Clinical Features and Main Determinants of Coronary Slow Flow Phenomenon in Iranian Patients

Mansour Moazenzadeh\(^1\), Behzad Sarvar Azimzadeh\(^2\), Jahangir Zare\(^3\), Mohammad Shokouhi\(^4\) & Mehrdad Sheikhvatan\(^5\)

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Keywords: coronary flow; risk; glucose tolerance; metabolism

ABSTRACT

Objectives: The present study addresses the associated clinical profile and main clinical determinants of coronary slow flow phenomenon (CSFP) among Iranians.

Background: CSFP may have a high incidence of clinical risk profiles as well as metabolic syndrome which leads to development of coronary microvascular dysfunction.

Methods: Our study population consisted of 46 patients with normal coronary arteries but documented CSFP on coronary arteriography and 92 control group patients with normal coronary arteries and normal coronary flow matched for age and gender. Coronary blood flow was measured quantitatively using the Thrombolysis in Myocardial Infarction (TIMI) frame count and slow flow was defined as TIMI grade 2 standard deviations (SD) from normal published range.

Results: Overall incidence of systolic hypertension and diabetes mellitus were significantly higher in the CSFP group. Opium addiction was also more frequent in those with CSFP. There were however no significant differences in age distribution, current smoking and hyperlipemia between the two groups. Multivariable logistic analysis showed that the two factors of opium addiction (OR = 3.807, p = 0.006) and diabetes mellitus (OR = 7.067, p = 0.020) were main independent predictors of CSFP with the presence of demographic variables as cofounders.

Conclusion: The presence of CSFP may be dependent on vascular dysfunction related to impaired glucose tolerance and regular opium use.

INTRODUCTION

Coronary slow-flow phenomenon (CSFP) is marked by a late 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\(^1\). Although exact etiopathogenesis of CSFP has been already unclear, some microvascular abnormalities have been suggested related to this syndrome such as vasomotor dysfunction, structural defects in small coronary vessels or microvascular resistance abnormality.

Totally, a combination of morphological and functional abnormalities in small vessels and epicardial coronary arteries contributes to the pathogenesis of CSFP\(^2\)-\(^4\). Besides, it has been known as an important clinical entity because of its crucial role in appearance of angina at rest or during exercise, acute myocardial infarction and hypertension\(^5\). Based on recent research, slow flow of the contrast in normal coronary arteries is not an infrequent finding in patients undergoing routine coronary angiography.

Overall, CSFP on is observed in approximately one per cent of patients undergoing coronary angiography\(^6\). An incidence of 7 per cent of CSFP was reported in patients suspected to have cardiovascular disease in another study\(^7\). Some studies suggested that impaired glucose tolerance might be an independent etiological factor for CSFP because of a strong link between impaired glucose tolerance and micro and macrovascular endothelial dysfunction\(^8\).

Some others showed the role of inflammatory biomarkers as predictors for slow flow appearance and demonstrated increased levels of soluble adhesion molecules in patients with CSFP that may be an indicator of endothelial activation and inflammation in these patients\(^9,10\).

Moreover, it was suggested that the patients with CSFP may have a high incidence of metabolic syndrome which leads to development of coronary microvascular dysfunction. The present study came to address the associated clinical profile and main clinical determinants of CSFP among Iranians.
**MATERIALS AND METHODS**

Patients with angiographically normal coronary arteries who underwent coronary angiography on suspicion of ischemic heart disease due to typical chest pain or ischemic findings on treadmill exercise test or myocardial perfusion scan were eligible for the study as the case group. Patients with the presence of atherosclerotic coronary artery disease, coronary ectasia, congenital coronary anomalies, uncontrolled hypertension, ventricular systolic dysfunction, left ventricular wall motion abnormalities, chronic obstructive pulmonary disease, severe anemia, history of cardiac revascularisation or patient refusal to give consent were excluded.

