

The association between coronary slow flow and platelet distribution width among patients with stable angina pectoris

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Abstract

Introduction: Coronary slow flow (CSF) is an angiographic phenomenon characterised by the delay of distal vessel opacification in the absence of significant stenosis of the epicardial coronary arteries. Some of the factors playing a role in CSF pathophysiology are increased thrombogenic activity and inflammation.

Aim: To examine the relationship between platelet distribution width (PDW) and CSF.

Material and methods: Taking into consideration the exclusion criteria, 136 patients with CSF and 152 patients with normal coronary angiographies (control group) were included in the study. The association between thrombolysis infarction frame count (TFC) in myocardial and laboratory and other clinical parameters were evaluated.

Results: The stated parameters were significantly higher in the group with CSF than in the normal coronary angiography group (control group). The PDW (16.6 ± 0.7 vs. 16.4 ± 0.6 , $p = 0.002$), neutrophil lymphocyte ratio (NLR) (3.1 ± 3.4 vs. 2.4 ± 1.1 , $p = 0.027$), haemoglobin (Hb) (14.1 ± 1.3 vs. 14.7 ± 1.1 , $p < 0.001$), and red cell distribution width (RDW) (13.6 ± 0.7 vs. 14.1 ± 2.8 , $p = 0.026$) were significantly higher in the CSF group than in the control group. Moreover, our study showed that $PDW > 16.15$ and $Hb > 13.75$ were predictors of the presence of CSF with sensitivities of 83% and 73% and specificities of 40% and 42%, respectively.

Conclusions: This study has demonstrated that compared to normal coronary flow, PDW, Hb, NLR, and RDW are significantly higher in CSF patients. We believe that further studies are needed to clarify the role of PDW and Hb in patients with CSF.

Key words: coronary slow flow, platelet distribution width.

Introduction

The phenomenon of coronary slow flow (CSF) is an angiographic clinical entity characterised by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis [1]. Diagnostic criteria for CSF include the absence of coronary atherosclerosis. What is important here is the atherosclerosis plaque, which visually forms significant or non-significant stenosis. Clinical data indicates that CSF is present in approximately 1–7% of coronary angiography screenings [2], and although not a particularly rare condition, the underlying pathophysiological mechanisms of CSF are poorly understood. Proposed aetiologies for CSF include small vessel disease, microvascular vasomotor dysfunction, diffuse

atherosclerosis, endothelial dysfunction, inflammation, increased platelet aggregation, and factors related to anatomic variation [1, 3–6]. Recently-published data associates CSF with poor prognostic outcomes, including cardiac dysfunction, acute coronary syndrome, fatal arrhythmias, and sudden cardiac death [5–8]. Platelet distribution width (PDW) is a direct measure of the variation in platelet size and a marker of platelet activation [9]. A recent study demonstrated a significant association between coronary artery disease (CAD) and PDW. Interestingly, PDW has also been linked to saphenous vein graft patency among patients who underwent coronary artery bypass [10]. Haemoglobin (Hb) is a key determinant of blood viscosity [11]. Red cell distribution width

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(RDW) is a direct measure of the variation in erythrocyte size that is easily measured as a component of routine blood counts [12]. The RDW is a well recognised indicator of chronic inflammation and oxidative stress, and elevated RDW is strongly associated with poor clinical outcomes among patients with CAD [13, 14]. Neutrophil/lymphocyte ratio (NLR), derived from the white blood cell count (WBC), is a common prognostic indicator in cardiovascular disease [15, 16].

Aim

The aim of the present study is to evaluate the relationships between CSF, PDW, and other haematological parameters in an effort to identify useful clinical indicators in patients undergoing coronary angiography.

Material and methods

Patient selection

A retrospective evaluation of consecutive patients undergoing coronary angiography was conducted. All patients enrolled in the study underwent coronary angiography as a result of chest pain and objective signs of ischaemia during treadmill exercises or myocardial SPECT testing. Routine laboratory and clinical parameters (e.g. diabetes mellitus (DM), hypertension (HT), hypercholesterolemia, tobacco use, family history of cardiovascular disease) were obtained from the patient medical records. Study exclusion criteria included coronary ectasia, mild-severe valve disease, heart failure, anaemia, renal failure, inflammatory diseases, malignancy, peripheral and cerebral arterial disease, thyroid gland dysfunctions (hypo-hyperthyroidism), and LV (left ventricle).

Echocardiography

All patients underwent transthoracic echocardiography performed using a system V (Vingmed, GE) device and a 2.5 MHz phased-array transducer. Recordings were made with the patients in the left lateral decubitus position. LV ejection fraction was measured using the modified Simpson's rule according to the most recent guidelines.

