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Original article

Plateletcrit and red cell distribution width are independent predictors of the slow coronary flow phenomenon

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ABSTRACT

Background and purpose: Endothelial dysfunction may play a role in the pathogenesis of the slow coronary flow (SCF) phenomenon. A detailed examination of blood cellular components has not been performed for this condition. We investigated the relationship between SCF and whole blood cell counts.
Method: Records of 17,315 patients who underwent coronary angiography between January 2006 and December 2012 were evaluated retrospectively. A total of 146 patients with SCF were compared with 148 patients with normal coronary arteries according to demographic data, complete blood count, and biochemical parameters.
Results: The following parameters were significantly higher in SCF patients than in patients with normal coronary arteries: percentage of smokers (36.3% vs. 25%, $p = 0.036$), body mass index (26.69 ± 2.84 vs. 26.07 ± 3.15, $p = 0.049$), white blood cells (WBCs) ($7.52 \pm 1.43 \times 10^3$ mm^{-3} vs. $7.01 \pm 1.42 \times 10^3$ mm^{-3}, $p = 0.002$), red cell distribution width (RDW) ($13.68 \pm 1.42\%$ vs. $13.15 \pm 1.13\%$, $p < 0.001$), platelets ($250.29 \pm 50.96 \times 10^3$ mm^{-3} vs. $226.10 \pm 38.02 \times 10^3$ mm^{-3}, $p < 0.001$), plateletcrit (PCT) ($0.214 \pm 0.40\%$ vs. $0.184 \pm 0.29\%$, $p < 0.001$), mean platelet volume (8.63 ± 1.10 fL vs. 8.22 ± 0.83 fL, $p < 0.001$), platelet distribution width (PDW) ($16.58 \pm 0.76\%$ vs. $16.45 \pm 0.57\%$, $p = 0.028$), and neutrophils ($4.44 \pm 1.25 \times 10^3$ mm^{-3} vs. $4.12 \pm 1.24 \times 10^3$ mm^{-3}, $p = 0.029$). Positive PCT values [odds ratio (OR), 4.165; 95% confidence interval (CI), 2.493–6.959; $p < 0.001$) and RDW (OR, 1.304; 95% CI, 1.034–1.645; $p = 0.025$) were independent predictors of SCF.
Conclusion: Although within the normal range, the increased numbers of WBCs and neutrophils in patients with SCF suggest that SCF may be a subclinical inflammatory condition. Furthermore, increased RDW and PDW in SCF patients may cause microvascular blood flow resistance due to impaired cell deformability. The PCT provides reliable data regarding total platelet mass and may be a useful predictor of SCF.

Introduction

The slow coronary flow (SCF) phenomenon is seen on coronary angiography as a delayed opacification of distal vessels, suggesting increased resistance toward the distal coronary segments, in the absence of significant epicardial coronary stenosis. The etiopathogenesis of SCF is unknown, although several studies have shown that endothelial and microvascular dysfunction, inflammation, increased platelet activation, and homocysteine may play roles in this condition [1–7]. The clinical implications and outcomes of SCF are usually favorable, but it may be associated with adverse cardiac conditions such as recurrent angina pectoris, acute myocardial infarction, hypertension, and sudden cardiac death [8,9].

Microvascular flow resistance can result from changes in blood rheological properties. Patel et al. showed that increased red cell distribution width (RDW) was associated with impaired deformability of erythrocytes [10]. Variations and heterogeneity of blood cell shape are expressed by RDW for erythrocytes and

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platelet distribution width (PDW) for platelets; however, no such parameter is available for leucocytes. Cell distribution widths of platelets and erythrocytes have not been evaluated simultaneously in patients with the SCF phenomenon. In the present study, the relationships between cellular components of blood and the SCF phenomenon were investigated.

