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Prevalence and Predictors of Coronary slow Flow in Patients with Angina and Normal Epicardial coronaries on Invasive Angiography amongst Asian Indians: *Papyrus Study*

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Abstract

Background: The Coronary Slow Flow Phenomenon (CSFP) is sometimes seen amongst patients presenting with ACS, in particular unstable angina and rarely with Normal Epicardial Coronaries (NECA). The study attempts to identify predictors of CSFP in patients with classical angina and normal epicardial coronaries in Asian Indians. *Materials and Methods:* This was a prospective, open label, observational study of 3000 consecutive patients undergoing invasive coronary angiography that was carried out a tertiary level cardiac care center between August 2016 to December 2018. After identifying the prevalence of CSFP using the corrected TFC method in all-comers, equal numbers of controls were analyzed for detailed evaluation for traditional risk factors, history, clinical examination, and laboratory investigation. *Results:* CSFP was more prevalent in men than in women (P=0.007). Histories of smoking and hypertension were more prevalent in CSFP patients than in NECA patients statistically significant (50% *vs* 20%; p 0.02) and (66.7% *vs* 33.3%, P 0.009) with Odds Ratio (OR) of 4(95% CI 1.27 to 12.58; P 0.02) for smoking and 4(95% CI 1.37 to 11.7; P0.01) for hypertension. Presence of LV dysfunction (16.7% versus 10%, P 0.45) with OR 0.56(95% CI 0.12 to 2.57; P 0.45), high level of hemoglobin in CSFP group (14.17±1.45 *vs* 11.95±1.38 mg/dl; p <0.0001), high level of LDL-c (153.77±13.02 *vs* 92.37±11.45 mg/dl; p <0.0001) and low HDL-C (33.93±6.71 *vs* 55.60±5.78mg/dl; p <0.0001) were also independent predictors of CSFP. Amongst single vessel CSFP, LAD was most common vessel (40.4%). *Conclusion:* Prevalence of CSFP amongst Asian Indians is 1%. High LDL-c, Low HDL-c level, Smoking, elevated hemoglobin and Hypertension are independent predictors of CSFP.

Keywords: Coronary Artery Disease; Coronary Slow Flow Phenomenon; Risk factors.

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Introduction

Slow Coronary Flow (CSFP) is an angiographic finding characterized by slow progression of contrast in the coronary arteries in the absence of coronary artery obstruction. The Coronary Slow-flow Phenomenon (CSFP) is observed in 1-7% of

all coronary angiographic studies performed for the evaluation of patients with stable angina and is associated with morbidity and even mortality on some occasions with lower prevalence amongst patients with normal epicardial coronaries without any obstruction.[1] Slow opacification of distal parts of normal epicardial coronary arteries in the absence of ventricular dysfunction, connective tissue disorder, valvular heart diseases and coronary spasm or ectasia characterize this phenomenon.[2] Although there has been a great interest in identifying the underlying mechanisms of CSFP, the etiology and pathogenesis still remain uncertain. Endothelial dysfunction, microvascular abnormalities, occult atherosclerosis and inflammatory processes are among the proposed factors that contribute to the pathogenesis of CSFP.[2]

Slow coronary flow can be quite subjective to make matters even more difficult. For the purpose of many clinical trials and the papers investigating potential mechanisms, a more specific, standardized definition was developed.[3] CSFP was defined by more than one expert angiographer as the presence of angiographically normal or near normal coronary arteries (i.e., <40% stenosis in any of the epicardial coronary arteries) and Thrombolysis In Myocardial Infarction (TIMI)-2 f low (i.e., requiring ≥3 beats to opacify prespecified branch points in the distal vasculature of at least one of the three major epicardial coronary vessels).[4] In an attempt to estimate prevalence of CSFP amongst Asian Indians with normal coronaries and also to identify it's noninvasive predictors, we conducted this study at our center.

Materials and Methods

This was a prospective, open label; observational study carried out at a tertiary level cardiac care center situated western India during a period of August 2016 to December 2019. The study was approved by the institutional ethics committee.

3000 consecutive patients with classical angina with normal or nonobstructive epicardial coronaries were included in the study. 30 patients out of these 3000 patients who had CSFP were then compared for traditional risk profile, clinical history and laboratory parameters with 30 patients with normal coronaries without CSFP. We excluded patients with significant coronary artery stenosis, coronary vasospasm, coronary ectasia, uncontrolled hypertension and severe LVH, Atrial fibrillation and cardiac rhythm other than sinus, angiography and stenting of acute myocardial infarction, heart failure and cardiomyopathy, valvular heart disease, connective tissue disease, tachycardia, anemia, thyrotoxicosis or malignancy. Patients with renal, hepatic dysfunction, acute and chronic infection and patients with current use of anti-inflammatory drugs were also excluded. Each patient gave written informed consent.

