Original Research

Prevalence, Risk Factors Profile And Treatment Outcomes Of Coronary Slow Flow Phenomenon In Angiographically Normal Coronary Arteries

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ABSTRACT

Background: Coronary slow flow (CSF) is an angiographic diagnostic finding characterized by delayed opacification of epicardial coronary arteries by slow progression of contrast agents in the coronary tree in the absence of coronary artery obstruction.The prevalence & risk factor profile is not well documented in CSF ,hence we intend to study prevalence, risk factors profile and treatment outcomes of CSF phenomenon in angiographically normal coronary arteries.

Materials and Methods: Allpatients who underwent coronary angiography between January 2018 and October 2018 in our center were evaluated for inclusion in this study. Consecutive patients with coronary slow flow phenomenon and similar no of consecutive controls with normal coronary flow were evaluated. Demographic variables, information on the traditional CAD risk factors and hematologic parameters were obtained before angiography. All patients with slow flow phenomenon got their treadmill exercise testing done before discharge and at follow up after 1 month with
emphasis on exercise time, ST segment changes and duke treadmill score (DTS).

Results: During study period, out of 5192 coronary angiograms performed in our institution, 511 patients with normal epicardial coronaries and 56 patients with coronary slow flow phenomenon as per our study protocol (i.e. 1.1% of all coronary angiograms and 10.96 % of normal coronary angiograms). CSF was more common in the males 44 (78.6 %) than female 12 (21.4%).Among patients with CSF most common presentation was CSA (39.3%) followed by USA(33.9 %), NSTEMI (19.6 %), STEMI (3.6%) and atypical chest pain (3.6%) . Depression, oral tobacco and smoking were significantly more common in case group than control group amongst clinical characteristics. Coronary slow flow was seen in all three vessels in 30(53.6 %) patients, LAD in 21 (37.5%) patients, RCA in (7.1%) and LCX in (1.8 %), patients out of 56 patients. In patients on Nicorandiland Diltiazem there was significant changes observed on exercise time and duke treadmill score, while there were no significant changes observed in pts on nitrates or statins.

Conclusion: Prevalence of CSF phenomenon was 1.1 % of all coronary angiograms and 10.96% of normal coronary angiograms. Gender, Depression, oral tobacco chewing and smoking had a significant and independent positive association with CSF phenomenon. In our study there was a significant improvement in functional status of patients nicorandil and Diltiazem which was not observed in pts on nitrates or statins.

Keywords: Coronary slow flow,TIMI frame count.

INTRODUCTION

Coronary slow flow (CSF) is an angiographic diagnostic finding characterized by delayed opacification of epicardial coronary arteries by slow progression of contrast agents in the coronary tree in the absence of coronary artery obstruction .[1] Prevalence of CSF phenomenon varies from 1 to 5% among patients undergoing coronary angiography.[2]

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). TIMI frame count was first introduced by Gibson et al, and it represents as the number of cine frame required for the contrast agent used during coronary angiogram to reach a well-defined prespecified distal coronary artery landmark.[3] For left anterior descending coronary artery (LAD) TIMI frame count is further corrected by normalizing for LAD length. The absolute TIMI frame count for LAD divided by 1.7 is the corrected TIMI frame count

(CFTC). CSF phenomenon is defined angiographically as CFTC > 2 standard deviation from normal values (21±3).

CSF phenomenon was initially defined in 1972 by Tambe et al, in 6 cases with chest pain, of which 4 had typical angina and 2 had atypical angina since then only a few studies have investigated the etiology and predisposing factors.[4]The exact pathophysiology of CSF phenomenon remains incompletely understood. Though endothelial dysfunction lies central to the pathogenesis of CSF, studies done in different ethnic populations have found varied clinical risk factors to be independently associated with CSF phenomenon.[5]slow flow phenomenon has been suggested as an early phase of atherosclerosis involving both the small and epicardial coronary arteries.[6]There are various mechanisms that may be involved in the CSF process, including small vessel dysfunction, diffuse atherosclerosis, inflammation, endothelial dysfunction, and increased platelet aggregability.[7]Importantly, 'primary' CSF phenomenon should be differentiated from the delay in the contrast opacification of the coronaries in the context of coronary reperfusion therapy such as angioplasty for acute myocardial infarction, or other "secondary" factors leading to coronary slow flow. These factors are mainly coronary artery ectasia, coronary artery spasm, heart failure, embolism, valvular heart disease, or connective tissue disorders.[8] The presentation of this phenomenon is extremely diverse ranging from stable or unstable angina, non-ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), nonsustained ventricular tachycardia (NSVT), and vague chest discomfort.[9] Even sudden cardiac death have been reported to be associated with CSF phenomenon. There are very scarce studies till date on the Indian population to assess the clinical risk factors and treatment outcome associated with CSFand hence the present study was undertaken.