Methods

The angiographic records of 17,315 patients who underwent coronary angiography, due to anginal symptoms or positive treadmill exercise and scintigraphy tests, between January 2006 and December 2012 were evaluated retrospectively. The patient recruitment process is shown in Fig. 1. In the first stage, two cardiologists obtained the names and hospital record numbers (ID numbers) of patients with the SCF phenomenon (519 patients) and those with normal coronary arteries (765 patients) from the non-digital (paper) record files. In the second stage, two different cardiologists, who had no knowledge of the patients' coronary angiographic diagnoses, collected demographic data and biochemical and hematological laboratory results from a digital recording system (PC records). In the third stage, another two different cardiologists, without knowledge of the patients' angiographic data, assessed all patients and selected those for the study based on the exclusion criteria. Patients meeting any of the following criteria were excluded: acute coronary syndrome; hematological, oncological, or inflammatory disease; white blood cell (WBC) count >10,000 mm^{-3}; hemoglobin level <12 g/dL; valvular disease or a cardiac valve operation; anticoagulant therapy; ejection fraction <50%; renal insufficiency; liver or thyroid dysfunction; thrombocytopenia or thrombocytosis; and missing data. In the fourth stage, two experienced interventional cardiologists, who were unaware of the demographic and laboratory data, evaluated coronary angiographic images and calculated thrombolysis in myocardial infarction (TIMI) frame counts. A total of 70 patients with significant atherosclerotic plaque and coronary ectasia were excluded because these conditions are thought to be present in patients with a slow blood flow [11,12]. Finally, 146 patients with the SCF phenomenon and 148 patients with normal coronary arteries were included in the study.

Transthoracic echocardiography (Vivid 7 Pro, GE, Horten, Norway) was performed with a 2.4 MHz phased array transducer. Left ventricular ejection fraction was estimated using Simpson's rule. Patients with arterial blood pressure >140/90 mmHg, as measured from the brachial artery, and those receiving antihypertensive therapy were considered to be hypertensive. Diabetes was defined by a fasting blood glucose >126 mg/dL or the use of antidiabetic drugs. Patients with total cholesterol >200 mg/dL, low density lipoprotein (LDL)-cholesterol >130 mg/dL, or triglycerides >150 mg/dL, and those using lipid-lowering drugs were considered to be hyperlipidemic. Past and current smokers were classified as smokers. This study was conducted with the approval of the local ethics committee.

