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RESEARCH ARTICLE

Relationship Between Plasma Atherogenic Index And Coronary Slow Flow Phenomenon

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Abstract

Introduction: Epidemiological studies indicated that patients suffering from coronary slow flow phenomenon (CSFP) are predisposed to dyslipidemia. However, there are limited studies evaluating the relationship between atherogenic index of plasma (AIP), which is a novel indicator of atherogenic dyslipidemia, and CSFP. This study aimed to investigate the prognostic role of the AIP in predicting CSFP among patients with undergoing coronary angiography. **Methods:** This retrospective study included 110 patients with CSFP diagnosed by methods of Thrombolysis in Myocardial Infarction (TIMI)-frame count (TFC) and 110 controls with normal coronary flow (NCF). AIP obtained as the base 10 logarithm of the ratio of triglycerides to HDL. **Results:** Mean AIP level was higher in the CSFP group than NCF group (0.6 ± 0.2 vs. 0.4 ± 0.2, $p < 0.001$). Multivariable regression analysis showed that AIP level (OR = 15.33, 95% CI = 4.11-57.18, $p < 0.001$), as well as neutrophil and platelets levels, were independent predictor of CSFP. The threshold value of the AIP in predicting CSFP was >0.7 with 64.5% sensitivity and 69.8% specificity (Area under the curve [AUC] = 0.714, $p < 0.001$). **Conclusion:** API was higher in CSFP patients and was determined as an independent predictor of CSFP. Prior to planned diagnostic coronary angiography, API exhibits significant diagnostic performance in predicting CSFP.

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Introduction

Coronary slow flow phenomenon (CSFP) is characterized by late opacification of contrast media into distal segment of one or more coronary arteries in patients with normal or near-normal coronary arteries during angiography.[1] There is still no clear consensus on the pathophysiology of CSFP. However, growing evidence suggested that some mechanisms, such as impaired lipid metabolism, atherosclerosis, endothelial or microvascular coronary dysfunction, platelet aggregation and inflammation, may play a role in the pathophysiology of CSFP.[2] Epidemiological studies indicated that patients suffering from CSFP are predisposed to dyslipidemia.[3-4] It is known that lipid metabolism is closely related to other mechanisms of CSFP such as atherosclerosis.[5] This is associated with the role of lipid metabolism in nitric oxide synthase activation, endothelial cell function, and induction of cytokines and coagulation factors.[6] Atherogenic dyslipidemia is characterized by elevated low-density lipoprotein cholesterol (LDL), apolipoprotein B and triglyceride levels and decreased high-density lipoprotein cholesterol (HDL) levels.[7] Atherogenic index of plasma (AIP) is a novel indicator of atherogenic dyslipidemia, and it is obtained as the base 10 logarithm of the ratio of triglycerides to HDL.[8] Meta-analysis studies indicated that AIP is an important predictor of cardiovascular diseases and events.[9-10] However, there are limited studies evaluating the relationship between AIP and CSFP.[11-12] These studies differ in the diagnostic performance of AIP in predicting CSFP. Therefore, more research is needed on the role of AIP on CSFP. Considering the relationship between lipid metabolism and other mechanisms of CSFP [13], we hypothesized that the AIP could be an important prognostic marker of CSFP. This study aimed to investigate the prognostic role of the AIP in predicting CSFP among patients with undergoing coronary angiography.

Material and Methods

This retrospective study included patients who had undergone diagnostic coronary angiograph in Ankara City Hospital Cardiology Clinic between January 2020 and January 2022. The study initiated with the approval of the Ankara City Hospital Ethics Committee (Date: 22.02.2023, Decision No: E1-23-3326) and was carried out in accordance with relevant ethical guidelines and the Declaration of Helsinki (revised in 2013, Brazil). The need for informed consent was waived by the local ethics committee due to the retrospective design. Based on a previous study, we determined the effect size of AIP as 0.74 in patients with and without CSFP (CSFP (+) = 0.70 ± 0.22 vs. CSFP (-) = 0.53 ± 0.24; p< 0.001).[11] Accordingly, it was determined by the G*Power program that the sample size should be at least 82 patients for each group with 5% alpha, 95% power, and 0.74% effect size.

