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Platelet Function Disorder in Patients with Coronary Slow Flow

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Summary

Background: Some patients evaluated for chest pain with angiographically normal coronary arteries show coronary slow flow phenomenon (CSFP) on angiography. Slow flow of dye in epicardial coronary arteries is also not an infrequent finding in patients during routine coronary angiography. The precise pathophysiology of CSFP is not known yet.

Hypothesis: This study investigates the presence of platelet function disorders in patients with CSFP.

Methods: The patient group included 24 patients with CSFP detected by coronary angiography via the TIMI "frame count" method, and a control group included 23 patients with normal coronary flow. Platelet aggregability induced by use of ristocetin, collagen, and adenosine diphosphate (ADP), was measured from all blood samples in both control and patient groups.

Results: The ratio of platelet aggregability increased significantly in patients with CSFP compared with patients with normal coronary flow (ristocetin 57.6 ± 15 vs. 45.4 ± 17.1, collagen 62.9 ± 16.4 vs. 48.9 ± 25.3, ADP 59.4 ± 18 vs. 42.4 ± 15.2, $p < 0.05$).

Conclusion: Platelet aggregability is increased in patients with CSFP.

Key words: coronary slow flow, platelet aggregability

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Introduction

One of the main physiologic functions of platelets is to aggregate and, thus, to participate in hemostasis. Chemical compounds such as adenosine diphospate (ADP), adrenalin, collagen, and ristocetin induce platelet aggregation.[8]

Although several platelet function abnormalities such as enhanced platelet aggregation and increase in platelet release reaction during stress in patients with myocardial ischemia have been recognized, the mechanism of these abnormalities is just beginning to be understood.[9, 10]

In this study we investigated the presence of platelet function disorders in patients with coronary slow flow (CSF).

Material and Methods

Between 1999 and 2001, 24 patients with angiographically proven CSF (patient group) and 23 patients who angiographically truly had normal coronary flow (control group) were included in the study, which was undertaken at Karadeniz Technical University Hospital. No patient had diabetes mellitus, thyroid dysfunction, history of arrhythmia, hypertension, left ventricular hypertrophy or dilatation, valvular dysfunction, or connective tissue disorder.

The patient group showed evidence of ischemia according to both treadmill exercise test and myocardial perfusion scintigraphy. The control group showed evidence of ischemia according to treadmill exercise test, but myocardial perfusion scintigraphy was positive in only two persons.

The group of 24 patients with CSF consisted of 18 men and 6 women. Their mean age was 51 (standard deviation [SD] ± 8 years, range 38–71). The control group consisted of 23 patients (16 men and 7 women) with a mean age of 52 ± 9 years, (range 37–79 years).

Coronary Angiography

All patients had ceased taking medication for 48 h prior to angiography. Selective coronary angiography was performed in the entire study population by using the Judkins technique. Coronary arteries were imaged in multiple views, including left and right anterior oblique views with cranial and caudal an-

gulation and right lateral view. Left ventriculography was performed in left and right anterior oblique views. To dispel any ambiguity, even the most distal coronary segments were imaged. Any suspicious lesions were clarified using cross-sectional imaging obtained in conventional places. Automatic injectors were used to administer radiopaque contrast. Iopromide contrast (Ultravist-370, Schering AG, Berlin, Germany) was used in all patients. All arteriograms were recorded on 35 mm cine film at 25 frames/s (Kodak, Paris, France).

The frame count was measured by two experienced observers blinded to the identity and the order of the angiograms after coronary angiography was completed and angiograms were developed. Any disagreements were resolved by a third observer. A Tagarno 35 Ax cine views frame counter (Elmo Co. Ltd for Nishimoto Sangyo Co. Ltd, Nagoya, Japan) was used for the measurement of frames.

The diagnosis of CSF was made using the Thrombolysis In Myocardial Infarction (TIMI) "frame count" method.[11] Frame counts extended from the origin of the coronary artery to its most distal segments. The diagonal reference points were the terminal bifurcations of the left anterior descending (LAD) and circumflex (CX) arteries, and the first side branch of the posterolateral artery on the right. The administration point of radiopaque material through the ostium of the coronary artery and first appearance of the coronary artery was regarded as the first frame and the most distal localization point of radiopaque material was regarded as the last frame. The number of frames necessary for filling of arteries was estimated by subtracting the number of the first frame from the number of the last frame.[11]

The corrected LAD artery frame rate was calculated by multiplying the frame rate by 0.7 as defined previously.[11]

We accepted the normal values as previously defined (36.2 ± 2.6 for the LAD artery, 22.2 ± 4.1 for the CX artery, and 20.4 ± 3.0 for the right coronary artery [RCA]). Arteries with values over the predicted normal frame counts were assessed as slow flow.[11]

Blood Samples

Blood samples for hemoglobin, hematocrit, leukocyte count, platelet count, prothrombin time, activated partial thromboplastin time, International Normalized Ratio (INR), fibrinogen, D-dimer, von Willebrand factor, adenosine diphosphate (ADP), ristocetin, and collagen were taken from the peripheral venous route in both patient and control groups 12 h after completion of coronary angiography.

