Case Report

Coronary Slow Flow Phenomenon: A Case Report

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Abstract
Angina pectoris and abnormally slow contrast propagation into the unobstructed coronary artery, the so-called coronary slow flow (CSF) phenomenon was first recognized four decades ago but the etiology remained unclear. We reported a case of CSF phenomenon presenting with acute coronary syndrome in a middle-aged man who had multiple coronary risk factors. Intracoronary ultrasound revealed no significant plaque burden in related epicardial arteries. The pathogenic mechanisms of small artery disease and the role of endothelial dysfunction are discussed and relevant literature has been reviewed.

Keywords: coronary slow flow, unstable angina, small coronary artery disease, endothelial dysfunction, intracoronary ultrasound

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Coronary slow flow phenomenon (CSF) is an abnormal angiographic finding described by a delayed passage of contrast media to the distal coronary artery with no obstructive lesion.[1,2] Patients with CSF could present with various clinical settings, from angina, acute myocardial infarction and sudden death.[1-3] Although the CSF phenomenon had been known for 43 years,[4] its pathogenic mechanisms remained unknown.[2,3] We reported a case of CSF where the angiography and intracoronary ultrasound imaging showed no significant plaque burden. The possible mechanisms and options of treatment are discussed in detail.

Case report

A 58 year-old man, heavy cigarette smoker, presented at Chandrubeksa Hospital, in February 2015, with 10/10 chest heaviness, radiating to both jaws. Past medical history included non-insulin dependent diabetes mellitus, hypercholesterolemia and chronic low back pain which often required non-steroidal anti-inflammatory drugs (NSAIDs). The electrocardiogram (ECG) showed sinus rhythm, rate 64 beats per minute (bpm) which had no significant ST-T changes (Figure 1). Serial troponin-T was negative. Thyroid function test and electrolytes were normal. Bedsides this, the echocardiogram showed relative hypokinesia of the distal septum and apical area with preserved left ventricle (LV) systolic function, ejection fraction (EF) of 0.50. After administration of aspirin 325 mg, clopidogrel 75 mg and heparin, he still had 5/10 chest pain so a coronary angiography was recommended. Coronary angiogram showed no notable stenotic lesion in any of the epicardial arteries. However, abnormal slow contrast flow was visualized in both left and right coronary arteries but predominantly observed in the left anterior descending (LAD) artery (see Figure 2). The slow flow was normalized after an intracoronary administration of 200 mcg of nitroglycerin to both left and right arteries. To delineate the plaque burden, a 64 elements intracoronary ultrasound sonography (ICUS), catheter (Eagle Eye, Endosonic company),

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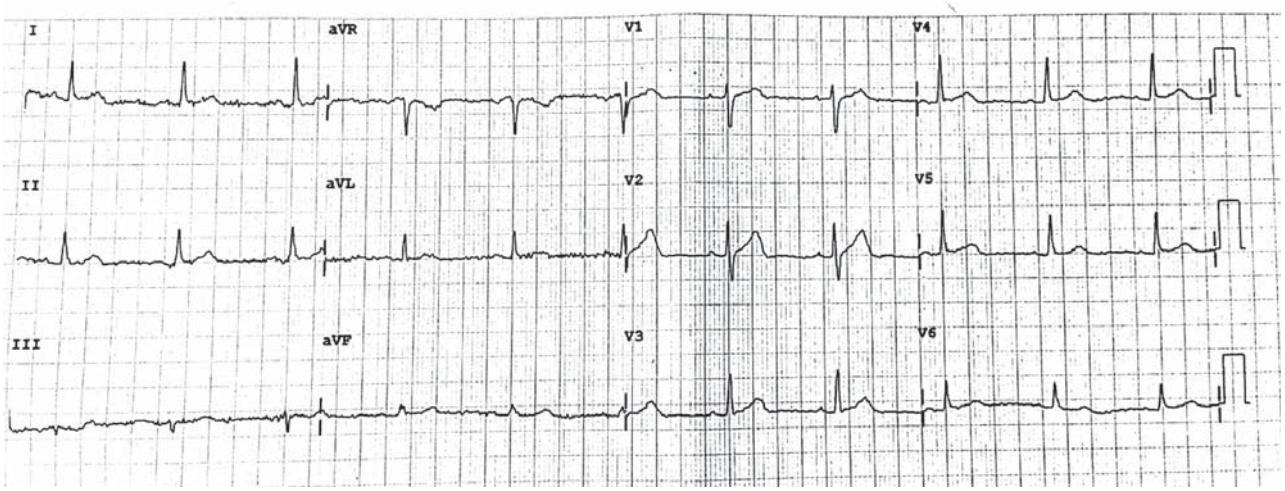

Figure 1: ECG during chest heaviness showed no remarkable ST-T changes.

