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Coronary Slow Flow Phenomenon: Clinical Findings and Predictors

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Background: In some patients with chest pain, selective coronary angiography reveals slow contrast agent passage through the epicardial coronary arteries in the absence of stenosis. This phenomenon has been designated the slow coronary flow (SCF) phenomenon.
Objectives: In this study, we aimed to describe the demographic and clinical findings and presence of common atherosclerosis risk factors in patients with the SCF phenomenon.
Patients and Methods: Between October 2014 and March 2015, demographic data, clinical histories, atherosclerosis risk factors, and laboratory and angiographic findings were recorded for all consecutive patients scheduled for coronary angiography and diagnosed with the SCF phenomenon, as well as a control group (patients with normal epicardial coronary arteries; NECA). SCF was diagnosed based on the thrombolysis in myocardial infarction frame count (TFC). A TFC > 27 indicated a diagnosis of SCF phenomenon.
Results: Among the 3600 patients scheduled for selective coronary angiography, 75 (2%) met the SCF criteria. SCF and NECA patients did not exhibit statistically significant differences in traditional risk factors except for hypertension, which was more prevalent in SCF than NECA patients (52% versus 31%, P = 0.008). A multivariable analysis indicated a low body mass index, presence of hypertension, low high-density lipoprotein cholesterol (HDL-c) level, and high hemoglobin level as independent predictors of the SCF phenomenon; of these, hypertension was the strongest predictor (odds ratio = 6.3, 95% confidence interval: 2.2 - 17.9, P = 0.001).
Conclusions: The SCF phenomenon is relatively frequent, particularly among patients with acute coronary syndrome who are scheduled for coronary angiography. Hypertension, a low HDL-c level, and high hemoglobin level can be considered independent predictors of this phenomenon.

Keywords: Coronary Angiography; Coronary Artery Disease; Slow Flow Phenomenon

1. Background

In some patients with chest pain who are scheduled for selective coronary angiography, slow contrast agent passage is observed through the epicardial coronary arteries in the absence of stenosis. This phenomenon has been designated the slow coronary flow (SCF) phenomenon (1-3).

Although some investigators have reported an SCF incidence rate of 7%, based on visual estimations, SCF is not a frequent finding in routine coronary angiograms, with an incidence of approximately 1% in patients undergoing coronary angiography (4, 5). The speed of contrast agent progression through the coronary arteries can be assessed and quantified with good accuracy and reproducibility using the Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) (6).

Since its initial definition by Tambe et al., only a few studies have investigated the etiology and predisposing factors of the SCF phenomenon (4, 5). This phenomenon has been suggested as an early phase of atherosclerosis that involves both the small and epicardial coronary arteries (7-10).

2. Objectives

In this study, we aimed to describe the demographic and clinical findings, as well as the presence of common atherosclerosis risk factors, in patients with the SCF phenomenon who presented at a tertiary center for cardiovascular diseases.

3. Patients and Methods

This was a case-control study. After receiving study approval from the research and ethics committee of Rajaie cardiovascular, medical, and research center, the demographic data, clinical histories, atherosclerosis risk factors, and laboratory and angiographic findings of all consecutive patients scheduled for coronary angiography and diagnosed with the SCF phenomenon between October 2014 and March 2015, as well as a control group, were recorded. SCF was diagnosed based on the TFC (6).

The exclusion criteria were the presence of congenital heart anomalies and heart rhythm disorders other than sinus tachycardia, and the concomitant presence of slow flow and stenotic lesions.

3.1. Control Group

The control group comprised an identical number of patients who underwent coronary angiography with a normal epicardial coronary artery angiogram (NECA). All patients in the control group were randomly selected from the subjects scheduled for coronary angiography.

3.2. Coronary Angiography and TFC

Standard left and right coronary angiography was performed in all case and control patients via the femoral approach, using Judkins catheters. The angiograms were assessed, and coronary flow quantification was performed using the corrected TFC method described by Gibson et al. The assessment was performed by an expert interventional cardiologist who was blinded to the clinical details of the study population (6). For TIMI frame counting, the first frame was defined as the first frame in which dye completely filled the entrance of the artery with antegrade flow, and the last frame was defined as the frame in which dye entered the distal landmark branch. Normal TFC values were defined as 36.2 ± 2.6 (range: 32 - 41) for the left anterior descending (LAD), 22.2 ± 4.1 (range: 16 - 31) for the left circumflex (LCX), and 20.4 ± 3.0 (range: 16 - 26) for the right coronary artery (RCA) (6).