Blood samples were drawn into vacuum-operated tubes that contained ethylene diamine tetraacetic acid (EDTA) (vacutainer; Becton Dickinson, Meylan, France) for hemoglobin, hematocrit, and platelet count measurements. Blood for the platelet aggregation test and other laboratory measurements was drawn into vacuum-operated tubes that contained 10% volume 3.13% trisodium citrate.

Plasma concentrations of fibrinogen were measured by the immunonepholemetric method using a commercial original kit (Dade Behring, Liederbach, Germany). The following tests were measured with enzyme-linked immunosorbent assay (ELISA) according to each manufacturer's instructions: D-dimer concentrations (Boehringer Mannheim, Germany); von Willebrand factor (IMTEC Immun-Diagnostica GmbH, Berlin, Germany).

For platelet aggregation tests, blood was centrifuged at 160 g for 5 min to prepare platelet-rich plasma (PRP) and at 2000 g for 10 min to prepare platelet-poor plasma (PPP) at 20°C. We added 1 µl of ADP, 1 µl of collagen, and 8 µl of ristocetin to 1 ml of PRP for each aggregant analysis of the aggregation test by using a Whole Blood Lumi-Aggregometer (Chrono-Log Corporation, Havertown, Penna., USA). Light transmission was accepted as 100% through PPP and as 0% through PRP.

Statistical Analysis

All measurement data, whether or not suitable for normal range, were analyzed using the Kolmogorov Smirnov test. Comparisons between the two groups were performed by means of an unpaired *t*-test for continuous variables. The chi-square test was used for categorical data.

Categorical data are presented as percent frequencies. Continuous variables are presented as mean (SD). A value of $p < 0.05$ was considered significant.

Results

Clinical characteristics of the study population are given in Table I. There was no difference with regard to age, gender, hypercholesterolemia, current smoker status, family history of coronary artery disease (CAD), symptoms, or body mass index (Table I), whereas scintigraphic findings were found to be significantly different between the groups: myocardial perfusion scintigraphy showed ischemia in 54.1% of patients with CSF, while only two persons (8%) in the control group had ischemia.

TABLE I Baseline clinical and angiographic characteristics

	Patient group (n = 24)	Control group (n = 23)
Age (years) (SD)	51 ± 8	52 ± 9
Sex (M/F)	18/6	16/7
Hypercholesterolemia	6/24	7/23
Current smokers	8/24	9/23
Proportion of patients taking nitrate	11/24	12/23
Proportion of patients taking ASA	13/24	12/23
Proportion of patients taking statin	6/24	5/23
Family history of CAD	2/24	4/23
Unstable/stable angina	4/18	4/19
Perfusion defect	13/24	2/23 [a]
Body mass index (kg/m^2)	23.6 ± 2.7	24.1 ± 2.8

[a] Between the patient group and control group, $p < 0.01$.
Abbreviations: ASA = acetyl salicylic acid, SD = standard deviation, M = male, F = female, CAD = coronary artery disease.

TABLE II TIMI frame count and vessel diameter

	Patient group (n = 24)	Control group (n = 23)
Mean vessel diameter		
LAD (mm)	3.21 ± 0.47	3.18 ± 0.53
CX (mm)	2.92 ± 0.35	2.89 ± 0.45
RCA (mm)	2.64 ± 0.31	2.61± 0.36
TIMI frame count		
LAD	63.2 ± 14.3	32.1 ± 4.1 [a]
CX	41.3 ± 7.1	23.1 ± 3.2 [a]
RCA	30.6 ± 4.2	19.3 ± 3.1 [a]

[a] Between patient group and control group, $p < 0.05$.
Abbreviations: LAD = left anterior descending artery, CX = circumflex artery, RCA = right coronary artery, TIMI = Thrombolysis In Myocardial Infarction.

TABLE III Laboratory results

Parameter	Patient group	Control group
WBC (×1000 ml)	11.6 ± 1.6	11.4 ± 1.64
Platelet (×1000 ml)	308.6 ± 52.1	304.8 ± 61.7
Hemoglobin (gr/dl)	14 ± 0.7	13.96 ± 0.9
Hematocrit (%)	42.3 ± 3.7	41.4 ± 4.3
PT (s)	13.4 ± 1.07	13.5 ± 1.04
APTT (s)	29.6 ± 2.8	29.5 ± 3.03
INR (%)	1.03 ± 0.18	1.04 ± 0.20
Collagen (%)	62.9 ± 16.4	48.9 ± 25.3 [a]
Ristocetin (%)	57.6 ± 15	45.4 ± 17.1 [a]
ADP (%)	59.4 ± 18	42.4 ± 15.2 [a]
Fibrinogen (mg/dl)	355.2 ± 75.3	346.7 ± 67.5
von Willebrand factor (%)	106.2± 13.4	103 ±11.7
D-dimer (mg/ml)	138.5 ± 39.9	136. ± 38.9

[a] Between patient group and control group, $p < 0.05$.
Abbreviations: WBC = white blood cell count, PT = prothrombin time, APTT = activated partial thromboplastin time, INR = International Normalized Ratio, ADP = adenosine diphosphate.

