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Original Article

Risk factors and angiographic profile of coronary slow flow (CSF) phenomenon in North Indian population: An observational study

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ABSTRACT

Background: "Coronary slow flow" (CSF) is delayed vessel opacification in the absence of epicardial stenosis. Studies in different ethnic groups have found variable risk factors associated with CSF.
Aim: of present study was to analyze the risk factors and angiographic profile of CSF in North Indian population, not studied till date.
Methods: 40 patients with CSF and 40 controls were studied. CSF was determined quantitatively by thrombolysis in myocardial infarction (TIMI) frame count method. Various clinical risk factors (age, sex, body mass Index (BMI), diabetes, hypertension, dyslipidemia, smoking), hematological and biochemical parameters (hematocrit, platelet count, uric acid, homocysteine, fibrinogen, high sensitivity C reactive protein (hsCRP), glycosylated hemoglobin (HbA1c) were assessed.
Results: Of the 40 patients with CSF, 37 (92.5%) were males. While 20 patients (50%) presented with chronic stable angina, rest 20 (50%) presented with acute coronary syndrome. [15 (37.5%) with unstable angina and 5 (12.5%) with non ST elevation myocardial infarction (NSTEMI)]. Patients with CSF had significantly higher BMI (27.27 ± 2.82 vs. 24.12 ± 2.35, $p < 0.001$), fibrinogen levels (398.48 ± 120.96 vs. 331.55 ± 162.6, $p = 0.04$) and smoking (24(60.0%) vs 14(35.0%), $p = 0.02$). On multivariable regression analysis, only BMI was found to have an independent association with CSF (odds ratio 1.613, 95% confidence interval 1.265–2.057, $p < 0.001$).
Conclusion: This is the first study to analyze clinical presentation, angiographic profile and risk factors associated with CSF in North Indian population. In this study, we found only BMI to have an independent association with CSF.

1. Introduction

Coronary slow-flow (CSF) phenomenon is characterized by delayed opacification of epicardial coronary arteries without occlusive disease as well as angiographically by a delayed progression of the contrast medium injected into the coronary tree. CSF phenomenon was reported first by Tambe et al. in 1972.[1] The prevalence of CSF phenomenon varies from 1 to 5%.[2,3] 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.[2,4–7] No study till date has been done on the Indian population to assess the clinical risk factors associated with CSF and hence the present study was undertaken.

2. Material and methods

Patients who underwent coronary angiography between April 2014 and October 2015 in our center were evaluated for inclusion in this study. We planned to study the North Indian Population (defined as Hindi speaking population residing from birth in the states of Delhi, Punjab, Haryana, Uttar Pradesh, Uttaranchal or Himachal Pradesh). A total of 40 consecutive patients with CSF phenomenon and 40 controls with normal coronary flow were evaluated in the present study.

Patients ≥18 years of age presenting with exertional chest pain or acute coronary syndrome (ACS) with normal epicardial

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coronaries on angiography but with slow coronary flow were selected as cases with the following exclusions:

1. Coronary artery disease (including plaque, spasm, ectasia, or obstructive lesion),
2. Myocardial bridge,
3. Cardiomyopathy,
4. Valvular heart disease,
5. Left ventricular systolic dysfunction (EF $\leq$ 40%),
6. Refusal to give informed consent.

The control group comprised of an identical number of patients who underwent coronary angiography with a normal epicardial coronary artery and normal flow on angiogram. Following recruitment of a patient with CSF, the next consecutive patient exhibiting normal coronaries with normal flow meeting our study's inclusion/exclusion criteria was recruited as control.

Informed consent was obtained from all subjects at the time of enrollment. Eligible subjects were evaluated by detailed history and physical examination. Apart from demographic profile, various risk factors reported to be associated with CSF like body mass index (BMI), hypertension, diabetes, dyslipidemia, smoking status were recorded in all subjects enrolled in the study. Various hematological (hematocrit, platelet count) and biochemical parameters (lipid profile, uric acid, glycosylated hemoglobin (HbA1c), homocysteine, fibrinogen, high sensitivity C reactive protein (hs CRP) were also assessed in all subjects. Measurement of Troponin T was done in patients presenting with ACS. The study conforms to the principles of Helsinki Declaration and was approved by our Institutional ethics committee.