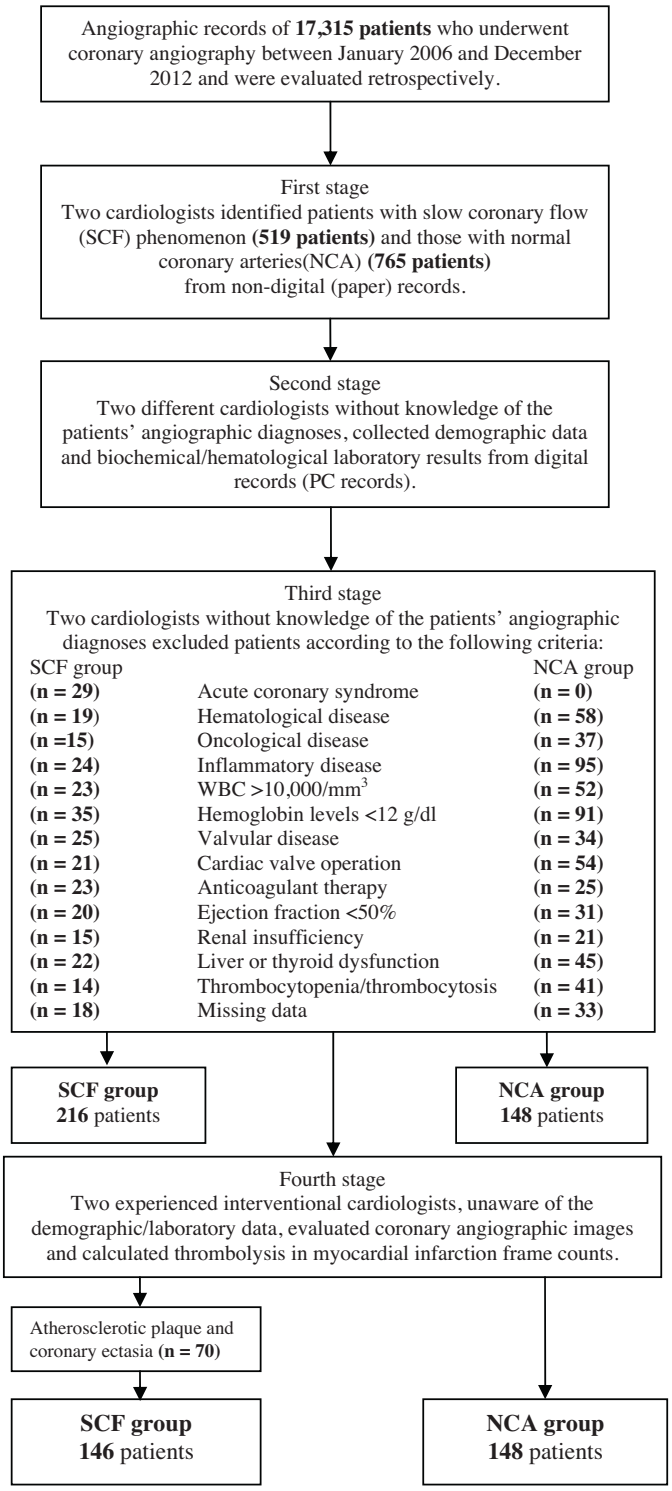

Fig. 1. Patients' recruitment diagram. WBC, white blood cell count.

Coronary angiography

Coronary angiography (Integris BH 5000; Philips, Amsterdam, the Netherlands) was performed via the femoral artery, using the standard Judkin's technique. The angiographic standard frame speed was 25 frames/s. Coronary angiography images of all patients included in the study were evaluated by two experienced interventional cardiologists who were unaware of the demographic and laboratory data. TIMI frame count values were calculated using the method of Gibson et al. [13].

Blood tests

Hematological parameters

Complete blood counts, performed using a Beckman Coulter LH 780 Analyzer (Miami, FL, USA), included 22 parameters: WBC count, 4.8×10^3 to 10.8×10^3 mm^{-3}; red blood cell count (RBC), 4.2×10^6 to 6.1×10^6 mm^{-3}; hemoglobin (HGB) concentration, 12–18 g/dL; hematocrit (HCT), 37–52%; mean cell volume (MCV), 80–99 fL; mean cell hemoglobin (MCH), 27–31 pg;

mean cell hemoglobin concentration (MCHC), 32–36 g/dL; RDW, 11.5–15.5; platelet count (PLT), 150×10^3 to 400×10^3 mm^{-3}; mean platelet volume (MPV), 7.4–10.4 fL; plateletcrit (PCT); PDW; lymphocyte count (Lym#), 1.3×10^3 to 2.9×10^3 mm^{-3}; monocyte count (Mo#), 0.3×10^3 to 0.9×10^3 mm^{-3}; neutrophil count (Neu#), 2.2×10^3 to 4.8×10^3 mm^{-3}; eosinophil count (Eo#), 0.06×10^3 to 0.18×10^3 mm^{-3}; basophil count (Ba#), 0.01×10^3 to 0.03×10^3 mm^{-3}; lymphocyte percentage (Lym%), 20.5–45.5; monocyte percentage (Mo%), 5.5–11.7; neutrophil percentage (Neu%), 45–75; eosinophil percentage (Eo%), 0.9–2.9; and basophil percentage (Ba%), 0.2–1%.

Biochemical parameters

The following parameters were analyzed with a Siemens ADVIA 2400 instrument (Tarrytown, NY, USA): fasting glucose (70–105 mg/dL), urea (10–50 mg/dL), creatinine (0.50–1.2 mg/dL), uric acid (3.4–7.0 mg/dL), aspartate transaminase (AST, 0–38 U/L), alanine aminotransferase (ALT, 0–41 U/L), total cholesterol (110–200 mg/dL), high density lipoprotein (HDL) cholesterol (35–65 mg/dL), LDL cholesterol (60–130 mg/dL), triglycerides (<150 mg/dL).