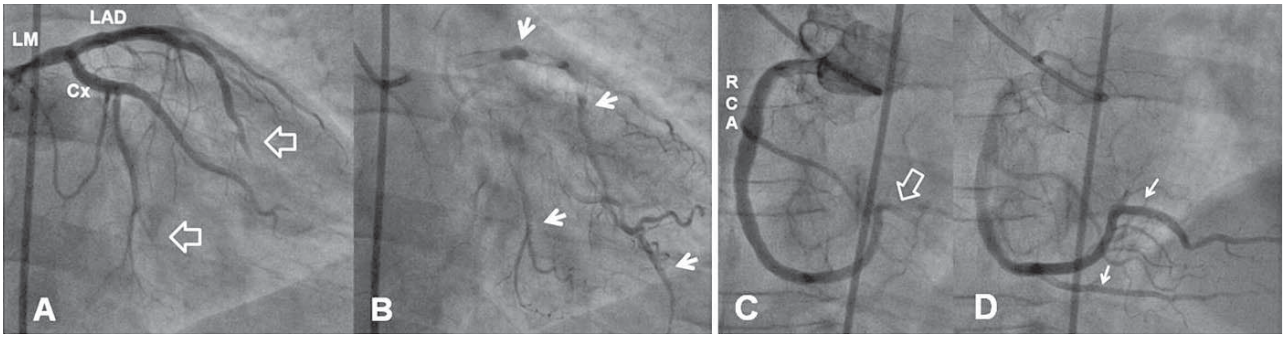

Figure 2: Coronary angiogram showed abnormally slow contrast flow (open arrow, A&C) in all three epicardial arteries and late filling in distal part (white arrow, B&D), LM: left main, LAD: left anterior descending, Cx: circumflex.

was examined and found only minimal concentric atheromatous plaque in the left main (LM), proximal to mid LAD artery (as shown in Figure 3). The patient was treated with Aspirin 81 mg/day, Clopidogrel 75 mg/day, Simvastatin 20 mg/day, Verapamil 120 mg/day and Glucophage 500 mg twice a day. He stopped smoking and took regular medication. He still had intermittent angina during the first three months and became pain free from then on.

Discussion

The Coronary Slow Flow (CSF) phenomenon

Coronary slow flow (CSF) was defined as a delay contrast filling to the distal part of epicardial coronary artery which had no significant luminal stenosis.[1,2] Its incidence ranged from 1-7% on diagnostic angiography.[1] Diagnosis of CSF is usually obtained by visual estimation of thrombolysis in myocardial infarction (TIMI) flow, grade 2 (which required ≥ 3 heart beats for complete distal contrast opacification) or worse.[2,3] A more precise diagnosis could be accomplished by using a corrected TIMI frame count (> 27 frame count).[5] After the original report by Tembe et al in 1972[4], CSF had been recognized as a distinct clinical entity, under various names, such as coronary flow syndrome,[6] coronary flow phenomenon,[7] a distinct subgroup of syndrome **"X"**[8] and syndrome **"Y"**.[9] Owing to the different mechanisms, CSF should be differentiated from the slow flow secondary to percutaneous coronary intervention (microvascular embolization and spasm), coronary ectasia (reduced flow velocity in enlarging vessel caliber), vasospasm (increase resistance in vasospastic epicardial artery), coronary stenosis (increase resistant in narrowed epicardial artery), heart failure and valvular heart disease (increased left ventricular end diastolic pressure).[2,3]

The diverse clinical manifestations

Patients with CSF could have various manifestations, ranging from mild chest discomfort, typical angina with no ST-T changes, to acute ST segment elevation myocardial infarction, syncope from non-sustained ventricular tachycardia and sudden cardiac death.[2,9-12] Like our case, most CSF patients are men, smokers and present with

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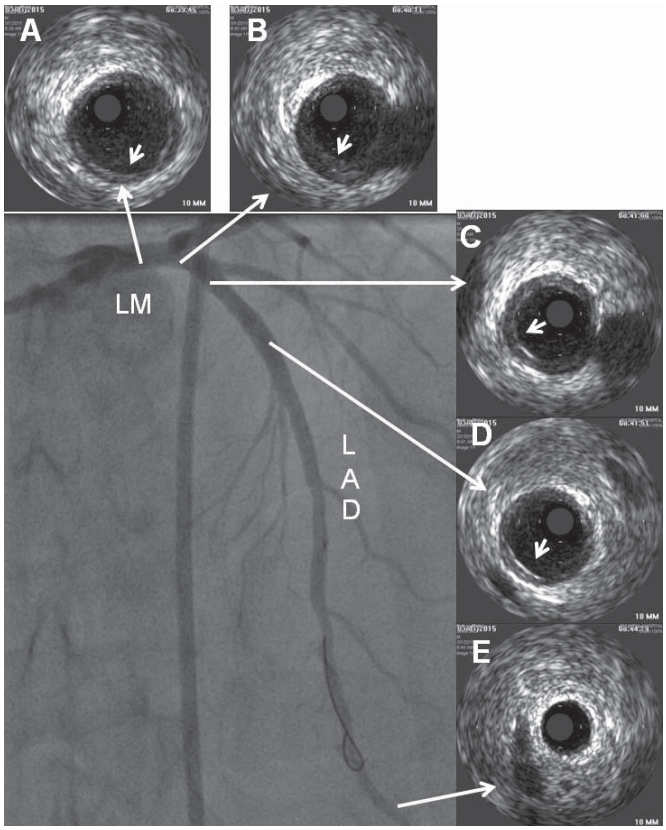

