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An Insight of Coronary slow-flow phenomenon (CSFP)

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Abstract

Background: Coronary slow-flow phenomenon (CSFP) is characterized by delayed distal vessel opacification of contrast, in the absence of significant epicardial coronary stenosis. CSFP has been reported as a cause of chest pain and abnormal noninvasive ischemic tests and is often underrecognized. CSFP also known as cardiac syndrome Y, is characterized angiographically by delayed distal vessel opacification in the absence of obstructive coronary artery disease and represents a pathology related to underlying dysfunction of microvascular resistance. The diagnosis of CSFP is made via coronary angiography based on either a reduced Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or increased corrected TIMI frame count of greater than 27 frames in one or more epicardial vessel.

Keywords: Coronary slow-flow phenomenon

Background

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 **(1).**

This condition, which may affect one or all coronaries, was originally described by **Tambe et al. (4)** 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 **(2).**

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 **(3).**

Table (1): Conditions associated with "secondary" coronary slow flow **(3)**

Conditions	Mechanism of slow flow
Coronary ectasia	Reduced coronary flow velocity
Coronary spasm	Increased epicardial resistances
Coronary stenosis	Increased epicardial resistances
Embolism	Microvascular plugging
Heart failure	Increased intracavitary pressure
Angioplasty and stenting of myocardial infarction	Reperfusion injury; imp rheology
Valvular heart disease	Increased left ventricle end-dia pressure
Connective tissue disorders	Impaired theology

Historical background

Tambe et al. **(4)** first described this slow coronary blood flow using angiography in 1972, which gave origin to its clinical interest that has accelerated over the past decade **(4)**.

From the initial description, small vessel dysfunction appeared to be implicated. Subsequent myocardial biopsy pathology analysis in the 1980s and 1990s further suggested this mechanism. Over the course of the past decade, both observational and control studies by **Beltrame et al. (5)** have helped delineate this disorder from Syndrome X or other chest pain presentations in the absence of significant epicardial coronary artery disease **(5).**

Following this observation, more has been reported on the topic, including analysis of the coronary artery microvascular resistance, reports of the not-so benign clinical impact and finally novel therapeutic approaches beyond traditional antianginal regimens, which often do not improve the symptomatology **(6).**

Prevalence

The prevalence of CSFP has been reported to range between 1% and 5% of diagnostic coronary angiograms and is classically described in young male smokers with recurrent chest pain **(5).**

Regarding the coronary vasculature, the left anterior descending (LAD) artery, even when corrected for length, is most often involved (50% to 90% of the time), followed by the right coronary artery (28% to 45%) and the left circumflex (20%) **(6).**

Coronary angiograms in patients with CSFP are often referred to as "normal" or "mild nonobstructive disease," which lends itself into classifying these phenotypical patients as having "chest pain with a negative cardiac catheterization." Perhaps due to the lack of a fully understood pathophysiology, CSFP is frequently not identified as a root cause of abnormal ischemic testing and recurrent chest pain symptoms **(7).**

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Clinical manifestation

Prior to more recent investigations and explanations of the root causes, CSFP had been associated with adverse clinical conditions such as increased atherosclerotic burden, impaired diastolic function, endothelial dysfunction and left bundle branch block. How clinical cardiologists deal with this condition and its associations hinges very much on the recognition and understanding of the entity of CSFP **(8).**

With recognition on initial angiography, invasive and general cardiologists can have an important impact making a correct diagnosis. CSFP is a diagnosis that has now been better characterized with a certain degree of clinical distinction and prognosis. By establishing a correct diagnosis, cardiologists can avoid the need for additional noninvasive and repeat invasive testing. The impact can be influential to patients with reassurance and avoidance of emergency room visits, which can have a profound impact on patients psychologically and on our healthcare system economically with cost savings **(6).**

Understanding this disorder is also critical from a prognostic standpoint. Previously the reassurance given to patients with 'normal coronary arteries' may have been reasonably appropriate in those patients with classic syndrome X; to give that same information to a patient with true CSFP may not be appropriate. Given the reported examples of significant ventricular arrhythmias and even sudden cardiac death being linked to this condition, physicians should not trivialize the importance of these findings **(9).**

By contrast, long-term follow-up (mean of 7 years) of patients with syndrome X confirmed no deaths, MIs or significant worsening of left ventricular function. Clearly there is potential morbidity and even mortality connected with CSFP. Whether or not pharmacologic interventions can improve these outcomes still remains an open question. **(6).**