2.1. Definitions

Hypertension was defined as diastolic blood pressure $\geq$90 mmHg, systolic blood pressure $\geq$140 mmHg, or the self-reported use of antihypertensive drug(s). Diabetes mellitus was diagnosed if HbA1c $\geq$6.5% or if the patient was on treatment with insulin or oral hypoglycemic agent(s). Dyslipidemia was defined as low-density lipoprotein (LDL) cholesterol $\geq$100 mg/dl and/or total cholesterol (TC) $\geq$200 mg/dl or high-density lipoprotein (HDL) cholesterol $<$40 mg/dl in men and $<$50 mg/dl in women and/or triglyceride (TG) $\geq$150 mg/dl.[8] BMI was calculated by dividing the weight in kilograms by the height in meters squared (kg/m^2).

2.2. Coronary angiography

All angiograms were performed using Standard Judkin's left and right 6 French diagnostic catheters with manual low osmolar contrast (Iohexol) injection. All patients received nitroglycerine during angiography in the form of intracoronary injection of 100–200 mcg. The angiograms were assessed and coronary flow quantification was performed using the corrected TIMI FRAME COUNT (TFC) method described by Gibson et al.[9] In brief, the first frame was considered as that at which a column of dye extended across the entire width of the origin of the artery touching both its borders with evidence of antegrade motion of the dye and the last frame was defined as the frame when the dye first entered a certain distal landmark branch (but did not necessarily fill) in each vessel. The following distal landmarks were used for analysis: For left anterior descending artery (LAD), the distal bifurcation was used (the moustache or whale's tail). For left circumflex artery (LCX), the most distal bifurcation of the obtuse marginal branch farthest from the coronary ostium was used as the distal landmark. For right coronary artery (RCA), the first branch of the posterolateral segment was used. The assessment was performed by two interventional cardiologists who were blinded to the clinical details of the study population. A corrected TIMI frame count exceeding 27 (i.e. greater than 2 standard deviations (SD) from normal published range of 21 + 3) was considered abnormal and indicative of CSF. This is based upon images acquired at 30 frames/second and a correction factor of 1.7 for the LAD (Left anterior descending).[9] The intra- and inter- observer coeffeicient of variation for LAD was 3.86% and 2.97%, for LCX: 3.13% and 3.36% and for RCA: 3.17% and 3.48%, respectively.

2.3. Laboratory measurements

Lipid profile (TC, HDL, LDL, TG), uric acid, homocysteine and hsCRP were estimated by Roche Cobas C501 autoanalyzer (Manheim Germany) using commercially available kits from Roche by photometric method. Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald equation. Fibrinogen was estimated by ACL ELITE PRO coagulation analyzer (MIAMI, USA) using commercially available reagent from IL (MIAMI, USA) by photoconductance method. HbA1c was estimated by BIO-RAD D-10 HPLC analyzer (USA) using commercially available kit from BIO-RAD (USA) by HPLC. Troponin T testing was done qualitatively using commercially available kit from Roche.

Table 1
Baseline demographic, clinical presentation and medications of CSF and control groups.

Variable	Case(n = 40)	Control(n = 40)	p-value
Age(years)	50.43 ± 10.18	51.38 ± 7.19	0.631
BMI(kg/m^2)	27.27 ± 2.82	24.12 ± 2.35	<0.001
	Number (%)	Number (%)	
SEX −Male [n (%)]	37(92.5)	35(87.5)	0.456
HTN [n (%)]	11(27.5)	13(32.5)	0.626
DM [n (%)]	15(37.5)	16(40.0)	0.818
Dyslipidemia [n (%)]	7(17.5)	14(35.0)	0.075
Smoking [n (%)]	24(60.0)	14(35.0)	0.025
CSA [n (%)]	20 (50)	34 (85)	<0.001
ACS(USA/NSTEMI)[n (%)]	20 (50)	6 (15)	<0.001
Antiplatelet [n (%)] (Aspirin and/or $P2Y_{12}$ Inhibitor)	37 (92.5)	39 (97.5)	0.30
Betablocker [n (%)]	17 (42.5)	16 (40)	0.82
Statin [n (%)]	18 (45)	20 (50)	0.65
Nitrate [n (%)]	30 (75)	28 (70)	0.61
ACE Inhibitor/ARB[n (%)]	10 (25)	09 (22.5)	0.80