Study population

A total of 4518 patients admitted to the hospital with stable or unstable angina pectoris and referred for diagnostic coronary angiography were evaluated retrospectively. The indication for diagnostic coronary angiography was positive ischemia in the exercise treadmill test or myocardial perfusion scintigraphy. Exclusion criteria were a history of heart failure, systemic inflammatory or autoimmune disease, thyroid dysfunction, coronary extasia, coronary artery stenosis (≥50%), valvular heart diseases, liver diseases, active hepatitis, malignancy, renal failure, lipid lowering drugs, and missing clinical data. After the exclusion process, a total of 225 CSFP patients with no stenosis in the main coronary arteries or their lateral branches greater than 2.0 mm were detected on coronary angiography results. For the control group, 250 subjects with normal coronary flow (NCF) findings on coronary angiography were selected. The groups were matched with the propensity match score using the 1:1 nearest neighbor matching method. The parameters used for matching were: age, gender, body mass index, comorbidities. Thus, 110 patients for each group were included in the analysis.

Analysis of patient data

The hospital's electronic information system and patient files were used to gather demographic and clinical data. In repeated measurements, blood pressure of >140/90 mmHg or use of antihypertensive drugs was defined as hypertension, and a fasting plasma glucose level of ≥126 mg/dL or use of antidiabetic drugs was defined as diabetes mellitus.

Blood samples were taken at the time of admission were measured using a Beckman Coulter LH 780 device (Mervue, Galway, Ireland). Levels of hemoglobin (photometrically), platelets (impedance method), C-reactive protein (immunoturbidimetric method), albumin (bromocresol green artery were evaluated. First side branch of right posterolateral artery for RCA, distal bifurcation for LAD, method), triglycerides and total cholesterol (enzymatic colorimetric method), and high-density lipoprotein (homogeneous enzymatic colorimetric method) were determined. The Friedewald formula was used to determine low-density lipoprotein levels. The AIP was calculated as follows: AIP = $\log_{10}$ (triglyceride / HDL ratio).

Coronary angiography

Angiographic data were analyzed in the cardiac catheterization laboratory by 2 cardiologists blinded to the clinical data of the patients. Patients underwent coronary angiograph through the femoral artery using the Judkins technique and were given an iopromide contrast medium (GE Healthcare, Cork, Ireland). Thrombolysis in myocardial infarction frame count (TFC) was used to evaluate coronary flow. In a nutshell, the cine frames number was recorded at 25 frames/s needed for the contrast to reach the standard distal coronary border point in the right coronary artery (RCA), left anterior descending (LAD) artery and left circumflex (LCX) artery were evaluated. First side branch of right posterolateral artery for RCA, distal bifurcation for LAD, and distal bifurcation of the major branch for LCX were defined as the distal ends of the coronary vessels. TFC is usually higher for LAD, which is longer compared to other main coronary arteries. Therefore, the TFC correction (cTFC) for LAD, obtained by dividing TFC by 1.7, was used.[14] The standard mean values of TFCs required for filling the coronary arteries have been previously defined.[14] In at least one coronary artery, CSFP was defined as ≥2 standard deviation of TFC values than published mean values.[14] The κ value for intra-observer and inter-observer variability between the two cardiologists was above 0.90 ($p < 0.001$).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Based on the results of the Kolmogorov-Smirnov test, normally distributed numerical data were presented as mean ± standard deviation and non-normally distributed variables were presented as median values (25th-75th quartiles). For comparisons between groups, the Student t-test and Mann-Whitney U test were used according to the normality of the distribution. Categorical variables were expressed as numbers and percentages, and comparisons between groups were evaluated with Chi-square and Fisher exact tests. Multivariable logistic regression analysis was performed to identify any possible independent predictors of CSFP. Receiver operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance. Youden index method was used for threshold values. Values of $p < 0.05$ were considered statistically significant.

