Research Article

Clinical Profile and Outcome in Patients with Coronary Slow Flow Phenomenon

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The coronary slow flow phenomenon (CSFP) is a poorly recognized clinical entity characterized by delayed distal vessel opacification in the absence of epicardial coronary stenosis and presently lack of specific data on the clinical profile and outcome. We investigated a cohort of 429 patients who fulfilled the criteria for CSFP to explore the clinical feature, outcome, and risk factor of prognosis. Two teams (clinical center and core lab) were blind to patient data for the assessment of coronary angiography using corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC). The study cohort consisted of 429 patients (294 men, 68.5%), aged from 30 to 78 years (mean, 54 years). Two hundred patients (46.6%) out of 429 patients had a history of hypertension, 72 (16.8%) had diabetes mellitus, and 222 (51.7%) had dyslipidemia. All the rates of agreement between two teams in evaluating whether normal flow (CTFC ≤ 27 frames) or slow flow (CTFC > 27 frames) were moderate (0.40 < κ < 0.75) for the three arteries. Follow-up (mean, 3.8 years) was done for 421 patients (98.1%). The major adverse cardiovascular events (MACE) occurred in 39 patients (9.3%) out of 421 patients. Multivariate analysis showed that the risk of MACE approximately doubles with age > 50 years (hazard ratio (HR) = 2.2, 95% CI: 1.0 to 4.9, and P = 0.042), hypertension (HR = 2.1, 95% CI: 1.1 to 4.2, and P = 0.021), and dyslipidemia (HR = 2.0, 95% CI: 1.0 to 3.9, and P = 0.042). CSFP affects predominantly patients at middle age and above but can occur in any age group; CSFP should be more concerned, particularly in patients > 50 years old with hypertension and dyslipidemia.

1. Introduction

The coronary slow flow phenomenon (CSFP) is characterized by the slow antegrade passage of dye through one or more vessels of the coronary tree without stenosis during coronary angiography. Since it was firstly described by Tambe et al. in 1972 [1], many studies focused on the risk factors of CSFP have been reported; however, there is a paucity of specific data on the clinical profile and outcome of these patients. Clinical center and angiographic core laboratory were blind to patient data for the assessment of coronary angiograph using corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) in this study. Moreover, the clinical profile and outcome of the patients were evaluated, and the prognostic factor was explored using proportional hazards. In the present study, it was sought to investigate the clinical feature and prognosis of the patients with CSFP.

2. Materials and Methods

2.1. Study Population. In this study, 1,67,494 consecutive patients who underwent coronary angiography in our clinical center between 2009 and 2017 were assessed by TIMI flow grade and excluded if they had any known or documented ischemic heart disease (previous or current infarction, revascularization, and ≥20% diameter coronary stenosis), coronary ectasia, coronary artery spasm, coronary
myocardial bridge, valvular heart disease (more than mild),
cardiomyopathy, heart failure, and malignancy, as well as
unavailable angiographic or clinical data. Then, 484 patients
with TIMI grade 2 flow (requiring three or more beats to
opacify the distal vessel) in at least one major vessel were
preliminarily subsumed.

This study was approved by our local research ethics
committee and conducted in accordance with the ethical
principles of the Declaration of Helsinki. Informed consent
was obtained from all the participants.

2.2. Assessment of Coronary Angiogram (CTFC). These pa-
tients preliminarily subsumed were reassessed by clinical
center and angiographic core laboratory, blind method,
using CTFC described by Gibson et al. [2]. For TIMI frame
counting, the first frame was defined as the frame in which
dye first completely filled the entrance of the artery with
antegrade flow, and the last frame was defined as the frame
in which dye first entered the distal landmark branch
(Figure 1). The left anterior descending coronary artery
(LAD) frame counts were divided by 1.7 for correction of
the longer length, and all the films should be corrected at
30 frames per second (fps). The CTFC above 27 frames for
at least one among three major vessels was defined to
CSFP, only if the qualitative results from clinical center
and angiographic core laboratory were consistent. Eventu-
tally, a cohort of 429 patients fulfilled the criteria for
CSFP.

2.3. Clinical Data Collection. Demographic data regarding
age, sex, body mass index (BMI), cardiovascular risk factors
(hypertension, diabetes, dyslipidemia, cigarette smoking,
etc.), and clinical presentation were recorded. Data of
electrocardiograph (ECG) and echocardiography were col-
clected. Then, the left ventricular mass index (LVMI) was
 calculated according to Devereux’s formula [3], and left
ventricular hypertrophy (LVH) was defined as LVMI >95 g/
 m² in females or LVMI >115 g/m² in males [4].