BMI: Body mass index; HTN: Hypertension; DM: Diabetes mellitus; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; CSA: Chronic stable angina; ACS: Acute coronary syndrome; USA: Unstable angina; NSTEMI: Non ST segment elevation myocardial infarction. Values presented as mean ± SD or n(%).

2.4. Statistical analysis

For comparing the statistical significance of categorical variables, Chi-square/Fishers exact test was applied. For determining statistical significance of quantitative variables, unpaired Student's *t*-test was applied. Leven's test was applied to check the equality of variances between the groups. In case of quantitative variables that did not follow a normal distribution, Mann Whitney *U* test was applied. Multivariable logistic regression was applied using enter method and those variables which by univariable methods had p-value less than 0.10 were included. The data was analyzed by the statistical software SPSS version 20.

2.5. Results

During the time period of study from 1st April 2014 to 31 October 2015, out of 4767 coronary angiograms performed at our institution which were analyzable as per our study protocol, we prospectively identified 692 patients with normal epicardial coronaries and 40 patients with CSF phenomenon (i.e. 0.8% of all coronary angiograms and 5.8% of normal coronary angiograms).

Cases were in the age group of 27–75 years with mean age of 50.43 ± 10.18 years and 92.5% (37/40) were males. Among cases (n = 40), 20 (50%) presented with chronic stable angina, 15 (37.5%) presented with USA and 5 (12.5%) presented with NSTEMI. Controls were in the age group of 36–70 years with mean age of 51.38 ± 7.19 years. Among controls (n = 40), 34 (85%) presented with chronic stable angina and 6 (15%) presented with USA (vide Table 1). There was no significant difference in age (mean 50.43 ± 10.18 vs 51.38 ± 7.19; p = 0.63) or sex (males 92.5% vs 87.5%; p = 0.46) between the two groups.

Amongst clinical characteristics, BMI and smoking were significantly higher in cases than controls ($p < 0.05$). Dyslipidemia was slightly higher in controls compared to cases (p = 0.07). There was no statistically significant difference with regard to hypertension, diabetes mellitus and baseline medications. ($p > 0.05$) (vide Table 1). Though only 18 (45%) patients with CSF were initially on statins, all the patients diagnosed with CSF were discharged on 40 mg simvastatin or equipotent doses of other statins as these drugs have been shown to improve endothelial function and coronary slow flow.[10]

Amongst hematological and biochemical variables, only fibrinogen was found to be significantly higher in cases than controls ($p < 0.05$). There was no difference with regard to hematocrit, platelet count, uric acid, HbA1c and hsCRP ($p > 0.05$) (vide Table 2).

The variables that were significant between the groups with p value <0.05 on unpaired *t*-test were BMI, Fibrinogen and Smoking. Variable with p value >0.05 but <0.1 on unpaired *t*-test was dyslipidemia. All the variables having p value <0.1 on univariate analysis were included in multivariable logistic regression analysis to assess the independent association of the variable with CSF.

Table 2
Hematological and biochemical variables in case and control groups.

Variable	Case(n = 40)	Control(n = 40)	p-value
Hematocrit (%)	42.54 ± 3.17	41.50 ± 3.0	0.137
Platelet count (lac/uL)	2.06 ± 0.59	2.01 ± 0.69	0.715
Uric Acid (mg/dL)	6.19 ± 1.73	5.70 ± 1.42	0.164
HbA1C (%)	6.39 ± 1.20	6.19 ± 1.35	0.491
Homocysteine (umol/L)	23.81 ± 16.73	23.55 ± 16.39	0.945
Fibrinogen (mg/dL)	398.48 ± 120.96	331.55 ± 162.6	0.040
	Median(IQR)		
hsCRP (mg/L)*	3.2(1.6–11.35)	2.7(1.1–6.5)	0.105

hsCRP: high sensitivity C reactive protein. Values are in mean ± SD or median* with interquartile range.

