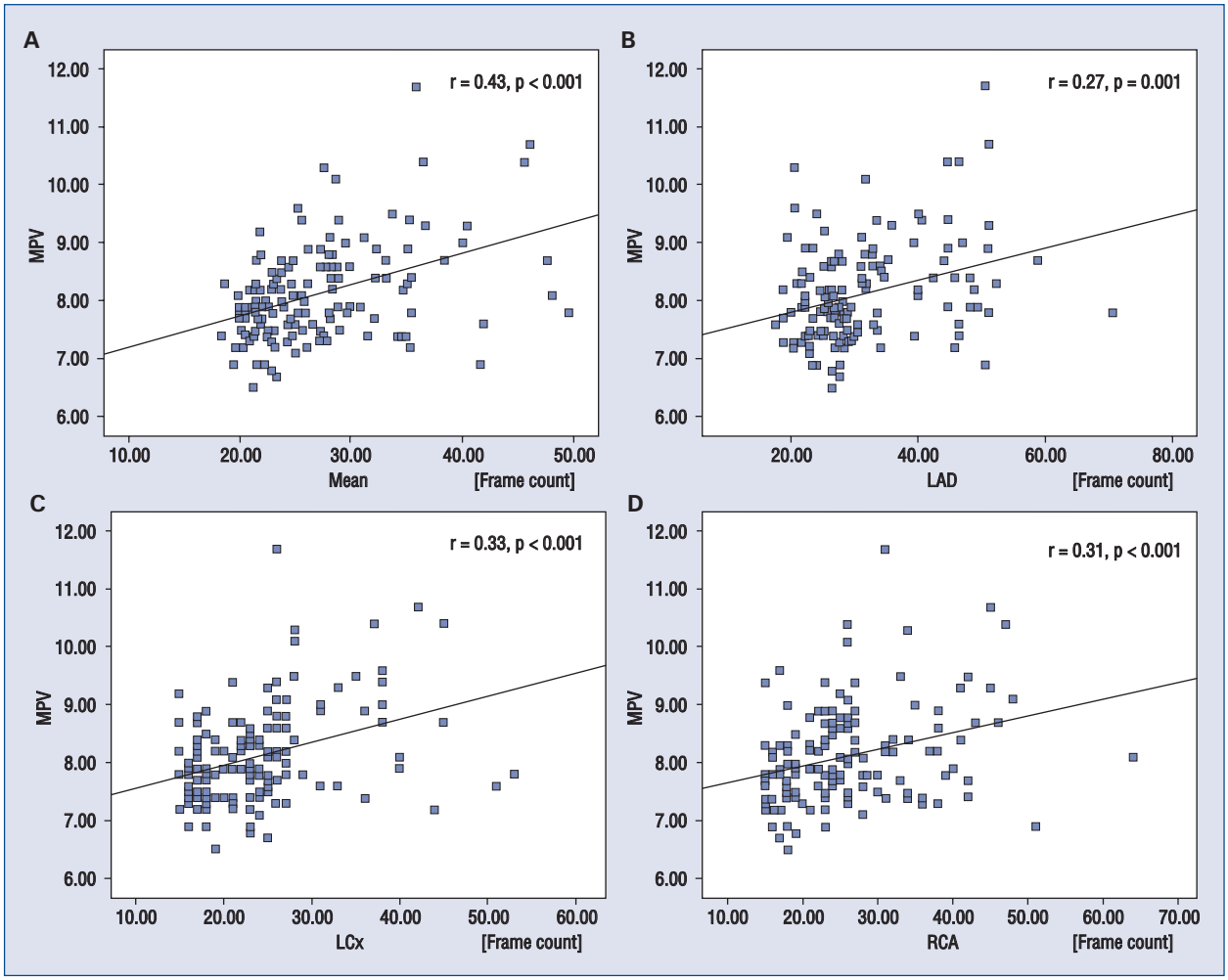

Figure 2. The relationship between mean platelet volume (MPV) and Thrombolysis In Myocardial Infarction (TIMI) frame count (TFC) values (mean and individual values for each artery); rest abbreviations as in Table 1.

Elevated thrombogenic tendency is one of the other subjects studied with regard to SCF pathogenesis [17]. Gokce et al. [7] showed that patients with SCF had increased platelet aggregability in the ristocetin, collagen and adenosine diphosphate groups than in the control group. Platelet volume is a index of platelet activation and it is measured by using MPV [13]. Increased MPV values suggest large platelets with more dense granules. Large platelets secrete high amounts of prothrombogenic thromboxane A2, serotonin and procoagulant membrane proteins like sP-selectin [15, 17, 25]. Moreover, large platelets are less sensitive to the antiaggregation and antisecretion properties of prostacyclin [16]. However, previous studies have reported that high MPV levels are related with cardiovascular risk factors [14] and were increased in cardiac conditions [15–17] with a poor prognosis [18]. In our study, we determined that MPV levels were not only associated with the presence of SCF, but also associated with the extent of SCF. These results show an association with a increase in MPV in patients with SCF.

The viscosity of blood is the resistance of blood against the flow and it is observed to increase in coronary artery disease patients [26]. Blood viscosity is a risk factor in cardiovascular events [27] and it is influenced by the same parameters, one of which is hematocrit [28]. In this study, we did not measure viscosity in SCF patients, however, previous studies have shown that SCF patients present with raised blood viscosity [29]. Our study shows for the first time that increased Hb values an associated with presence of SCF. As in atherosclerosis cases, blood viscosity is raised in SCF patients because of increased platelet adhesion to subendo-

thelium, elevated protein infiltration into the arterial wall, and altering local shear forces [30].

There is no consensus on the treatment protocols for SCF patients. Generally, as in coronary artery disease patients, those cases are treated by agents against angina attacks such as organic nitrates, beta–blockers and calcium channel blockers along with acetylsalicylic acid and statin therapy against a possible atherosclerotic pathogenesis. However, these therapies oftenly fail to control the angina attacks. In our study, we did not focus on the efficacy of a certain agent, however, because of patients with SCF have atherosclerosis, inflammation, endothelial dysfunction, and elevated thrombogenicity, they may need an aggressive antiplatelet therapy with modification of risk factors and reduces MPV values, particularly in patients with extensive SCF. However, further multicenter randomized prospective studies are required for verification.

Limitations of the study

First, this was a cross-sectional study, therefore, we did not perform long-term analyses. Second, since normal coronary artery was defined based on the angiographic appearance, all the atherosclerotic plaques could not be excluded.

Conclusions

An increased baseline MPV value was found to be an associated with presence and extent of SCF. Our study may assist in better understanding the SCF pathogenesis.

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