Statistical analysis

Statistical analyses were performed using SPSS 13.0 for Windows (Chicago, IL, USA) and MedCalc 9.2. Categorical variables are given as frequency and percentage. Continuous variables are given as mean ± standard deviation (SD). The Shapiro–Wilk test was used to determine normality. The Mann–Whitney *U*-test was used for two-group comparisons. Pearson's and Yate's chi-squared tests were used to compare categorical variables. Multivariate logistic regression analysis was used to identify the independent predictors of SCF. Univariate analysis was performed using age, gender, body mass index (BMI), smoking, ASA (acetylsalicylic acid) use, WBC, RDW, PCT group, and PDW as variables. Significant variables ($p < 0.05$) were included in a multivariate model. Values of $p < 0.05$ were considered to indicate significance. A cutoff point for PCT and RDW to predict the SCF phenomenon was calculated with a receiver operating characteristics (ROC) curve analysis and is expressed as the area under the curve (AUC) and sensitive-specific values with 95% confidence intervals (CIs).

Results

The demographic and biochemical data of the two groups are shown in Table 1. For the 146 patients with SCF (mean age, 58.4 ± 10.3 years; 68.5% male), mean PCT was 0.214 ± 0.40% and mean RDW was 13.68 ± 1.42%. Compared with the normal artery group, the SCF group had a higher percentage of smokers [36.3% (53 patients) vs. 25% (37 patients), $p = 0.036$] and a higher BMI (26.69 ± 2.84 vs. 26.07 ± 3.15, $p = 0.049$). No differences in the biochemical parameters were observed between the two groups.

Table 2 shows a comparison of the 22 complete blood count parameters between the two groups. The following parameters

Table 1
Demographic data and biochemical parameters of the patients.

	Slow coronary flow group ($n = 146$)	Normal coronary artery group ($n = 148$)	p-Value
Age (years)	58.4 ± 10.3	57.2 ± 9.2	0.387
Male, *n* (%)	100 (68.5)	102 (68.9)	0.937
Hypertension, *n* (%)	79 (54.1)	66 (44.6)	0.103
Diabetes mellitus, *n* (%)	41 (28.1)	39 (26.4)	0.739
Hyperlipidemia, *n* (%)	46 (31.5)	60 (40.5)	0.107
Family history, *n* (%)	56 (38.4)	42 (28.4)	0.070
Smoking, *n* (%)	53 (36.3)	37 (25)	**0.036**
Alcohol consumption, *n* (%)	36 (24.7)	27 (18.2)	0.180
ASA, *n* (%)	31 (21.2)	46 (31.1)	0.055
ACE inhibitor, *n* (%)	45 (30.8)	46 (31.1)	0.962
ARB, *n* (%)	16 (11)	19 (12.8)	0.751
Beta blocker, *n* (%)	29 (19.9)	38 (25.7)	0.235
Ca channel blocker, *n* (%)	25 (17.1)	32 (21.6)	0.329
Statin, *n* (%)	16 (11)	22 (14.9)	0.318
Fibrate, *n* (%)	17 (11.6)	23 (15.5)	0.330
EF (%)	60.5 ± 3.8	59.8 ± 4.0	0.147
BMI (kg/m^2)	26.69 ± 2.84	26.07 ± 3.15	**0.049**
Fasting glucose (mg/dL)	107.19 ± 19.99	108.32 ± 21.94	0.813
Urea (mg/dL)	26.08 ± 6.55	27.55 ± 8.69	0.151
Creatinine (mg/dL)	0.92 ± 0.11	0.90 ± 0.11	0.240
AST (U/L)	24.13 ± 6.78	23.47 ± 7.47	0.317
ALT (U/L)	22.44 ± 8.29	23.78 ± 8.22	0.067
Uric acid (mg/dL)	5.18 ± 0.99	5.06 ± 0.79	0.901
Total cholesterol (mg/dL)	185.78 ± 27.59	184.52 ± 27.27	0.364
LDL-cholesterol (mg/dL)	121.05 ± 21.47	124.26 ± 23.97	0.090
HDL-cholesterol (mg/dL)	43.87 ± 6.64	45.69 ± 8.78	0.051
Triglyceride (mg/dL)	123.23 ± 37.45	123.85 ± 45.48	0.620
TIMI frame count			
LAD	46.54 ± 2.44	33.09 ± 2.32	**<0.001**
LAD corrected	27.38 ± 1.43	19.46 ± 1.36	**<0.001**
RCA	31.63 ± 3.34	20.34 ± 2.38	**<0.001**
LCX	33.38 ± 3.69	21.68 ± 2.54	**<0.001**
Mean	31.07 ± 3.38	25.01 ± 1.95	**<0.001**
Coronary artery branches including SCF ($n = 207$)			
LAD, *n*	130		
RCA, *n*	46		
LCX, *n*	31		

