



Assessment of Left ventricular function in coronary slow flow by two-dimensional speckle tracking dobutamine stress Echocardiography.

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Abstract

Background: The Coronary Slow Flow Phenomenon (CSFP) is defined as delayed distal vessel contrast opacification without any evidence of obstructive epicardial coronary artery disease. Medical literature contains conflicting data regarding the effects of CSFP on left ventricular functions assessed by conventional echocardiography or tissue Doppler imaging.

Material and methods: Patients with chronic stable angina were referred for coronary angiography from February 2022 to December 2022 at the Department of Cardiology, Faculty of Medicine, Kafrelsheikh University Hospitals. 50 patients with CSFP and 50 age-and-sex-matched controls without CSFP were enrolled in the study. CSFP was diagnosed by TIMI Frame Count (TFC). GLS of LV was measured by two-dimensional (2D) STE in addition to other conventional and tissue Doppler parameters to assess LV diastolic and systolic functions.

Results: LV GLS was lower in CSFP group patients (-15 ± 2.73) compared to the control group (-17.19 ± 2.54) ($p=0.001$). There was a statistically significant negative correlation between mean TFC and LV GLS ($r=-0.33$, $p=0.002$). LVEF by the modified Simpson method was lower in the CSFP group ($57.77 \pm 5.66\%$) compared to the control group ($59.29 \pm 3.32\%$) but with no statistical significance ($p=0.18$). Left atrial diameter LAVI was larger in the CSFP group compared to the control group (p

Conclusions: CSFP impairs LV systolic and diastolic function, using 2D speckle tracking dobutamine stress echocardiography; the most pivotal findings reveal that dynamic assessments under different dobutamine infusion rates highlighted substantial alterations in left ventricular function. Specifically, left ventricular strain (LS), strain rate during systole (LSRs), and strain rate during early diastole (LSRed) demonstrated significant differences across varying infusion rates, with notable decrements in LS and LSRs as dobutamine dosage increased.

Keywords: Dobutamine; Stress Test; Coronary slow flow; Ischemia; Echocardiography; Speckle tracking

Background

Coronary slow flow (CSF) is defined as a microvascular coronary artery disorder that angiographically shows increased microvascular resistance to flow with no evidence of obstructive coronary heart

disease (CHD) [1, 2]. Recent data indicates that the prevalence of CSF is about 2-8% [3]. It is always associated with poor prognostic outcomes [1, 4]. However, the pathophysiological mechanism of CSF remains unclear. Up to now, there is still a lack of effective treatment and assessment to prevent the occurrence of cardiovascular events.

In another definition Coronary Slow Flow (CSF) is an angiographic clinical condition, characterized by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis [5].

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, In the clinical practice CSF is usually underestimated maybe due to the yet unknown mechanisms, its relative rarity, and the subsequent difficulties in conducting randomized trials to evaluate different treatment options [6]. Two-dimensional (2D) Speckle Tracking dobutamine stress echocardiography is a new technology that measures strain and strain rate by tracking speckles in 2D grayscale echocardiographic images. It can measure myocardial motion in any direction irrespective of the direction of the beam, and provides strain in all dimensions; longitudinal, radial, and circumferential [7]. It is, comprehensive, and noninvasive methodology that can detect and evaluate myocardial diastolic and systolic performance. Abnormalities of strain and strain rate can be found early in the development of many pathophysiologic states, and thus provide a sensitive means for detecting myocardial dysfunction [8].

The objective of this study was to evaluate whether there is impairment of GLS of the left ventricle obtained by 2D speckle tracking dobutamine stress echocardiography in patients with Coronary Slow Flow.

Material and methods

Design

The researchers prospectively investigated the patients with chronic stable angina referred for coronary angiography from February 2022 to December 2022 at the Department of Cardiology, Faculty of Medicine; Kafrelsheikh University Hospitals. 50 patients with CSF and 50 age-and sex-matched controls without CSFP were en-rolled in the study.

Inclusion criteria

All patients with chronic stable angina who underwent cardiac catheterization were recruited.