Coronary angiography

Coronary angiography was performed using a GE imaging system (General Electric Advantx LC +, Milwaukee, Wisconsin, US). The standard selective coronary angiography procedure in our clinic includes at least four views of the left coronary system and two views of the right coronary artery using the Judkins technique and 6-French right and left heart catheters and no nitroglycerin. Iohexol (GE Healthcare Omnipaque 350 ml, Ireland) was used as the contrast agent for all patients and control subjects. Coronary flow rates were measured using the Myocardial

Infarction (TIMI) frame count (TFC) method, with cineangiography at 30 frames per second. Coronary angiograms included at least four images of the left cardiac system and two images of the right cardiac system. These are in the form of cranial and caudal angulations of the left and right oblique images. Images with the best resolution were used for TFC evaluations of the left coronary artery system, and TFC evaluations of the right coronary artery were performed with the left anterior image with cranial angulation. In the cases, invasive haemodynamic evaluations were performed during the coronary angiography. Therefore, haemodynamic changes resulting from catheterisation and vasovagal syndrome could be evaluated with pressure trace; data indicating slow flow as a result of catheterisation and vasovagal syndrome were excluded. Coronary angiograms were assessed independently for objective quantification of coronary flow by two invasive cardiologists blinded to the clinical findings.

Laboratory parameters

Prior to coronary angiography, eight-hour postprandial venous blood was collected from all patients for routine laboratory testing. Haematological measurements were made using a Mindray Haematology Analyser (BC-6800, China) and were evaluated for complete blood count (CBC). LDL cholesterol analysis was performed using an Olympus AU 2700 Plus Chemistry-ImmunoAnalyser (USA).

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. In accordance with World Health Organization criteria, anaemia was defined as a baseline haemoglobin concentration < 13 mg/dl in men or < 12 mg/dl in women. Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease Equation [17]. Renal insufficiency was defined as GFR < 60 ml/min/1.732 m². The TFC was derived according to the methods of Gibson *et al.* [18]. The first frame was defined as the frame in which radiocontrast agent was first visualised in the ostial region of the coronary artery. The last frame was defined as the frame in which the radiocontrast agent reaches the distal index point of the relevant coronary artery. The LAD is longer than all other coronary arteries; therefore, the corrected TFC (cTFC) is the LAD frame number divided by 1.7. SCF was defined as cTFC greater than two standard deviations from the normal range (40.8 frames for LAD, 29.8 frames for LCx, and 27.3 frames for RCA), while normal coronary was defined as cTFC within two standard deviations of the normal range reported for a particular vessel. All study parameters were reviewed and approved by the Local Ethics Committee.

Statistical analysis

The statistical package for social sciences (SPSS, version 15) was used for all data analysis. Continuous data are expressed as mean ± standard deviation (SD), and categorical data are reported as percentages. The Student's *t*-test was used to compare continuous parametric variables. The χ^2 test was used to compare distributions of categorical variables. Cut-off values of PDW and Hb concentration for the prediction of SCF and their respective sensitivity and specificity values were estimated using receiving operating characteristic (ROC) curve analysis. The threshold of statistical significance was established at $p < 0.05$.

Results

The study population consisted of 6280 consecutive patients undergoing coronary angiography. Out of the total population, 136 patients with SCF were included in the study group. The control group consisted of 152 age-matched subjects with normal coronary angiograms selected consecutively during the same study period as the study group. The same exclusion criteria were applied to the study and control groups. The distribution of cardiovascular risk factors, demographic characteristics, and laboratory parameters in the two groups are shown in Table I. The mean age of the CSF group was 53 ± 9 years with a male gender dominance of 61.03%. Among known CAD risk factors, diabetes mellitus and smoking history were more prevalent in the CSF group than in the control group (29% vs. 17%, $p = 0.019$ and 58% vs. 46%, $p = 0.028$, respectively, Table I). The PDW (16.6 ± 0.7% vs. 16.4 ± 0.6%, $p = 0.002$), NLR (3.1 ± 3.4 vs. 2.4 ± 1.1, $p = 0.027$), haemoglobin (14.1 ± 1.3 g/dl vs. 14.7 ± 1.1 g/dl, $p < 0.001$), and RDW (13.6 ± 0.7% vs. 14.1 ± 2.8%, $p = 0.026$) were significantly increased in the CSF group relative to the control group (Table II). A PDW of 16.15 predicted CSF with a sensitivity of 83% and a specificity of 40% (ROC AUC: 0.618, 95% CI: 0.554–0.683, $p = 0.001$) (Figure 1 A)