Corrected TIMI-LAD is equal to TIMI-LAD/1.7. Mean TIMI equals (TIMI-LAD + TIMI-RCA + TIMI-LCX)/3. ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; Ca, calcium; EF, ejection fraction; BMI, body mass index; AST, aspartate transaminase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TIMI, thrombolysis in myocardial infarction; LAD, left anterior descending; RCA, right coronary artery; LCX, circumflex; SCF, slow coronary flow.

Table 2
Comparison of 22 parameters complete blood count values between two groups.

	Slow coronary flow group ($n = 146$)	Normal coronary artery group ($n = 148$)	p-Value
WBC ($\times 10^3$ mm^{-3})	7.52 ± 1.43	7.01 ± 1.42	**0.002**
RBC ($\times 10^6$ mm^{-3})	4.76 ± 0.47	4.74 ± 0.46	0.684
HGB (g/dL)	14.26 ± 1.24	14.23 ± 1.30	0.859
HCT (%)	41.78 ± 3.55	41.60 ± 3.85	0.671
MCV (fL)	87.75 ± 5.51	87.92 ± 4.82	0.656
MCH (pg)	30.18 ± 2.06	30.19 ± 1.87	0.865
MCHC (g/dL)	34.13 ± 0.79	34.20 ± 0.90	0.816
RDW (%)	13.68 ± 1.42	13.15 ± 1.13	**<0.001**
PLT ($\times 10^3$ mm^{-3})	250.29 ± 50.96	226.10 ± 38.02	**<0.001**
MPV (fL)	8.63 ± 1.10	8.22 ± 0.83	**<0.001**
PCT (%)	0.214 ± 0.40	0.184 ± 0.29	**<0.001**
PDW (%)	16.58 ± 0.76	16.45 ± 0.57	**0.028**
Lym# ($\times 10^3$ mm^{-3})	2.24 ± 0.82	2.10 ± 0.61	0.232
Mo# ($\times 10^3$ mm^{-3})	0.60 ± 0.26	0.60 ± 0.27	0.852
Neu# ($\times 10^3$ mm^{-3})	4.44 ± 1.25	4.12 ± 1.24	**0.029**
Eo# ($\times 10^3$ mm^{-3})	0.20 ± 0.19	0.17 ± 0.18	0.265
Ba# ($\times 10^3$ mm^{-3})	0.04 ± 0.16	0.02 ± 0.04	0.277
Lym%	29.82 ± 9.04	30.55 ± 8.64	0.419
Mo%	7.74 ± 2.36	8.32 ± 2.67	0.080
Neu%	59.07 ± 10.02	57.91 ± 9.81	0.316
Eo%	2.65 ± 2.39	2.10 ± 1.75	0.059
Ba%	0.57 ± 0.41	0.50 ± 0.40	0.127

WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; HCT, hematocrit; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; RDW, red cell distribution width; PLT, platelet count; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; Lym#, lymphocyte count; Mo#, monocyte count; Neu#, neutrophil count; Eo#, eosinophil count; Ba#, basophil count; Lym%, lymphocyte percentage; Mo%, monocyte percentage; Neu%, neutrophil percentage, Eo%, eosinophil percentage and Ba%, basophil percentage.