Results

The mean age of the 110 CSFP patients included in this study was 56.2 ± 8.3 years, the majority of them were male (70%). The baseline characteristics of the patients are reported in Table 1. The distributions of age, gender, and comorbidities were similar between the CSFP and NCF groups. Mean blood pressures and mean left ventricular ejection fraction did not differ significantly between the CSFP and NCF groups. Mean LAD-TFC (46.4 ± 2.5 vs. 22.4 ± 2.2, $p < 0.001$), mean LCX-TFC (34.5 ± 2.4 vs. 16.1 ± 2.1, $p < 0.001$) and mean RCA-TFC (31.3 ± 2.4 vs. 14.7 ± 2.2, $p < 0.001$) were higher in the CSFP group than NCF group (Table 1). The median neutrophil count (5.7 vs. 4.1 ×103 μL, $p < 0.001$), mean platelets count (256.5 ± 56.2 vs. 203.6 ± 42.4 ×103 μL, $p < 0.001$) and mean monocyte count (0.6 ± 0.2 vs. 0.5 ± 0.1×103 μL, $p < 0.001$) was higher in the CSFP group than NCF group, while mean lymphocyte count was lower (2.1 ± 0.6 vs. 2.3 ± 0.7 ×103 μL, $p = 0.024$). The levels of lipid profile also significantly differed between the groups ($p < 0.05$). Mean AIP level was higher in the CSFP group than NCF group (0.6 ± 0.2 vs. 0.4 ± 0.2, $p < 0.001$) (Table 2). Variables associated with CSFP (Tables 1 and 2) were considered as potential confounding factors. Among these factors, the components of the

AIP were not included in the regression analysis due to multicollinearity. Multivariable regression analysis showed that AIP level (OR = 15.33, 95% CI = 4.11-57.18, p < 0.001), as well as neutrophil and platelets levels, were independent predictor of CSFP. Accordingly, it was determined that a 1-unit increase in AIP level increased the probability of CSFP by 15.33-folds (Table 3). The diagnostic performance of AIP in predicting CSFP is shown in Figure 1. The threshold value of the AIP in predicting CSFP was >0.7 with 64.5% sensitivity and 69.8% specificity (Area under the curve = 0.714, p < 0.001) (Figure 1).

Discussion

The mechanism of CSFP, which has a wide presentation from mild chest pain to acute coronary syndrome, has not yet been elucidated.[15] The main mechanisms proposed for CSFP are thrombosis tendency, microvascular injury or disease, endothelial dysfunction and atherosclerosis.[2] Previous studies have shown that male gender, high body mass index, smoking, diabetes, hypertension and hyperlipidemia increase the risk of CSFP.[16-17] To more objectively assess the relationship between AIP and CSFP, we aimed to adjust for the effects of these potential confounding factors by creating a control group paired with propensity match score analysis. The main findings of the study were as follows: 1) AIP levels were higher in patients with CSFP. 2) Increased AIP was an independent predictor of CSFP. 3) The AIP score exhibited superior diagnostic performance in predicting CSFP.