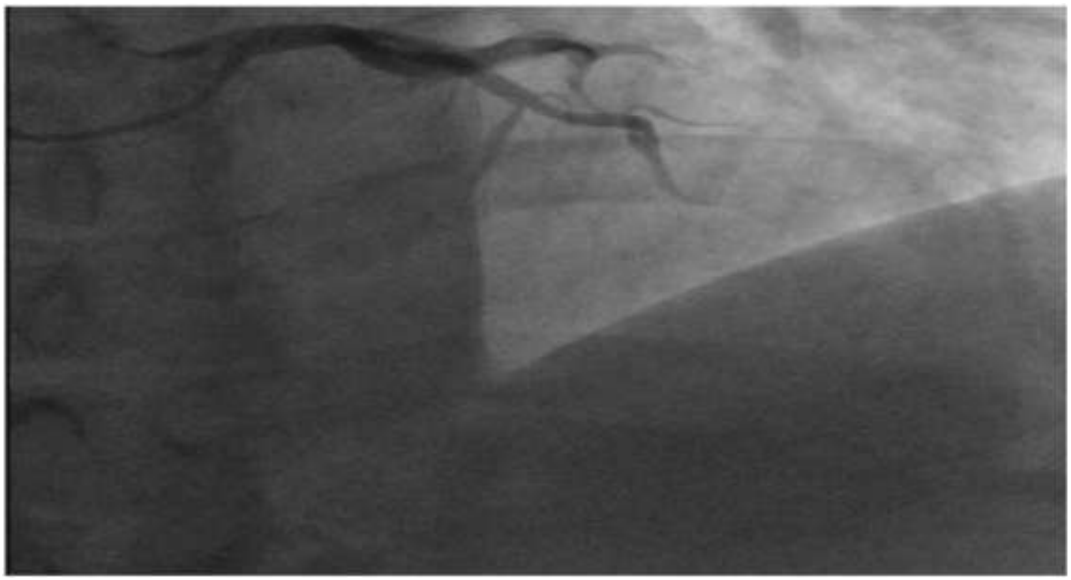

Figure (1): Coronary slow flow in both the left anterior descending (LAD) and left circumflex (LCX). Coronary angiogram at the 25th cine frame (utilizing 30 frames per

second acquisition) revealing contrast opacification only up to the mid-vessel segment of the LAD and LCX **(7).**

Clinically, this phenomenon occurs most commonly in young men and smokers, and patient admitted with acute coronary syndrome. These patients present with rest angina rather than with exertional symptoms, often bringing them to the emergency department. They often have resting ECG abnormalities (in up to a third of patients) yet normal exercise ECGs, normal myocardial stress ECGs and imaging, as well as normal resting ECGs **(2).**

It is not until proceeding to cardiac catheterizations, sometimes more than once, that the observation and diagnosis is made, which is often a source of frustration for patients and clinicians alike. Their typical initial clinical diagnosis is of unstable angina (Braunwald Class IIIB); a minority of patients may have ECG and cardiac biomarker evidence of MI (5–10%), which is clearly different than in patients with the classic and relatively benign syndrome X **(1).**

Proposed mechanisms

The coronary circulation consists of epicardial vessels and microvasculature. In the absence of epicardial stenosis, microvascular dysfunction may explain the pathophysiology of coronary slow flow phenomenon. Supporting this hypothesis, biopsy studies have revealed structural microvascular coronary abnormalities in slow flow patients. Reduced endothelium dependent flow-mediated dilatation (FMD) of the brachial artery has been detected in patients with coronary slow flow phenomenon, suggesting that endothelial dysfunction is implicated in the etiology. However, there are still multiple questions and controversies regarding the underlying pathophysiology and whether this pathology is limited to coronary arteries or is a manifestation of systemic vascular or endothelial disease remains to be answered **(2).**

Various medications have been evaluated for the treatment of CSFP. However, the actual efficacies of the majority of these pharmacological agents have not been established. Oral calcium channel blockers (CCBs) can attenuate the microvascular effects associated with coronary slow flow. Studies have utilized intracoronary (IC) CCBs to improve the TIMI frame count in patients with CSFP on catheterization. To our knowledge, however, no previous studies have uniformly evaluated the subsequent use of oral CCBs in patients who's angiographic slow-flow resolved with IC CCBs **(10).**

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. 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 **(5).**

Diagnosis and evaluation

CSFP in coronary angiographic studies was initially described subjectively by visual judgement. 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 **(11).**

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 **(2).**

The Corrected TIMI Frame Count vs the TIMI Frame Count

The raw TIMI Frame Count is the number of cine frames required for contrast to reach a standardized distal coronary landmark in the culprit vessel normalized to 30 frames /second. This value is not the "Corrected TIMI Frame Count (CTFC)," which adjusts for vessel length as well. A 1.7 correction factor is used to correct the TIMI frame counts for the average shorter length of the LCx or RCA, as compared with the LAD. When this correction is applied, this is called the corrected TIMI Frame Count (CTFC). A 1.6 correction factor is used to correct the TIMI frame counts for the average greater length of SVG's, as compared with the LCx or the RCA **(12).**