Patients underwent detailed evaluation including history, clinical examination, and laboratory investigation. Detailed history regarding risk factors of coronary slow flow was taken in all patients. All patients underwent basic and relevant biochemical investigations. The angiograms were assessed, and coronary flow quantification was performed using the corrected TFC method described by Gibson et al.[5]

Slow coronary flow estimated by using formula asframe counts in the LAD/1.7. Based on Gibson's study, a frame count > 27 was considered indicative of CSFP.

Statistical Methods

All statistical analysis was performed using SPSS *vs* 20.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess normal distributions. Categorical variables were expressed as numbers and percentages; quantitative variables were expressed as means and standard deviations (SDs). Categorical data were compared using the *chi*-square test and Student's t-test; quantitative variables were compared using an analysis of variance (ANOVA). A binary logistic regression analysis was performed for the multivariate analysis. P values < 0.05 were considered significant.

Results

Among the 3000 patients scheduled for selective coronary angiography 30(1%) met the criteria for CSFP. Of these, 24(80%) patients were male and 6(20%) females. The age of the CSFP subjects was 49.47±9.12 years. In 5 (16%) subjects, the indication for coronary angiography was the presence of angina or dyspnea with a high-risk categorization on noninvasive test. Otherwise, 25 (83%) patients underwent coronary angiography following an episode of acute classical angina.

The CSFP was more prevalent in men than in women (P 0.007). Histories of smoking and hypertension were more prevalent in CSFP patients than in NECA patients and this difference was statistically significant (50% *vs* 20%; p 0.02) and

(66.7% *vs* 33.3%, P 0.009) with Odds Ratio (OR) of 4(95% CI 1.27 to 12.58; P 0.02) for smoking and 4(95% CI 1.37 to 11.7; P 0.01) for hypertension as shown in Table 1. The left Ventricular Ejection Fraction (LVEF) was significantly lower in the CSFP group than in the NECA group (38.67±2.92 *vs* 50.0±4.15; P <0.001). There was no statistically significant difference seen in diastolic dysfunction between two groups (16.7% *vs* 10%, P 0.45).

The two study groups did not significantly differ in most laboratory parameters, except for hemoglobin, low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c). As shown in Table 2, the levels of Hb (14.17±1.45 *vs* 11.95±1.38 mg/dl; p <0.0001) and LDL-c (153.77±13.02 *vs* 92.37±11.45 mg/dl; p <0.0001) were higher in the CSFP group relative to the NECA group, and the HDL-c level (33.93±6.71 *vs* 55.60±5.78mg/dl; p <0.0001) was significantly lower in the CSFP group. To assess the adjusted association between the CSFP phenomenon and the study variables mentioned in Tables 1 and 2 a

Table 1: Comparison of clinical data between CSFPand NECA subjects.

Variables	CSFP (N = 30)	NECA (N = 30)	P Value
Age, years	49.47± 9.12	48.63±7.68	0.72
Gender			
Male	24(80)	14(46.7)	0.007
Female	6(20)	16(53.3)	
Dyspnoea	5(16.7)	3(10)	0.46
Chest pain	27(90)	14(46.7)	<0.0001
Fatigue	18(60)	7(23.3)	0.003
Syncope	2(6.7)	6(20)	0.13
HR	87.93±12.87	85.73±10.46	0.47
BMI kg/m2	21.74±2.79	24.15±1.87	<0.0001
BP	127.87±11.97	121.73±7.53	0.02
Hypertension	20(66.7)	10(33.3)	0.009
Diabetes mellitus	5(16.7)	5(16.7)	1.00
Smoking	15(50)	6(20)	0.02
Dyslipidemia	10(33.3)	6(20)	0.38
Family history	3(10)	4(13.3)	1.00

CSFP– Coronary slow flow phenomenon; NECA– Normal epicardial coronary arteries; HR– Heart rate; BMI– Body mass index; BP– Blood pressure

Table 2: Comparison of laboratory findings in CSFP andNECA Subjects.

Variables	CSFP (N = 30)	NECA (N = 30)	P value
Blood Glucose mg/dL Range	101.77±23.70 (78-178)	101.43±1.83 (78-130)	0.947
TG,mg/dL Range	141.63±9.54 (110-160)	140.30±11.79 (125-159)	0.632
TC,mg/dL Range	192.24±36.33 (133-222)	188.53±14.44 (154-210)	0.606
LDL-C,mg/dL Range	153.77±13.02 (120-180)	92.37±11.45 (59-120)	<0.0001
HDL-C,mg/dL Range	33.93±6.71 (40-45)	55.60±5.78 (42-68)	<0.0001
Hb, mg/dL Range	14.17±1.45 (10.70-16.20)	11.95±1.38 (10.40-18.0)	<0.0001
WBC, count/µL Range	9958.33±9614.73 (4580-59970)	10488.67±17220.31 (5220-101300)	0.883
Platelet count/ µL Range	282606.37±81431.5 (167000-476000)	286466.67±66558.1 (170000-470000)	0.841
Creatinine mg/dL Range	0.91±0.21 (0.58-1.38)	1.0±0.18 (0.7-1.3)	0.079

TG–Triglycerides; TC–Total cholesterol; LDL-C–Low density lipoprotein cholesterol; HDL-C–High density lipoprotein cholesterol; Hb–Hemoglobin; WBC–White blood cell

Table 3: Multivariable regression of independent predictors of the CSFP Phenomenon.