MATERIAL AND METHODS

This was a case control study. After receiving study approval from the research and ethics committee all patients who underwent coronary angiography between January 2018 and October 2018 in our center were evaluated for inclusion in this study with prior consent. Total consecutive patients with coronary slow flow phenomenon and similar no of consecutive controls with normal coronary flow were evaluated in the present study.Inclusion criteriawere patients> 18 years of age presenting with acute coronary syndrome (ACS) or effort angina and normal epicardial coronary arteries on angiography but with slow coronary blood flow.Exclusion criteria were the presence of coronary artery disease (including obstructive lesion, ectasia, plaque, myocardial bridge or spasm) on coronary angiography,Cardiomyopathy, Valvular heart disease, left ventricular systolic dysfunction (EF - 40%), Renal or Hepatic failure,anemia, neoplastic disordersand refusal to give informed consent. Following enrollment of a patient having coronary slow flow, the next consecutive patient with normal coronary angiography meeting all the inclusion and exclusion criteria were enrolled as control. CoronaryAngiography was performed using the standard Judkins technique from radial or femoral arterial route with 6 French diagnostic catheters with low osmolar contrast agents injected manually. Angiographic images were obtained in standard views using right and left, and cranial and caudal angulations. Angiograms of all included subjects were reviewed by two trained cardiologist and TIMI frame counts was determined for each coronary vessel, with cinemography at 15 frames per second. In brief, the first frame was considered to be that at which a column of dye extended across the entire width of the origin of artery touching both its border with antegrade filling. The final frames we determined was when dye opacification reached a certain distal landmark in each vessel. For the left anterior descending artery (LAD), the distal bifurcation was used ("whale's tail"). The most distal bifurcation of the obtuse marginal branch furthest from the coronary ostium was used as the distal landmark for the left circumflex artery (LCX). The first branch of the posterolateral segment was used for the right coronary artery (RCA). Frame counts in the LAD was divided by a factor of 1.7 to correct for its longer length. Any corrected frame count exceeding 27 was considered to be abnormal and indicative of slow flow based on the recommendations of Gibson et al. [3]Detailed history, physical examination and demographic profile was evaluated in all eligible subjects. Demographic variables pertaining to age, race, and sex was collected. Information on the following traditional CAD risk factors: hypertension, diabetes, dyslipidemia, depression, tobacco chewing, smoking and Body mass index (BMI) was collected.Hemoglobin, along with other hematologic parameters was measured, the neutrophil/ lymphocyte (N/L)ratio obtained by dividing the total count of neutrophils by the lymphocytes count. Blood urea, serum creatinine, serum uric acid, fasting blood sugar and serum lipids was measured before angiography. Medication used at the time of CAG was recorded with emphasis on cardio active drugs, antiplatelet agents, and anticoagulants. All patients with slow flow phenomenon got their treadmill exercise testing done before discharge and at follow up after 1 month with emphasis on exercise time, ST segment changes and duke treadmill score (DTS).

Statistical analysis-

Subjects with coronary slow flow phenomenon were compared with those having normal coronary flow.

Categorical variables wereanalyzed using chi-square or Fisher's exact test, as applicable. Continuous variables were analyzed using unpaired t-test or 1-way analysis of variance (ANOVA), as applicable. Logistic regression analysis was used to assess predictors of slow flow. Continuous variables are

expressed as means ± standard deviation. A 2-sided P<0.05 was considered statistically significant.

