Ventricular Dysfunction in Patients with Coronary Slow-Flow Phenomenon: A Single-center Case–control Study

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ABSTRACT

Background: Coronary slow-flow phenomenon (CSFP), characterized by delayed distal vessel opacification of contrast, in the absence of significant epicardial coronary stenosis, has effects on exercise capacity and clinical outcomes. The aim of this study was to explore the systolic and diastolic function of patients with CSFP and to compare it with a group of controls with normal coronary anatomy and flow.

Materials and Methods: In this case–control study, 45 consecutive CSFP patients and 45 age-, body mass index-, and presentation season-matched controls with normal coronary arteries and normal coronary flows were enrolled from Seyyedosohada Heart Center from March 2015 to March 2016. A transthoracic echocardiography was done by a blinded echocardiographer using both conventional and tissue Doppler imaging techniques.

Results: Patients with CSFP were more likely to be male (P = 0.006) and smoker (P = 0.02) compared to controls. Other risk factors were not different between the two groups. There were no differences between groups in terms of the peak early (E) and late (A) diastolic velocities, deceleration time, early (E') and late (A') peak diastolic velocities at the mitral annulus, and the systolic mitral annular velocity (S'). Global longitudinal strain and peak systolic strain rates was lower in patients with CSFP compared to controls (−16.7% ± 2.4% vs. −18.9% ± 1.6%, P < 0.001 and 1.10 ± 0.1 vs. 1.24 ± 0.3, P = 0.008, respectively).

Conclusion: Patients with CSFP showed signs of the left ventricular systolic dysfunction in tissue Doppler echocardiography, which underlines the importance of close follow-up in these patients. Patients with CSFP should be screened for ventricular function preferably by tissue Doppler echocardiography.

Key words: Case–control, coronary slow-flow phenomenon, echocardiography

INTRODUCTION

Coronary slow-flow phenomenon (CSFP), that was first described by Tambe et al., in 1972,[1] is characterized by delayed distal vessel opacification of contrast, in the absence of significant epicardial coronary stenosis.[2] For diagnosis, first, the alternate mechanisms of delayed coronary contrast progression, including coronary artery disease, coronary artery spasm, distal embolization, no-reflow as a consequence of coronary intervention, and coronary artery ectasia causing turbulent nonlaminar blood flow need to be ruled out.[3]

Its incidence is estimated to be up to 7% among patients with suspected cardiovascular disease who...
undergo coronary angiography. CSFP impairs exercise capacity, and majority of patients present to the emergency department and they are hospitalized for recurrent chest pain.

CSFP is purported to represent a pathology related to coronary microvasculature, and endothelial dysfunction. Increased plasma levels of endothelin-1, and decreased levels of nitric oxide are proposed as potential mechanisms for this phenomenon.

Histopathologic studies have reported cellular edema, microvacular thickening with luminal narrowing, myofibril disorganization, and fibromuscular hyperplasia in patients with CSFP. CSFP is also linked to some levels of myocardial ischemia. For example, cardiac magnetic resonance spectroscopy data in these patients have shown reduced myocardial ratio of phosphocreatine to adenosine triphosphate, consistent with cellular ischemia.

Whether the above-mentioned pathophysiologic changes affect the cardiac function or not is yet to be established. At present, there is controversy about whether the diastolic function, systolic function, or both are impaired in patients with CSFP.

Roughly, two-thirds of CSFP patients were shown to have functional and perfusion abnormalities that match the coronary territories demonstrating the delayed vessel opacification with contrast.

In this study, the aim was to explore the systolic and diastolic function of patients with CSFP and to compare it with a group of controls with normal coronary anatomy and flow.

MATERIALS AND METHODS

This case-control study was approved by the Institutional Review Board and the Ethics Committee of the Urmia University of Medical Sciences. Written informed consent was obtained from all participants prior to their enrollment to the study.

In the Seyyedoshohada Heart Center of Urmia University of Medical Sciences (Urmia), a total of 900 patients underwent coronary angiography for the acute chest pain suspicious of coronary artery disease between March 21, 2015 and March 19, 2016. 45 patients among these 900 was diagnosed with CSFP and were enrolled as "case" into this study.

The participants were selected among those who presented to the hospital with acute chest pain, clinically diagnosed as "unstable angina," had a positive noninvasive diagnostic test including exercise tolerance test, stress echocardiography, or myocardial perfusion imaging, and were a candidate for coronary angiography. Patients with the diagnosis of ST-segment elevation and non-ST elevation myocardial infarction were not included.

