Original Article
Abnormal nail fold capillaroscopic findings in patients with coronary slow flow phenomenon

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Abstract: The coronary slow flow phenomenon (CSFP) is the delayed opacification of coronary arteries in the absence of significant stenosis. The pathogenesis of CSFP has not been completely understood yet. There are several proposed mechanisms such as the structural and functional abnormalities in coronary microcirculation. Nail fold capillaroscopy is a simple, noninvasive examination of the microvasculature and suggested to be a useful technique for analysis in various inflammatory and autoimmune diseases. In this study; we hypothesized that; CSFP is a part of systemic vascular entity rather than a problem confined to coronary vasculature and our aim was to investigate the nail fold capillaries of the patients with CSFP and compare to those with normal coronary flow (NCF). The study was designed as a case-control study and total 25 patients (10 male, mean age 55 ± 9 years) with documented CSFP, and 24 patients (15 male, mean age 55 ± 11 years) with NCF were recruited. Nail fold capillaroscopy examinations were performed by video dermatoscopy in all patients and results were compared between two groups. The demographic and clinical characteristics were similar between patients of CSFP and NCF groups. Nail fold capillary abnormalities including dilatation, tortuosity and microhemorrhage were present in 15 (60%) patients in CSFP group and 5 (21%) patients in NCF group (p < 0.05 OR: 5.7 95% C.I 1.602-20.279). In this study, we found that the abnormalities in nail fold capillaries suggesting the presence of inflammation and anatomical changes were significantly higher in patients with CSFP.

Keywords: Coronary slow flow phenomenon, capillaroscopy, inflammation, microvascular, nail fold capillary, coronary artery disease

Introduction

The coronary slow flow phenomenon (CSFP) was first described by Tambe et al in six subjects presenting with chest pain syndromes [1]. It is an angiographic clinical entity in which the distal opacification of the coronary artery is delayed in the absence of significant coronary artery disease [2]. The reported prevalences for the CSFP range between 1-7% [3-5]. Clinically, this phenomenon occurs most commonly in young men and smokers, and patients admitted with acute coronary syndrome [2]. In addition to angina it has been associated with life-threatening arrhythmias and sudden cardiac death [6, 7].

The exact pathogenesis of CSFP has not been identified yet and is probably multi-factorial. Local and systemic pathologies including functional and morphological abnormalities in the microvasculature, endothelial dysfunction, inflammation, atherosclerosis and anatomical factors of epicardial arteries have all been implicated [8].

Nail fold capillaroscopy is a simple, noninvasive way for the examination of the microvasculature. During capillaroscopy, morphology of nail fold capillaries is evaluated by using a magnification system [9, 10]. Different nail fold capillary changes were defined and used to identify several rheumatic disorders [9, 11]. It has been studied mainly in systemic sclerosis, dermatomyositis, systemic lupus erythematosus, Sjögren’s syndrome, antiphospholipid syndrome, familial Mediterranean fever are some diseases in which nail fold capillaroscopy was
Capillaroscopic findings in coronary slow flow patients

reported to be a useful technique for microvascular analysis [11-13].

In this study, we evaluated the presence of capillaroscopic changes representing the abnormalities of the microvasculature in CSFP patients. We also compared nail fold capillary abnormalities with those of patients with normal coronary flow (NCF).

Materials and methods

Patient selection

Twenty-five patients (15 male, mean ages; 55 ± 11 years) with CSFP in at least one major epicardial coronary artery and 24 patients (10 male, mean ages; 55 ± 9 years) with NCF were included in the study. Patients’ past medical history and current medications were recorded. A detailed physical examination and an electrocardiographic and transthoracic echocardiographic evaluation were performed in all patients.

Patients with noncritical or critical stenosis and plaques in coronary arteries, valvular heart disease, cardiomyopathy, left ventricular systolic dysfunction, diabetes mellitus, thyroid disease, any autoimmune and connective tissue disease, malignancy, infection, and renal or hepatic failure were excluded from the study.

The study was conducted in accordance with Declaration of Helsinki. The institutional ethical committee approved the protocol, and written informed consent was obtained from all patients.

Coronary angiography protocol

The coronary angiographies were performed using the standard Judkins technique. Angiographic images were taken in standard right and left oblique views using cranial and caudal angulations. All patients received nitroglycerin during angiography either in the form of sublingual spray or intracoronary injection.

Figure 1. Capillaroscopy findings including normal (A), capillary dilatation (B), microhemorrhage areas (C), and tortuous capillaries (D).
Coronary angiograms of all patients were reviewed and TIMI frame counts (TFC) were determined for each coronary vessel as described by Gibson et al. [14]. The first frame was considered to be that at which > 70% lumen opacification with antegrade filling was noted. The final frames were determined 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 circumflex artery (Cx). The first branch of the posterolateral segment was used for the right coronary artery (RCA). Images were acquired at 15 frames/s and thus all values were multiplied by 2. Frame counts in the LAD were divided by a correction factor of 1.7 for its longer length. Any frame count exceeding 27 was considered to be abnormal and indicative of coronary slow flow based on the recommendations of Gibson et al. [14].