In the present study, CSFP patients had lower HDL levels and higher triglyceride and LDL levels. This is consistent with the findings of epidemiological studies that patients with CSFP had a worsened lipid profile.[17] It has been shown that there is a significant correlation between hypertriglyceridemia and impaired coronary vasodilation in the absence of significant coronary stenosis.[18] Triglyceride-rich lipoproteins affect HDL levels and particle sizes, resulting in rapid catabolization of rich triglyceride and poor HDL-cholesterol ester particles. This atherogenic property contributes to atherosclerosis.[19] Dyslipidemia may cause in decreased aortic elastic properties. This result in impaired coronary blood flow. Increased reactive oxygen species and oxidized LDL induce vascular dysfunction and endothelial cell apoptosis.20 Small HDL and small dense LDL particles, which are more atherogenic than plasma LDL cholesterol, have limited use in clinical practice because of their cost and measurement complexity.21 AIP is an indirect indicator of small dense LDL levels. It has also been shown to be an important predictor of atherosclerosis and cardiovascular diseases and events.[9-10]

Previous rare studies have shown that the non-logarithmic triglyceride/HDL ratio is higher in patients with CSFP.[22-23] However, the logarithmic transformation of the triglyceride/HDL ratio is thought to better reflect atherogenic dyslipidemia.[8] In the present study, AIP was higher in patients with CSFP compared to the NCF group, despite similar demographic characteristics. The results of this study both support and extend the findings of previous limited studies that examined the relationship between AIP and CSFP. To the best of our knowledge, there were only two studies that investigated the relationship between AIP and NCFP. Afsin et al.[11] reported that patients with stable or unstable angina pectoris with CSFP had higher AIP compared to the NCF group. In a study conducted by Adalı et al.[12] on patients undergoing coronary angiography, AIP was approximately 2-folds higher in patients with CSFP than NCF patients. In these studies, confounding factors such as male gender, age, proportion of smokers, and presence of hypertension were higher in the CSFP group.[11-12] These confounding factors may have contributed in favor of CSFP, as they may be associated with a worse lipid profile.[24] The main difference between the present study and these studies is that the potential effects of these confounding factors were adjusted with a matched control group. On the other hand, consistent with the results of the studies mentioned above, AIP was identified as an independent predictor of CSFP. Current evidence supported that patients with CSFP may be predisposed to atherogenic dyslipidemia.

The AIP showed significant diagnostic performance in distinguishing patients with CSFP. The threshold value of AIP classified approximately 65% of patients with CSFP as true positive, while approximately 70% of individuals with NCF classified them as true negative. Afsin et al.11 reported the threshold value of AIP as 0.66 with 59% sensitivity and 73% specificity,

Table 1. Demographic and clinical findings in patients with and without slow coronary flow phenomenon.

Variables	CSFP group n = 110	NCF group n = 110	p
Demographic findings			
Gender, n (%)			
Female	33 (30.0)	34 (30.9)	0.884
Male	77 (70.0)	76 (69.1)	
Age, years	56.2 ± 8.3	55.6 ± 7.8	0.581
BMI, kg/m2	29.1 ± 3.8	28.9 ± 3.4	0.681
Smoking, n (%)	59 (53.6)	54 (49.1)	0.500
Diabetes mellitus, n (%)	40 (36.4)	33 (30.0)	0.316
Hypertension, n (%)	59 (53.6)	55 (50.0)	0.589
Dyslipidemia, n (%)	51 (46.4)	43 (39.1)	0.275
Clinical findings			
Systolic BP, mmHg	130.2 ± 24.3	128.1 ± 22.8	0.509
Diastolic BP, mmHg	78.3 ± 14.5	76.2 ± 13.3	0.264
LVEF, %	66.4 ± 7.8	67.8 ± 7.1	0.165
TFC, frame			
LAD	46.4 ± 2.5	22.4 ± 2.2	<0.001*
CX	34.5 ± 2.4	16.1 ± 2.1	<0.001*
RCA	31.3 ± 2.4	14.7 ± 2.2	<0.001*

Values are mean±SD or median (IQR) or number (%). * p<0.05 indicates statistical significance. Abbreviations: BMI: Body Mass Index; BP: Blood Pressure; CSFP: Slow Coronary Flow Phenomenon; Cx: Left Circumflex Coronary Artery; LAD: Left Anterior Coronary Artery; LVEF: Left Ventricular Ejection Fraction; NCF: Normal Coronary Flow; RCA: Right Coronary Artery; TFC: Thrombolysis in Myocardial Infarction Frame Count.