Variables	Beta	P Value	95% CI
BMI	0.001	0.86	-0.015 to 0.018
Hypertension	0.30	0.01	0.064 to 0.544
Smoking	0.29	0.02	0.045 to 0.548
HDL-c	-0.015	<0.0001	-0.019 to 0.010
LDL-c	0.009	<0.0001	0.007 to 0.011
Hemoglobin	0.014	0.299	-0.013 to 0.041

BMI– Body mass index; HDL-C– High density lipoprotein cholesterol; LDL-C– Low density lipoprotein cholesterol.

multivariable regression model with a backward elimination method was applied; The squared multiple correlation coefficient (R^2) was 0.96. This model revealed a low HDL-c –0.015(95% CI –0.019 to 0.01; P <0.0001) level is negatively associated with CSFP and presence of hypertension 0.30 (95% CI 0.064 to 0.544; P 0.01), smoking 0.29 (95% CI 0.045 to 0.548; P 0.02) and high LDL-c 0.009 (95% CI 0.007 to 0.011; P <0.0001) is positively associated independent predictors of the CSFP phenomenon, showed in Table 3. Single vessel involvement was more common in CSFP 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.

Discussion

There are a limited number of studies focused on CSFP. Therefore, the underlying pathophysiological mechanisms and the clinical importance of CSFP are not known clearly.[6] In this study, we investigated characteristics of CSFP subjects. 1% of the patients scheduled for coronary angiography in this study were found to exhibit the CSFP phenomenon. The prevalence of the CSFPphenomenon varies among studies.[7-9] Hawkins et al. used a TFC-based definition of CSFP and reported a prevalence of 5.5% among patients referred for coronary angiography.[7] In other studies, the prevalence of the CSFP phenomenon was 1% among patients referred for coronary angiography, based on the TFC definition.[10,11] However, Diver et al. found that approximately 5% of patients presenting with acute coronary syndrome in the TIMI-IIIA trial exhibited evidence of CSFP without obstructive Coronary Artery Disease (CAD), and a prevalence of 24%–34% was previously reported in a NECA population.[12]

In our study, approximately 1% of the patients with evidence of CSFP were scheduled for coronary angiography because of acute angina. It has been suggested that differences in atherosclerotic burdens among general populations might explain these discrepancies. The CSFP 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.[2] 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.[7] In our study, LAD was most frequently involved, with a rate exceeding 90% of overall population which was similar to the study by Sanati el al. The reason for this difference is unclear, although it might be related to racial differences or technical errors in CSFP quantification.[13]

Several studies have attempted to define the demographic and clinical characteristics and independent predictors of patients with the CSFP phenomenon. Fineschi et al. investigated 8 patients with the CSFP phenomenon and found no difference between subjects with CSFP and NECA in terms of atherosclerosis risk factors.[14] Although the Fineschi et al. study involved a small sample size, Hawkins et al. compared 92 patients with CSFP and 62 subjects with normal coronary arteries and found no correlation between traditional atherosclerosis risk factors and CSFP.[7,14] 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 CSFP in normal coronaries and NECA subjects.

A comparison of the CSFP and NECA groups showed that the groups did not differ in terms of traditional risk factors, except for LDL-c, HDL-c, Hypertension and smoking. Several studies have suggested independent predictors of the CSFP phenomenon. In a study by Arbel et al. smoking was found to be the strongest predictor of the CSFP phenomenon.[15] Hawkins et al. suggested male sex, a higher BMI, and a low HDL-c level as independent predictors of the CSFP phenomenon following a multivariable analysis, and demonstrated that male sex was the strongest independent predictor of this phenomenon.[7] Other studies have also suggested

BMI and male sex as predictors of the CSFP phenomenon.[16,17] This result is similar to our study.

Our study also showed that a male gender, low HDL-c, high LDL-c level and high hemoglobin level are independent predictors of the CSFP phenomenon. We also found no association between white blood cell or platelet counts with CSFP. Akpinar et al. had investigated the relationship between whole blood cell counts inCSFP and suggested the platelet count and red cell distribution width as independent predictors of this phenomenon.[18]

Conclusion

Prevalence of CSFP amongst Asian Indians is 1%. High LDL-c, Low HDL-c level, smoking, elevated hemoglobin, LV systolic dysfunction and Hypertension were independent predictors of CSFP amongst Asian Indians.

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Conflicting Interest: None declared

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