2.4. Follow-Up and Outcome. Follow-up evaluation was
attempted for all patients by telephone or visit, which in-
cluded major adverse cardiovascular events (MACE), con-
comitant symptoms, and long-term medications after
discharge. In this study, MACE was defined as cardiac death,
nonfatal myocardial infarction (MI), revascularization,
hospitalization due to unstable angina pectoris, and nonfatal
stroke. In case the patient had died, an attempt was made to
identify the cause (cardiac and noncardiac).

2.5. Statistical Analysis. Data were expressed as mean and
standard deviation (SD) or frequency percents. Analyses
were conducted on the raw data. Variable differences were
assessed by paired t-test for continuous variables and ¥²-test
for discrete variables; crosstab analysis and kappa value (k
statistic) were used in the consistency evaluation. The sur-
vival follow-up data were analyzed by univariate and mul-
tivariate Cox proportional hazards regression. Missing data
were omitted, where samples with invalid data are discarded
from further analysis. All analyses were conducted with SAS
version 9.3 software (SAS Institute Inc., Cary, NC). Two-
tailed P values less than 0.05 were considered to be statis-
tically significant.

3. Results

3.1. Clinical Feature. The study cohort consisted of 429
patients (294 men, 68.5%). In the initial evaluation, the age
range was from 30 to 78 years (mean, 54 years). As dem-
onstrated in Figure 2, 67% of patients were >50 years old.
Baseline characteristics are displayed in Table 1. The mean
body mass index (BMI) was 26.3 kg per square meter. Two
hundred patients (46.6%) of 429 had a history of hyper-
tension, 72 (16.8%) had diabetes mellitus, 222 (51.7%) had
dyslipidemia, 205 (47.8%) were previous or current smokers,
102 (23.8%) were moderate to heavy alcohol drinkers, 12
(2.8%) had obstructive sleep apnea-hypopnea syndrome, 68
(15.9%) had family history of coronary artery disease, and
421 (98.1%) had symptom of chest pain; only 22 (5.1%) were
diagnosed with “acute coronary syndrome” at the time of
discharge.

3.2. Electrocardiography and Echocardiography. The 12-lead
ECG at the time of the initial admission was reviewed in 403
patients and demonstrated complete right bundle branch
block in 10 (2.5%) out of 403 patients, complete left bundle
branch block in 2 patients (0.5%), ST-segment depression in
36 patients (8.9%), and ST-segment elevation in 5 patients
(1.2%). Nonspecific ST-T-wave abnormalities were noted in
74 patients (18.4%), and 276 patients had a normal ECG
(69%).

The echocardiographic findings in our study cohort
were summarized in 338 patients. Average left ventricular
end-diastolic diameter was 47.1 mm (range, 35 to 55 mm).
Left ventricular ejection fraction was assessed quantita-
tively, and the ejection fraction averaged 66% (range, 53%
to 80%). The echocardiography demonstrated regional
wall motion abnormality in 13 (3.8%) out of 338 patients,
and 28 patients (8.3%) were assessed as left ventricular
hypertrophy.

3.3. Coronary Angiography

3.3.1. TIMI Flow Grades for Coronary Arteries by Clinical
Center and Core Lab. As to the left anterior descending
coronary artery (LAD), 215 patients (50.1%) out of 429
were assessed as TIMI grade 2 flow by clinical center and
287 (66.9%) by angiographic core laboratory (P < 0.001). The
patients with TIMI grade 2 flow for the left circumflex artery
(LCX) amounted to 327 (76.2%) assessed by clinical center
and 92 (21.4%) by angiographic core laboratory (P < 0.001).
As for the right coronary artery (RCA), 317 patients (73.9%)
oroutof429patientswereassessedasTIMIgrade2flow
by clinical center and 157 (36.6%) by angiographic core lab-
oratory (P < 0.001). The results of TIMI flow grades for
coronary arteries are displayed in Table 2.
3.3.2. Agreement in Assessment of Conventional TIMI Flow Grades between Clinical Center and Core Lab. As mentioned above, TIMI flow grades were evaluated by two teams (clinical center and core lab), respectively. Furthermore, the rate of agreement between clinical center and core lab in the evaluation of TIMI flow (TIMI grade 2 flow or TIMI grade 3 flow) was assessed with use of \( \kappa \) statistic (range of values, \(-1\) to \(+1\)). The value of \( \kappa > 0.75 \) indicates excellent agreement between two observers; however, value \(< 0.40 \) indicates poor agreement. Agreement was poor in assessment of TIMI flow. 