whereas Adalı et al.[12] reported 0.68 with 72% sensitivity and 42% specificity. Similar diagnostic performance has been reported in rare studies evaluating the non-logarithmic triglyceride/HDL ratio.[22-23] When the findings of this study are evaluated in the light of the existing literature, AIP may be an important indicator of CSFP. Threshold values in the 0.6-0.7 range of AIP in distinguishing CSFP are consistent across studies. Therefore, AIP before coronary angiography can be an important screening tool for estimating CSFP.

Another important finding of this study was that elevated neutrophil and platelet levels were an independent risk factor for CSFP in addition to AIP. Besides, higher monocyte levels were found in CSFP patients. This could be due to the relationship between atherogenic lipids and inflammation. It is postulated that HDL protects endothelial cells against the undesirable effects of LDL and exhibits both anti-inflammatory and antioxidant effects by preventing the oxidation of LDL molecules.[25] Atherogenic lipids, which cause low-grade inflammation in endothelial cells, may contribute to endothelial damage and acceleration of atherosclerosis.[5] Triglyceride-rich lipoproteins, which easily accumulate in the arterial wall, play a role in the accumulation of macrophages by causing endothelial damage and leukocyte activation.[19] Platelets play a key role in thrombotic events and blood rheology. The tendency to thrombogenicity causes slowing of blood flow and development of CSFP.[26] Some studies have indicated that platelet dysfunction associated with the development of CSFP.[27-28] In thromboinflammatory conditions, platelet-neutrophil interaction occurs and they regulate each other's functions.[29] An experimental study showed that activated polymorphonuclear neutrophils cause vasoconstriction and endothelial dysfunction in coronary arteries isolated from low-flow perfusion reperfused hearts.[30] Consistent with these findings, increased neutrophil and platelet levels were identified as an independent predictor of CSFP.

This study has some limitations. In addition to the small sample size, it had a single-center and

Table 2. Laboratory findings in patients with and without slow coronary flow phenomenon.

Variables	CSFP group n = 110	NCF group n = 110	p
FBG, mg/dL	92.1 ± 20.4	88.7 ± 19.4	0.207
Hemoglobin, g/dL	13.1 ± 2.3	13.5 ± 2.5	0.218
WBC, ×103/mm3	7.6 ± 2.3	7.3 ± 2.0	0.303
Neutrophil, ×103 µL	5.7 (3.4-8.1)	4.1 (2.3-6.0)	<0.001*
Lymphocyte, ×103 µL	2.1 ± 0.6	2.3 ± 0.7	0.024*
Platelets, ×103 µL	256.5 ± 56.2	203.6 ± 42.4	<0.001*
Monocyte, ×103 µL	0.6 ± 0.2	0.5 ± 0.1	<0.001*
RDW, %	13.8 ± 2.5	13.5 ± 1.8	0.308
Total cholesterol, mg/dL	200.4 ± 43.5	188.2 ± 37.1	0.026*
LDL, mg/dL	123.1 ± 28.0	115.2 ± 25.6	0.030*
HDL, mg/dL	39.1 ± 8.5	42.4 ± 9.2	0.006*
Triglyceride, mg/dL	145 (108-185)	122 (81-145)	0.010*
AIP	0.6 ± 0.2	0.4 ± 0.2	<0.001*

Values are mean±SD or median (IQR). * p<0.05 indicates statistical significance.
Abbreviations: AIP:Atherogenic Index of Plazma; CSFP: Slow Coronary Flow Phenomenon; FBG: Fasting Blood Glucose; HDL: High-Density Lipoprotein Cholesterol; LDL: Low-Density Lipoprotein Cholesterol; NCF: Normal Coronary Flow; RDW: Red Distribution Width; WBC: White Blood Cell.