were significantly higher in patients with SCF than in patients with normal coronary arteries: WBC ($7.52 \pm 1.43 \times 10^3$ mm^{-3} vs. $7.01 \pm 1.42 \times 10^3$ mm^{-3}, $p = 0.002$), RDW ($13.68 \pm 1.42\%$ vs. $13.15 \pm 1.13\%$, $p < 0.001$), PLT ($250.29 \pm 50.96 \times 10^3$ mm^{-3} vs. $226.10 \pm 38.02 \times 10^3$ mm^{-3}, $p < 0.001$), PCT ($0.214 \pm 0.40\%$ vs. $0.184 \pm 0.29\%$, $p < 0.001$), MPV (8.63 ± 1.10 fL vs. 8.22 ± 0.83 fL, $p = 0.001$), PDW ($16.58 \pm 0.76\%$ vs. $16.45 \pm 0.57\%$, $p = 0.028$), and neutrophil count ($4.44 \pm 1.25 \times 10^3$ mm^{-3} vs. $4.12 \pm 1.24 \times 10^3$ mm^{-3}, $p = 0.029$).

A ROC analysis was performed for all platelet parameters and RDW. The PCT cutoff value was 0.200 (AUC: 0.715; $p < 0.001$; 95% CI: 0.656–0.773; 66% sensitivity; 72% specificity) (Fig. 2). All patients were categorized into two groups according to their PCT value: patients with PCT <0.200 were assumed to be PCT negative, and all others were assumed to be PCT positive. The RDW cutoff value was 13.15 (AUC: 0.636; $p < 0.001$; 95% CI: 0.572–0.699; 58% sensitivity; 57% specificity) (Fig. 3).

Age, gender, BMI, smoking, ASA use, WBC, RDW, PDW, and PCT group (PCT negative or positive according to the cutoff value) were analyzed in a univariate analysis. Smoking, RDW, WBC, and PCT group were included in a multivariate logistic regression analysis (Table 3). A positive PCT value [odds ratio (OR): 4.165; 95% CI: 2.493–6.959, $p < 0.001$] and RDW (OR: 1.304; 95% CI: 1.034–1.645, $p = 0.025$) were independent predictors of the SCF phenomenon.

Discussion

The SCF phenomenon is observed on coronary angiography as a delayed distal vessel opacification in the absence of significant coronary stenosis. The mechanism of this angiographic clinical entity remains unknown, although several hypotheses have been proposed, including inflammation, endothelial dysfunction, changes in blood rheological properties, increased uric acid, and conditions associated with increased platelet volume [14–17]. The cellular components of the blood in patients with SCF have not been evaluated comprehensively.

In our study, 22 complete blood count parameters were compared between patients with the SCF phenomenon and those with normal coronary artery flow. Similar to previous reports, the MPV was higher in the SCF group than in the normal artery group in the present study [18,19]. Platelets play critical roles in inflammation, thrombosis, and cardiovascular physiopathology. Additionally, increased MPV is associated with acute coronary syndrome, carotid artery disease, sepsis, deep vein thrombosis, pulmonary embolism, and coronary collateral vessels [20–25]. Only MPV and platelet count have been evaluated in most earlier investigations of SCF parameters, and PDW and PCT, which reflect the total platelet mass, have been ignored. PCT has been assumed to indicate the number of circulating platelets in a unit volume of blood, analogous to the hematocrit for erythrocytes [26]. Sahin et al. demonstrated that PCT is correlated with C-reactive protein (CRP) levels in patients with chronic inflammatory diseases such as tuberculosis [27].

In addition to an increased RDW value, PDW was significantly higher in the SCF group than in the normal artery group. Some studies have suggested that PDW is more specific than MPV for indicating platelet activation. Vagdatli et al. reported that PDW is a simple, practical, and specific activation marker for coagulation [28]. However, insufficient data on the clinical significance of PDW are available. Increased distribution width of red and white blood cells may be associated with impaired deformability of these cells and thus increased microvascular resistance [29–31].

