Original Research Article

Evaluation of prevalence, clinical presentation and risk factors of coronary slow flow phenomenon: a single-center study

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ABSTRACT

Background: The coronary slow flow phenomenon has been revealed to be associated with life-threatening arrhythmias and sudden cardiac death. Currently, clinical features and risk factors of patients with the coronary slow flow phenomenon are incompletely understood. The present study aimed to evaluate the prevalence, clinical presentation, risk factors and evidence of ischemia in patients with coronary slow flow.

Methods: This observational study was conducted at a tertiary-care center in India between February 2013 and August 2014. A total of 60 consecutive patients whose coronary angiogram revealed coronary slow flow were included in the study. According to the number of blood vessels involved, patients were divided into group-1 (29 patients with single-vessel disease), group-2 (22 patients with double-vessel disease), and group-3 (9 patients with triple-vessel disease). Clinical presentation and risk factors were compared among groups.

Results: Prevalence of coronary slow flow was 2.97% with greater prevalence amongst male patients (p=0.030). Unstable angina was the most common presentation (p=0.030). Among the traditional risk factors, there was a significantly higher prevalence of smoking (p=0.036), family history of coronary artery disease (p=0.049) and dyslipidemia (p=0.045) in group-3 patients compared to other groups. Among all groups, triglycerides (p=0.020), low-density lipoprotein cholesterol (p=0.046), highly sensitive C-reactive protein (p=0.007) levels, homocysteine (p=0.481), and patterns of ECG abnormalities were significantly different between the three groups. In addition, mean frame counts with coronary slow flow phenomenon in left anterior descending artery (p<0.001), left circumflex artery (p<0.001) and right coronary artery (p=0.005) increased significantly with increase in number of vessels involved.

Conclusions: Coronary slow flow was relatively common among patients who presented with unstable angina. Male sex, smoking, and dyslipidemia can be considered as independent risk factors for this phenomenon.

Keywords: Coronary angiography, Coronary slow flow, Homocysteine, Thrombolysis in myocardial infarction, Unstable angina

INTRODUCTION

The coronary slow flow phenomenon is an angiographic clinical entity characterized by delayed opacification of the distal vessel in the absence of significant epicardial coronary stenosis.1-3 Coronary slow flow was first described by Tambe et al in 1972 in six patients presenting with chest pain syndrome.4 According to a recent study, the overall prevalence of coronary slow flow phenomenon has been reported as 1% among...
patients undergoing coronary angiography especially in patients presenting with acute coronary syndrome. The diagnosis of coronary slow flow can be distinguished by using coronary angiography based on either reduced thrombolysis in myocardial infarction (TIMI) flow grade 2 or increased TIMI frame count of >27 frames in one or more epicardial vessel. Similarly, coronary slow flow associated with coronary artery spasm, coronary artery ectasia, myocardial dysfunction, valvular heart disease and certain connective tissue disorders involving coronary microvasculature is easy to understand. Sometimes, coronary slow flow phenomenon may occasionally result from inadvertent air-embolism during angiography or may be due to an overlooked ostial lesion. Hence, patients with coronary angiograms with coronary slow flow phenomenon are often referred to as normal or mild non-obstructive disease patients.

Coronary slow flow has also been described to be associated with life-threatening arrhythmias and sudden cardiac death probably due to increased QT interval depression. Although well-known to interventional cardiologists, myocardial biopsy studies have demonstrated the presence of coronary microvascular disease in some patients exhibiting coronary slow flow, the pathogenic mechanisms have not been extensively studied. Some studies have mentioned it as microvascular or endothelial dysfunction while others considered it a preliminary stage of atherosclerotic coronary artery disease (CAD). Currently, clinical features and risk factors of patients with this coronary slow flow are incompletely understood. In order to provide information for further exploration of potential mechanisms of coronary slow flow phenomenon, this study was conducted to evaluate the prevalence, clinical presentation, risk factors and evidence of ischemia in patients with a coronary slow flow.