TIMI frame count and vessel diameters are given in Table II. There was a difference in point of TIMI frame count, but mean vessel diameters for LAD, CX, and RCA were not found to be significantly different between the groups.

Frame counts found in patients with CSF were considerably higher compared with those of controls. In control patients, average frame count was 32.1 ± 4.1, 23.1 ± 3.2, and 19.3 ± 3.1 for LAD, CX, and RCA, respectively. In patients with CSF, the average frame count was 63.2 ± 14.3, 41.3 ± 7.1, and 30.6 ± 4.2 for CAD, CX, and RCA, respectively ($p < 0.001$).

Laboratory Results (Table III)

There was no difference in hemoglobin, white blood cell count, platelets count, hematocrit, prothrombin time, activated partial thromboplastin time, INR, fibrinogen, D-dimer, and von Willebrand factor between the groups.

In platelet aggregation tests performed using ristocetin, ADP, and collagen, the ratio of platelet aggregability was significantly higher in the patient group than in the control group in all cases (ristocetin 57.6 ± 15 vs. 45.4 ± 17.1, ADP 59.4 ± 18 vs. 42.4 ± 15.2, collagen 62.9 ± 16.4 vs. 48.9 ± 25.3) (all $p > 0.05$).

Discussion

The main finding emerging from our study was that the ratio of platelet aggregability increased in patients with CSF, and this finding may be helpful for explaining the pathogenesis of the underlying mechanism in CSF phenomenon (CSFP).

Ionic agents are reported to have greater antithrombotic potential while nonionic agents are more thrombogenic.[12, 13] We used a nonionic contrast agent (Iopromide, Ultravist-370, Schering AG) during coronary angiography in this study. We did not know whether or not this contrast agent had an effect on CSFP; therefore, blood was taken from both patient and control groups 12 h after completion of coronary angiography, thus eliminating the contrast agent effect on CSFP.

In 1972, Tambe *et al.*[2] first described the clinical and hemodynamic features of a group of six patients with angina pectoris and slow flow velocity of contrast agent in coronary arteries. The authors suggested that an abnormal increase in small vessel resistance was the cause of the slow progression of the dye at selective coronary arteriography.

Coronary slow flow phenomenon is an important clinical entity because it may be the cause of angina at rest or during exercise, acute myocardial infarction, and hypotension.[14–18]

It has been proposed that true myocardial ischemia does occur in a subset of patients with CSFP as evidenced by increased myocardial lactate extraction during atrial pacing or isoproterenol infusion, decreased coronary sinus oxygen saturation during atrial pacing or inadequate increase in coronary flow during dipyridamole infusion.[19, 20]

Mangieri *et al.*[6] reported that histopathologic examination of left ventricular endomyocardial biopsies in patients with CSF showed thickening of vessel walls with luminal size reduction, mitochondrial abnormalities, and glycogen content reduction. In some patients with CSFP functional obstruction of microvessels seems to be implicated.

Some studies have supported impaired coronary microvascular function as a mechanism for CSF.[2, 5, 6, 20–22]

Mangieri *et al.*[6] reported a 7% incidence of CSF among patients with angina and normal epicardial coronary arteries.

Cannon *et al.*[20] proposed a heightened sensitivity of coronary microvasculature to vascoconstrictor stimuli along with a reduced microvasculature dilator capacity.

Van Lierde *et al.*[23] showed that slow blood flow velocity, coronary flow reserve, and calculated coronary blood flows with intracoronary Doppler measurements were within normal range in one patient with CSFP. They postulated that CSFP may be linked to marked coronary artery ectasia of epicardial arteries.

Friedman[24] suggested that CSFP may have a neurobiologic aspect.

Lanza *et al.*[25] showed that platelet aggregability at rest was increased in patients with syndrome X, compared with patients with coronary artery disease and healthy subjects. They postulated that platelet aggregability was reduced by exercise in patients with syndrome X; however, they studied patients with syndrome X whereas we studied patients with CSF.

Angina in patients with CSF is generally atypical. Resting electrocardiogram is normal or nonspecific. Myocardial ischemia may be detected by myocardial perfusion scintigraphy or exercise stress testing.[5, 26]

Cesar *et al.*[26] found ischemia in 76.4% of patients with CSFP on myocardial perfusion scintigraphy. In our study, we also found a high ratio of myocardial ischemia with myocardial perfusion scintigraphy in patients with CSFP (54.1%).

There has been much debate with regard to classifying CSF as a subset of syndrome X.[2, 15, 18, 23] Goel *et al.*[15] suggest that patients with CSF constitute a definite subset within the wide spectrum of syndrome X. Some previous studies have proposed that patients with CSFP be closely followed[6, 26] and that they receive some medication with antiplatelet properties, such as acetylsalicylic acid or clopidogrel.

While the causes of platelet aggregability in patients with CSFP are unknown, the ratio of platelet aggregability is increased in the presence of microvascular dysfunction or slow flow, including high shear stress and impairment of the endothelial barrier.

Conclusion

We found that platelet aggregability is increased in patients with CSFP. This result may be of help for devising a treatment strategy for these patients.

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