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Original article

# The Impact of Coronary Slow Flow Phenomenon on Diastolic Function Trajectory in Patients with Non-ST Segment Elevation Acute Coronary Syndrome

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## Abstract

**Background:** Non-ST Segment Elevation Acute Coronary Syndrome (NSTE-ACS) patients often present with complex cardiac pathophysiology, including coronary slow flow phenomenon (CSFP) and diastolic dysfunction (DD). This study aimed to better understand the short-term alterations and indicators of improved diastolic function in CSFP patients presenting with NSTEMI. **Methods:** This prospective research was conducted on 100 NSTE-ACS patients undergoing coronary angiography. Echocardiographic measures were employed to determine diastolic function, and the TIMI frame count approach was employed to determine the presence of CSFP. At the start of the study and after three months, clinical and angiographic data were gathered. **Results**: The mean age of the studied patients was 46 ±4 years. Significant improvements were noted in several diastolic function parameters at three months. At three months, there were significantly lower percentages of average E/Em > 14 (2% vs. 16%, $p < 0.001$), LAVI > 34 mL/m2 (46% vs. 76%, $p < 0.001$), lateral Em < 10 (61% vs. 76%, $p < 0.001$), and TR velocity (41% vs. 76%, $p < 0.001$) compared to baseline. Kaplan Meier analysis was done to calculate MACE-free survival. It showed that at 1.5 months, the MACE-free survival was 97.8% and 92.7% in those with improved and non-improved diastolic dysfunction, respectively. **Conclusion:** Our study shows the positive impact of diagnosing CSFP in NSTE-ACS patients, as it may lead to improved diastolic function over a relatively short period.

**Keywords:** NSTE-ACS; Coronary Slow Flow Phenomenon; Diastolic Function; Major Adverse Cardiac Events; Echocardiography.

## Introduction

The coronary slow flow phenomenon (CSFP), initially explained by Tambe and associates, is characterized by a delay in the visibility of the distal coronary arteries during coronary angiography, even when there are no substantial coronary artery obstructions (1). The fundamental processes

that lead to CSFP are not well understood. Myocardial ischemia, acute myocardial infarction (MI), and sudden cardiac mortality have all been linked to CSFP (2).

Numerous case series investigations have repeatedly indicated that CSFP tends to afflict a certain demographic, particularly middle-aged males with a varying pattern of angina marked by recurrent episodes, considerably affecting their quality of life (3). With or without an elevation in cardiac biomarkers, patients with CSFP may present with chronic stable angina (CSA) or acute coronary syndromes (ACS). Unstable angina, ST elevation MI (STEMI), and non-ST elevation MI (NSTEMI) are some examples of these ACS occurrences (4).

The exact causes of CSFP remain unclear, but several proposed mechanisms include abnormalities in microvascular reserve, elevated vasoconstrictor mediators, reduced nitric oxide levels, and inflammation. Diastolic dysfunction (DD), which frequently occurs in people with coronary artery disease (CAD) and typically arises before apparent abnormalities in left ventricular (LV) wall motion, is a predictive indication for poor results in acute MI patients (5, 6).

Various investigations have revealed improvements in DD following revascularization in ACS or ischemic cardiomyopathy patients (7, 8). Additionally, gradual improvement in DD has been observed after MI, especially with thrombolytic therapy, primarily attributed to the gradual recovery of stunned myocardium during the acute MI phase and the effects of drugs such as beta-blockers (9).

Patients with CSFP have had their diastolic function examined, and most of the time, an impairment was revealed. Still, there has not been any prior research on the rapid development of DD in CSFP patients who present with NSTEMI. In contrast to those with obstructive epicardial CAD who experience MI and are likely to see improvements in DD after revascularization, the pathophysiological mechanisms underlying myocardial ischemia in CSFP are distinct and not yet fully understood (10).

The purpose of this research was to analyze the impact of CSFP on the trajectory of diastolic function in patients with NSTE-ACS, to determine the predictors of diastolic dysfunction non-improvement, and to assess the clinical consequences related to these findings.

## Patients and methods

This prospective investigation research was performed within the Coronary Care Units of Benha University Hospital and Ahmed Maher Teaching Hospital on 100 patients with NSTE-ACS who experienced coronary angiography. The study lasted over one year, from April 2022 to March 2023.

The patients signed an informed consent form. A description of the study's objectives and a secret code number were given to each patient. Before the study was conducted, it received approval from the Benha University Faculty of Medicine Research Ethics Committee.

**The key inclusion criteria** included the registration of 100 NSTE-ACS patients who were slated to get coronary angiography. NSTE-ACS, which comprises unstable angina (UA) and NSTEMI: NSTEMI was defined as a rise and reduction in cardiac biomarkers; preferably, troponin values should have at least one value that is higher than the 99th percentile upper reference limit and it had to be accompanied by any one of the subsequent criteria: ischemia symptoms, new ST-segment/T-wave alterations (such as ST depression or T-wave inversions), emergence of pathological Q waves on the ECG, imaging evidence indicating loss of viable myocardium, or new regional wall motion abnormality (11). On the other hand, UA was identified by clinical signs and symptoms of myocardial ischemia, such as newly developing angina, modifications in the typical angina pattern, angina that occurs while resting, or variations in the typical angina equivalent (12). Notably, UA was characterized by the lack of myocardial necrosis, shown by normal cardiac indicators of injury, such as troponin, even when ECG alterations, such as ST-segment depression or T-wave inversions, might have existed.