Our study population consisted of 46 patients with normal coronary arteries, but documented slow coronary flow on coronary arteriography (30 (%65.2) male, 51±10 years) and 92 control group patients with normal coronary arteries and normal coronary flow (30 (%65.2) male, 51±11 years) matched for age and gender. Patients’ demographics and medical history were obtained by an interviewing or from hospital recorded files. The subjects were defined as hypertensive if their blood pressure was ≥140/90 mmHg or if they were receiving any antihypertensive medication. Diabetes mellitus was defined as the presence of a history of antidiabetic medication usage or fasting glucose level above 126 mg/dl. Current cigarette smoking was defined as regular smoke of tobacco product/products one or more times per day within the 30 days prior to admission. Hypercholesterolemia was also defined as total cholesterol level ≥5.0 mmol/l, HDL-cholesterol level ≥1.0 mmol/l in men, or ≥1.1 mmol/l in women, and triglyceride level ≥2.0 mmol/l). we also defined opium use according to the DSM-IV Criteria for Substance Dependence as regularly consumption of inhalatory opium more than three times per week and/or oral opium daily (11). Coronary arteriography was performed by a femoral approach using the standard Judkins technique. Coronary blood flow was measured quantitatively using the Thrombolysis in Myocardial Infarction (TIMI) frame count which was derived from the number of cine-frames recorded from the first entrance of contrast to its arrival at the distal end of the left anterior descending artery, circumflex artery or right coronary artery.

TIMI frame counts were evaluated by an experienced observer blinded to the clinical status of the patients. CSFP was defined as TIMI grade 2 standard deviations (SD) from normal published range for that particular coronary vessel (5) and was determined using angiography by an expert cardiologist. The study was approved by the ethics committee of Kerman University of Medical Sciences and written informed consent was obtained from all patients.

Results were reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Student’s t-test for the continuous variables and the chi-square test (or Fisher’s exact test if required) for the categorical variables.

Multivariable logistic regression analyses were used to assess the predictive role of demographics and clinical profiles on slow flow appearance. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

The mean age of patients with CSFP was 51 ± 11 years (range 22 to 73 years). The most prevalent general risk factors for coronary disease in CSFP patients were cigarette smoking (56.5%) and hyperlipidemia (47.8%). The demographics and clinical characteristics of the patients are outlined in Table 1 and compared between the CSFP and the control group.

Overall incidence of systolic hypertension and diabetes mellitus were significantly higher in the CSFP group (p = 0.034 and p = 0.028, respectively). Opium addiction was also more frequent in those with CSFP (p = 0.008). There were however no significant differences in age distribution, current smoking and hyperlipidaemia between the two groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Slow flow group (n=46)</th>
<th>Normal group (n=92)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.67 ± 10.61</td>
<td>50.54 ± 10.54</td>
<td>0.556</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>21 (45.7)</td>
<td>39 (42.4)</td>
<td>0.716</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (34.8)</td>
<td>17 (18.5)</td>
<td>0.034</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (13.3)</td>
<td>3 (3.3)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>22 (47.8)</td>
<td>31 (33.7)</td>
<td>0.108</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>26 (56.5)</td>
<td>50 (54.3)</td>
<td>0.809</td>
</tr>
<tr>
<td>Opium addiction</td>
<td>20 (43.5)</td>
<td>20 (21.7)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number (%)
Multivariable logistic analysis showed that the two factors of opium addiction (OR = 3.807, 95% CI: 1.461 – 9.919, p = 0.006) and diabetes mellitus (OR = 7.067, 95% CI: 1.356 – 36.827, p = 0.020) were main independent predictors of CSFP with the presence of demographic variables as cofounders (Table 2).

**DISCUSSION**

Despite frequent risk factors for atherosclerotic coronary artery disease have been extensively studied; there are limited data about the etiology and clinical manifestations of CSFP and specific data on underlying predisposing factors for this phenomenon is insufficient in the medical literature. To our knowledge, there are only a few reports suggesting the clinical significance of this phenomenon.

Our intention was to explore this area. Recent reports estimated an incidence of 7% of this phenomenon in patients suspected to have cardiovascular disease. In those reports, main clinical features of CSFP were young age, chest discomfort or angina pectoris for a longer duration without accompanying cardiovascular disease or any coronary risk factors or muscle bridge by angiographic examination, but show significant distal CSFP in multiple vessels (5).