Exclusion criteria

Patients with recent ACS, Chronic heart failure, valvular heart disease, congenital heart disease, dilated cardiomyopathy, Chronic kidney disease (glomerular filtration rate < 60 ml/min/1.73 m²), or Severe arrhythmia (e.g., history of frequent premature ventricular contraction, ventricular tachycardia, bundle branch block, or persistent/paroxysmal atrial fibrillation/flutter).

Conventional Echocardiography: -

Echocardiography will be performed using the (PHILIPS EPIQ-7C) - (S5-1 & X5-1 transducers). To obtain ultrasound images of the resting heart, ECG gated study. Three consecutive cardiac cycles will be recorded with the patient in the left lateral position. Ventricular wall motion is observed from the parasternal long and short axis views (at the level of the mitral valves, papillary muscles, and apex), and apical four- and two-chamber views. Left ventricular ejection fraction (LVEF) will be calculated with Simpson's biplane method.

Speckle Tracking Echocardiography:

- Under continuous electrocardiography, dobutamine was infused at 0, 5, 10, 15, and 20 µg/kg/min, respectively. LV peak systolic longitudinal strain (LS), LV peak systolic longitudinal strain rate (LSRs), LV peak early diastolic longitudinal strain rate (LSRed), LV systolic circumferential strain (CS).
- Three consecutive cardiac cycles were recorded to automatically track the endocardium and epicardium throughout each heart cycle and divide the LV myocardium into six segments in each apical view. Heart cycle data were excluded from analysis if tracking was found to be inaccurate in more than two segments after manual adjustment. The LV strain and strain rates were derived by averaging measurements from three consecutive heart cycles. Only global strain values were obtained.
- The infusion was terminated after the target heart rate was reached or one of the following endpoints was met: (1) systolic blood pressure (SBP) > 220 mmHg or diastolic blood pressure > 120 mmHg; (2) ventricular arrhythmia; (3) a decrease in SBP of >40 mmHg, as compared with baseline, or a measurement of ≤100 mmHg; (4) new abnormal ventricular wall motion; (5) achievement of 85%–90% of the age-predicted maximal heart rate; and (6) patient request.

Post-exercise echocardiography stress protocol: -

- Standard DES protocol for ischemia was used after discontinuation of B-blocker for 48h. the test endpoint is target heart rate [$0.85 \times (220 - \text{age})$] started with 10 mic/kg/min and increase every 3 minutes to 20,30,40 mic/kg/min. If 85% of APMHR is not achieved at 40 mic/kg/min then a 3 min 50 mic/kg/min may be used. If dobutamine alone is not effective, then atropine may be used. The EF will be measured at the resting stage and when maximum heart rate achieved.

The statistical analysis:

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by ANOVA (F) test with post hoc test (Tukey). Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant.

Results:

A total of 50 patients (36 males, 14 females; mean age, 52.54 ± 15.79 years) were assigned to the CSF group and 50 (32 males, 18 females; mean age, 50.86 ± 15.09 years) to the control group.

There was no statistically significant difference in age, sex ratio, weight, Height or BMI between the CSF and control groups ($P > 0.05$); (Table 1)

There was no statistically significant difference regarding history of hypertension/diabetes /Smoking between the CSF and control groups ($P > 0.05$); (Table 2)

Table 1: Demographic data of the studied groups

		CSF group (n=50)	Control group (n=50)	P value
Age (years)	Mean ± SD	52.54 ± 15.79	50.86 ± 15.09	0.588
	Range	22 - 73	24 - 75	
Sex	Male	36 (72%)	32 (64%)	0.391
	Female	14 (28%)	18 (36%)	
Weight (kg)	Mean ± SD	79.78 ± 10.92	77.08 ± 10	0.200
	Range	59 - 101	61 - 94	
Height (cm)	Mean ± SD	168.12 ± 7.13	167.76 ± 5.49	0.778
	Range	154 - 182	157 - 180	
BMI (kg/m ²)	Mean ± SD	28.25 ± 3.66	27.48 ± 3.85	0.306
	Range	20.7 - 33.9	19.7 - 33.7	

Table 2: Comorbidities of the studied groups

	CSF group (n=50)	Control group (n=50)	P value
Hypertension	32 (64%)	29 (58%)	0.539
DM	16 (32%)	14 (28%)	0.663
Smoking	19 (38%)	17 (34%)	0.677

DM: Diabetes mellitus.