3.3. Definition of Slow Coronary Flow

The frame counts in the LAD were divided by 1.7 to correct for the increased length. Based on Gibson's study, a frame count > 27 was considered indicative of SCF (6).

3.4. Statistical Analysis

IBM SPSS Statistics, version 19.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. The Kolmogorov-Smirnov test was used to assess normal distributions. Categorical variables were expressed as numbers and percentages; quantitative variables were expressed as means [standard deviations (SDs)] or medians [interquartile ranges (IQRs)] as appropriate. Categorical data were compared using the chi square test and Student's t-test; quantitative variables were compared using an analysis of variance (ANOVA) or the Mann-Whitney test, as appropriate. A binary logistic regression analysis was performed for the multivariate analysis. P values < 0.05 were considered significant.

4. Results

4.1. Patients' Characteristics

Among the 3600 patients scheduled for selective coronary angiography between October 2014 and March 2015, 75 (2%) met the criteria for SCF.

Of these, 53 (71%) patients were male. The mean (SD) age of the SCF subjects was 57 (10.8) years. In 19 (25.3%) subjects, the indication for coronary angiography was the presence of angina or dyspnea with a high-risk non-invasive test. Otherwise, 56 (74.7%) patients underwent coronary angiography following an episode of acute coronary syndrome, in which 8 (10.7%) patients presented with ST segment elevation myocardial infarction (STEMI).

Table 1 presents a comparison of demographic and clinical data from SCF subjects and control subjects (NECA).

The mean age did not differ between the SCF and NECA groups. However, as shown in Table 1, SCF was more prevalent in men than in women (P < 0.001). Histories of smoking and cerebrovascular events (CVE) were more prevalent in SCF patients than in NECA patients. However, this difference was not statistically significant.

The SCF and NECA groups did not exhibit statistically significant differences in traditional risk factors except for hypertension, which was more prevalent in the SCF group than the NECA group (52% versus 31%, P = 0.008).

Table 2 presents the laboratory and echocardiography findings for each study population.

Table 1. Comparison of Demographic and Clinical Data Between SCF Subjects and Control Subjects (NECA) [a,b]

Variables	SCF, (n = 75)	NECA, (n = 75)	P Value
Age, y	57 (10.8)	57 (10.4)	0.1
Gender			< 0.001
Female	22	48	
Male	53	27	
BMI, kg/m²	26.9 (3.8)	28.6 (4.8)	0.004
Hypertension	39 (52)	23 (31)	0.008
Diabetes Mellitus	20 (27)	22 (30)	0.5
Smoking	24 (32)	15 (20)	0.09
Dyslipidemia	28 (38)	35 (47)	0.2
Family history	12 (16)	13 (17)	0.8
History of RF	0	2 (2.7)	0.1
History of CVE	4 (5.3)	1 (1.3)	0.1

[a] Abbreviations: BMI, body mass index; CAD, coronary artery disease; CVE, cerebrovascular events; NECA, normal epicardial coronary arteries; RF, renal failure; SCF, slow coronary flow.
[b] Data are presented as means (SD) for intervals (age and BMI) and counts (%) for categorical variables.

Table 2. Comparison of echocardiographic and laboratory findings in SCF and control (NECA) subjects [a,b]

	SCF (n = 75)	NECA (n = 75)	P value
LVEF, %	44.8 (11.1)	51.9 (5.7)	< 0.001
Normal RV function	62 (82.7%)	73 (97.3%)	0.003
FBS, mg/dL	104 (95 - 137)	111 (98 - 135)	0.4
TG, mg/dL	150 (120 - 210)	152 (114 - 202)	0.9
TC, mg/dL	156 (43)	175 (70)	0.05
LDL-C, mg/dL	98 (34)	114 (47)	0.02
HDL-C, mg/dL	39 (35 - 44)	41 (36 - 48)	0.008
Hb, mg/dL	14 (12 - 15)	13 (12 - 14)	0.06
WBC, count/μL	8056 (2400)	8865 (2045)	0.4
Platelet, count/μL	216000 (62000)	210000 (45000)	0.5
Creatinine, mg/dL	0.8 (0.7 - 1)	0.8 (0.7 - 1)	0.5
Uric acid, mg/dL	5.2 (1.1)	5.7 (1.3)	0.4
ALT, mg/dL	21 (16 - 26)	18 (13 - 23)	0.07
AST, mg/dL	23 (15 - 35)	21 (15 - 37)	0.9

