



Original Article

Clinical, demographic, risk factor and angiographic profile of coronary slow flow phenomenon: A single centre experience



Sanjeev Sanghvi, Rohit Mathur, Anil Baroopal*, Aditya Kumar

Department of Cardiology, DR. S.N. Medical College, Jodhpur, India

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ABSTRACT

Background: The coronary slow flow phenomenon (CSFP) is an angiographic finding characterized by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis. Although it is well-known to interventional cardiologists for approximately four decades, the etiopathogenesis still remains unclear.

Aims and objectives: In this study, we aimed to determine the clinical, demographic, risk factor and angiographic profile of patients with CSFP.

Methods: Clinical, demographic, risk factor and angiographic profile were recorded in all consecutive patients who had undergone coronary angiography between September 2016 and March 2017 and showed features of CSFP and a control group who showed normal coronary flow (NCF). The CSFP was diagnosed on the basis of the corrected thrombolysis in myocardial infarction frame count.

Results: CSFP was significantly more prevalent in male patients. Among the traditional risk factors, there was significantly more prevalence of hypertension (31.25% versus 6.67%, $p < 0.001$), dyslipidemia (40% versus 7.5%, $p < 0.001$) and history of tobacco use (47.5% versus 10.0%, $p < 0.001$) in CSFP patients as compared to NCF patients. On multivariable regression analysis hypertension, dyslipidemia, history of smoking and tobacco chewing were found to have independent association with CSFP. Acute coronary syndrome (ACS) was the most common mode of presentation in CSFP patients.

Conclusion: CSFP was relatively common among patients who presented with ACS. Hypertension, dyslipidemia, smoking and tobacco chewing can be considered independent risk factors for this phenomenon. Therefore, CSFP should be considered as a pathological entity and not an entirely benign condition.

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1. Introduction

The coronary slow flow phenomenon (CSFP) is an angiographic finding characterized by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis or myocardial bridge. The CSFP was first described by Tambe et al¹ in 1972. Although it is well-known to interventional cardiologists for approximately four decades, the pathogenic mechanisms are incompletely understood. The overall prevalence of CSFP has been reported as 1% among patients undergoing coronary angiography, especially in patients presenting with acute coronary syndrome (ACS).² In the TIMI-III study, the prevalence of CSFP was approximately 4% among patients who presented with unstable angina and had no or insignificant epicardial coronary artery disease (CAD).³ Whereas Hawkins et al⁴ reported overall

prevalence of 5.5% among patients undergoing coronary angiography. Over 80% of these patients experience recurrent chest pain and one third of them require readmission for an acute exacerbation.^{2,5} Amasyali et al⁶ reported a case of aborted sudden death due to malignant ventricular fibrillation who had coronary slow flow in all coronary arteries. This study was undertaken to assess the clinical risk factors for CSFP. To the best of our knowledge, only two studies have been done in Indian population till date.^{7,8}

2. Methods

The present cross sectional observational study was done between September 2016 and March 2017 in the department of cardiology, Dr. S.N. Medical College, Jodhpur, India, which included study group comprising 80 consecutive patients who had undergone coronary angiography and showed features of CSFP and control group comprising 120 consecutive patients who had undergone coronary angiography and showed normal coronary flow (NCF).

* Corresponding author at: MDM Hospital, Room No. 102, PG Hostel, Jodhpur, Rajasthan, India.

E-mail address: anisabarupal@yahoo.com (A. Baroopal).

2.1. Inclusion criteria

Between September 2016 and March 2017 all consecutive patients of age >18 years, who presented with ACS, stable angina, atypical chest pain or dyspnea on exertion whose coronary angiogram showed normal coronaries with CSFP (n = 80) and NCF (n = 120) were included in study.

2.2. Exclusion criteria

- 1 Valvular heart disease and mitral valve prolapse
- 2 Cardiomyopathy (dilated, hypertrophic and restrictive)
- 3 Connective tissue diseases
- 4 Patients with severe anemia, leucopenia, bleeding diathesis
- 5 Patients with liver disease
- 6 Patients with deranged renal function
- 7 Patients with acute decompensated heart failure