Table I. Distribution of baseline characteristic of all patients

Variables	Normal flow (n = 152)	Slow flow (n = 136)	Value of p
Age [years]	52 ± 10	53 ± 9	0.379
Male gender, n (%)	71 (47)	83 (61)	0.015
Family history, n (%)	34 (22)	33 (24)	0.704
Smoking, n (%)	46 (30)	58 (43)	0.028
Diabetes mellitus, n (%)	17 (11)	29 (21)	0.019
Hyperlipidaemia, n (%)	51 (34)	62 (46)	0.037
Hypertension, n (%)	58 (38)	43 (32)	0.246
LDL-c [mg/dl]	116 ± 25	112 ± 33	0.476
SBP [mm Hg]	124 ± 17	121 ± 16	0.008
DBP [mm Hg]	76 ± 11	75 ± 9	0.17
Heart rate [bpm]	77 ± 12	74 ± 13	0.046
TIMI frame count	23 ± 2.8	33 ± 6.4	< 0.001
LAD cTFC	26.8 ± 4.3	38.1 ± 13.9	< 0.001
LCx TFC	20.9 ± 3.7	30.2 ± 9.5	< 0.001
RCA TFC	20.7 ± 3.6	33.3 ± 11.5	< 0.001

Values are mean (SD). LDL-c – low density lipoprotein cholesterol, SBP – systolic blood pressure, DBP – diastolic blood pressure, LAD – left anterior descending coronary artery, LCx – left circumflex coronary artery, RCA – right coronary artery, TFC – TIMI frame count, cTFC – corrected TIMI frame count

Table II. Distribution of the haematological parameters of all cases

Variables	Normal flow (n = 152)	Slow flow (n = 136)	Value of p
Haemoglobin [g/dl]	14.1 ± 1.3	14.7 ± 1.1	< 0.001
WBC	7.6 ± 1.7	7.9 ± 2.4	0.289
MCV	87.2 ± 7.6	88.3 ± 5.6	0.164
Platelet [$\times 1000/\text{mm}^3$]	244 ± 46	244 ± 66	0.989
RDW [%]	13.6 ± 0.7	14.1 ± 2.8	0.026
MPV [fl]	8.5 ± 1.1	8.7 ± 1.1	0.079
PDW [%]	16.4 ± 0.6	16.6 ± 0.7	0.002
NLR	2.4 ± 1.1	3.1 ± 3.4	0.027

WBC – white blood cell count, MCV – mean corpuscular volume, RDW – red blood cell distribution width, MPV – mean platelet volume, PDW – platelet distribution width, NLR – neutrophil/lymphocyte ratio

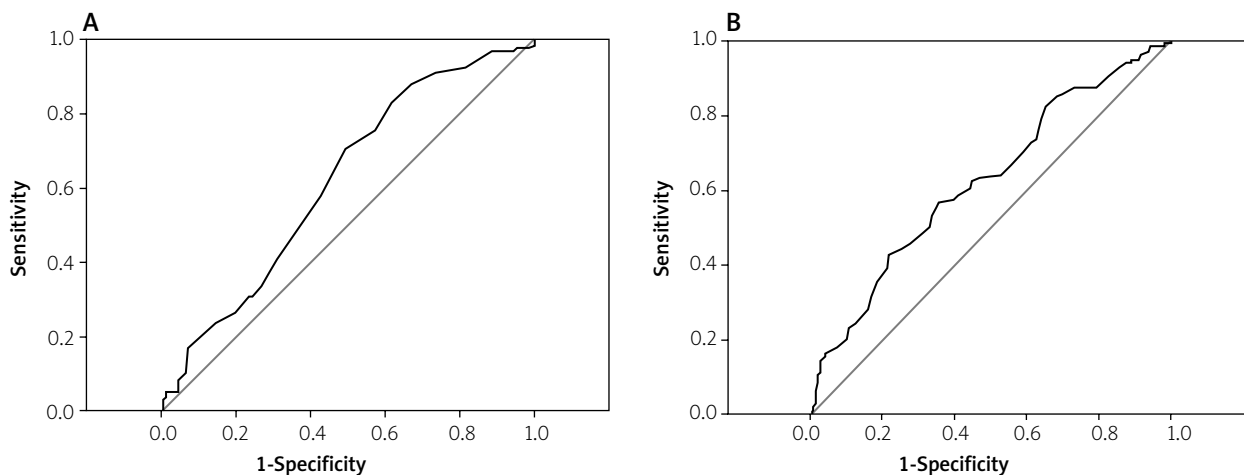


Figure 1. Receiver operating characteristics (ROC) analysis of PDW (A) and Hb (B) concentration

and an Hb concentration of 13.75 g/dl predicted CSF with a sensitivity of 73% and a specificity of 42% (ROC AUC: 0.625, 95% CI: 0.561–0.690, $p < 0.001$) (Figure 1 B).