**Table 1**: Baseline characteristics of the patients with CSFP.

| Feature                                      | Overall (n = 429) | Mean (SD)/n (%) |
|----------------------------------------------|-------------------|-----------------|
| Age (yrs)                                    | 54.4 (8.9)        |                 |
| Male                                         | 294 (68.5)        |                 |
| BMI (kg/m\(^2\))                             | 26.3 (3.5)        |                 |
| Hypertension                                 | 200 (46.6)        |                 |
| Diabetes mellitus                            | 72 (16.8)         |                 |
| Dyslipidemia                                 | 222 (51.7)        |                 |
| Current or previous smoker                   | 205 (47.8)        |                 |
| Moderate to heavy alcohol drinker            | 102 (23.8)        |                 |
| Obstructive sleep apnea-hypopnea syndrome    | 12 (2.8)          |                 |
| Family history of coronary artery disease    | 68 (15.9)         |                 |
| Symptom of chest pain                        | 421 (98.1)        |                 |
| Diagnosis of acute coronary syndrome         | 22 (5.1)          |                 |

CSFP = coronary slow flow phenomenon; BMI = body mass index.
for LAD, with a 62.3% rate of agreement between clinical center and core lab ($\kappa = 0.24 \pm 0.05$). There was a poor rate (42.0%) of agreement in assessment of TIMI flow for LCX ($\kappa = 0.11 \pm 0.05$). Furthermore, for assessment of TIMI flow for RCA, the rate of agreement was also poor at 54.8% ($\kappa = 0.20 \pm 0.05$).

### 3.3.3. CTFC for Coronary Arteries by Clinical Center and Core Lab

The CTFC for LAD averaged 37 (SD, 12) frames by clinical center and 44 (SD, 14) frames by core lab ($P < 0.001$). The mean CTFC for LCX was 47 (SD, 17) frames by clinical center and 54 (SD, 21) frames by core lab ($P < 0.001$). The CTFC for RCA averaged 47 (SD, 22) frames by clinical center, which was significantly higher than that (averaged 42 (SD, 21) frames) assessed by core lab ($P < 0.001$). The results of CTFC for coronary arteries are displayed in Table 3.

### 3.3.4. Agreement in Evaluating Whether It Is Normal Flow or Slow Flow (Using CTFC) between Clinical Center and Core Lab

The coronary flow result whether normal flow (CTFC $\leq 27$ frames) or slow flow (CSFP, CTFC $> 27$ frames) was evaluated by clinical center and core lab, and the rate of agreement between clinical center and core lab in the evaluation of CSFP or not was also assessed with use of $\kappa$ statistic. Agreement was moderate in assessment of CSFP or not for LAD, with a 92.3% rate of agreement between clinical centers and angiographic core laboratory ($\kappa = 0.65 \pm 0.05$). There was a moderate rate (92.8%) of agreement in assessment of CSFP or not for LCX ($\kappa = 0.48 \pm 0.05$). Furthermore, for assessment of CSFP or not for RCA, the rate of agreement was also moderate at 87.9% ($\kappa = 0.62 \pm 0.05$). According to the identical results assessed by clinical center and core lab, 429 patients had slow flow coronary phenomenon in at least one major vessel.

### 3.4. Follow-Up

Follow-up was done for 421 patients (98.1%) out of 429 patients, with a mean duration of 3.8 years (range, 0.7 to 9.3 years). Sixteen patients (3.8%) returned to our center; for the remaining 405 patients, follow-up information was obtained by phone with the patient in the flesh if alive and with the next of kin if passed away. Five patients (1.2%) had died. Death was attributed to cardiac cause in 3 patients (sudden cardiac death) and noncardiac cause in 2 patients (lung cancer; melanoma). Among the 416 survivors, 154 patients had relapses of angina pectoris, 28 had hospitalization due to unstable angina pectoris, 11 had repeated coronary examinations (among these patients, 4 still showed CSFP), 12 had recurrent syncope, 1 had non-sustained ventricular tachycardia, 9 had atrial fibrillation, 3 patients had nonfatal myocardial infarction (MI), none had revascularization, and 11 had stroke (10 was ischemic; 1 was hemorrhagic and ischemic). For some patients, there were some overlaps or concurrences for these events.

