Atherogenic and hematologic inflammatory indexes: What is the most useful predictor of coronary slow flow?

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Atherogenic and hematologic inflammatory indexes in coronary slow flow

Abstract
Aim: Previous studies reported that inflammation and atherosclerosis are linked to coronary slow flow (CSF). The predominant pathological mechanism has not been elucidated yet. Hence, we aimed to compare hematologic inflammatory and atherogenic indexes simultaneously between patients with normal coronary flow (NCF) and CSF.

Material and Methods: In a single-center retrospective analysis, 91 consecutive NCF patients and 90 consecutive CSF patients constituted two groups according to Thrombolysis in Myocardial Infarction frame count (TFC). Hematological indexes consist of the neutrophil-lymphocyte ratio (NLR), the lymphocyte to monocyte ratio (LMR), and the platelet-lymphocyte ratio (PLR), and the atherogenic indexes consist of an atherogenic index of plasma (AIP), atherogenic coefficient (AC), and Castelli’s risk index (CRI). Baseline clinical parameters were compared beside the indexes.

Results: NLR, LMR, PLR were similar in groups. AIP, AC and CRI were significantly higher in the CSF group (p<0.05). In correlation analysis, only CRI has a significantly positive correlation with mean TFC (r: 0.419 p <0.001). In multivariate regression analysis, CRI was found as independently predictor of CSF (Odds ratio = 2.74, 95% CI= 1.21-6.207; p=0.016). Discussion: An elevated CRI may be an independent predictor for the presence of CSF. Additionally, it can be said that the inflammatory activity in CSF is transformed into atherosclerotic structures.

Keywords
Coronary Circulation; Inflammation; Coronary Atherosclerosis; Dyslipidemias
Introduction
Coronary slow flow (CSF), classified as heart syndrome Y or non-obstructive coronary artery disease (INOCA), is an angiographic phenomenon characterized by late dye transfer to the distal coronary vascular bed during angiography in patients without obstructive coronary lesions [1,2]. CSF is a considerable clinical entity because it causes acute cardiac ischemic effects as well as complaints reminiscent of myocardial ischemia in general [3]. CSF has well-established mechanisms based on inflammation, atherosclerosis, endothelial dysfunction, and microvascular resistance [4]. However, the proportion of this relationship between the factors involved in the pathological mechanism is still unclear.

Hematological inflammatory indexes consisting of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR), associated with inflammation in cardiovascular diseases have been previously specified [5,6]. Studies have shown that there is a significant association between decreased density lipoprotein cholesterol (HDL-c) level, increased low-density lipoprotein cholesterol (LDL-c) level, and the incidence of cardiovascular diseases and adverse events [7,8]. Recently, researchers have defined atherogenic indexes, consisting of the Atherogenic plasma index (AIP), the Atherogenic coefficient (AC), and Castelli’s risk index (CRI) to better define cardiovascular diseases based on atherosclerosis [9, 21-23].

Although many studies have been conducted on patients with CSF, as far as we know, no studies have been conducted comparing these hematologic inflammatory and atherogenic indexes in slow coronary flow. We aimed to compare the possible roles of atherogenic and hematological indexes in CSF, which includes both inflammation and atherosclerosis in its basic pathology.

Material and Methods
Patient selection
The present study was a retrospective and single-center study. Patients who attended to cardiology clinic for stable angina pectoris between January 2015 and December 2018, who underwent coronary angiography and had angiographically normal or close to normal coronary arteries were retrospectively analyzed [4]. At the beginning of our study, 129 patients with coronary slow flow (CSF) were detected. Exclusion criteria are as follows: left ventricular ejection fraction <50%, history of the previous revascularization, acute coronary syndrome, obstructive coronary lesion (>20%), myocardial bridging, coronary ectasia, coronary spasm, infection, current anti-inflammatory and lipid-lowering medication usage, autoimmune disease, renal failure, anemia, hematological disease, and malignancy. After exclusion criteria, 181 patients were included in the final analysis, 90 consecutive patients with slow flow in either of their coronary arteries, versus 91 consecutive patients with normal coronary flow (NCF). Hypertension was defined as diastolic blood pressure ≥ 90 mm Hg or systolic blood pressure ≥ 140 mm Hg or with the use of any reported antihypertensive therapy. Diabetes mellitus (DM) was defined as the use of any antidiabetic agent. The study was in compliance with the principles in the Declaration of Helsinki and approved by the Local Institutional Ethics Committee (Ethics committee approval code numbered 2020-16/07 was obtained on 17.06.2020).

Statistical Analysis
All analyses were performed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). The compliance of the data
to normal distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean ± standard deviation, while continuous variables that were not normally distributed were specified as median with interquartile range (25–75th percentiles). Categorical variables were specified as the number with a percentage. Student’s t-tests were used to compare parametric continuous variables, and the Mann-Whitney U test was used to compare nonparametric continuous variables. Chi-square analysis was used to compare categorical variables. The correlation between CRI and mTFC was tested with the Spearman rho analysis. Logistic regression analysis was performed to assess the association of clinical and laboratory parameters with the presence of CSF. Univariate analyses were performed by including parameters that were significantly different between the groups. The Hosmer-Lemeshow test was used to determine sufficient goodness of fit for the regression model. Then, all significant parameters in univariate analysis were evaluated individually in a multivariate model with possible confounding factors (mTFC, age, gender, hypertension, smoking). All odds ratios were presented with their respective 95% confidence intervals (CI). A two-sided p<0.05 was considered significant.