OBSERVATION AND RESULTS

During study period, out of 5192 coronary angiograms performed in our institution, we prospectively identified 511 patients with normal epicardial coronaries and 56 patients with coronary slow flow phenomenon as per our study protocol (i.e., 1.1% of all coronary angiograms and 10.96 % of normal coronary angiograms). A total of 112 subjects were recruited for analysis. These 112 subjects included 56 cases with normal coronaries with slow flow and 56 controls with normal coronaries with normal flow.CSFP was most prevalent in age group 36- 50 yr. (28 pts.) f/b 51- 65 yrs. (19 pts.) age group. NFCA was more prevalent in age group 51 – 65 yrs. (30 pts.) f/b 36 – 50 yrs. (21 pts). No significant difference was observed in the age intervals.CSFP was more common in the males 44 (78.6 %) than female 12 (21.4%), whereas in normal flow was more in female 34 (60.7%) than male 22 (39.3). Among patients with CSFPmost common presentation was CSA (39.3%) followed by USA (33.9 %), NSTEMI (19.6 %), STEMI (3.6%) and atypical chest pain (3.6%). Among control group most common presentation was CSA (55.4%), USA (21.4), atypical chest pain (17.9 %) and NSTEMI (5.4%). No patient among control group presented with STEMI. Patients having slow flow presented more commonly with acute coronary syndrome (57.1 %) than among control group (26.8%).

Tab 1. Baseline distribution of risk factor

Risk Factors Present	Cases N (%)	Controls N (%)	p-value
HTN	20 (35.7)	22(39.3)	0.696
DM	10(17.9)	13(23.2)	0.483
Depression	11(19.6)	3(5.4)	0.022
Dyslipidemia	12(21.4)	8(14.3)	0.975
Oral tobacco chewing	21(37.5)	10(17.9)	0.020
Smoker	16(28.6)	3(5.4)	0.045

Depression,oral tobacco and Smoking were significantly more common in case group than control group amongst clinical characteristics. No any statistically significant difference was observed among hypertension, diabetes mellitus& dyslipidemia. Therewas no any significant difference observed amongst various hematological and biochemical parameters like hemoglobin, total leucocyte count, Neutrophil/ lymphocyte ratio, blood urea, serum creatinine, serum uric acid, and various lipids parameters. (Table 2).

Tab 2. Hematological and biochemical variables

	Groups	N	Mean	Std. Deviation	p-value
AGE	Cases	56	50.27	10.54	0.054
	Controls	56	53.79	8.49	
BMI	Cases	56	27.66	1.88	0.339
	Controls	56	27.34	1.65	
HB	Cases	56	13.42	1.57	0.095
	Controls	56	12.90	1.21	
TLC	Cases	56	7900.40	2057.35	0.789
	Controls	56	8002.10	1955.74	
N/L RATIO	Cases	56	3.43	0.51	0.188
	Controls	56	3.54	0.33	
BLOOD UREA	Cases	56	28.89	8.39	0.818
	Controls	56	28.51	9.17	
S. CREATININE	Cases	56	0.96	0.21	0.178
	Controls	56	0.91	0.19	
S. URIC ACID	Cases	56	4.69	0.64	0.953
	Controls	56	4.69	0.65	
TOTAL CHOLESTEROL	Cases	56	186.86	44.31	0.056
	Controls	56	178.16	37.94	

HDL	Cases	56	39.38	5.72	0.381
	Controls	56	38.46	5.23	
LDL	Cases	56	123.34	40.15	0.080
	Controls	56	110.46	36.84	
VLDL	Cases	56	22.14	6.73	0.371
	Controls	56	21.09	5.63	
TG	Cases	56	117.88	44.68	0.521
	Controls	56	112.95	35.82	

Tab 3. Angiographic profile of slow flow

Slow flow	N=56
All vessels	30 (53.6 %)
LAD	21(37.5 %)
RCA	4(7.1%)
LCX	1(1.8%)

Coronary slow flow was seen in all three vessels in30(53.6 %) patients, LAD in 21 (37.5%) patients, RCA in (7.1%) and LCX in (1.8 %), patients out of 56 patients (Table 3).