However, LS, LSRs and LSRed were insignificantly different between CSF group and control group ; (Table 3).

LS, LSRs and LSRed were significantly different among five groups (P value<0.001). LS was significantly lower in (5 µg/kg/min group and 10 µg/kg/min group) than at rest group than (P value<0.001) while LS was insignificantly different between at rest group and (15 µg/kg/min group and 20 µg/kg/min group). LS was significantly higher in 5 µg/kg/min group than 10 µg/kg/min group (P value<0.001) while LS was insignificantly different between 5 µg/kg/min group and (15 µg/kg/min group and 20 µg/kg/min group) and between 15 µg/kg/min group and 20 µg/kg/min group. LS was significantly lower in 10 µg/kg/min group than (15 µg/kg/min group and 20 µg/kg/min group) (P value<0.001).

LSRs was significantly lower in (5 µg/kg/min group, 10 µg/kg/min group, 15 µg/kg/min group and 20 µg/kg/min group) than at rest (P value<0.001). LSRs was significantly higher in 5 µg/kg/min group than (10 µg/kg/min group and 15 µg/kg/min group) (P value<0.001) while LSRs was insignificantly different between 5 µg/kg/min group and 20 µg/kg/min group. LSRs was significantly

lower in 10 µg/kg/min group than 20 µg/kg/min group (P value<0.001) while LSRs was insignificantly different between 10 µg/kg/min group and 15 µg/kg/min group.

LSRed was significantly higher in 5 µg/kg/min group than at rest (P value<0.001) while LSRed was insignificantly different between at rest group and (10 µg/kg/min group, 15 µg/kg/min group and 20 µg/kg/min group). LSRed was significantly higher in 5 µg/kg/min group than (10 µg/kg/min 15 µg/kg/min group and 20 µg/kg/min group) (P value<0.05).

LSRed was significantly higher in 10 µg/kg/min group than 20 µg/kg/min group (P value<0.001) while LSRed was insignificantly different between 10 µg/kg/min group and 15 µg/kg/min group. (Table 4).

Table 3: LV longitudinal function at rest of the studied group

		CSF group (n=50)	Control group (n=50)	P value
LS (%)	Mean ± SD	-19.3 ± 2.38	-20.26 ± 2.81	0.068
	Range	-23 - -15	-24 - -16	
LSRs (sec-1)	Mean ± SD	-1.1 ± 0.33	-1.2 ± 0.22	0.092
	Range	-1.6 - -0.6	-1.5 - -0.7	
LSRed (I/s)	Mean ± SD	1.21 ± 0.45	1.3 ± 0.46	0.324
	Range	0.3 - 1.9	0.5 - 2.1	

LS: Longitudinal strain, LSRs: Systolic longitudinal strain rate, LSRed: diastolic longitudinal strain rate

Table 4: LV longitudinal function in response to different dobutamine infusion rates

		At rest group (n=50)	5 µg/kg/min group (n=50)	10 µg/kg/min group (n=50)	15 µg/kg/min group (n=50)	20 µg/kg/min group (n=50)
LS (%)	Mean ± SD	-19.5 ± 2.27	-21.7 ± 2.53	-25.1 ± 2.44	-20.8 ± 2.78	-20.5 ± 2.78
	Range	-23 - -15	-27 - -16	-30 - -20	-28 - -15	-25 - -15
	P1		<0.001*	<0.001*	0.096	0.358
	P2			<0.001*	0.404	0.115
	P3				<0.001*	<0.001*
	P4					0.964
LSRs (sec ⁻¹)	Mean ± SD	-1.1 ± 0.33	-1.4 ± 0.32	-1.9 ± 0.35	-1.8 ± 0.35	-1.5 ± 0.35
	Range	-1.6 - -0.6	-1.9 - -0.8	-2.6 - -1.3	-2.4 - -1.1	-2.2 - -1.1
	P1		<0.001*	<0.001*	<0.001*	<0.001*
	P2			<0.001*	<0.001*	0.294
	P3				0.059	<0.001*
	P4					<0.001*
LSRed (sec ⁻¹)	Mean ± SD	1.2 ± 0.45	1.7 ± 0.45	1.4 ± 0.44	1.3 ± 0.44	1 ± 0.44
	Range	0.3 - 1.9	0.7 - 2.4	0.5 - 2.1	0.4 - 1.9	0 - 1.9