Results
The comparison of the main clinical characteristics and laboratory findings of the groups are shown in Table 1. There was no significant difference between the groups with respect to BMI, family history of premature coronary artery disease (CAD), DM, systolic blood pressure. Age (55.76 ± 12.16 years; 52.03 ± 11.94 years, p = 0.047), female gender (n=27 [30.3%]; n=61 [67%], p <0.001), smoking (n=26 [28.9%]; n=14 [15.4%], p =0.022), hypertension (n=41 [45.6%]; n=27 [29.7 %], p=0.020) were significantly higher in patients with CSF. When the CSF and NCF groups were compared with the laboratory parameters, there was no significant difference between the CRP and glomerular filtration rate. In complete blood count, hemoglobin was significantly higher in patients with CSF (14.66 ± 1.8 g/dL; 13.91 ± 1.7 g/dL, p =0.003). On the other hand, platelet count was significantly higher in the NCF group (244.69 ± 73.52 x10^3/mm3; 265.66 ± 63.57 x10^3/mm3, p =0.008). Neutrophil count, monocyte count and lymphocyte count were similar among groups. On a lipid scale, the TG levels were similar in the groups. Total cholesterol (134 ±100.75-216) mg/dL, 123.5 ±93-175.75 mg/dL, p <0.001) and LDL-c (116.98 ± 41.71 mg/dL, 90,42 ± 13.91 ± 1.7 g/dL, p <0.001) were lower in patients with CSF. HDL-c (31 ±25-37, 14 ±12-16, p <0.001) was significantly higher in the CSF group. Comparisons of the hematological inflammatory indexes and atherogenic indexes are shown in Table 1. NLR, LMR, and PLR were similar between the groups. AIP (3.4 [2.1-5.4], 2.2 [1.8-3.8], p =0.027), AC (3.59 ± 1.66, 2.34 ± 1.9), p <0.001, and CRI (2.92 [1.94-3.84], 1.72 [1.17-2.53], p <0.001) were significantly higher in the CSF group. Univariate and multivariate logistic regression analyses were used to evaluate independent predictors of CSF and are shown in Table 2. In multivariate regression analysis, total cholesterol (OR = 1.946; 95% CI = Table 1. Comparison of baseline clinical, laboratory parameters and indexes of study groups

| Variables | Patient with CSF (n=90) | Patient with NCF (n=91) | p  |
|-----------|-------------------------|-------------------------|----|
| **Clinical parameters** | | | |
| Age, years | 55.76±12.16 | 52.03±11.94 | 0.047 |
| Female gender | 27(30.3 %) | 61(67 %) | < 0.001 |
| BMI, kg/m² | 27.1(25-30.1) | 26.62(73-31.2) | 0.671 |
| Smoking | | | |
| | 26.2(8.9 %) | 14(15.4 %) | 0.022 |
| Family history premature CAD | 20(22.2 %) | 14(15.4 %) | 0.162 |
| Diabetes mellitus | 10(11.1 %) | 14(15.4 %) | 0.265 |
| Hypertension | 41(45.6 %) | 27(29.7 %) | 0.020 |
| **Hematological blood pressure, mmHg** | 127.5(120-140) | 125(110-130) | 0.140 |
| **Laboratory parameters** | | | |
| eGFR, ml/min | 90(85.8-90) | 90(85.8-90) | 0.247 |
| CRP, mg/L | 3.4(2.2-6.7) | 3.1(3.5-5.5) | 0.176 |
| Hemoglobin, g/dL | 14.6±1.8 | 13.91±1.7 | 0.003 |
| Platelet, X 10^9/mm³ | 244.69±73.52 | 265.66±63.57 | 0.008 |
| Neutrophil, X 10^9/L | 4.7(3.6-5.72) | 4.5(3.5-6.09) | 0.627 |
| Monocyte, X 10^9/L | 0.48(0.36-0.64) | 0.48(0.38-0.62) | 0.989 |
| Lymphocyte, X 10^9/L | 2.15(1.62-2.56) | 2.52(1.93-2.68) | 0.100 |
| Triglyceride mg/dL | 134(100.75-216) | 123(93-175.75) | 0.191 |
| Total cholesterol, mg/dL | 187.11±52.65 | 154.64±38.36 | <0.001 |
| LDL-c, mg/dL | 116.98±41.71 | 90,42±29.81 | <0.001 |
| HDL-c, mg/dL | 40(34-48) | 50(42-60) | <0.001 |
| mTFC | 31(25-37) | 14(12-16) | <0.001 |