METHODS

Study design and patient population

This was an observational study conducted at a tertiary-care center in India between February 2013-August 2014. Consecutive patients whose coronary angiography showed coronary slow flow were included in study. Patients were divided into three groups based on the number of vessels involved: group-1: patients with single-vessel disease (SVD); group-2: patients with double-vessel disease (DVD); and group-3: patients with triple-vessel disease (TVD). Patients with normal coronary angiograms and patients whose coronary angiograms displayed obstruction were excluded from the study. Written informed consent was obtained from all study patients. The study was approved by institutional ethics committee.

Data collection

Data for patient demographics, history, cardiovascular risk factors, and clinical presentation was recorded. Laboratory blood investigations such as complete blood count, fasting and postprandial blood sugar, fasting lipid profile, serum homocysteine, serum uric acid, serum creatinine, and serum highly sensitive C-reactive protein (hsCRP) were done within 24 hours of admission. Electrocardiogram examination was done. Echocardiographic examination was performed using Siemens ACUSON CV-70 machine and two-dimensional, M-mode and color Doppler evaluation were carried out according to ACC/AHA guidelines.

Treadmill exercise test

A symptom-limited treadmill exercise test was performed using the standard Bruce protocol with a 12-lead electrocardiography recording for each minute of the exercise and continuous monitoring of leads V2, V5 and aVF. Anti-ischemic medication was administered 48 hours before the test. The criteria for interrupting the treadmill test were targeted heart rate (220 beats/min), severe chest pain, complex ventricular arrhythmias, hypertension, exhaustion, ST-segment depression (2 mm) and ST-segment elevation (2 mm). Rest and exercise myocardial perfusion scan were done using standard 99 technetium sestamibi CZT-single photon emission computed tomography (SPECT) imaging technique.

Study intervention

All patients involved in the study underwent selective coronary angiography using the standard Judkins technique. Peripheral access was achieved by using a radial or femoral arterial route. Angiographic images were obtained in standard views using right and left, and cranial and caudal angulations. Angiograms of all included subjects were studied and TIMI frame count was determined for each coronary vessel. Objective and quantitative measurement of slow flow was done by corrected TIMI frame count. In brief, images were acquired at 15 frames/sec and thus all values were multiplied by 2. Frame counts in the left anterior descending (LAD) were divided by a factor of 1.7 to correct for its longer length. Any frame count exceeding 27 was considered to be abnormal and indicative of slow flow based on the recommendations of Gibson et al.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared using the student’s t test. Categorical variables were expressed as frequencies and percentages and compared using the chi square test. Analysis of variance (ANOVA) was used to compare three or more quantitative variables. Spearman correlation test was used to quantify the association between two variables. A p value<0.05 was considered as statistically significant. Statistical analysis was performed using epidemiological information software (EPI info™, Atlanta, Georgia, version 3.5.3).
RESULTS

A total of 60 patients whose coronary angiogram showed coronary slow flow were included in the study. Of the 60 patients, group-1 consisted of 29 patients with single-vessel disease (SVD), group-2 consisted of 22 patients with double-vessel disease (DVD), and group-3 consisted of nine patients with triple-vessel disease (TVD). Out of 2,018 angiographies done during the study period, only 60 patients showed significant coronary slow flow as diagnosed by corrected TIMI frame count. So, the prevalence of the coronary slow flow in this study was found to be 2.97%.

Demographic characteristics

The mean age of the study population was 51.8±10.9 years. There was a male predominance (78.3%) among the study population, with a significant difference among the three groups as group-3 comprised 100% male patients compared to 75.9% males in group-1 and 72.7% males in group-2 (p=0.030). The mean body mass index at presentation was 24.5±0.4 kg/m². At the time of admission, unstable angina (p=0.030) was found to be significantly higher in group-1 patients (55.2%) compared to other presentations, while chronic stable angina (p=0.030) was found to be significantly higher in group-2 (40.9%) and group-3 (55.6%) patients than other presentations. Group-3 patients also showed a significantly higher prevalence of coronary risk factors such as smoking (77.8%, p=0.036), dyslipidemia (88.9%, p=0.045) and family history of CAD (55.6%, p=0.049) compared to other groups. The baseline demographic characteristics of the study population are delineated in Table 1.