Table 3
Multivariable logistic regression analysis.

Variable	B(SE)	p-value	OR	95% CI of OR
BMI (per 1 unit)	0.478 (0.124)	<0.001	1.613	1.265–2.057
Fibrinogen (per 10 unit)	0.030 (0.020)	0.137	1.031	0.990–1.073
Smoking (yes)	0.788 (0.563)	0.162	2.200	0.729–6.638
Dyslipidemia (yes)	−0.287 (0.635)	0.651	0.750	0.216–2.607

Total number of case = 80, positive = 40 and negative n = 40; −2LL = 79.133.
Model overall model chi-square = 31.771, df = 4, p = 0.000; <0.001.
Nagelkerke R-square 0.437.

On multivariable logistic regression analysis, out of the four variables, only BMI was found to have an independent and significant association with CSF (vide Table 3).

Out of 40 cases, 13 had slow flow in all 3 vessels (32.5%), 19 had slow flow in 2 vessels (47.5%) and 8 had slow flow in 1 vessel (20%). The most common artery involved was LAD [n = 36 (90%)], followed by LCX [n = 29 (72.5%)] and RCA [n = 19(47.5%). The median TIMI frame count in LAD [35(IQR 30–46) vs 17 (IQR 15–20), $p < 0.001$], LCX [36 (IQR 30–45) vs 18 (IQR 16–20), $p < 0.001$] and RCA [34 (IQR 30–42) vs 18 (IQR 16–20), $p < 0.001$] exhibiting slow flow was significantly higher compared to controls (Table 4).

3. Discussion

This study utilizing a case control study design studied the angiographic profile and clinical risk factors associated with CSF phenomenon in the North Indian population. In our study, BMI was found to have an independent association with CSF which is in agreement with studies reported by other authors.[5,11,12] Yilmaz et al[5] in a study in Turkish population have reported BMI to have an independent association with CSF. Similarly, Hawkins et al[12] have reported BMI to be an independent predictor of CSF in the North American population.

Risk factors and pathophysiology of CSF phenomenon is still unclear and studies done in different ethnic populations have found variable risk factors to be associated with CSF phenomenon. In a study performed by Beltrame et al[2] in an Australian population, male sex and smoking were found to be independent risk factors for CSF while a study done in Chinese subjects reported hyperuricemia, hyperglycemia, thrombocytosis and hsCRP all of which cause endothelial dysfunction to be independent risk factors associated with CSF.[6] A study done on Iranian population identified diabetes mellitus, hypertension and opioid abuse to be independent risk factors associated with CSF.[7] However, none of these factors were found to be predictors of CSF in our population. One possible explanation for this is that, due to high and similar rates of prevalence of diabetes mellitus and hypertension in both cases and

Table 4
TIMI frame count in subjects of slow flow versus controls.

Artery involved		Normal	Slow Flow	p value
LAD	Median [IQR]	17 [15–20]	35 [30–46]	$p < 0.001^{\#}$
	Mean + SD	17.69 + 2.65	38.47 + 9.40	
LCX	Median [IQR]	18 [16–20]	36 [30–45]	$p < 0.001^{\#}$
	Mean + SD	17.72 + 1.98	39.38 + 11.20	
RCA	Median [IQR]	18 [16–20]	34 [30–42]	$p < 0.001^{\#}$
	Mean + SD	18.21 + 2.30	35.58 + 6.79	

LAD: Left anterior descending artery.
LCX: Left circumflex artery.
RCA: Right coronary artery.
SD: Standard Deviation.
IQR: Interquartile Range.
Mann Whitney *U* test testing the distribution of LAD, LCX and RCA.