Overall, MACE with a mean duration of 2.5 years (range, 0.2 to 7.2 years) after discharge occurred in 39 patients (9.3%) out of 421 patients, which was a composite of cardiac death, nonfatal MI, revascularization, hospitalization due to unstable angina pectoris, and nonfatal stroke in the study. Univariate analysis demonstrated that MACE with CSFP was not significantly related to sex, age, body mass index, diabetes mellitus, smoking, drinking, or medications. However, MACE with CSFP was related to hypertension (hazard ratio ($HR = 2.1, 95\% CI: 1.1$ to $4.0$, and $P = 0.029$) and dyslipidemia ($HR = 2.0, 95\% CI: 1.0$ to $3.9$, and $P = 0.043$) (Figure 3). Multivariate analysis showed that the risk of MACE was significantly independently associated with age $>50$ years ($HR = 2.2, 95\% CI: 1.0$ to $4.9$, and $P = 0.042$), hypertension ($HR = 2.1, 95\% CI: 1.1$ to $4.2$, and $P = 0.021$), and dyslipidemia ($HR = 2.0, 95\% CI: 1.0$ to $3.9$, and $P = 0.042$).

### 4. Discussion

Although dozens of formal definitions have been put forward, the CSFP essentially consists of the delayed progression of contrast injected into an epicardial coronary artery without stenosis during coronary angiography. In virtue of discrepancies in defining CSFP, incidence range of 1–7% in serial angiographies, and up to 5% in cases of acute coronary syndromes, has been reported [1, 5]. Most previous patient series were hampered by heterogeneity of included patients, angiographic inclusion criteria; however, our study emphasizes that the CSFP, an independent clinical entity, is “primary” CSFP, which should be distinguished from coronary reperfusion therapy-induced slow flow, or other “secondary” causes of coronary slow flow. These causes include coronary artery ectasia, coronary artery spasm, pulmonary arterial hypertension, valvular heart disease, cardiomyopathy, connective tissue disorders, or heart failure. Slightly unlike Beltrame criteria for diagnosing primary coronary slow flow [6], we strictly exclude obstructive epicardial coronary artery disease (no lesions $\geq 20\%$). So, this

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| Coronary artery | Clinical center $n$ (%) | Core lab $n$ (%) | $P$ value |
|-----------------|------------------------|-----------------|-----------|
| LAD, TIMI grade 2 | 215 (50.1) | 287 (66.9) | $< 0.001$ |
| LCX, TIMI grade 2 | 327 (76.2) | 92 (21.4) | $< 0.001$ |
| RCA, TIMI grade 2 | 317 (73.9) | 157 (36.6) | $< 0.001$ |

TIMI = thrombolysis in myocardial infarction; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery.

| Coronary artery | Clinical center Mean (SD) | Angiographic core laboratory Mean (SD) | $P$ value |
|-----------------|---------------------------|--------------------------------------|-----------|
| LAD, frames | 37 (12) | 44 (14) | $< 0.001$ |
| LCX, frames | 47 (17) | 54 (21) | $< 0.001$ |
| RCA, frames | 47 (22) | 42 (21) | $< 0.001$ |

CTFC = corrected thrombolysis in myocardial infarction (TIMI) frame count; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery.

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Univariate analysis demonstrated that MACE with CSFP was not significantly related to sex, age, body mass index, diabetes mellitus, smoking, drinking, or medications. However, MACE with CSFP was related to hypertension (hazard ratio ($HR = 2.1, 95\% CI: 1.1$ to $4.0$, and $P = 0.029$) and dyslipidemia ($HR = 2.0, 95\% CI: 1.0$ to $3.9$, and $P = 0.043$) (Figure 3). Multivariate analysis showed that the risk of MACE was significantly independently associated with age $>50$ years ($HR = 2.2, 95\% CI: 1.0$ to $4.9$, and $P = 0.042$), hypertension ($HR = 2.1, 95\% CI: 1.1$ to $4.2$, and $P = 0.021$), and dyslipidemia ($HR = 2.0, 95\% CI: 1.0$ to $3.9$, and $P = 0.042$).
study aims to evaluate clinical profile and prognosis of the patients with primary CSFP.

CSFP is more common in middle-aged and old men (M:F, 2.2:1) in our study; some studies have regarded male gender as a predictor of CSFP, while others have found no relation between sex and CSFP [7]. CSFP is most common in patients admitted with symptom of chest pain; rest or mixed-pattern angina with durations of symptom from several minutes to tens of minutes is a distinguishing characteristic of CSFP. Most importantly, CSFP has been delineated to be associated with life-threatening arrhythmias and sudden cardiac death [8, 9]. Generally speaking, in all but severe cases of unstable hemodynamics, no special physical findings are in patients with CSFP.