2.3. Corrected TIMI frame count

Corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) is a quantitative and reproducible index of coronary artery flow. It represents the number of cine frames required for contrast to reach the standardized distal coronary artery landmarks. We measured the number of cine frames required for contrast to reach standard distal coronary landmarks in the left anterior descending (LAD) artery, left circumflex (LCX) artery and right coronary artery (RCA) using the cine viewer frame counter. The first frame is defined as the frame in which dye fully enters the artery, it extends across entire width and touches both borders of origin of artery with antegrade flow. Last frame was defined as the one in which dye enters but not necessarily completely opacifies the distal landmark branch. The distal landmark branch used for analysis was pitchfork, mustache, or whale's tail at the apex of heart for LAD artery. The distal landmark branch used for analysis of LCX artery was distal bifurcation of the major obtuse marginal or main LCX artery whichever was longer. In the left and balanced dominant systems, the target branch used for LCX artery was no further distal than the obtuse marginal branch that lies at the border of the inferior and lateral walls, usually the third or fourth obtuse marginal. The distal landmark branch used for analysis of RCA was the first branch arising from the posterior lateral extension of the RCA after the origin of the posterior descending artery regardless of the size of this branch.⁹

The TIMI frame count of the LAD and LCX arteries were assessed in either the right or left anterior oblique views with caudal angulation, and the RCA was assessed in the left anterior oblique projection with cranial angulation. The normal frame counts for LAD artery (36.2 ± 2.6 frames) are 1.7 times greater than that for LCX artery (22.2 ± 4.1 frames) and RCA (20.4 ± 3.0 frames). So the longer LAD artery frame counts were divided by 1.7 to derive the CTFC of 21.1 ± 1.5 frames.⁹ This ratio is consistent with the mean ratio of 1.55 predicted by use of three dimensional vector algebra devised by Dodge et al¹⁰ to calculate the distance to the TIMI landmarks in the normal human heart. In the present study CSFP was defined as CTFC greater than 24 frames for LAD, 26 for RCA and 30 for LCX.⁹ In patients with multiple vessel involvement; CSFP was diagnosed if CTFC was more than cutoff in one or more vessels.

Intra-observer and inter-observer variability were examined in 20 randomly selected subjects. Intra-observer variability was assessed by the same observer, repeating the measurement in these subjects after 2 weeks and blinding for initial measurements. A second independent observer repeated the measurements for inter-observer variability. Coefficient of variation for intra-observer and inter-observer variability was found to be 2.79% and 2.91%, respectively.

2.4. Data analysis

Categorical data were expressed as number and percentage. Quantitative data were expressed as mean and standard deviation. Categorical data were analyzed using Chi square test/ Fischer exact test as appropriate and difference in mean was analyzed using unpaired *t*-test or Mann Whitney *U* test (depending on normality). Multivariable logistic regression analysis was performed using enter method to include factors with $p < 0.10$ on univariable analysis. Statistical significance was considered at the p value < 0.05 . The statistical analysis was performed using SPSS trial version 20.

3. Results

A total of 2424 coronary angiograms were performed during the study period from September 2016 to March 2017 at our institution. The CSFP was detected in 80 patients thus giving a prevalence of 3.3% of all coronary angiograms. Table 1 presents demographic profile, risk factors, co-morbid conditions and mode of clinical presentation of both groups. The study population (CSFP group) consisted of 50 (62.5%) male and 30 (37.5%) female; the

Table 1
Demographic profile, risk factors, co-morbid conditions and mode of clinical presentation.

Variable	CSFP group (n = 80)	NCF group (n = 120)	p value
Mean age (years)	51.36 \pm 10.24	51.66 \pm 11.05	0.831
Sex			
Male	50 (62.5%)	52 (43.3%)	0.012
Female	30 (37.5%)	68 (56.7%)	
Hypertension	25 (31.25%)	8 (6.67%)	<0.001
Diabetes mellitus	20 (25%)	18 (15%)	0.114
Dyslipidemia	32 (40%)	9 (7.5%)	<0.001
Family history of coronary artery disease	10 (12.5%)	12 (10.0%)	0.747
Tobacco use	38 (47.5%)	12 (10.0%)	<0.001
(A) Smoking	20 (25%)	7 (5.83%)	<0.001
(B) Tobacco chewing	18 (22.5%)	5 (4.17%)	<0.001
Acute coronary syndrome	34 (42.5%)	30 (25%)	0.015
Myocardial infarction	7 (8.75%)	8 (6.67%)	0.784
Unstable angina	27 (33.75%)	22 (18.33%)	0.021
Stable angina	18 (22.5%)	42 (35%)	0.083
Atypical chest pain	20 (25%)	33 (27.5%)	0.819
Dyspnea on exertion	8 (10%)	15 (12.5%)	0.715

Table 2
Multivariable logistic regression analysis.

Variable	B	S.E.	p value	Exp (B)/ odds ratio	95% CI for EXP (B)	
					Lower	Upper
Hypertension	1.778	0.490	<0.001	5.919	2.265	15.471
Dyslipidemia	1.565	0.461	0.001	4.781	1.935	11.811
Smoking	1.719	0.540	0.001	5.577	1.935	16.075
Tobacco chewing	1.828	0.588	0.002	6.219	1.966	19.676
Male sex	0.375	0.373	0.315	1.455	0.700	3.023
Constant	-1.673	0.291	<0.001	0.188		

Nagelkerke R square = 0.399.