Figure 3: Intracoronary ultrasound sonogram delineated only minimal plaque burden in LM, proximal and mid LAD artery (white arrow, A-D) and no plaque in distal LAD artery (E). LM: left main, LAD: left anterior descending.

recurrent chest pain.[2,13] According to Beltrame JF et al.[13] a case control, observation study of 47 CSF patients and 47 controls delineated that the CSF group had a higher prevalence of current smokers (32% vs 9%, $p < 0.01$) presenting with rest angina and required admission (74% vs 21%, $p < 0.001$).

Underlying mechanism, small size artery pathology and endothelial dysfunction

Despite the uncertain etiologies, recent studies suggested the role of endothelial dysfunction in CSF syndrome. In 2006, Binak et al.[14] reported the association between the impaired fasting glucose and CSF phenomenon. Later, Yilmaz et al.[15] reported the higher values of fasting glucose, total and low-density lipoproteins (LDL) cholesterol, body mass index, among CSF patients compared with those of the control group. All of these conditions were the known causes of endothelial dysfunction[16] and they also presented in our reported case. The sick endothelium could not produce enough coronary vasodilating substances, i.e. prostacyclin and nitric oxide, and potentially enhanced microvascular vasoconstriction, causing the CSF phenomenon. The normalized CSF, after intracoronary administration of nitroglycerin, and the unremarkable plaque burden in our reported case also supported this endothelia dysfunction hypothesis.

While the pathology of epicardial coronary artery was not significant, like our case, abnormal pathologic findings were observed in the smaller size artery (< 400 micron) which was known as a resistant vessel for regulating myocardial blood flow.[17,18] Mosseri M, et al.[17] reported an edematous, thickening and degenerative endothelial cell, in conjunction with intimal proliferation, hypertrophic vascular media and fibromuscular proliferation of small vessel coronary artery disease. In addition, Mangieri et al.[18] found the abnormal mitochondria and vascular wall thickening in the intramural artery of the biopsied left ventricle. These findings indicated pathologic structural changes of the small coronary artery which regulated myocardial blood flow and possibly causing endothelial dysfunction.

Treatment and prognosis

Cigarette smoking is a known cause of endothelial damage and smoking cessation is mandatory. All coronary risk factors should be controlled to improve endothelial function. Nitroglycerin, the endothelial independent vasodilator, could normalize the CSF as shown in our patient. In nitroglycerin resistant cases, reversed CSF could be achieved by dipyridamole and mibefradil.[19,20] It was suggested that both drugs might affect the very small arteries (size < 200 micron) which could be the

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responsible site of CSF.[2] The new beta-blocking agent with its distinct property of releasing nitric oxide, nebivolol, had been reported to improve angina and quality of life in CSF patients.[21,22] Both simvastatin and atorvastatin had been shown beneficial in CSF patients, possibly from the anti-inflammatory effects.[23-25] In our case, after the patient stopped smoking and with treatment with simvastatin, verapamil, his angina was still present but to a lesser degree and required another hospitalization only once. No ECG changes or elevated biomarker was observed during this admission. After three months, his angina disappeared and he has been well since then until the present time. It was possible that his endothelial function might be improving after treating underlying dyslipidemia, diabetes mellitus and smoking cessation. It should be mentioned that the non-steroidal anti-inflammatory drugs, especially COX-2 inhibitor, must be avoided in CSF cases since they can inhibit COX-2 dependent prostacyclin synthesis and reduce nitric oxide production.[26,27] The majority of CSF cases usually have a favorable outcome[2,13] but recurrent chest pain is expected. In Beltrame JF, et al.[13] report of 64 CSF cases, 84% of patients still reported recurrent chest pain during the median follow-up period of 21 months.

Conclusion

CSF phenomenon is a rare distinct syndrome that could present in various clinical settings such as acute coronary syndrome, syncope and sudden arrhythmic death. Recent findings suggested the role of endothelial dysfunction, which occurred at the level of the resistant small coronary artery. Our reported case supported this hypothesis since no significant atheroma was found in the LM, LAD artery identifiable by means of intracoronary ultrasound imaging. The angina disappeared three months after controlling all risk factors, including smoking cessation, and with administration of aspirin, statin and verapamil. We hope that this reported case will raise our medical colleagues' awareness in an attempt to control all of the coronary risk factors to prevent the potentially lethal CSF phenomenon.

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