Nail fold capillaroscopy

Nail fold capillaroscopy was performed by a videodermatoscope (Molemax II, ×30). All patients had rest for at least 15 minutes before the procedure in the examination room in where the temperature was kept approximately 24°C.

All ten fingers except those affected by recent trauma were examined by videodermatoscope for the dilatation or tortuosity of the capillaries, and microhemorrhages. During procedure a transparent gel was used between the probe and the nail fold of each finger to improve image resolution and images were recorded with ×30 magnification.

Nail fold capillaries were evaluated regarding capillary morphology according to Maricq criteria modified by Bergman et al [15]. Capillary morphology was assessed as dilatation, tortuosity, and microhemorrhages (Figure 1). Dilatation was considered when there was homogeneous or local expansion of the capillary throughout its course. Microhemorrhage was defined in the presence of at least two punctate bleeding around a single capillary.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentage. The student t test was used to compare the normally distributed continuous variables. The Mann-Whitney U test was used to compare the continuous variables not distributed normally. For categorical data, Chi-square test and Fisher’s exact test were used. All analyses were conducted using SPSS statistical software, version 20 (SPSS, Chicago, Illinois). All statistical tests were two-sided, and statistical significance was determined at a p value < 0.05.

Results

The baseline demographic and clinical characteristics of coronary slow flow phenomenon (CSFP) and normal coronary flow (NCF) groups were similar (Table 1). Conventional transthoracic echocardiographic parameters including left ventricle dimensions and ejection fraction were also not different.

Patients in the CSFP group had significantly higher corrected TIMI frame count (TFC) in all of the major epicardial coronary arteries than those in the NCF group (Table 2). In CSFP group patients; CSFP was present in at least 1 coronary artery of 8 (32%), 2 arteries of 11 (44%) and 3 arteries of 6 (24%) patients. Right coronary artery (20 patients, 80%) was the predominant artery in which CSFP was detected, followed by circumflex (16 patients, 64%) and left anterior descending (12 patients, 48%) arteries.

Nail fold capillaroscopy findings of CSFP and NCF groups were given in Table 3. Dilatation in nail fold capillaries was the most common abnormality in CSFP group patients. Capillaroscopic abnormalities were present in 15 (60%) patients in CSFP group and 5 (21%) in the NCF group (Odds Ratio 5.7 95% confidence interval [1.602-20.279] p < 0.05).

Discussion

In this study, we demonstrated that the capillaroscopic abnormalities including dilatation, haemorrhage, and tortuosity were 5.7 times more common in patients with coronary slow flow phenomenon (CSFP) compared to those with normal coronary flow (NCF).

The coronary slow flow phenomenon is an angiographic clinical entity in which the distal opacification of the coronary artery is delayed in the
absence of significant coronary artery disease [2]. Male sex, body mass index, glucose levels, lipid level abnormalities, and metabolic syndrome were found as the significant predictors of CSFP [5, 16]. In patients with CSFP, different pathophysiological mechanisms were suggested. These mechanisms include; small vessel disease, endothelial dysfunction, atherosclerosis, inflammation, imbalance of vasoactive substances, anatomic abnormalities [2, 4, 17-24]. When all of these mechanisms are considered, it can be concluded that CSFP was a generalized vascular disease rather than a local abnormality affecting only the coronary blood flow. The studies performed on other vascular systems in patients with CSFP support this hypothesis. For example Karakaya et al found that cerebral blood flow velocity is significantly lower in patients with CSFP [25]. Camsari et al reported a significant correlation between coronary intima media thickness and carotid intima media thickness [26].

Small vessel disease is one of the important mechanisms suggested in pathogenesis of CSFP. Fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, as well as endothelial edema, thickening and degeneration in the coronary microvessels were reported [17]. Additionally, Mangieri et al found thickening of vessel walls with lumenal size reduction, mitochondrial abnormalities, and glycogen content reduction in left ventricular endomyocardial biopsies [4]. The results of our study showed that small vessel disease was a generalized condition rather than a local phenomenon related to coronary arteries.

Endothelial dysfunction and inflammation play important role in pathogenesis of CSFP. As an important indicator of endothelial dysfunction, endothelin-1 plasma concentrations were higher and nitric oxide plasma concentrations were lower in slow coronary flow patients [23, 27]. Additionally investigators found elevated levels of other markers of endothelial dysfunction such as plasma homocysteine, asymmetric dimethylarginine, adiponectin and paraoxonase activity [22, 28-30]. Regarding the inflammation, increased levels of the plasma concentration of high-sensitivity C-reactive protein, interleukin-6, plasma soluble adhesion molecules and E-selectin were reported [20, 21]. Although we did not perform an analysis of an inflammatory marker in this study, having similar capillaroscopic results with the other capillaroscopy studies performed on different inflammatory diseases might be the indicator of diffuse inflammation in CSFP patients.