Clinical and angiographic characteristics

Analysis of lipid profile revealed a significant difference for triglyceride levels (p=0.020) and low-density lipoprotein (LDL) cholesterol levels (p=0.046) between three groups, with group-3 patients exhibiting higher levels (202.1±44.7 and 140.0±25.4 mg/dL, respectively). On the other hand, high-density lipoprotein (HDL) cholesterol levels were lower in group-3 (39.8±3.4 mg/dL) patients compared to group-1 (41.9±4.7 mg/dL) and group-2 (41.8±4.8 mg/dL) patients (p=0.477).

Proportion of patients with hsCRP ≥2.0 mg/L were increasing significantly with an increase in number of vessels involved as indicated by 31.0, 36.4 and 88.9% patients in group-1, group-2, and group-3 respectively (p=0.007). Similarly, hyperhomocysteinemia (i.e., homocysteine ≥12 µmol/L) was significantly higher in group-3 patients (22.2%) compared to group-1 (6.9%) and group-2 (0%) patients (p=0.041). The ECG changes in patients with coronary slow flow showed that left bundle branch block (LBBB) or right bundle branch block (RBBB) was observed in 13.8% patients in group-1, 18.2% patients in group-2, and 22.2% patients in group-3, while ST/T wave changes were observed in 48.3% patients in group-1, 68.2% patients in group-2, and 66.7% patients in group-3 (p<0.05). Among the three groups of the study population, regional wall motional abnormality (RWMA) was noted in 23.3% patients and global hypokinesia was noted in 10% patients. There was a statistically significant difference between three groups for RWMA with group-1 comprising 34.5% patients with RWMA as compared to 13.6% and 11.1% patients in group-2 and group-3 (p=0.043).

Treadmill test (TMT) was found to be positive in 37 (61.7%) patients, of which, group-1 (41.4%) patients were numerically lower compared to group-2 (77.3%) and group-3 (88.9%) patients (p<0.001). Mean frame counts with coronary slow flow phenomenon in LAD (p<0.001), LCx (p<0.001) and RCA (p=0.005) were increasing significantly with an increase in no. of vessels involved. Detailed clinical and angiographic characteristics of study population are displayed Table 2.

Myocardial perfusion abnormality

SPECT showed reversible perfusion defect (RPD) in 18.3% cases, no defect in 53.3% and was not done in 28.3% patients. The patients without perfusion defect were significantly higher than patients with perfusion defect in double and triple-vessel group but it was almost equal in single-vessel group.

Table 1: Baseline demographic characteristics of the study population.

| Characteristics          | Total (N=60) (%) | Group-1 (N=29) (%) | Group-2 (N=22) (%) | Group-3 (N=9) (%) | P value |
|--------------------------|-----------------|-------------------|-------------------|------------------|--------|
| Age (year)               |                 |                   |                   |                  |        |
| ≤40                      | 10 (16.7)       | 6 (20.7)          | 2 (9.1)           | 2 (22.2)         | 0.465  |
| 41-50                    | 22 (36.7)       | 11 (37.9)         | 7 (31.8)          | 4 (44.4)         |        |
| 51-60                    | 26 (43.3)       | 10 (34.5)         | 13 (59.1)         | 3 (33.3)         |        |
| 61-70                    | 2 (3.3)         | 2 (6.9)           | 0 (0.0)           | 0 (0.0)          |        |
| Male                     | 47 (78.3)       | 22 (75.9)         | 16 (72.7)         | 9 (100.0)        | 0.030* |
| Body mass index (kg/m²)  |                 |                   |                   |                  |        |
| <25                      | 36 (60.0)       | 16 (55.2)         | 15 (68.2)         | 5 (55.6)         | 0.615  |
| >25                      | 24 (40.0)       | 13 (44.8)         | 7 (31.8)          | 4 (44.4)         |        |

Continued.
By utilizing this observational study, we have examined the prevalence of the coronary slow flow phenomenon differ markedly from other patients in their mode of clinical presentation. The prevalence of the coronary slow flow in this study was noticed to be 2.97% which is equivalent to the other studies conducted in the past.\textsuperscript{2,11,16}
The coronary slow flow phenomenon is more often encountered in male sex and smoking patients. Hawkins and Arbel et al found male sex and smoking to be the strongest predictors of the coronary slow flow phenomenon. Similarly, a study done in the Australian population revealed male sex and smoking to be the independent risk factors for coronary slow flow phenomenon. This study is in line with similar prior reports, as 78.3% of the study population were males (mean age of 51.87±10.92 years) with 41 (68.3%) of the 60 patients classified as either active or former smokers.

