

# The functional importance of the left atrium in patients with coronary slow flow phenomenon

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## Abstract

The coronary slow flow phenomenon (CSFP) is relatively common in patients scheduled for coronary angiography, characterized by the delayed distal vessel opacification of contrast in the absence of significant epicardial coronary stenosis. Rather than a simple angiographic oddity, CSFP has significant clinical implications. Its etiology and pathophysiologic mechanisms have not been well elucidated so far, although several possible mechanisms have been proposed. The left atrial (LA) dysfunction initially attracted attention after the recognition of left ventricular (LV) systolic/diastolic dysfunction in patients with CSFP. In this commentary, we will address the clinical manifestations, possible pathophysiologic mechanisms, and the significance of LA function assessment in patients with CSFP, according to our research and existing literature.

**Keywords:** Coronary slow flow phenomenon (CSFP), Left atrial (LA) function, Two-dimensional speckle tracking echocardiography (2D-STE), Strain, Strain rate

## Introduction

The coronary slow flow phenomenon (CSFP), also known as cardiac syndrome Y, is relatively common in patients scheduled for coronary angiography. The incidence varies from 1% to 5.5% [1-4]. Since its original description by Tambe in 1972 [5], it has garnered intensive attention among interventional cardiologists. Currently, it is believed that CSFP is not just a simple angiographic curiosity, but rather, it has significant implications in clinic. Patients with CSFP can present with various symptoms, ranging from severe, such as acute coronary syndrome, fatal ventricular arrhythmias [6,7] and sudden cardiac death [8], to mild symptoms, such as chest tightness or discomforts [7,9]. Studies have shown that younger patients are more likely to develop CSFP, and its prevalence is higher in men [2,3]. Additionally, CSFP is more likely seen in smokers [7], patients with metabolic syndrome and high body mass index (BMI) [10], patients with anxiety, depression [11] and sleep apnea [12], patients with high uric acid level [13], and in patients with impaired renal function [14]. Hypertension, low high density lipoprotein cholesterol (HDL-c) levels, and high hemoglobin levels were also considered as independent predictors of this phenomenon [15].

The current adapted diagnostic criteria were proposed by John Beltrame in 2012 [16], in which CSFP is defined as delayed distal vessel opacification of contrast in the absence of significant epicardial coronary stenosis (where coronary artery stenosis  $\leq$  40%), with the Thrombolysis in Myocardial Infarction (TIMI) blood flow grade of 2, or corrected TIMI frame count (cTFC) of greater than 27 frames in one or more epicardial vessel. However, unlike the relatively clear definition, the pathophysiology of CSFP is not fully understood although several possible mechanisms have been proposed. In this commentary, we will summarize the possible pathophysiological mechanisms and the alteration of cardiac function, especially the changes of left atrial (LA) functions in patients with CSFP according to our research and existing literatures. Our purpose is to provide further insight into its clinical significance and management strategies.

## The Pathophysiological Mechanism

The exact pathophysiology of CSFP remains unclear so far. Several possible mechanisms have

been proposed, including the endothelial dysfunction theory [17], early atherosclerosis [18], microvascular disease [19,20], platelet dysfunction [21], changes in hemorheology [22,23], the ratio of monocyte-to-HDL cholesterol [24], and oxidative stress and local/systemic inflammatory response [19,25]. In addition, lipoprotein-associated phospholipase A2 [26], plasma choline [27], and serum salusin beta level [28] have also been identified as a predictive or diagnostic biomarker for CSFP in recent studies. In our most recent study [4], we found the percentage of monocytes is higher in patients with CSFP than that in control patients. Given the important role of monocytes in the occurrence and development of atherosclerosis [29,30], and the findings from coronary intravascular ultrasounds [18,31], we speculate that CSFP may be an early manifestation of coronary atherosclerosis or part of systemic atherosclerosis, initiating from endothelial dysfunction and microvascular dysfunction.

Endothelial dysfunction is a key event and represents one of the earliest events in the pathogenesis of many cardiovascular disorders [32]. Many risk factors of cardiovascular diseases, such as hypertension, diabetes mellitus (DM), hypercholesterolemia, smoking and obesity, can induce endothelial dysfunction through oxidative stress [33,34] or an imbalance in the production of vasodilatory agents [10,35]. Once endothelial dysfunction is present, it predisposes the vessel to vascular lesions, inflammation, vasoconstriction, thrombosis, atherosclerotic plaque formation and rupture. Therefore, endothelial dysfunction was considered as the “risk of the risk factors” [36]. Several studies have revealed high percentage of smoking, obesity, DM, dyslipidemia or hypertension in patients with CSFP [7,10,15]. This is consistent with our observation [4] that there were more smokers and subjects with high BMI in CSFP group.