Table 1. The demographic and clinical characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>NCF Group n=24</th>
<th>CSFP Group n=25</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55 ± 9</td>
<td>55 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Male Gender (%)</td>
<td>10 (41)</td>
<td>15 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>13.4 ± 1.6</td>
<td>14.2 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>201 ± 68</td>
<td>208 ± 48</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>48.0 ± 14.5</td>
<td>51.4 ± 10.4</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>118.8 ± 50.5</td>
<td>121.4 ± 38.5</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>154.6 ± 108.9</td>
<td>176.4 ± 84.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>23.3 ± 9.2</td>
<td>21.6 ± 9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>69 ± 10</td>
<td>75 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>59 ± 9</td>
<td>58 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>48.3 ± 5.2</td>
<td>51.3 ± 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>31.3 ± 5.8</td>
<td>36.8 ± 11.4</td>
<td>NS</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>35.5 ± 4.1</td>
<td>38.8 ± 7.9</td>
<td>NS</td>
</tr>
<tr>
<td>RV (mm)</td>
<td>26.0 ± 2.6</td>
<td>27.5 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic root (mm)</td>
<td>36.5 ± 6.4</td>
<td>37.1 ± 6.5</td>
<td>NS</td>
</tr>
</tbody>
</table>


Table 2. The mean corrected TIMI frame counts of groups

<table>
<thead>
<tr>
<th></th>
<th>NCF Group n=24</th>
<th>CSFP Group n=25</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>17.6 ± 4.4</td>
<td>28.6 ± 9.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Cx</td>
<td>20.9 ± 4.6</td>
<td>34.01 ± 10.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RCA</td>
<td>22.5 ± 4.6</td>
<td>38.8 ± 15.4</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Abbreviations: CSFP: coronary slow flow phenomenon, Cx: circumflex, LAD: left anterior descending, NCF: normal coronary flow, SBP: systolic blood pressure.
Capillaroscopic findings in coronary slow flow patients

Table 3. Normal and abnormal nail fold capillaroscopic findings of patients in coronary slow flow phenomenon and normal coronary flow groups

<table>
<thead>
<tr>
<th></th>
<th>NCF Group</th>
<th>CSFP Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=24 (%)</td>
<td>n=25 (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>19 (79)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>5 (21)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Dilatation</td>
<td>4 (17)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Microhemorrhage</td>
<td>1 (4)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Tortuosity</td>
<td>0</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: CSFP: coronary slow flow phenomenon, NCF: normal coronary flow.

Certain anatomic properties of coronary arteries were also reported to be correlated with CSFP [24, 31]. Kantarci et al showed that angulations of the main coronary arteries from the aorta detected by multidetector computed tomographic coronary angiography imaging were correlated with CSFP [31]. Nie et al showed that higher tortuosity and more distal branches in coronary arteries were associated with CSFP [24]. Although all of the reported anatomical properties were related to the coronary system, the abnormal dilatation and tortuous capillaries detected in this study were the anatomic abnormalities in a different vascular bed may suggest the idea of generalized anatomical disruption.

Nail fold capillaroscopy has been used for evaluation of microvascular abnormalities found in different disorders [11]. The most common one is systemic sclerosis, which includes vascular damage as the primary event in its pathogenesis [32]. Primary and secondary Raynaud’s phenomena are easily distinguished by nail fold capillaroscopy [33]. Nail fold capillaroscopic examinations were also performed diseases such as systemic lupus erythematosus, dermatomyositis, polymyositis, rheumatoid arthritis, primary Sjögren’s syndrome, familial Mediterranean fever [12, 34]. Abnormal capillaries were suggested to present an increased risk for connective tissue disease [35]. Capillaroscopy was reported to help to the noninvasive diagnosis and follow-up of several autoimmune systemic diseases [33].

Nail fold capillaroscopy has been also used for examining the microangiopathies in non-rheumatic systemic disorders [36]. A significant reduction in capillary density was found in hypertensive patients. Besides, a correlation was recognized between capillary density and mean diastolic blood pressure [37]. In another study, changes in the microvasculature were detected in subjects with early and subtle elevations in blood pressure [38]. In type 1 diabetics; the capillary diameters and density were found to be different compared to healthy controls. Gorska et al reported the nail fold capillaroscopy as a useful tool to screen premature atherosclerosis in patients with juvenile idiopathic arthritis [39].

Once the findings of our study interpreted with the results of other studies on the current literature, it can be concluded that the coronary slow flow phenomenon is a primarily an abnormality of coronary blood flow as a reflection of a generalized pathology affecting different microvascular systems accompanied by generalized inflammation.

Disclosure of conflict of interest

None.

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Capillaroscopic findings in coronary slow flow patients


Capillaroscopic findings in coronary slow flow patients