Forty-five age-, body mass index (BMI)-, and presentation season-matched controls with normal coronary arteries and normal coronary flows were also included. We excluded patients with bundle branch block, atrial fibrillation, paced rhythm, atroventricular block, moderate-severe valvular heart disease, prosthetic heart valve, any form of cardiomyopathies and heart failure, congenital heart disease, coronary artery ectasia, major coronary spasm, previous history of myocardial infarction, uncontrolled hypertension, systemic diseases including hyperthyroidism, hypothyroidism, malignancy, pulmonary, hepatic, renal, hematological disorders, and those with poor echocardiographic images.

Coronary angiography

All patients underwent coronary angiography using the Judkins technique. Coronary flow was quantified according to the thrombolysis in myocardial infarction frame count (TFC) method for the left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA) arteries.

This technique counts the number of cineangiographic frames, recorded at 25 frames/sec, from initial contrast opacification of the proximal coronary artery to opacification of the distal arterial landmarks. Distal bifurcation of the LAD and LCX and the first branch of posterolateral segment in the RCA were used as the landmark arterial landmarks.

Since the LAD is usually longer than the other two major coronary arteries, TFC for LAD was corrected by dividing it by 1.7. TFC measurements were performed for LAD and LCX in the right anterior oblique projection with caudal angulation and RCA in the left anterior oblique projection with cranial angulation.

Coronary slow-flow phenomenon

CSFP was defined as TFC of > 27 frames in the coronary angiography of at least one epicardial vessel in the absence of any angiographic lesion ≥ 40%.

Echocardiography

Transsthoracic echocardiography was done the day before undergoing coronary angiography in all patients and controls in the left lateral decubitus position and according to the guidelines of the American Society of Echocardiography. The echocardiography images were acquired at the frame rate of 58 Hz.

The left ventricular (LV) wall thickness and diameter were measured in the parasternal long-axis view using the two-dimensional M-mode echocardiography. Doppler assessments were done by placing the pulse-wave Doppler sample volume at the tips of the mitral valve on apical four-chamber view. Tissue synchronization images were obtained for all individuals in three standard apical views using the Vivid 6 (General Electric) system, and 3–5 consecutive cardiac cycles during quiet respiration were stored to be analyzed offline later.
Segmental longitudinal strain and strain rates (SR) were analyzed in a 12-segment model of the left ventricle. The echocardiographer who analyzed the stored images was blinded to the patient’s clinical condition and angiographic findings.

**Statistical analysis**
Categorical variables were summarized as frequency and percentages and compared between CSFP and control groups using the Pearson Chi-square test or Fisher’s exact test, as appropriate. Continuous variables were summarized as mean with standard deviation and compared using the independent t-test.

**RESULTS**

Among 900 patients, who underwent coronary angiography for the investigation of acute chest pain between March 2015 and February 2016, 45 patients were identified as CSFP and enrolled in this study.

The CSFP was observed in all three major coronary vessels in 14 (31.1%) patients, in two vessels in 16 (35.6%) patients, and in a single epicardial vessel in 15 (33.3%) cases. LAD, LCX, and RCA were involved, respectively, in 34 (75.5%), 25 (55.5%), and 28 (62.2%) of patients. Forty-five age-, BMI-, and presentation season-matched healthy controls were also selected randomly for the control group. Patient’s demographic and clinical characteristics are presented in Table 1.

Patients with CSFP were more likely to be male (62.2% vs. 33.3%, $P = 0.006$) and smoker (42.5% vs. 18.4%, $P = 0.02$) compared to controls. Other cardiac risk factors were not different between the two groups [Table 1].

Echocardiographic measures of LV systolic and diastolic function were compared between patients with CSFP and controls in Table 2. LV ejection fraction was normal (≥55%) for all patients in both groups. There were no differences in the peak early (E) and late (A) diastolic velocities, deceleration time, left atrial and LV dimensions among patients with CSFP and controls. Right atrial and ventricular dimensions were also comparable between the two study groups.

The only significant difference observed between groups in conventional echocardiography was the significantly higher thickness of interventricular septum in the CSFP groups compared to their counterparts ($1.05 \pm 0.20$ vs. $0.95 \pm 0.13$, $P = 0.009$).