Taken together, CSFP may be caused by gradual progression of endothelial dysfunction, microvascular disease, or early atherosclerosis, which then results in microvascular luminal narrowing. Moreover, the interplay between local and systemic inflammatory response further promotes this process.

### **The LV Functions in Patients with CSFP**

The effect of CSFP on LV function is still controversial [37-40]. Nurkalem et al. [37] analyzed LV systolic function of 45 patients with CSFP and compared with 21 normal subjects, they observed significant impairment in longitudinal left ventricular systolic function in patients with CSFP although LV-EF was preserved. However, in a study with a patient-to-patient matched design (including age, sex, hypertension and diabetes mellitus), Narimani et al. [40] had opposite conclusion. They didn't find the impaired longitudinal LV systolic and diastolic functions. Although the data on LV functions wasn't presented in our current study [4], we did observe significant impairment of LV systolic and diastolic functions in patients CSFP, our findings are consistence with most of current studies [37-39]. The discrepancy causing the different conclusion needs further investigation, however several factors should be taken into consideration, such as sample size, the method for cardiac function assessment. The studies with large sample size usually showed LV dysfunctions in patients with CSFP [37-39,41].

### **The Functional Importance of LA in Patients with CSFP**

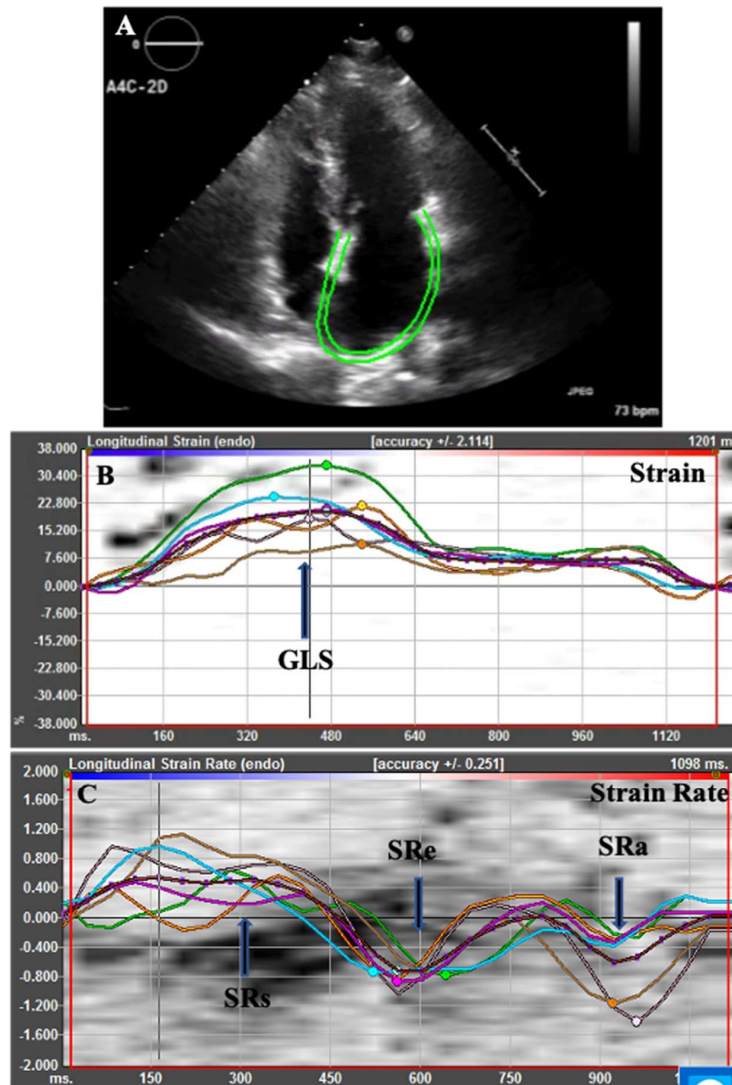
The left atrium (LA) plays an important role in ensuring proper performance of left ventricular (LV) function and systemic circulation. It is not simply just a conduit for LV filling. From the