Tab 4. Angiographic characteristics

	Groups	N	Mean	Std. Deviation	p-value
LAD CFTC	Cases	56	35.43	4.99	<0.001*
	Controls	56	16.46	1.84	
LCX CFTC	Cases	56	26.20	8.72	<0.001*
	Controls	56	16.18	1.90	
RCA CFTC	Cases	56	27.23	8.52	<0.001*
	Controls	56	16.52	1.99	

Applied unpaired t test for significance. *Significant.

Corrected TIMI frame count for LAD, LCX and RCA were 35.43± 4.99, 26.20± 8.72 and 27.23± 8.52 respectively among CSPF patients. Among control group corrected TIMI frame count for LAD, LCX and RCA were 16.46± 1.84, 16.18 ±1.90, and 16.52 ±1.99. respectively (Table 5).Among CSFP, 16 patients were prescribed calcium channel blockers, 15 pts nicorandil, 15 pts nitrates and 10 patients nitrate for one month duration.

Tab: 5 Treatment outcome in patients

CCB (N- 16)	Pre TMT	Post TMT	Mean difference	p-value
ET (min)	7.031±0.64	7.61±0.51	-0.58	<0.001*
ST depression(mm)	1.25±0.44	0.91±0.37	0.34	0.016
DTS	-1.12±2.41	2.27±1.96	-1.15	<0.001
NIKORANDIL N – 15				
ET (min)	6.94±0.65	7.41±0.62	-0.47	<0.001
ST depression(mm)	1.23±0.37	1.1±0.28	0.13	0.262
DTS	-2.49±2.98	0.5±2.58	-2.99	<0.001
NitratesN- 15				
ET (min)	7.27±0.96	7.32±0.88	-0.05	0.334
ST depression (mm)	1.40±0.63	1.26±0.53	0.14	0.104
DTS	-1.86±3.69	- .81±3.76	-1.05	0.067
StatinsN- 10				
ET (min)	6.89±0.71	7.01±0.84	-0.12	0.279
ST depression(mm)	1.05±0.43	1.15±0.24	0.10	0.443
DTS	-0.32±2.06	-0.01±1.89	-0.31	0.26

patients on CCB'S,Nicorandil there was significant changes observed on exercise time and duke treadmill score on treadmill exercise test. While there were no significant changes observed on treadmill exercise test in patients on nitrates and statins.