To assess coronary flow, as we all know, both TIMI flow grade and CTFC can be used. TIMI flow grade is a valuable and widely used qualitative measure in angiographic clinical and trials, while it is limited by its variable, categorical, and subjective nature [2]. On the contrary, the TIMI frame-counting method (CTFC) is reproducible, quantitative, and relatively objective. In our study, two teams (clinical center and core lab) were blind to patient data for the assessment of coronary angiograph using corrected TIMI frame count (CTFC). It was demonstrated that the results assessed by CTFC method have higher frequency of agreement than that by TIMI flow grade method between clinical center and angiographic core laboratory, which proved CTFC method to be more reproducible and reliable. So, different from Beltrame criteria [6] for diagnosing primary coronary slow flow, which defined CSFP by either TIMI 2 flow or CTFC > 27 frames, we define CSFP only by CTFC method (CTFC > 27 frames).

In addition, some studies showed that Doppler echocardiographic-derived coronary flow velocity had prognostic value [10, 11]; however, due to anatomic factors and technological limitation (e.g., the application was confined to LAD), the noninvasive demonstration of coronary flow pattern (transthoracic Doppler echocardiography, TTDE) does not widely apply to the assessment of coronary flow, including the CSFP.

Little is known about the prognosis of true primary CSFP, because the most published literature has included patients with known heart failure, near-normal coronary arteries (<40% stenosis), and other unexplained diseases [12, 13], and as a result, their outcome was not substantially the same as that observed in this study. In this study, we have tried to exclude patients with a possible secondary form of CSFP and other disease states as has been said before by sticking to very strict inclusion and exclusion criteria. Furthermore, in our study, two teams (clinical center and core lab) participate in the assessment of patient imaging, which can guarantee the accuracy of outcome in the maximum extent.

As previously mentioned, there is a paucity of specific data on the outcome of the patients with CSFP, not only that, there is considerable controversy regarding the prognosis. Sadamatsu et al. and Chaudhry et al. reported that patients with CSFP had a favorable long-term prognosis [13, 14], while Fragasso et al. investigated 12 patients with CSFP by an averaged follow-up of 15 years and thought that patients with CSFP were associated with a worse cardiac prognosis and should be carefully followed-up [15]. Besides that, the number of patients reported was limited (from a dozen to over a hundred); so, this phenomenon (CSFP) remains poorly understood. Our study, compared with those published reports, had relatively adequate sample size and explored the risk factor of prognosis for the first time in forever. The observed overall major adverse cardiovascular events (MACE) occurred in 39 (9.3%) out of 421 patients. The risk of MACE by multivariate analysis was significantly independently associated with age > 50 years (HR = 2.2, 95% CI: 1.0 to 4.9, and \( P = 0.042 \)), hypertension (HR = 2.1, 95%
involved in CSFP are not fully interpreted and are the di-
lipidemia, is associated with adverse outcome. This phe-
mineralization, and functional abnormalities in the coronary microcircu-
play an important role, resulting in transient or persistent myocardial hypoperfusion. To date, treatment is
not well defined and is mainly directed at influencing
functional obstruction in arterioles (<200 μm) with dipyridamole or mibefradil [16, 17], controlling abnormal
cholesterol and vascular inflammation with statins [18, 19],
and improving endothelial function as well as alleviating symptoms [20, 21]. In addition, hypertension and dysli-
pidemia need better control in patients with CSFP, on the
basis of our finding.

Our study has several limitations. This is a single cohort study (lack of control group) that required data collection
over 9 years, during which few patients returned for follow-
up, and a large proportion was contacted by telephone. As a
result of the retrospective design of this study, the hypothesis that CSFP may result in myocardial hypoperfusion was not
tested, which could have been achieved by cardiac magnetic
resonance imaging or radionuclide myocardial perfusion. Although we have attempted, to the best of our ability, to
reduce the deficiency, these limitations are innate to the
retrospective design of the study. Future work is encouraged
to initiate further large-scale prospective studies that reveal
the pathogenesis involved in CSFP, better characterize this
phenomenon, and most importantly, investigate therapeutic
approaches and long-term prognosis.

To sum up, the coronary slow flow phenomenon (CSFP)
characterized by delayed distal vessel opacification without
epicardial coronary stenosis, as assessed quantitatively using
the corrected TIMI frame count (CTFSC), should be more
concerned. This study describes the clinical, electrocardio-
graphic, and echocardiographic features as well as coronary
angiographic presentation of patients with CSFP. Although these features of CSFP are nonspecific, our study reveals that
the presence of age above 50 years, hypertension, and dys-
lipidemia, is associated with adverse outcome. The patho-
genesis, therapeutic approach, and long-term prognosis
involved in CSFP are not fully interpreted and are the di-
rections of much ongoing research.

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request.

**Disclosure**

The funding agencies had no influence on the analysis and interpretation of data, in the writing of the report, or in the
decision to submit the paper for publication.

**Conflicts of Interest**

The authors have no conflicts of interest to disclose.

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