RDW is a marker of the variation in erythrocyte shape and morphology. Hemolysis and various nutritional deficiencies, such as iron, vitamin B12, and folate deficiencies, may increase the RDW value. Regardless of the hemoglobin level, an increased RDW has predictive importance for mortality and morbidity in terms of atherosclerotic disease and heart failure [32,33]. The relationship between RDW and SCF has been shown in only one study, which found, similar to our study, that RDW was an independent predictor of the SCF phenomenon [34]. The presence of a significant correlation between increased RDW and high-sensitivity CRP levels suggests that RDW may be a useful marker associated with inflammation [35].

In our study, although the WBC count was within the normal range in both groups, WBC and neutrophils were present in

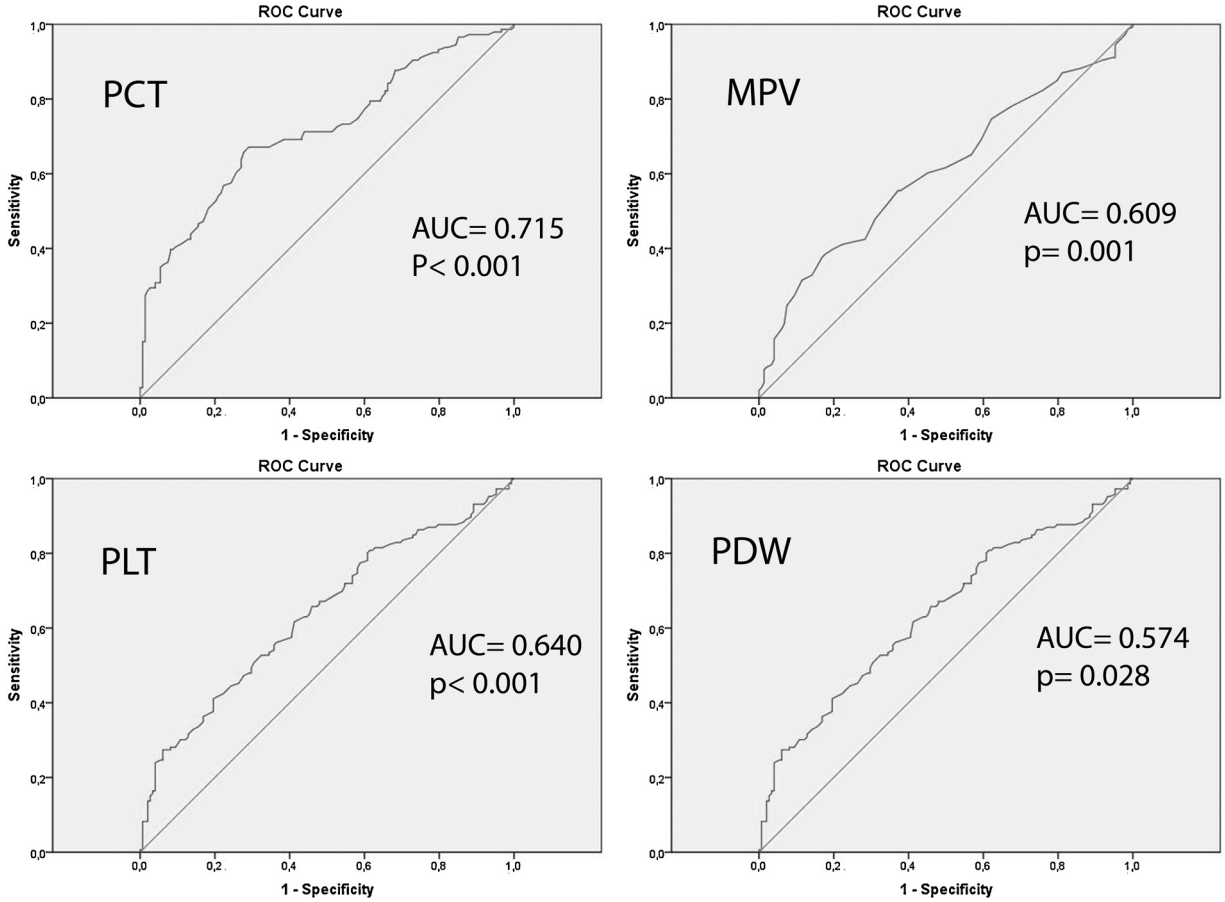

Fig. 2. Receiver operating characteristics (ROC) analysis of all platelet parameters. AUC, area under the curve; PCT, plateletcrit; MPV, mean platelet volume; PLT, platelet count; PDW, platelet distribution width.