[a] Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CVE, cerebrovascular events; FBS, fasting blood sugar; HDL-c, high density lipoprotein cholesterol; Hg, hemoglobin; LDL-c, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NECA, normal epicardial coronary arteries; RF, renal failure; RV, right ventricle; SCF, slow coronary flow; TC, total cholesterol; WBC, white blood cell.
[b] Data are presented as means (standard deviations) or medians (interquartile ranges) for intervals and counts (%) for categorial variables (normal Rv function).

As shown in Table 2, the median (IQR) of the left ventricular ejection fraction (LVEF) was significantly lower in the SCF group than in the NECA group (P < 0.001). The right ventricular (RV) function was within the normal range in 82.7% of SCF group subjects, compared with 97.3% of NECA group subjects (P = 0.003).

The two study groups did not significantly differ in most laboratory tests, except for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c). As shown in Table 2, the levels of TC and LDL-c were higher in the NECA group relative to the SCF group, and the HDL-c level was significantly lower in the SCF group.

4.2. Slow Coronary Flow Pattern

LAD single vessel involvement was more common in SCF patients (40.4%). The LAD was involved in more than 90% of cases, and whereas RCA and LCX were involved in 37% and 48% of cases, respectively.

Figure 1 shows the slow flow patterns and numbers of involved vessel in our study population.

There was no association between traditional risk factors and the number of involved vessels in subjects with the SCF phenomenon (all P values > 0.5)

4.3. Independent Predictors of the SCF Phenomenon

To assess the adjusted association between the SCF phenomenon and the study variables mentioned in Tables 1 and 2, a multivariable regression model with a backward elimination method was applied; this model revealed a low body mass index (BMI), presence of hypertension, low HDL-c level, and high hemoglobin level to be independent predictors of the SCF phenomenon (Table 3). Of these, the presence of hypertension was the strongest predictor of the SCF phenomenon [odds ratio = 5.3, 95% confidence interval (CI): 2.3 - 12.4, P < 0.001].

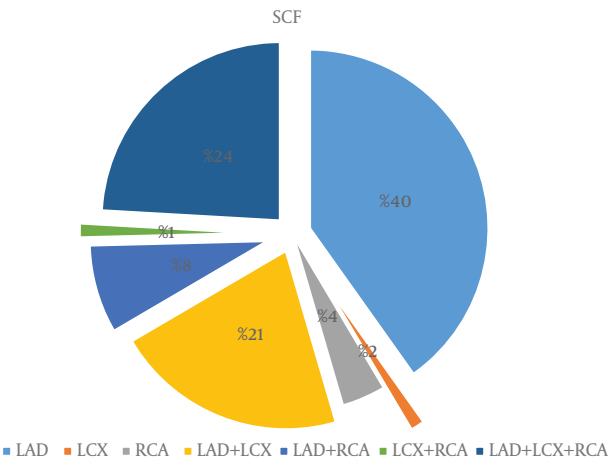

Figure 1. Slow Flow Pattern (Number of Involved Vessels) in our Study Population (n = 75)

Table 3. Independent Predictors of the SCF Phenomenon [a]

	Beta	P Value	Odds Ratio	95% CI
BMI	-0.15	0.003	0.8	0.7 - 0.9
Hypertension	1.8	< 0.001	5.3	2.3 - 12.4
HDL-c	-0.09	0.001	0.9	0.8 - 1
Hemoglobin	0.4	0.004	1.4	1.1 - 1.9

[a] Abbreviations: BMI, body mass index; CI, confidence interval; HDL-c, high-density lipoprotein cholesterol; SCF, slow coronary flow.