hemodynamic perspective, the LA is divided into three phases: 1) the LA reservoir, acting as a reservoir for blood during LV systole and isovolumic relaxation, 2) a conduit, acting as a conduit function for transit of blood from the pulmonary veins to the LV during early diastole, and 3) a pump function, acting as an active contractile chamber to augment LV filling during late diastole, all of which contribute to LV filling [42-45]. Conversely, LV function influences LA function. LA reservoir function is affected by LV contraction and LA compliance. LA pump function is influenced by LV end-diastolic pressure, LV compliance, and LA contractile properties, while LA conduit function is dependent on LV diastolic properties [44,45]. Abnormal left atrial function can affect LV filling and cause a decrease in cardiac output. Therefore, LA function can be considered as a direct or indirect indicator for reflecting the status of cardiac function, particularly the LV diastolic function. It is well known that diastolic dysfunction is associated with the development of heart failure and is predictive of all-cause mortality [46]. Studies have also shown that LA function has an important clinical and prognosis impact and has proven to be an essential marker for cardiovascular disease prevention, as well as a recognized prognostic marker for diverse cardiovascular conditions [43,44,46,47].

In our recent study [4], we found a significant impairment of LA reservoir function and booster function in patients with CSFP despite the fact that the LA structure (size) has no significant differences between the CSFP group and the control group, which in turn indicates that the parameters of LA function is a sensitive marker for reflecting the changes of cardiac function. Furthermore, correlation tests have revealed a negative correlation between LA global longitudinal strain (LA-GLS) and mTFC, suggesting that the overall LA function will further decrease in conjunction with the decrease of coronary blood flow velocity. Our results were in-line with several other research groups consisting of the same kind of patients [48,49]. They had also found an impaired diastolic function of LV and LA dysfunction in patients with CSFP, assessed with conventional parameters and with two-dimensional speckle tracking echocardiography (2D-STE) analysis.

The significance of our study was to emphasize the importance of monitoring LA function in patients with CSFP. Recent studies have revealed that LA dysfunction may be an important factor in the pathophysiology of some cardiovascular diseases (e.g. heart failure with preserved ejection fraction (HFpEF)) rather than simply a secondary consequence of LV diastolic dysfunction although it is closely related with LV functions. It can also be used to reflect the severity of HFpEF [44,50], and LA dysfunction may represent a potential therapeutic target in patients with CSFP.

Another area of focus that should be highlighted and expanded upon is the method used for assessing LA function. Traditional methods using 2D echocardiography and the Doppler technique for the assessment of left atrial function were limited by hemodynamic loading and geometric measurements of the heart [44], making it so that it did not completely present information of the LA function. In our study, along with a number of other studies, 2D-STE was used for quantitative evaluation of LA function [4,44,51,52]. This technology quantifies the movement of the myocardium by tracking the trajectory of the myocardial acoustic spot during the cardiac cycle (Figures A, B, C). It gives an excellent assessment of the atrial deformation profile during an entire cardiac cycle by closely following the LA physiology [51,52]. In contrast to Doppler-



**Figure Schematic diagram of LA Strain and Strain Rate of Apical 4 Chamber Chamber**

**A:** Apical 4 chamber view; **B:** Strain curve: The global longitudinal LA strain curve (GLS); **C:** Strain rate curve: The longitudinal LA strain rate curve had a positive systolic peak (SRs), an early negative peak at early diastole (SRe), and a late negative peak at late diastole (SRa). GLS and SRs represented the LA reservoir function, SRe reflected the LA conduit function, and SRa was the indices of the LA booster function. For the strain measurement, LA was divided as 6 segments and each colored line presents different LA segment. The value of LA strain or strain rate is the average of the 6 segments (shown as red line with dot).

derived parameters, speckle tracking has the advantages of being angle-independent, less load-dependent than ejection fraction, and less affected by reverberations, side lobes, and drop out artifacts [51,52]. 2D-STE was found to be a feasible, reproducible, and sensitive method to assess LA function [4,50-53]. Several studies have shown that strain imaging can detect LA dysfunction before the manifestation of LA structural changes [53-55]. Reduction in the LA strain was found to be an important predictor in separating patients with clinical HFpEF and asymptomatic diastolic dysfunction [38].

To summarize, CSFP is a multifactorial entity in which endothelial dysfunction and local/systemic inflammatory status may play key roles. Patients with CSFP have impaired LA function, which could be used as a measurement of the severity of cardiac function and may represent a potential therapeutic target in the future. Further large-scale studies are warranted to determine the cut-off value of LA strain for scaling and their clinical outcome in patients with CSFP and LA dysfunction.

## Conflict of Interests Statement

The authors declare no conflict or competing interest with respect to the authorship and publication of this article. The authors have no financial relationship with any organization.

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## Consent for Publication

All authors have read and agreed to the published version of the manuscript.

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