The coronary slow flow phenomenon: characteristics, mechanisms and implications

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Abstract: The coronary slow flow phenomenon (CSFP) is an important, angiographic entity characterized by delayed progression of the injected contrast medium through the coronary tree. It is a frequent finding, typically observed in patients presenting with acute coronary syndromes. Although it is well known to interventional cardiologists for approximately four decades, the pathogenic mechanisms remain unclear. The clinical implications are significant, with over 80% of patients experiencing recurrent chest pain, resulting in considerable impairment in quality of life. This article will address in detail the characteristics, possible mechanisms, and clinical implications of this entity to provide further insight into its clinical significance and management strategies.

Key Words: coronary slow flow phenomenon; coronary tree; chest pain

Introduction

The coronary slow flow phenomenon (CSFP) is an angiographic clinical entity, characterized by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis. Although it is well-known to interventional cardiologists for approximately four decades, the pathogenic mechanisms are incompletely understood. Rather than representing a simple angiographic curiosity, CSFP has direct clinical implications, as it has been linked to clinical manifestations of myocardial ischemia, life-threatening arrhythmias, sudden cardiac death, and recurrent acute coronary syndromes (1-4). However, current clinical practice tends to underestimate the impact of CSFP due to the yet unknown mechanisms, its relative rarity, and the subsequent difficulties in conducting randomized trials to evaluate different treatment options. In this article, we will summarize the characteristics, possible mechanisms, and clinical implications of this entity to provide further insight into its clinical significance and management strategies.

Definition

Although a number of formal definitions have been proposed, the CSFP essentially consists of a delay in the progression of the contrast injected into the coronary arteries during coronary angiography. Representative angiographic images of CSFP and normal subjects are shown in Movie 1,2. This condition, which may affect one or all coronaries, was originally described by Tambe et al. in 1972 (5). Since then it has been accepted as an independent clinical entity, which is called ‘CSFP’, ‘coronary slow flow syndrome’ ‘syndrome Y’, or “primary” coronary slow flow (6-9). Importantly, ‘primary’ CSFP should be distinguished from the delay in the contrast progression in the context of coronary reperfusion therapy such as angioplasty or stenting for acute myocardial infarction, or other “secondary” causes of coronary slow flow. These include coronary artery ectasia, coronary artery spasm, valvular heart disease, or connective tissue disorders (8-10) (Table 1).

Clinical manifestation

CSFP is a frequent angiographic observation, with a reported incidence of 1%-7% in patients undergoing diagnostic angiography because of clinical suspicion of cardiovascular...
disease (6,11). Clinically, this phenomenon occurs most commonly in young men and smokers, and patient admitted with acute coronary syndrome (12). The clinical course is complicated, with over 80% of patients experiencing recurrent chest pain, most occurring at rest, necessitating readmission to the coronary care unit in almost 20% of affected patients (12). Most importantly, coronary slow flow has been described to be associated with life-threatening arrhythmias and sudden cardiac death (3, 4), probably due to increased QTc dispersion in these patients (13).

Further, Yilmaz et al. (14) recently delineated the clinical and laboratory features of CSFP compared to the control subjects without CSFP. Metabolic syndrome was more frequent in CSFP in the presence of higher total cholesterol, low-density lipoprotein-cholesterol, fasting glucose and body mass index levels. These data are in line with the observations that insulin resistant states (15) and impaired glucose tolerance (16) correlate with CSFP occurrence. These data suggest that a common underlying pathophysiologic mechanism of the metabolic syndrome and CSFP may be endothelial dysfunction.

**Diagnosis and evaluation**

CSFP in coronary angiographic studies was initially described subjectively by visual judgement (5). A semi-quantitative assessment of coronary blood flow is the thrombolysis in myocardial infarction (TIMI) flow grade classification, which reflects the speed and completeness of the passage of the injected contrast through the coronary tree (17). Although this widely used method of grading coronary flow has been a valuable tool for comparison of flow data in clinical trials, variability in the visual assessment may limit the broad clinical applicability. In contrast, as an objective, quantitative index of coronary flow, corrected TIMI frame count (CTFC) facilitates the standardization of TIMI flow grades and flow assessment. It represents the number of cine-frames required for contrast to first reach standard distal coronary landmarks (18).