DISCUSSION

The present study utilizing a case control study design studied the prevalence, risk factors profile and treatment outcomes of coronary slow flow phenomenon in angiographically normal coronary arteries. In our study prevalence of CSF phenomenon was 1.1 % of all coronary angiograms and 10.96% of normal coronary angiograms, which is similar to that reported by Mukhopadhyay at al[10]of 0.8 % in north India population among all coronary angiograms and 1% in the Australian population by Beltrame et al. [1]The prevalence of CSFP of 10.96 % among the normal flow normal coronary arteries was higher than the study by Mukhopadhyay et al (5.5%), in the Chinese study[11] (4.5%) and North American white population (5.5%)[12], in an Iranian population by S A Mohammed the prevalence of slow flow was 6. 6 %.[13] Goel P K et al in Indian population reported CSF phenomenon in 23.7% of the normal coronary angiograms.[14]The presentation of slow flow phenomenon is extremely diverse ranging from stable or unstable angina (USA), non-ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI) as well as atypical chest pain.[15]In our study 57.1 % patients with CSFP presented with acute coronary syndrome (USA 33.9 %, NSTEMI 19.6 % and STEMI 3.6%), 39.3 % with chronic stable angina and 3.6% with atypical chest pain. Among control group most common presentation was CSA (55.4%), USA (21.4), atypical chest pain (17.9 %) and NSTEMI (5.4%). No patient among control group presented with STEMI. Patients having slow flow presented more commonly with acute coronary syndrome than among control group.In a recent study by Mukhopadhyaya et al, 50% of patients with CSF presented with chronic stable angina and remaining 50% with ACS (35% with USA and 15% with NSTEMI).[10] Presentation with ACS was more common in cases with CSF than controls. In contrast in a study by YaronArbel et. al in Israel, most common presenting complaint was non-specific chest pain (71.9%) followed by ACS (18.4%) and stable angina (8.8%).[16] Similarly in a recent study in Iranian population, 75% of the patients with CSF presented with ACSof which 10.7% patients had ST segment elevation myocardial infarction (STEMI) on presentation.[17]In our study Coronary slow flow was seen in all three vessels in 53.6 % patients, LAD in 37.5% patients, RCA in 7.1% and LCX in 1.8 %, patients.There are very limited data on demographic variables associated with CSFP. In our study 78.6% patients were male which is similar with an Iranian study which demonstrated this in 76 %. Earlier some of the studies have reported male gender as a predictor of CSFP, while others refuted its association with gender. In our study male sex, tobacco chewing, smoking and depression were significantly associated with CSF. Whereas no significant difference was noted for variables like diabetes, hypertension, dyslipidemia, hypothyroidism, CVA. There was also no any significant difference could be demonstrated among groups in term of various biochemical variables like hemoglobin, total leucocyte count, Neutrophil/ lymphocyte ratio, blood urea, serum creatinine, serum uric acid, and lipids parameters. Beltrame et al, in an Australian population among various factors male sex, young age and nicotine use were demonstrated to be associated with CSFP significantly[1]. Yilmaz et al. in a study in Turkish population have reported BMI, glucose levels, lipid derangements, and metabolic syndrome to have an independent association with CSF. [7]A study done in Chinese population by Xia s et al reported that hyperuricemia, hyperglycemia, thrombocytosis and hsCRP(high sensitive C reactive protein) were independent risk factors of CSF, all of which were causative factors of endothelial dysfunction .[11] Mukhopadhyay at all reported BMI as an independent factor associated with CSF in a case control study in north Indian population.[10]In a study by Arbel et al. smoking was found to be the strongest predictor of the SCF phenomenon [16]. Hawkins et al. suggested male sex, a higher BMI, and a low HDL-c level as independent predictors of the CSF phenomenon following a multivariable analysis, and demonstrated that male sex was the strongest independent predictor of this phenomenon [12]. Naing et al. identified a significant correlation between uric acid levels and CSF and suggested serum uric acid levels as an independent predictor of CSF.[18] CSF patients have usually good prognosis, although the disease progress subsequently and patients present frequently with remitting, relapsing anginal chest pain which results in considerable impairment in quality of life. Unfortunately, currently available pharmacological agents are of limited clinical value. To date, no large clinical trial has been conducted to test pharmacological treatment approach, and the available evidences have been derived from the smaller studies with nonhomogeneous inclusion and exclusion criterias.[19]In our study, among patients on calcium channel blocker had significantly improved exercise time, ST segment changes and duke treadmill score on TMT. Patients on nicorandil treatment had significant improvement in exercise time and DTS. Whereas there was no significant improvement noted in patients on nitrates or statins. Recently, several studies have demonstrated that nebivolol and statins can improve endothelial function and ameliorate symptoms, hence improving quality of life in these patients.[20-22]Simvastatin has shown to improve myocardial perfusion in patients with CSFP [23]. In a study by Fan et al. significant improvement in coronary flow reserve was shown after atorvastatin treatment for eight weeks [24]. Dipyridamole abolishes functional obstruction in coronary arteries with

diameters less than 200 micrometers and is considered superior in treating CSFP as compared to nitroglycerine. [25]In a study regarding clinical and angiographic benefits of mibefradil, there was significant reduction of total angina episodes and angiographically,13 out of 18 vessels had abolition of the slow flow [26]

Our study shows the various risk factors and determinants which may lead to slow flow along with different treatment modalities which may have an impact on functional status. This study provides a basis for further long term follow up studies to understand the pathophysiology and decide a specific treatment for this intriguing entity.

CONCLUSION

Prevalence of CSF phenomenon was 1.1 % of all coronary angiograms and 10.96% of normal coronary angiograms. Gender, Depression, oral tobacco chewing and smoking had a significant and independent positive association with CSF phenomenon. In our study there was a significant improvement in functional status of patients on Nicorandil and Diltiazem which was not observed in pts on nitrates or

LIMITATIONS

Causality could not be established as this was a cross-sectional study. Nonetheless, an independent significant positive association was demonstrated between oral tobacco chewing, smoking and depression to CSF phenomenon. Sample size was small in our study. Longitudinalstudies should be done for an adequate sample size with an extended follow up period in order to determine cause effect relationship.

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