In the present study, hypertension and diabetes were not significantly associated with coronary slow flow patients whereas family history of CAD and dyslipidemia were found to be the significant predictors. These results were similar to a study done by Goel et al. showing that hypertension and diabetes were not associated with coronary slow flow phenomenon. In particular, coronary slow flow phenomenon was typically observed in patients undergoing coronary angiography for acute coronary syndrome, usually unstable angina (36.7%) and few (11.6%) had evidence of myocardial infarction. To our knowledge, this was the first study to compare the association between lipid profile and coronary slow flow patients and it was observed that coronary slow flow patients showed significant association with triglycerides, HDL and LDL. Hence, elevated serum lipid profile levels can be considered as the etiological factor and play an important role in the pathogenesis of this coronary slow flow phenomenon.

In this study, the majority of the study population had low levels of hsCRP and homocysteine values. This study is in contrast with other reports showing that patients with slow coronary flow had elevated homocysteine and hsCRP levels. The occurrence of coronary slow flow is also believed to be strongly associated with raised plasma homocysteine levels which cause a detrimental effect on endothelial function. However, there is still a controversy on lack of a clear and positive relationship between hsCRP and coronary slow flow. Hence, further research in this regard seems worthwhile. A study conducted by Beltrame et al displayed that majority of the population had abnormal ST/T changes and stress testing with standard ECG yielded positive results which can be compared with the present study. Also, LBBB/RBBB was observed in 16.7% of study population which can be compared to a previous report showing that new onset intermittent LBBB has also been reported in association with coronary slow flow phenomenon in patients presenting with the acute coronary syndrome. The SVD was most commonly observed in this study population followed by DVD and TVD. In a similar way, a study conducted by Hawkins et al showed that majority of the coronary slow flow patients are with single vessel involvement.

In this study, myocardial perfusion scan was performed by using SPECT and displayed a good anatomic correlation between the vessel showing slow flow and area of reversible perfusion defect (RPD). Evidence of perfusion abnormality in non-invasive tests must justify anti-ischemic treatment strategies in these patients. The rate of RPD obtained in this study can be compared to previous studies. Although the majority of patients developed anginal pain, only a few developed myocardial ischemia. Thus, in most of the patients, angina pectoris does not originate from the myocardial ischemia as demonstrated by the metabolic parameters. However, of the patients who showed evidence of metabolic ischemia, the majority showed that perfusion defect was an anatomically correlated well with the vessel showing coronary slow flow phenomenon by using SPECT.

Thus, this study supports prior reports showing that coronary angiography is one of the best tools for diagnosis and assessment of coronary slow flow. Inflammation is a contributing factor to several cardiovascular conditions and inflammatory mechanisms have also been observed in the context of coronary slow flow phenomenon showing that plasma concentration of hsCRP, and homocysteine levels was increased in coronary slow flow patients. This study also suggests that male sex and smoking play an integral role in the development of coronary slow flow.

**Limitations**

A limitation to this report stems primarily from being an observational single-center study with small sample size and with no assessment regarding response to therapy. Further randomized trials are required to reveal the exact pathogenesis involved in coronary slow flow phenomenon and proper follow-up is needed to know the definitive treatment.

**CONCLUSION**

The coronary slow flow phenomenon is an important angiographic finding typically observed in patients presenting with CAD, in particular, unstable angina. Male sex, smoking, and dyslipidemia can be considered as independent risk factors for this phenomenon. Elevated hsCRP levels supported the role of endothelial function as the pathogenic factor for coronary slow flow. Significant ECG changes, positive TMT and few patients showing reversible perfusion defect strongly indicate that coronary slow flow phenomenon is not an entirely benign condition.

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