Currently, by using CTFC as a quantitative index of coronary flow, coronary angiography is the only tool for the diagnosis and assessment of CSFP. Yet, owing to its invasiveness, this method does not permit long-term clinical follow-up and dynamic treatment evaluation. Recent advances of transthoracic Doppler echocardiography (TTDE) have enabled the non-invasive demonstration of coronary flow patterns in the left anterior descending (LAD) coronary artery (19-24). In this context, we measured coronary flow in the distal LAD using TTDE technique with a high success rate (92.3%) (Figure 1). Patients with CSFP exhibited lower coronary diastolic velocities of LAD, which was negatively correlated with CTFC (Figure 2). TTDE may provide a useful tool for the monitoring of treatment effect and long-term follow-up for CSFP. However, there is a lack of confirmation in clinical trials, and there is need for further evaluation of TTDE in the diagnosis of CSFP.

**Pathogenic mechanisms**

**Small vessel disease**

The coronary circulation is traditionally considered as a two-compartment model. The first compartment consists of epicardial vessels, which are also referred to as “conductance vessels”, because they do not pose any resistance to blood flow. The second compartment consists of “small vessels” of <400 μm (“resistive vessels”), which primarily regulate myocardial blood flow in the absence of any significant obstructive epicardial stenosis (25,26). Small vessel dysfunction has been typically involved in the pathogenesis of CSFP since its first description (5).

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**Table 1 Conditions associated with “secondary” coronary slow flow**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Mechanism of slow flow</th>
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<tbody>
<tr>
<td>Coronary ectasia</td>
<td>Reduced coronary flow velocity</td>
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<tr>
<td>Coronary spasm</td>
<td>Increased epicardial resistances</td>
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<tr>
<td>Coronary stenosis</td>
<td>Increased epicardial resistances</td>
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<tr>
<td>Embolism</td>
<td>Microvascular plugging</td>
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<tr>
<td>Heart failure</td>
<td>Increased intracavitary pressure</td>
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<td>Angioplasty and stenting of acute myocardial infarction</td>
<td>Reperfusion injury; impaired rheology</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Increased left ventricle end-diastolic pressure</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>Impaired rheology</td>
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Confirming this hypothesis, investigators reported fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, as well as endothelial edema, thickening and degeneration in the coronary microvessels (27). In parallel to these data, Mangieri et al. (11) found thickening of vessel walls with luminal size reduction, mitochondrial abnormalities, and glycogen content reduction in left ventricular endomyocardial biopsies. Subsequently, Beltrame et al. (28) indicated that CSFP was associated with a chronically elevated resting coronary microvascular tone characterized by low coronary sinus oxygen saturation as well as blunted responses to endothelial stimuli such as cold pressor or acetylcholine testing. Based on these data, it can be suggested that a combination of structural and functional abnormalities coexists in the coronary microcirculation.

**Endothelial dysfunction**

A growing body of evidence has suggested that the endothelium plays an integral role in the regulation of vascular tone, platelet activity, leukocyte adhesion, vascular smooth muscle proliferation, and is intimately involved in the development of atherosclerosis. It has been reported that reduced endothelium dependent flow-mediated dilatation (FMD) of the brachial artery was detected in patients with CSFP, suggesting that endothelial dysfunction is implicated in etiology of CSFP (29). Noteworthy is the recent finding demonstrating that baseline and peak exercise...
endothelin-1 plasma concentrations were higher and nitric oxide plasma concentrations were lower in slow coronary flow patients (30,31). In addition, patients with slow coronary flow had raised level of plasma homocysteine (32,33) and asymmetric dimethylarginine (34), a nitric oxide synthase inhibitor, both of which have a detrimental effect on endothelial function. More recently, decreased adiponectin concentrations (35) and paraoxonase activity (36), two significant markers of endothelial dysfunction have also been shown to be responsible for the etiopathogenesis of CSFP.

Subclinical atherosclerosis

Utilizing IVUS technique and flow rate measurements, Cin et al. (37) demonstrated that patients with CSFP have diffuse intimal thickening, widespread calcification along the coronary vessel wall, and non-obstructive atheromatous coronary changes. In line with these results, Pekdemir et al. (38) showed that most patients with CSFP have longitudinally extended massive calcification throughout the epicardial coronary arteries. These data are evidence that CSFP may reflect diffuse, non-obstructive atherosclerotic disease of epicardial vessels together with microvascular disease. These findings are supported by previous IVUS study indicating that diffuse atherosclerosis is often present in angiographically normal coronary arteries.