P1	<0.001*	0.517	0.988	0.152
P2		0.005*	<0.001*	<0.001*
P3			0.818	0.001*
P4				0.045*

*: significant as P value ≤ 0.05 . P1: P value compared to at rest group, P2: P value compared to 5 $\mu\text{g}/\text{kg}/\text{min}$ group, P3: P value compared to 10 $\mu\text{g}/\text{kg}/\text{min}$ group and P4: P value compared to 15 $\mu\text{g}/\text{kg}/\text{min}$ group.

Discussion:

Coronary slow flow (CSF) is recognized as a microvascular coronary artery disorder, characterized angiographically by increased microvascular resistance in the absence of obstructive coronary heart disease. The condition affects approximately 1-7% of the population, presenting a significant health concern due to its association with adverse prognostic outcomes. Despite this, the underlying pathophysiological mechanisms of CSF remain poorly understood, and there are currently no effective strategies for the prevention of cardiovascular events related to CSF [9].

Dobutamine stress echocardiography (DSE) is widely used as a diagnostic imaging tool for coronary heart disease, leveraging its ability to detect myocardial ischemia-induced local wall motion abnormalities. Over the years, multiple studies have underscored the high accuracy and prognostic value of DSE for diagnosing [10].

Recent advancements in echocardiographic techniques have introduced two-dimensional (2D) speckle tracking as a method to enhance the detection capabilities of DSE. Specifically, speckle tracking echocardiography, particularly in the early recovery period post-DSE, has proven effective in assessing systolic or post-systolic strain, thus aiding in the identification of hemodynamically significant coronary artery stenosis [11].

However, there is a gap in the literature concerning the evaluation of left ventricular (LV) function in CSF patients under stress conditions. Preliminary studies have shown inconsistent results regarding LV function at rest in CSF patients, and no studies have yet assessed LV response to dobutamine-induced stress. To address this, our study aims to evaluate LV function in CSF patients utilizing 2D speckle-tracking echocardiography during dobutamine stress testing, potentially providing new insights into the condition's impact on cardiac performance [12].

Therefore, this study aimed to assess the changes to left ventricular (LV) function of patients with the coronary slow flow (CSF) with 2D speckle tracking dobutamine stress echocardiography.

This prospective cohort study was conducted on 50 patients with coronary slow flow and 50 healthy controls who were admitted to cardiology department –Kafr El-Sheikh University Hospitals during the period from February 2023 to February 2024. Participants underwent full clinical evaluation, conventional echocardiography, and Speckle tracking echocardiography.

Regarding LV longitudinal function in response to different dobutamine infusion rates, LS, LSRs and LSRed were significantly different among five groups (P value <0.001).

Lower LS at lower infusion rates (5 and 10 $\mu\text{g}/\text{kg}/\text{min}$) compared to rest suggests that at lower doses, dobutamine might initially lead to a decrease in myocardial performance in patients with coronary slow flow. This could be attributed to the inability of the ischemic or micro-vascularly compromised myocardium to respond adequately to inotropic stimulation, which is usually expected to enhance myocardial function. A study by Mohammed Mehkiemer et al. showed similar findings, where patients with microvascular dysfunction exhibited decreased LS under low dose dobutamine [13].