Model over all chi square = 69.948 at df = 5; p value < 0.001.

mean age of participants was 51.36 ± 10.24 years. The mean age did not differ between the CSFP and NCF group, however CSFP was significantly more prevalent in males than females ($p = 0.012$). Among the traditional risk factors, there were significantly more prevalence of hypertension (31.25% versus 6.67%, $p < 0.001$), dyslipidemia (40% versus 7.5%, $p < 0.001$) and history of tobacco use (47.5% versus 10.0%, $p < 0.001$) in CSFP patients as compared to NCF patients. Diabetes mellitus (25% versus 15%, $p = 0.114$) and positive family history of CAD (12.5% versus 10.0%, $p = 0.747$) were more prevalent in CSFP group compared to NCF group; however, this difference was not statistically significant. Acute coronary syndrome was most common mode of presentation in CSFP patients and was also statistically more prevalent than NCF patients (42.5% versus 25%, $p = 0.015$). Among ACS patients, unstable angina presentation (33.75% versus 18.33%, $p = 0.021$) was significantly more common in CSFP group compared to NCF group. Stable angina, atypical chest pain and dyspnea on exertion were more common mode of clinical presentation of NCF patients compared to CSFP patients. However, the difference was not statistically significant.

On multivariable logistic regression analysis hypertension, dyslipidemia, smoking and tobacco chewing were found to have independent association with CSFP and hypertension was the strongest predictor as shown in Table 2.

Out of the 80 cases, 23 had slow flow in all 3 vessels (28.75%), 42 had slow flow in 2 vessels (52.5%) and 15 had slow flow in 1 vessel (18.75%). The CSFP was found in LAD artery in 66 (82.5%) patients, in LCX artery in 54 (67.5%) patients and in RCA in 48 (60%) patients. The CTFC for LAD artery was significantly more in CSFP group compared to NCF group (43.2 ± 18.4 versus 23.2 ± 4.2 , $p < 0.001$). Similarly, CTFC for LCX artery (51.7 ± 12.5 versus 25.4 ± 6.1 , $p < 0.001$) and for RCA (48.4 ± 10.2 versus 24.8 ± 7.3 , $p < 0.001$) were significantly more in CSFP group compared to NCF group as shown in Table 3.

4. Discussion

The exact pathophysiological mechanism of CSFP is not clear. Endothelial injury caused by elevated homocysteine level, decreased nitric oxide levels with elevated levels of nitric oxide synthetase inhibitor and asymmetric dimethyl arginine are considered as pathophysiological mechanisms of CSFP.^{11–13} There is a genetic variation in different ethnic groups regarding predisposition to CSFP. Gupta et al¹⁴ had shown strong association

between Glu298Asp gene polymorphism of nitric oxide synthase and CSFP in the North Indian population, but no such association could be seen in the Turkish population. The name cardiac syndrome Y has been suggested for CSFP due to the possible role of Neuropeptide Y in the pathophysiology of the CSFP.^{15,16} Mosseri et al¹⁷ histopathologically demonstrated marked hypertrophy of myofibres, severe fibromuscular hyperplasia and thickening of media of small coronary arteries in patients with angina pectoris with CSFP. Electron microscopy showed endothelial degeneration, lipofuscin deposits and degenerative foci in myofibres. Some underlying etiologies such as abnormally high microvascular resistance and widespread atherosclerosis of coronary arteries have been proposed. Among these, small vessel dysfunction is one of the most typical of the pathogenesis of CSFP.

Left ventricular dysfunction due to significant alterations in the LV myocardial deformation parameters assessed by speckle tracking echocardiography (STE) was demonstrated by Gulel et al¹⁸ in the patients of CSFP. In particular circumferential deformation parameters (averaged peak systolic strain, systolic strain rate (SR), and early diastolic SR) were significantly lower in patients of CSFP compared to patients of NCF. Wang et al¹⁹ measured left atrial (LA) and right atrial (RA) global longitudinal strain and strain rate during systole (Ss, SRs), during early diastole (Se, SRe), and during late diastole (Sa, SRa) for evaluation of LA and RA function in patients of CSFP using two-dimensional STE. They demonstrated decreased LA (decreased LA Se and SRe) and RA conduit function (decreased RA Se and SRe) and increased LA contractile function (increased LA Sa and SRa) in patients of CSFP. Intravascular ultrasound imaging studies have shown diffuse intimal thickening, widespread atheroma and calcification along the vessel wall without luminal irregularities, and abnormalities in the fractional flow reserve thereby indicating subclinical diffuse atherosclerosis in the patients with CSFP.²⁰ The CSFP may have various clinical modes of presentations including life threatening situations such as ST-segment elevation myocardial infarction, ventricular arrhythmias and sudden cardiac death.^{21–25}