The main finding of current study is that the higher overall prevalence of diabetes mellitus is associated with CSFP, whereas, there are no significant differences in terms of hypertension, hyperlipidemia or cigarette smoking between the two groups with and without this syndrome. In our study, the prevalence of diabetes in those with CSFP was estimated as 13.3% that was lower than the reported range in similar studies (14.6 to 33.3%) (Table 3).

### Table 2: Main determinants of slow flow coronary syndrome among Iranians

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Multivariate p-value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.723</td>
<td>1.228</td>
<td>0.395 – 3.821</td>
</tr>
<tr>
<td>Age</td>
<td>0.825</td>
<td>0.995</td>
<td>0.953 – 1.039</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.074</td>
<td>2.769</td>
<td>0.905 – 8.472</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.020</td>
<td>7.067</td>
<td>1.356 – 36.827</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.355</td>
<td>1.454</td>
<td>0.658 – 3.212</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>0.895</td>
<td>0.929</td>
<td>0.310 – 2.785</td>
</tr>
<tr>
<td>Opium addiction</td>
<td>0.006</td>
<td>3.807</td>
<td>1.461 – 9.919</td>
</tr>
</tbody>
</table>

Hosmer – Lemeshow goodness of fit: $\chi^2 = 19.120$, $p = 0.014$

Area under the ROC curve: $c = 0.609$ (95% CI: 0.493 – 0.724)

### Table 3: Review of studies on medical profiles in slow coronary flow patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>Hypertension</th>
<th>Hyperlipidemia</th>
<th>Diabetes mellitus</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bae</td>
<td>China</td>
<td>2008</td>
<td>33.3</td>
<td>27.3</td>
<td>33.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Celebi</td>
<td>Turkey</td>
<td>2007</td>
<td>56.3</td>
<td>---</td>
<td>14.6</td>
<td>41.7</td>
</tr>
<tr>
<td>Nurkalem</td>
<td>Turkey</td>
<td>2009</td>
<td>43.0</td>
<td>---</td>
<td>17.0</td>
<td>44.0</td>
</tr>
<tr>
<td>Tekin</td>
<td>Turkey</td>
<td>2007</td>
<td>33.3</td>
<td>58.3</td>
<td>25.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Our study</td>
<td>Iran</td>
<td>2010</td>
<td>34.8</td>
<td>47.8</td>
<td>13.3</td>
<td>56.5</td>
</tr>
</tbody>
</table>
Not only, potential role of diabetes as a major risk factor for atherosclerosis has been clearly confirmed (12), the increased risk of major coronary event and its-related mortality in non-diabetic subjects with glucose intolerance has been also demonstrated (13). Putative mechanisms underlying the association between elevated glucose concentrations in the non-diabetic range and atherosclerosis include low density lipoprotein oxidation, hemostatic factors, advanced glycation end product formation on the vessel walls, increased endothelin 1 and inflammatory factors (14). Potential mechanisms by which hyperglycemia induces vascular dysfunction also include hyperglycemia mediated formation of oxygen derived free radicals and activation of protein kinase c (15).

Similar to ours, Binak et al. revealed that impaired glucose tolerance and postprandial hyperglycemia might play a role in CSFP pathogenesis independent of other factors (8). Some investigators did not detect any difference in fasting plasma glucose and insulin levels between CSFP and normal coronary flow subjects. In their studies, although insulin levels of CSFP patients were higher, it didn’t reach statistical significance (16). However, with respect to the relationship between other coronary risk profiles and CSFP, our study is in accordance with theirs so that fasting plasma lipid was not different between our two groups.

It was also shown that endothelial function measured by flow-mediated dilatation of the brachial artery may be impaired in people with CSFP in the absence of any cardiac risk factors such as smoking, diabetes and hyperlipidemia (17). It seems that larger studies to confirm our findings and to search for confirming role of diabetes and other coronary risk factors are needed.

This study also suggests that the presence of CSFP may be dependent on the regular opium use. Opium addiction is a major problem for every society including developing countries such Iran. The prevalence of opium addiction has estimated 2.0 to 2.8% among premenopausal female patients with slow coronary flow. In their studies, although insulin levels of CSFP patients were higher, it didn’t reach statistical significance (16). However, with respect to the relationship between other coronary risk profiles and CSFP, our study is in accordance with theirs so that fasting plasma lipid was not different between our two groups.

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REFERENCES