Table 2. Univariate and multivariate logistic regression analyses of independent variables of SCF

| Variables | Univariate Logistic Regression Analysis | Multivariate Logistic Regression Analysis* |
|-----------|----------------------------------------|------------------------------------------|
| Odds Ratio | 95% CI | p value | Odds Ratio | 95% CI | p value |
| Hemoglobin | 1.302 | 1.091-1.553 | 0.003 | | | |
| Platelet | 0.995 | 0.991-1.000 | 0.035 | | | |
| Total cholesterol | 1.012 | 1.004-1.020 | 0.002 | 1.946 | 1.359-2.787 | 0.024 |
| LDL-c | 1.017 | 1.008-1.026 | <0.001 | 1.032 | 1.005-1.059 | 0.018 |
| HDL-c | 0.984 | 0.964-1.003 | 0.103 | | | |
| AIP | 1.101 | 0.97-1.251 | 0.138 | | | |
| AC | 1.662 | 1.269-2.177 | <0.001 | | | |
| CRI | 1.94 | 1.44-2.61 | <0.001 | 2.74 | 1.21-6.207 | 0.016 |

Abbreviations: AC, atherogenic coefficient; AIP, atherogenic index of plasma; BMI, body mass index; CAD, coronary artery disease; CRI, Castelli’s risk index; CRP, C-reactive protein; CSF, coronary slow flow; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LMR, lymphocyte to monocyte ratio; mTFC, mean TIMI frame count; NCF, normal coronary flow; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; TIMI, thrombolysis in myocardial infarction.

*Multivariate logistic regression analyses were performed for each parameter adjusted for mTFC, age, sex, hypertension, and smoking coefficients, and only significant results were presented.
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Discussion

In the present study, we found that CRI, LDL-c, and total cholesterol were independent predictors of the presence of CSF. We also found that CRI activity was moderately correlated with mTFC.

CSF is a term professionally known to interventional cardiologists that delays opacification in distal segments without >40% angiographic lesions in main epicardial coronary arteries [1]. Previous studies have shown that CSF is a condition involving systemic inflammatory factors rather than just locally acting inflammation [13]. Systemic inflammatory effects can alter the parameters and rates of blood count. PLR, LMR, and NLR are inexpensive systemic inflammatory markers. Considering the relationship between many cardiovascular diseases in which cardiovascular risk factors are well documented by various previous studies, these parameters can be used as markers for conditions involving an inflammatory process [5,6]. PLR, NLR, and LMR were similar between groups in our study. Inflammatory infrastructure pattern was recessive in CSF. These results may be explained by the presence of near-normal coronary arteries in our patient selection, because inflammation has been blamed in the initial stage rather than the advanced stage of the atherosclerotic process [15].

The benefits of increasing HDL-c level as well as lowering LDL-c level for the prevention of atherosclerotic cardiovascular disease are well known and potential benefits have been reported in patients at an early age [16]. Besides, it has been reported that statin therapy reduces CSF and increases coronary flow reserve in patients with CSF [17]. Decreased coronary reserve in CSF required a new definition as INOCA [2]. The increased microvascular tone has been blamed in the CSF examined in the INOCA subgroup. In the increase of coronary microvascular tone, oxidative stress and pro-inflammatory process in which adipokines are blamed together with sympathetic hyperactivity [18]. Recent adipokine gene studies have found significant regulatory and correlative effects of adipokines on LDL-c and total cholesterol in obese male and female patients [19]. According to the results of our study, the increased LDL-c and total cholesterol level associated with atherosclerosis and increased microvascular tone is an independent predictor of CSF.

CSF may include diffuse atherosclerosis not only in the epicardial coronary arteries but also in the coronary microvascular circulation [20]. The relationship of atherogenic indexes with cardiovascular diseases and cardiovascular death based on atherosclerosis has been defined [9,12]. A recent study found that the SYNetergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score, which indicates the severity of obstructive coronary artery disease, is associated with AIP [21]. Besides, saphenous vein graft stenosis associated with distal flow insufficiency, endothelial damage, and accelerated atherosclerosis has been associated with AIP and AC [22]. Furthermore, in a study based on intracoronary imaging in CAD, there was a significant relationship between plaque lipid content and plaque sensitivity and CRI [23].

In our comparison of the CSF group with the NCF group, AIP, AC, and CRI were found to be significantly higher in the CSF group. CRI, the equivalent of LDL-c/HDL-c, was an independent predictor of CSF.

The present study has some limitations that need to be mentioned. First, this study used a retrospective study design with a relatively small sample size based on single-center experience. Second, since we used a single CRI value and a limited number of patients for our analysis, rather than a transient trend, no prognostic values were determined on cardiovascular outcomes. Third, Cohen's kappa value was not determined to detect inter-observer and intra-observer variations in TFC measurements. Finally, we did not evaluate for endothelial dysfunction and microvascular tone.

Our findings suggested that higher total cholesterol level, LDL-c level, and CRI were independently related to the presence of CSF. In addition to that, CRI was significantly positively correlated with mTFC. The findings of our study also confirmed that CRI had a moderate positive correlation with mTFC. Studying these markers may provide more informative data about the pathogenesis of microvascular atherosclerosis in patients with CSF. Additionally, it can be said that the inflammatory activity in CSF changes into atherosclerotic structures but more studies are needed to confirm our findings in CSF.

Scientific Responsibility Statement

The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.
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Conflict of interest
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