The early (E’) and late (A’) peak diastolic velocities of the mitral annulus displacement, and the peak systolic mitral annular velocity (S’) were not different between patients with CSFP and controls. Nevertheless, when accounted for the confounding factor of sex, female CSFP patients had a significantly lower S’ as compared to the female controls ($6.8 \pm 1.0$ vs. $7.5 \pm 1.0$, $P = 0.03$), while there was no difference between the two groups in men ($7.7 \pm 1.1$ vs. $8.1 \pm 0.9$, $P = 0.28$).

Global longitudinal strain (GLS) was impaired and lower in all three standard views in patients with CSFP when compared to controls, with an average GLS of $−16.7\% \pm 2.4\%$ in the CSFP group versus $−18.9\% \pm 1.6\%$ in the control group ($P < 0.001$). Peak systolic strain rates (SRs) were lower in basal segments in CSFP patients when compared to controls ($1.10 \pm 0.1$ vs. $1.24 \pm 0.3$, $P = 0.008$).

**DISCUSSION**

The prevalence of CSFP has been reported to range from 1% to 7% among diagnostic coronary angiograms.[2-4] Its prevalence in our cohort of patients who underwent coronary angiography was 5%, which was similar to several previous studies.[17-19] Patients are generally described as young male smokers with recurrent chest pain,[2,20-21] hypertension[22] and metabolic syndrome.[23]

Similar to previous studies, which showed male sex to be an independent predictor of CSFP,[17,22,24] male sex was associated with CSFP in our study population. There was no significant difference between groups in terms of other risk factors, an observation that was also reported in several other studies.[25]

Echocardiographic parameters of cardiac function measured by both conventional echocardiography and tissue Doppler imaging (TDI) technique did not show evidence in favor of systolic or diastolic dysfunction in this study, but the longitudinal strain and SR were significantly lower in the CSFP group. Using conventional echocardiography, Sezgin et al. found higher A velocity, decreased ratio of early to late transmural filling velocities (E/A), prolonged isovolumic relaxation time, but no systolic dysfunction in patients with CSFP as compared to controls.[26]

Similarly, Chen et al. reported lower E peak value and E/A ratio in the CSF group compared to controls.[27]

In this study, the diastolic or systolic function was not different between CSFP patients and controls using.

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**Table 1: Patients characteristics in two study groups**

| Age (year) | CSFP (n=45) | Control (n=45) | P  |
|------------|-------------|---------------|----|
|            | 52.6±9.7    | 53.2±8.3      | 0.74 |
| Male sex, n (%) | 28 (62.2%) | 15 (33.3%) | 0.006 |
| BMI (kg/m²) | 29.2±4.5    | 28.4±4.5      | 0.38 |
| Familial history of CAD, n (%) | 5 (12.5) | 6 (15.8) | 0.67 |
| Medical history, n (%) |            |               |    |
| HTN | 8 (20.0) | 13 (34.2) | 0.15 |
| DM | 5 (12.5) | 3 (7.9) | 0.50 |
| Dyslipidemia | 5 (12.5) | 9 (23.7) | 0.19 |
| Current/previous smoker | 17 (42.5) | 7 (18.4) | 0.021 |

BMI: Body mass index, CSFP: Coronary slow-flow phenomenon, DM: Diabetes mellitus, HTN: Hypertension, CAD: Coronary artery disease
Table 2: Echocardiographic findings in patients with coronary slow‑flow phenomenon and controls

|                         | CSFP (n=45)     | Control (n=45) | P     |
|-------------------------|-----------------|----------------|-------|
| **LVEDD (cm)**          | 4.44±0.41       | 4.36±0.47      | 0.40  |
| **LVESD (cm)**          | 3.26±0.50       | 3.13±0.40      | 0.18  |
| **IVS (cm)**            | 1.05±0.20       | 0.95±0.13      | 0.009 |
| **LA area (cm²)**       | 14.41±2.75      | 14.11±2.59     | 0.59  |
| **LA diameter (cm)**    | 2.93±0.38       | 2.81±0.22      | 0.09  |
| **RA area (cm²)**       | 12.18±2.11      | 11.68±2.48     | 0.50  |
| **RV diameter (cm)**    | 2.73±0.19       | 2.71±0.27      | 0.77  |
| **E (cm/s)**            | 0.62±0.13       | 0.67±0.14      | 0.10  |
| **A (cm/s)**            | 0.69±0.14       | 0.69±0.11      | 0.94  |
| **DT (ms)**             | 208.69±37.85    | 207.07±37.60   | 0.83  |
| **Tissue Doppler imaging** |                |                |       |
| **E’ (cm/s)**           | 8.53±2.09       | 8.87±2.13      | 0.45  |
| **A’ (cm/s)**           | 9.11±1.60       | 9.21±1.69      | 0.77  |
| **S’ (ms)**             | 7.40±1.19       | 7.73±1.07      | 0.16  |
| **Average GLS (%)**     | 16.72±2.49      | 18.96±1.65     | <0.001|
| **GLS A2C (%)**         | 16.77±2.99      | 19.82±2.16     | <0.001|
| **GLS A4C (%)**         | 17.05±2.44      | 19.26±2.33     | <0.001|
| **GLS PLAX (%)**        | 16.34±3.47      | 17.93±2.32     | 0.012 |
| **Average SR basal segments** |         |                |       |
| **SR BA (s⁻¹)**         | 1.10±0.17       | 1.24±0.30      | 0.008 |
| **SR BI (s⁻¹)**         | 1.27±0.29       | 1.37±0.53      | 0.28  |
| **SR BL (s⁻¹)**         | 0.91±0.23       | 1.06±0.24      | 0.002 |
| **SR BS (s⁻¹)**         | 1.41±0.45       | 1.54±0.54      | 0.24  |