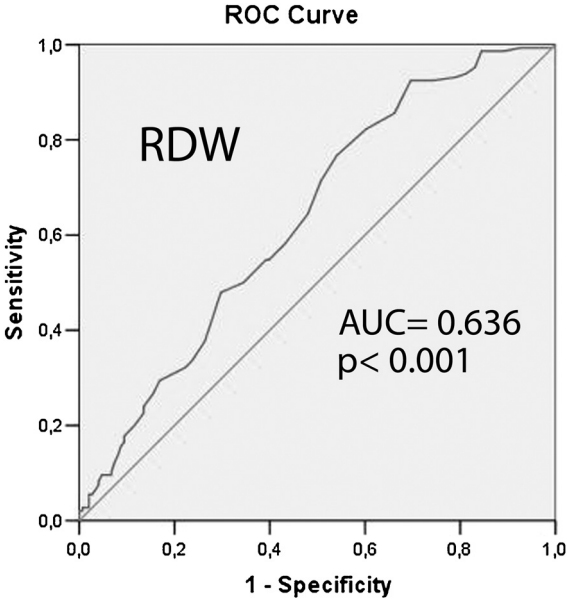

Fig. 3. Receiver operating characteristics (ROC) analysis of red cell distribution width. RDW, red cell distribution width; AUC, area under the curve.

Table 3
Independent predictors of slow coronary flow in multivariate logistic regression analysis.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age	1.012	0.989–1.037	0.305			
Gender	0.980	0.599–1.605	0.937			
BMI	1.072	0.992–1.158	0.079			
Smoking	1.710	1.035–2.825	**0.036**	1.506	0.869–2.611	0.145
ASA use	0.598	0.353–1.013	0.056			
WBC	1.280	1.087–1.507	**0.003**	1.145	0.959–1.368	0.135
RDW	1.445	1.161–1.799	**0.001**	1.304	1.034–1.645	**0.025**
PCT positive group	5.011	3.050–8.232	**<0.001**	4.165	2.493–6.959	**<0.001**
PDW	1.361	0.948–1.954	0.095			

BMI, body mass index; ASA, acetylsalicylic acid; WBC, white blood cell count; RDW, red cell distribution width; PCT, plateletcrit – PCT group, patients with PCT <0.200 were assumed to be PCT negative and all others were assumed to be PCT positive; PDW, platelet distribution width.

significantly higher numbers in the SCF group compared with the normal artery group. These increases along with the increased RDW suggest that SCF is a subclinical inflammatory condition.

Conclusions

To the best of our knowledge, our study is the first that investigates the predictive value of PCT in patients with SCF. Platelets are associated with inflammation and cardiovascular events. Many studies regarding the SCF phenomenon have investigated only mean platelet volume and platelet count among the possible SCF parameters. In this study, for the first time, patients with SCF were compared with patients who had normal coronary artery flow, according to 22 complete blood count parameters, including PCT and PDW. The PCT cutoff value for SCF in our study was 0.200. Positive PCT value (>0.200) and RDW were independent predictors of SCF. In patients with SCF phenomenon, positive PCT may be used as a marker for more aggressive antiplatelet treatment. For patients with positive PCT (over 0.200), whether recovery of slow coronary flow to normal coronary flow after antiplatelet therapy will be another area of study. Further large-scale and comprehensive studies are needed to support these results.

Limitations

Because high-sensitivity CRP is not evaluated routinely in patients undergoing elective coronary angiography in our department, this test was not included to compare inflammatory status between the groups. Owing to the retrospective nature of this study, no patient was evaluated by intravascular ultrasonography. For this reason, the existence of minimal atherosclerotic plaques could not be definitively ruled out.

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Disclosures

The authors declare no conflicts of interest.

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