Table 3. Independent predictors of slow coronary flow phenomenon.

Variables	Univariable				Multivariable			
	OR	95% CI		p	OR	95% CI		p
		lower	upper			lower	upper	
Neutrophil	1.21	1.09	1.35	<0.001*	1.15	1.02	1.29	0.011*
Lymphocyte	0.97	0.94	0.99	0.024*	-	-	-	-
Platelets	1.07	1.03	1.11	<0.001*	1.05	1.01	1.10	0.030*
Monocyte	1.03	1.01	1.08	<0.001*	-	-	-	-
Total cholesterol	1.06	1.01	1.12	0.026*	-	-	-	-
LDL	1.08	1.02	1.15	0.030*	-	-	-	-
AIP	17.0	4.91	58.97	<0.001*	15.33	4.11	57.18	<0.001*
					Nagelkerke R2: 0.326, p<0.001*			

Components of AIP were not included in the regression analysis. * p<0.05 indicates statistical significance.
Abbreviations: AIP: Atherogenic Index of Plazma; CI: Confidence Interval; LDL: Low-Density Lipoprotein Cholesterol; OR: Odds Ratio.

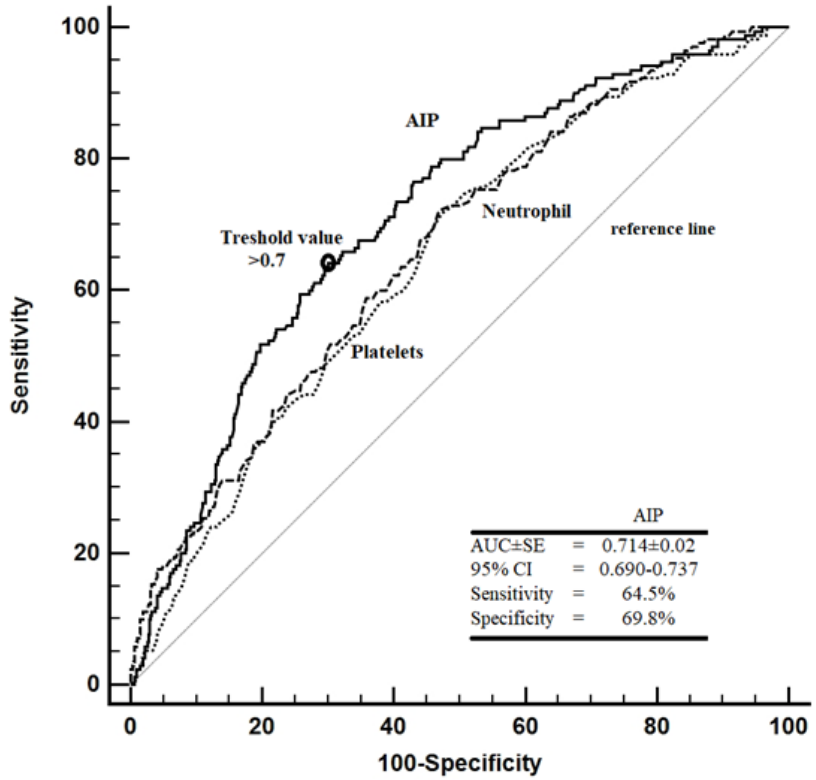

Figure 1. Diagnostic performance of the AIP in predicting slow coronary flow phenomenon.

retrospective design. The fact that the majority of patients were male may have contributed to the deterioration of homogeneity. Atherosclerosis-related inflammatory markers such as high-sensitivity C-reactive protein and interleukin-6 could not be studied due to the retrospective design. This limited the importance of the relationship between CSFP and inflammation. Apolipoprotein B and small dense LDL levels, which better reflect atherogenic dyslipidemia, could not be evaluated. In addition, endothelial dysfunction, which is involved in the pathology of CSFP, could not be evaluated by flow-mediated dilatation or pulse wave velocity.

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