As the dose increases, the myocardium may show a "catch-up" response, where initially unresponsive myocardial segments begin to respond to higher pharmacologic stimulation. This phase-dependent response could indicate varying degrees of myocardial viability within the CSF population which explains the insignificant change between rest and higher doses (15 and 20 $\mu\text{g}/\text{kg}/\text{min}$) [14].

Decreased LSRs at all dobutamine doses compared to rest is a consistent decline across all infusion rates that might suggest an overall compromised myocardial contractility in the CSF group, potentially linked to intrinsic myocardial dysfunction rather than just load-dependent changes. This supports findings by Pastorini et al., where diminished strain rates were associated with myocardial energy inefficiency in microvascular disease [15].

The significant variability in LSRs between the lower doses (5 $\mu\text{g}/\text{kg}/\text{min}$ more than 10 $\mu\text{g}/\text{kg}/\text{min}$) and minimal differences at higher doses could reflect a non-linear myocardial response to increasing inotropic challenge, further complicating the interpretation of myocardial health and suggesting differential segments of myocardial reserve [16].

The initial increase in diastolic strain rate at the lowest infusion rate could be reflective of an enhanced early diastolic relaxation response to mild inotropic stimulation, which could be beneficial in demonstrating early diastolic function improvement before systolic strain catches up. However, as the strain rate does not maintain this improvement at higher doses, it could indicate a ceiling effect of dobutamine on improving diastolic function in CSF patients, as suggested by studies like those by Liu et al., which noted a peak improvement in diastolic parameters at low doses in patients with subclinical myocardial dysfunction [17].

A study was conducted by Wu et al. to evaluate LV function in patients with coronary slow flow by the dobutamine stress echocardiography. They found comparable results to our study where LS initially increased at a moderate dose (10 $\mu\text{g}/\text{kg}/\text{min}$) but decreased as the dose was further increased. This suggests a biphasic response where initial mild to moderate dobutamine stimulation might transiently improve myocardial function in CSF patients, but higher doses fail to sustain this benefit, possibly due to the exhausted myocardial reserve or worsening ischemia under stress. Additionally, they reported significant variability in LSRs across different dobutamine doses showing a similar trend where increased doses initially led to improvement but ultimately resulted in a decrease, indicative of limited myocardial adaptability in CSF [18].

Both studies underline the early diastolic strain rate (LSRed) as a sensitive indicator, with significant increases at lower doses, demonstrating that diastolic function might initially improve with mild stress but is not sustained at higher stresses. The agreement between both studies underscores the

utility of speckle-tracking echocardiography in identifying nuanced changes in myocardial function under pharmacologic stress in CSF patients. [19].

Limitations

This study has several limitations that should be acknowledged. Firstly, The results were obtained from a single medical center (Kafrelsheikh University Hospitals).

Secondly, the sample size was relatively small, which may limit the generalizability of the findings. Furthermore, the Clear delineation of endocardial borders was difficult in some patients, especially obese patients or patients with causes of poor echo window. Lack of follow-up of the patients to evaluate the efficacy of treatment and prognosis of CSF is another limitation, as invasive measurements are considered the gold standard. Therefore, it is important to interpret the results cautiously. To overcome these limitations, future research should be conducted.

Conclusions

In this prospective cohort study assessing LV function in patients with CSF using 2D speckle tracking dobutamine stress echocardiography, the most pivotal findings reveal that dynamic assessments under different dobutamine infusion rates highlighted substantial alterations in left ventricular function. Specifically, left ventricular strain (LS), strain rate during systole (LSRs), and strain rate during early diastole (LSRed) demonstrated significant differences across varying infusion rates, with notable decrements in LS and LSRs as dobutamine dosage increased. These findings underscore the sensitivity of speckle-tracking echocardiography in detecting subtle but clinically relevant functional impairments in CSF patients.

LIST OF ABBREVIATIONS

CSF = Coronary Slow Flow

CS = Systolic Circumferential Strain

CAG = Coronary Angiography

STE = Speckle-Tracking Echocardiography

LVEF = Left Ventricular Ejection Fraction

Type of article: Original Article

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