controls of our study (unlike the Iranian study) along with lack of statistically significant difference in levels of uric acid, hsCRP or platelets in our studied subjects (unlike the Chinese study), these factors could not be included in the logistic regression analysis model and failed to act as predictors of slow flow in our studied population. Hence we find that the literature to date has not demonstrated any consistent demographic feature or co morbidity associated with CSF, though accumulated evidence suggests that endothelial dysfunction is the main factor responsible for CSF phenomenon. As there is difference in the prevalence of comorbidities described to be independently associated with slow flow in different ethnic groups, one possible explanation is that anyone or multiple number of these comorbidies causing endothelial dysfunction may be responsible for manifestation as CSF. Similarly there is also genetic variation in different ethnic groups regarding predisposition to CSF. Gupta et al[13] had shown a strong association between polymorphism of nitric oxide synthetase gene and CSF in the North Indian population, but no such association could be seen in the Turkish population.

The presentation of this phenomenon is extremely diverse ranging from atypical chest pain, stable or unstable angina (USA), non-ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI).[2,14,15] In our study, 50% of patients with CSF presented with chronic stable angina and remaining 50% with ACS (35% with USA and 15% with NSTEMI). Presentation with ACS was more common in cases with CSF than controls. Similarly in a recent study in Iranian population, 75% of the patients with CSF presented with ACS.[16] In contrast in a study by Yaron Arbel et al.[17] in Israel, most common presenting complaint was non-specific chest pain (71.9%) followed by ACS (18.4%) and stable angina (8.8%).

In our study, prevalence of CSF phenomenon was 0.8% of all coronary angiograms which is similar to that reported by Beltrame et al of 1% in the Australian population.[2] Similarly, the prevalence of slow flow of 5.5% among normal coronary angiograms is similar to that reported in the Chinese[6] (4.5%) and North American white population[12] (5.5%).

The most common artery involved was LAD [n = 36 (90%)], followed by LCX [n = 29 (72.5%)] and RCA [n = 19(47.5%)], which is similar to that reported in other studies.[14,16]

Endothelial dysfunction lies central to the pathogenesis of CSF phenomenon[2] and obesity has been shown to be independently associated with coronary and systemic endothelial dysfunction.[18] The endothelial dysfunction in obesity is mediated by a large number of adipokines like visfatin, leptin, tumor necrosis factor alpha (TNF-a), and interleukin-6 (IL-6)[19,20] by induction of an insulin resistant state.[21,22] Obesity is also associated with hypoadiponectinemia[23] which produces endothelial dysfunction by inducing an insulin resistant state[24,25] and has been shown to be associated with CSF.[26] The insulin resistant state produced by various adipokines leads to endothelial dysfunction by inducing reactive oxygen species production that causes breakdown of endogenous vasodilator nitric oxide.[27] This link between obesity and coronary endothelial dysfunction suggests a major independent role of obesity in the pathogenesis of CSF phenomenon. Pontiroli et al[28] showed that reduction in BMI after gastric banding procedures is associated with improvement in markers of endothelial dysfunction. As BMI has been shown to be an independent predictor of slow flow in our population, studies in future should be carried out to see whether reduction in BMI improves coronary flow.

3.1. Limitations

This is a cross-sectional study and hence causality could not be determined. Nonetheless, a significant and independent positive association was demonstrated between BMI and CSF phenomenon. In order to determine causality, longitudinal studies with an extended follow up should be carried out.

Secondly, the coronary flow reserve or endothelial function using acetyl choline was not assessed. Future studies should also be done assessing these indices in Indian subjects.

4. Conclusion

This is the first study in North Indian population to evaluate the clinical risk factors independently associated with CSF. In this study we found only BMI to have an independent association with CSF phenomenon in the North Indian population. It also provides foundation for future studies that should be done likewise in other ethnic groups residing in different parts of India. It also emphasizes the need for further studies to study in detail the various specific adipokines and/or inflammatory markers contributing to CSF phenomenon in Indian patients which might provide new insight into the pathophysiology of this intriguing entity that might be of diagnostic and/or therapeutic use.

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