5. Discussion

In this study, we investigated characteristics of SCF subjects at a tertiary center for cardiovascular medicine. Approximately 2% of the patients scheduled for coronary angiography in this study were found to exhibit the SCF phenomenon. The prevalence of the SCF phenomenon varies among studies (4, 5, 7, 9, 11). Hawkins et al. used a TFC-based definition of SCF and reported a prevalence of 5.5% among patients referred for coronary angiography (4). In other studies, the prevalence of the SCF phenomenon was 1% among patients referred for coronary angiography, based on the TFC definition (1, 2). However, Diver et al. found that approximately 5% of patients presenting with acute coronary syndrome in the TIMI-IIIA trial exhibited evidence of SCF without obstructive coronary artery disease (CAD), and a prevalence of 24% - 34% was previously reported in a NECA population (21).

In our study, approximately 75% of the patients with evidence of SCF were scheduled for coronary angiography because of acute coronary syndrome. It has been suggested that differences in atherosclerotic burdens among general populations might explain these discrepancies. The SCF phenomenon is a systemic phenomenon caused by microvascular dysfunction; it is possibly secondary to an early atherosclerotic process and could be considered within the atherosclerosis spectrum (14-17).

The vessel involvement frequencies observed in our study differed from those in other studies. In a study by Hawkins et al., LAD, LCX, and RCA were involved in 67%, 69%, and 58% of cases respectively (4). In our study, LAD was most frequently involved, with a rate exceeding 90%. The reason for this difference is unclear, although it might be related to racial differences or technical errors in SCF quantification.

5.1. Clinical Characteristics and Predictors of the SCF Phenomenon

Several studies have attempted to define the demographic and clinical characteristics and independent predictors of patients with the SCF phenomenon. Fineschi et al. investigated 8 patients with the SCF phenomenon and found no difference between subjects with SCF and NECA in terms of atherosclerosis risk factors (9, 17). Although the Fineschi et al. study involved a small sample size, Hawkins et al. (4) compared 92 patients with SCF and 62 subjects with normal coronary arteries and found no correlation between traditional atherosclerosis risk factors and SCF. Those authors have stated that the high frequency of risk factors in their general population might have diluted any existing differences.

In the current study, we compared SCF patients in both NECA subjects and patients with CAD (4).

5.2. Comparing SCF and NECA Subjects

A comparison of the SCF and NECA groups showed that the groups did not differ in terms of traditional risk factors, except for hypertension. Hypertension was more common in the SCF group than in the NECA group, and a multivariate analysis showed that hypertension was the strongest independent predictor of the SCF phenomenon.

Several studies have suggested independent predictors of the SCF phenomenon (5, 7, 11-13, 18-20). In a study by Arbel et al. smoking was found to be the strongest predictor of the SCF phenomenon (13). Hawkins et al. suggested male sex, a higher BMI, and a low HDL-c level as independent predictors of the SCF phenomenon following a multivariable analysis, and demonstrated that male sex was the strongest independent predictor of this phenomenon (4). Other studies have also suggested BMI and male sex as predictors of the SCF phenomenon (11, 13). In contrast to other studies, our study found an association between a lower BMI and the SCF phenomenon. Although we randomly selected our control group, the NECA group might have been selected from among patients with higher weights.

Our study also showed that a low HDL-c level and high hemoglobin level might be independent predictors of the SCF phenomenon.

Endothelial dysfunction, inflammation, increased uric acid levels, conditions associated with changes in platelet properties, and changes in blood rheological properties have also been proposed as mechanisms associated with the SCF phenomenon (2, 7, 11, 13, 15, 18-21). In our study, we found no association between white blood cell or platelet counts and SCF. Akpinar et al. investigated the relationship between whole blood cell counts and SCF and suggested the platelet count and red cell distribution width as independent predictors of this phenomenon (18).

Naing et al. identified a significant correlation between uric acid levels and SCF and suggested serum uric acid levels as an independent predictor of SCF (12). However, in this study, we found no association between the uric acid level and the presence of SCF.

5.3. Study Limitations

First, this study only recorded the presence or absence of slow flow after quantification. Second, the patients' medication usage was not recorded. Third, the lack of

any follow-up data could be considered another study limitation.

In conclusion, the SCF phenomenon is relatively frequent, particularly among patients scheduled for coronary angiography for acute coronary syndrome. Hypertension and a low HDL-c level can be considered independent predictors of this phenomenon. The presence of significant differences in SCF predictors among studies suggests the presence of unknown confounders, which should be addressed in other studies.

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