For example, if dye reached fully entered the Left Main Coronary Artery at frame 8 of a 15 frames per second cinefilm and reached the distal landmark of the LAD at frame 28, the unadjusted frame count would be 20, the raw TIMI Frame Count would be 40, and the Corrected TIMI Frame Count would be 68 **(13).**

Adjusting for different film speeds

30 frames/second is the standard film speed used in U.S. cardiac catheterization laboratories (more recently 30 frames/sec filming rates are widely available at international catheterization laboratories). Alternatives include 15 frames/second and 60 frames/second. The European equivalents of U.S. 30 frames/second and 15 frames/second are 25 frames/second and 12.5 frames/second, respectively. If the frame count was collected at a rate of 15 frames/second, then the frame count is multiplied by 2 to arrive at the CTFC **(14).**

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One of the more interesting observations learned with the use of the CTFC is the fact that flow in non-culprit arteries in the setting of acute coronary syndromes is "abnormal." For instance, the CTFC in uninvolved arteries in acute STEMI (30.5 frames) is in fact 40% slower than normal Adjunctive and rescue PCI following fibrinolysis restores flow in culprit vessels that is nearly identical to that of non-culprit arteries in the STEMI setting, but this flow remains slower than normal (21 frames) **(15).**

It is notable that PCI of the culprit lesion is also associated with improvements in the non-culprit artery after the intervention in both the STEMI and UA/NSTEMI settings **(14).**

Washout TIMI Frame Count

The washout TIMI Frame Count is the number of frames required for dye to exit the infarct related artery (clearance of dye from the ostium to the standardized distal TIMI landmark). In the first frame, unopacified blood occupies at least 70% of the ostium of the artery with antegrade motion down the artery. In the last frame, unopacified blood first enters (but does not completely fill) the standard distal TIMI landmark **(16).**

TIMI Myocardial Frame Count (TMFC) = frame when blush is the brightest minus frame when blush first appears.

Coronary flow reserve

Coronary flow reserve (CFR) is the maximum increase in blood flow through the coronary arteries above the normal resting volume. Its measurement is often used in medicine to assist in the treatment of conditions affecting the coronary arteries and to determine the efficacy of treatments used. Coronary flow reserve can be measured through a variety of methods including **(17)**:

- Digital subtraction cine angiography with coronary catheterization.
- Doppler echocardiography.
- Positron emission tomography (PET).
- Fractional flow reserve
- In ischemic heart disease, deciding which narrowing is the culprit lesion is not always clear-cut.

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 **(18).**

In the acute setting in the cardiac catheterization lab, certain vasodilators that have effects on the microvasculature (<200 μm in diameter), which include dipyridamole, adenosine

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and papaverine, can all yield significant improvements in coronary flow. Mangieri et al. observed that in this CSFP patient population flow could return to normal limits with infusion of dipyridamole, which was attributed to the microvascular dilation effect. Vasodilators, which dilate epicardial coronary arteries >200 μm in diameter, such as nitroglycerin do not successfully normalize the TIMI frame count (i.e., coronary flow) in the acute or chronic situations **(2).**

Reported clinical experience has shown that basic antianginal medical therapy has been limited in effectiveness in chronic treatment of the CSFP condition. Calcium channel blockers have shown some promise in treating microvascular dysfunction (although those more appropriately labeled as syndrome X) broadly, not those specifically with CSFP. One major exception to these generalizations has been a unique calcium T-channel blocker in addition to calcium L-channel blockade, with mibefradil. Rat studies by Gustafsson et al. demonstrated the predominance of T-channels in the microvasculature **(19).**

This abundance of T- versus L-channels in the microperiphery of the coronary beds may account for the lack of response to classic antianginal therapies, specifically the calcium channel blocker verapamil. It is sought to take advantage of these properties and use such an agent, mibefradil, to block these particular calcium channels. **(20).**

An important nonpharmacologic intervention that should not be overlooked in treating CSFP patients is smoking cessation. Smoking has clearly been associated with CSFP. This association is consistent with the observed impaired postischemic skin blood flow motion (depicted by laser Doppler flowmetry of the skin microcirculation) present in chronic healthy smokers, which suggests an early sign of endothelial and smooth muscle microvascular dysfunction **(21).**

Patients with chronic obstructive pulmonary disease, a systemic inflammatory disorder, were associated with a higher TIMI frame count (slow flow). This link could reflect microvascular impairment throughout vascular beds in chronic smokers. In addition, several authors have demonstrated that chronic smoking can result in increased plasma viscosity and fibrinogen levels and thus further increase microvascular resistance contributing to increased slow coronary flow. Although clinical studies exploring the impact of smoking cessation on CSFP are lacking, from a theoretical standpoint it would be appropriate to promote smoking cessation in addition to general coronary artery disease prevention measures **(2).**

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