Discussion

In this study we examined the relationship between CSF, PDW, and other haematological parameters. The CSF was independently associated with PDW, Hb, NLR, and RDW. Moreover, our study data demonstrate that PDW $> 16.15\%$ and Hb > 13.75 g/dl predict the presence of CSF with sensitivities and specificities of 83% and 73%, and 40% and 42%, respectively.

A limited number of studies have been performed examining the pathophysiology of CSF since the first description of the disease by Tambe *et al.* in 1972. Several competing hypotheses explaining the aetiology of CSF have emerged. These include atherosclerosis and increased thrombogenic activity. Inflammation plays an important role in the onset, development, and progression of atherosclerosis. Atherosclerosis is itself considered an inflammatory disease. Microvascular atherosclerosis may contribute to the development of CSF. Recent studies have demonstrated the relationship between CSF and inflammation.

Vagdatli *et al.* [19] have proposed that PDW is a more specific indicator of platelet activation than MPV in the absence of platelet swelling. Elevated PDW directly measures the variability in platelet size during platelet distension and serves as a marker of platelet activation [20]. Increased platelet number, size, and the presence of pseudopodia may influence PDW. Khandekar *et al.* reported a significant elevation of PDW among patients with acute myocardial infarction and unstable angina pectoris [21]. Our study data demonstrate a significant association between PDW and CSF. A study conducted by Jindal *et al.* identified a significant association between PDW and microvascular dysfunction among diabetic patients [22]. The CSF may be a symptom of microvascular and circulatory dysfunction. Numerous factors contribute to microvascular and circulatory dysfunction, including coronary microvascular imbalance and increased tonus, endothelial thickening of small vessels and endothelial nitric oxide imbalance, and blood viscosity. Hb concentration is a determinant of blood viscosity, and a significant relationship between CSF and Hb concentration has been demonstrated previously [11]. The SCF patients frequently present with elevated blood viscosity [23]. Similar to atherosclerosis, blood viscosity is elevated in SCF patients as a result of increased platelet adhesion to the subendothelium, elevated protein infiltration into the arterial wall, and alterations to local shear forces [24]. Our data supports a significant relationship between CSF and haemoglobin concentration, a component of blood viscosity.

The NLR is associated with the onset and progression of atherosclerosis in the coronary arteries [25], and re-

cent studies suggest that NLR is an excellent indicator of cardiovascular disease [15, 16, 26]. As a result, NLR has emerged as a new prognostic indicator [16, 27]. Among patients with acute coronary syndrome, neutrophils are functionally activated, and the presence of localised neutrophil infiltration in atherosclerotic lesions has been documented, suggesting that neutrophils play a role in the mediation and destabilisation of atherosclerotic plaques [28]. The present study demonstrates a significant correlation between the presence of CSF and NLR, an inflammatory marker linked to CAD and atherosclerosis.

Chronic inflammation and neuro-humoral activation can act synergistically to elevate RDW, enhancing the atherosclerotic process [29]. The RDW is an independent predictor of mortality and coronary morbidity among patients with myocardial infarction [13, 14]. Similar to the report by Kalay *et al.* [25], the present study confirms a significant association between CSF and RDW. A recent study by Akpınar *et al.* involving a comparable number of patients reported elevated PDW, RDW, and NLR similar to our CSF study group [30].

The relationship between cardiovascular disease and increased platelet activity is well known. In this study, we found a significant relationship between CSF and PDW, an established indicator of platelet activity. In addition, we detected a significant relationship between CSF and NLR, an indicator of systemic inflammation, and Hb concentration, a component of blood viscosity. These predictive parameters are easily measured and are inexpensive in routine clinical practice. In case, it is supported in other studies; in patient with chest pain care the high value of PDW can be ranked in CSF diagnosis algorithm.

In this study we evaluated the coronary arteries using coronary angiography. Although it is well known that IVUS provides a more precise evaluation of coronary atherosclerosis, we were unable to perform intravascular ultrasound (IVUS) assessment. In addition, the study data is reflective of the cross-sectional design and may not reflect the long-term clinical status of the patients.

Conclusions

Our study data support a statistically significant association between PDW and CSF. Further studies of CSF will continue to advance our understanding of its etiology.

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