Inflammation

Inflammation is a contributing factor to several cardiovascular conditions and inflammatory mechanisms have also been observed in the context of CSFP. Li et al. (39) showed that the plasma concentration of high-sensitivity C-reactive protein and interleukin-6 was increased in CSFP patients. Similarly, coronary slow flow was associated with higher levels of plasma soluble adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin (40). Other inflammatory markers, such as red cell distribution width and serum uric acid levels, were also shown to be correlated with CSFP occurrence (41,42). Collectively, abnormalities in inflammatory parameters might be an indicator of endothelial dysfunction, both of which contribute to coronary slow flow.

Anatomic factors

Blood flow patterns in epicardial coronary arteries depend on the geometry and motion of these vessels (43). Disturbed laminar blood flow occurs in arterial segments with geometric irregularities such as curvatures, branches, and bifurcations (44). It is in these complex regions that low blood velocity rates tend to occur. Confirming this theory, recent observation with multidetector CT coronary angiography demonstrated that in patients with CSFP, the angulations of the main coronary arteries from the aorta were smaller determined (45). Based on this theory, we recently performed a case-control study to explore the correlation between anatomic properties of coronary arteries and CSFP occurrence. The results showed that the presence of CSFP was associated with higher tortuosity.
and more distal branches in coronary arteries. Accordingly, it is reasonable to assume that certain anatomic properties of coronary arteries could be predisposing to disturbed coronary flow and endothelial damage, ultimately leading to CSFP occurrence.

CSFP: a local or systemic condition?

Previous studies have suggested that a combination of morphological and functional abnormalities in small vessels and epicardial coronary arteries accounts for the etiology of CSFP. Another feature of CSFP, probably requiring special consideration is its frequent occurrence in association with more widespread vascular abnormalities.

Karakaya et al. (46) found that cerebral blood flow velocity is significantly lower in patients with CSFP. Endothelial abnormality appears to be a generalized process affecting both coronary and peripheral vasculature. Furthermore, in intravascular ultrasound investigation, Camsari et al. (47) found that there was a significant correlation between coronary intima-media thickness (IMT) and carotid IMT. In contrast, aortic distensibility and aortic strain, another predictor of subclinical atherosclerosis, were lower in patients with CSFP (48). It is reasonable to assume that early atherosclerosis is not restricted to the coronary circulation but also extends to large peripheral conduit arteries in patients with CSFP. Based on these data, our group hypothesized that CSFP is not an isolated local observation but may be part of generalized vascular disturbance (49). Taken together, CSFP may be caused by the interplay between local features coronary arteries and systemic pathophysiologic factors.

Therapy

Despite good prognosis of CSFP patients, the subsequent progress is frequently characterized by remitting, relapsing anginal episodes resulting in considerable impairment in quality of life. Unfortunately, currently available anti-anginal agents are of limited clinical value. To date, no large trial testing pharmacological approaches has been conducted, and the evidence available derives from small studies with inhomogeneous inclusion criteria. It was shown that dipyridamole and mibefradil, which both influence functional obstruction in arteries <200 μm, normalized CTFC but nitroglycerine, which dilates arteries with diameters >200 μm, did not (50,51). Importantly, statins appear beneficial for patients with CSFP, likely in part due to their anti-inflammatory properties (52-54). More recently, several studies demonstrated that nebivolol can both improve endothelial function and markedly ameliorate symptoms, thereby improving quality of life in patients with CSFP (55-57). Besides its beta-receptor blocking activity, nebivolol can cause endothelium-dependent vasodilatation through increased nitric oxide release (55).

Conclusions

CSFP is an important, angiographic finding typically observed in patients presenting with acute coronary syndrome, in particular unstable angina. This phenomenon should be considered a separate clinical entity with peculiar characteristics, pathogenic mechanisms, and defined diagnostic criteria. Previous studies have shown that small vessel disease, endothelial dysfunction, subclinical atherosclerosis, inflammation, and anatomic properties of coronary arteries are related to the occurrence of CSFP. Current findings support the hypothesis that CSFP may be part of systemic vascular disturbance.

Our current understanding is incomplete, but clinicians should be aware of this condition and its clinical significance. Further experimental investigations are needed to reveal the pathogenesis involved in CSFP. In addition, large-scale clinical studies are warranted to better characterize these phenomenon, and most importantly, investigate potential therapeutic approaches.

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