A: Late diastolic mitral inflow velocity, A’: Early diastolic velocity at mitral annulus, A2C: Apical 2 chamber view, A4C: Apical 4-chamber view, BA: Basal anterior segment, BI: Basal inferior segment, BL: Basal lateral segment, BS: Basal septum segment, CSFP: Coronary slow-flow phenomenon, DT: Deceleration time of the mitral E-wave, E: Early diastolic mitral inflow velocity, E’: Early diastolic velocity at the mitral annulus, GLS: Global longitudinal end-systolic strain, IVS: Interventricular septum, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LVEDD: Left ventricular end-diastolic diameter, PLAX: Parasternal long-axis view, SR: Peak systolic strain rate, S’: Peak systolic mitral annular velocity

the conventional echocardiography. Other studies also failed to find LV systolic dysfunction in patients with CSFP using conventional echocardiography.[26,28]

Conventional echocardiography might not be the best modality to screen for functional dysfunctions in patients with CSFP, and other echocardiographic methods such as TDI could be considered. TDI is demonstrated to have excellent ability to quantify regional myocardial dysfunction,[8] and better performance in patients with CSFP.[28]

In this study, TDI-driven transmitral velocities were not different between the study groups, but there were significantly lower GLS and SRs in patients with CSFP. TDI allows quantitative assessment of regional myocardial systolic and diastolic dysfunction, and several studies have shown LV systolic and diastolic function abnormalities when assessed this patient population by TDI.[8,28,29]

In this study, the peak systolic SR was significantly lower in basal myocardial segments in patients with CSFP compared to controls. Few studies in the literature that used speckle tracking echocardiography for evaluating patients with CSFP have reported variable results,[29,30] but most reported reduced SR in all basal, mid, and apical segments.

The differences could be due to various epicardial artery or microvascular involvement, or anatomic features such as curvatures and branches, but this needs further investigation in future studies.

Impaired LV systolic function observed in CSFP patients underlines the necessity of close follow-up in these patients for risk stratification, lifestyle modification, and potential treatment.[5] Several pharmacologic therapies have been proposed with different mechanisms of effect, including oral or intracoronary calcium channel blockers, anti-angina, and vasodilator medications, for example, nicorandil, platelet cAMP-phosphodiesterase inhibitors such as dipyridamole, statins, angiotensin-converting enzyme inhibitors, and alpha channel blockers.[2]

The study had several limitations that are noteworthy. Although we have studied several major risk factors in our study population, there might be other covariates missing here. Despite the advantages of echocardiography, such as being noninvasive and widely available in almost all hospitals in the world, it is sensitive to patient echogenicity. However, TDI-driven LV systolic assessment is less influenced by body habitus as shown by previous studies.[31]

In this study, we have not evaluated whether the number of affected coronary arteries may further influence the myocardial function in patients with CSFP. This can be explored further in future studies.

CONCLUSION

Five percent of patients who undergo diagnostic treatment due to various epicardial artery or microvascular involvement, or anatomic features such as curvatures and branches, but this needs further investigation in future studies.
coronary angiography were diagnosed with CSFP, and these patients showed signs of LV systolic dysfunction, which underlines the importance of close follow-up in these patients. Patients with CSFP should be screened for ventricular function preferably by tissue Doppler echocardiography.

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**Conflicts of interest**

There are no conflicts of interest.

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