Hawkins et al⁴ suggested male sex and a higher body mass index (BMI) as independent predictors of the CSFP following a multivariable analysis, and demonstrated that male sex was the strongest independent predictor of this phenomenon. In a study performed by Arbel et al²⁶ smoking was found to be the strongest predictor of the CSFP, while a study done in Australian population, male sex and smoking were found to be independent risk factors for CSFP.² CSFP was significantly more common in male patients in

Table 3
Corrected TIMI frame counts.

Vessel	CSFP group (n = 80)	NCF group (n = 120)	p value
Left anterior descending artery	43.2 ± 18.4	23.2 ± 4.2	<0.001
Left circumflex artery	51.7 ± 12.5	25.4 ± 6.1	<0.001
Right coronary artery	48.4 ± 10.2	24.8 ± 7.3	<0.001

the present study although on multivariable regression analysis no independent association of male sex with CSFP was found. In a study performed by Mukhopadhyay et al⁷ in North Indian population, higher BMI, higher fibrinogen levels and smoking were significantly associated with CSFP but on multivariable regression analysis only BMI was found to have independent association with CSFP. In the present study hypertension, dyslipidemia, smoking and tobacco chewing were independently associated with CSFP patients and hypertension was found the strongest predictor. However in a study done by Goel et al¹⁸ none of the risk factors such as hypertension, diabetes mellitus and smoking were associated with CSFP. Hypertension, diabetes mellitus and opioid abuse were found to be independent risk factors for CSFP in a study done on Iranian population.²⁷ Left anterior descending artery (82.5%) was most commonly involved vessel followed by LCX artery (67.5%) and RCA (60%) in our study which is similar to that reported in other studies.^{7,19} ACS (42.5%) was most common mode of clinical presentation in the present study. Our findings also correlate with a previous study by Beltrame et al² in which LAD artery was most commonly involved vessel in 86% of cases and ACS was most common mode of clinical presentation in 75% cases.

Treatment modalities for CSFP are not well established. Dipyridamole, which has a vasodilator effect on the coronary microvasculature, abolishes functional obstruction in coronary arteries with diameters less than 200 μm and is used in treating CSFP.²⁸ Beltrame et al²⁹ assessed the acute and long-term clinical benefits of mibefradil, a long-acting calcium T-channel antagonist in patients with CSFP by exploring its beneficial effects on microvessels. The CSFP was abolished in approximately three fourth of the vessels at 30 min after 50 mg mibefradil injection. Due to reported lethal drug-drug interactions with many drugs, mibefradil is not currently in use. Statins such as simvastatin and atorvastatin have been shown to be beneficial in CSFP, possibly from the anti-inflammatory effects.^{30–32} Nitric oxide potentiating beta blocker nebivolol in a dose of 5 mg per day for 12 weeks was shown to be effective in improving endothelial function in patients with CSFP. Relief in chest pain was reported in 90% of patients along with decrease in C reactive protein and significant improvement in coronary flow.³³ Nicorandil, an anti-anginal drug that mediates its vasodilator effects by increasing the cGMP, in a dose of 5 mg three times daily has been reported to decrease chest pain episodes and improve LV function in CSFP patients, possibly via an increase in NO release and decrease in endothelin-1 levels.³⁴ A comparison of the effect of nicorandil and isosorbide dinitrate on the TIMI frame count in patients affected with the CSFP showed that intracoronary injection of nicorandil was superior to isosorbide dinitrate, leading to a more significant reduction in the TIMI frame count.³⁵ Ozdogru et al³⁶ demonstrated that intracoronary calcium channel blocker diltiazem in a dose of 5 mg and intracoronary nitroglycerin in a dose of 250 μg improve CSFP, and intracoronary diltiazem is superior to nitroglycerin in reducing TIMI frame count in CSFP. Trimetazidine, an anti-anginal drug that inhibits fatty acid beta oxidation, lead to decrease in anginal symptoms in patients of CSFP.³⁷

4.1. Limitations of the study

This was an observational single centre study with a small sample size and the response to pharmacological therapy was not assessed.

5. Conclusion

The CSFP is relatively common among patients who present with ACS. Hypertension, dyslipidemia, smoking and tobacco

chewing can be considered independent risk factors for this phenomenon. Therefore, CSFP should be considered as a pathological entity and not an entirely benign condition.

Conflict of interest

The authors declare that there is no conflict of interest.

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