The key exclusion criteria were patients with atrial fibrillation, obstructive CAD, and coronary slow-flow phenomenon (CSFP) related to various pathologic diseases such as myocarditis, thromboembolic infarctions, or coronary ectasia, left ventricular ejection fraction (LVEF) below 40%, severe pulmonary hypertension, pericardial diseases, a paced rhythm, significant valvular heart disease, patients with previous ischemia, PCI or CABG, or those with suboptimal echocardiographic windows. Initially, all patients were exposed to complete medical history taking, thorough physical examination, and electrocardiogram.

**Coronary angiography**

The TIMI frame count (TFC) technique of cine frames will be used to diagnose CSFP, with frames being filmed at 30 frames per second (13).

TFC is the contrast needed to allow the leading edge to first touch recognized distal coronary markers as measured by the cine-viewer frame counter. The image with the contrast filling at least 70% of the artery ostium's diameter is the initial counting frame. The final frame is where the contrast starts to fill the last landmark in the picture. The mustache segment, distal bifurcation segment, and the first branch of the posterolateral artery, respectively, served as the last points of reference for the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) (14). Each patient's TFC was evaluated independently by two interventional cardiologists. Any conflicts were settled when a third observer was present.

**Transthoracic echocardiography**

Two echocardiographic tests were performed during transthoracic echocardiography on each patient. The first research occurred during the index hospitalization for NSTE-ACS, while the second one happened three months later. All evaluated variables met the standards set out by the American Society of

Echocardiography (15). The size and wall thickness of the left ventricle (LV) were assessed using M-mode echocardiography. Simpson's biplane rule calculated the left ventricular ejection fraction (LVEF) in the apical 2- and 4-chamber views at the end of systole and diastole. The positioning of the pulsed-wave sample volume for Doppler imaging allowed for the measurement of early diastolic flow (E), atrial contraction wave (A), and E deceleration time (DT). Additionally, pulsed-wave Doppler was employed to measure isovolumic relaxation time (IVRT). Tissue Doppler imaging was subsequently employed to measure the velocities of the septal and lateral mitral annuli (16), evaluating the lateral and septal annular sides' peak systolic (Sm) and early (Em) and late (Am) diastolic velocities.

When more than two of the (16) following conditions were met, LVDD was considered to exist, while the existence of two or fewer conditions either excluded or rendered DD diagnosis uncertain (16). (1) Average E/Em was more than 14; (2) Septal Em velocity was less than 7 cm/s or lateral Em velocity was less than 10 cm/s; (3) Tricuspid regurgitation (TR) velocity was more than 2.8 m/s; and (4) LA volume index was more than 34 mL/m2. When a parameter, such as TR velocity, could not be measured during the study, it was given a negative value for DD.

Diastolic dysfunction was also graded according to the following: Normal pattern: E/A was > 0.8, DT was 160–240 msec, IVRT was 70–90 msec, and (E/Em) was < 10; Grade I: E/A was < 0.8, DT was > 240 msec, IVRT was > 100 msec, and (E/Em) was < 10; Grade II: E/A was 0.8–2, DT was 160–240 msec, IVRT was 70–100 msec, and E/Em was 10–14; Grade III: E/A was > 2, DT was < 160 msec, IVRT was < 70 msec, and E/Em was > 14.

**Endpoints:**

The study had two primary endpoints. First, the echocardiographic endpoint involved evaluating the mean change in diastolic function parameters at the 3-month follow-up compared to baseline, with stratification by the diastolic dysfunction (DD) grade. Secondly, the clinical endpoint centered on assessing major adverse cardiac events (MACE), encompassing cardiac death, reinfarction, and heart failure (HF), among the study participants during a three-month follow-up.

**Approval code: Ms1.6.2022**

**Statistical analysis**

Data management and statistical analysis were done utilizing SPSS version 28. (IBM, Armonk, New York, United States). Kolmogorov-Smirnov test, Shapiro-Wilk test, and direct data visualization techniques were performed to determine whether the quantitative values were normal. Quantitative data were summarized utilizing medians and ranges or means and standard deviations following normality. Numbers and percentages served as a summary of categorical data. The independent t-test or Mann-Whitney U test for normally and non-normally distributed quantitative variables, respectively, were employed to compare

quantitative data concerning the status of diastolic dysfunction at three months. Comparing categorical data was done utilizing either Chi-square or Fisher's exact test. Utilizing paired t-test or Wilcoxon signed ranks test for quantitative variables with normal or non-normal distribution, respectively, echocardiographic parameters were compared between baseline and three-month time points. Kaplan-Meier analysis was done to estimate MACE-free survival according to the status of diastolic dysfunction at three months. The log-rank test was employed to compare survival curves. Diastolic dysfunction non-improvement was predicted utilizing multivariate logistic regression analysis. The odds ratios were calculated along with their 95 % confidence intervals. Statistical tests were two-sided. The threshold of significance was 0.05.

## Results

Baseline characteristics & coronary angiographic findings:

The mean age of the studied patients was 46 ±4 years. There was a male predominance (73%). Hypertension and diabetes were reported in 45% and 36%, respectively. Dyslipidemia was reported in 40%. The mean BMI was 25.1 ±2. Abnormal ECG was reported in 44%. The median peak troponin level was 280, ranging from 40 - 580. The mean heart rate was 82 ±8. The mean systolic and diastolic blood pressure were 132 ±13 and 84 ±9 mmHg, respectively. The mean TIMI frame count was 45 ±3 for LAD, 38 ±2 for LCX, 34 ±4 for RCA, and 38.8 ±1.6 for all vessels. The most frequent in-hospital medication used was CCB (94%), while the least frequent was beta-blockers (40%). Table 1

Patients with improved diastolic dysfunction exhibited significantly lower hypertension (20% vs. 65.5%, $p < 0.001$), diabetes (17.8% vs. 50.9%, $p < 0.001$), dyslipidemia (4.4% bs 69.1%, $p < 0.001$), body mass index (23.4 ±0.9 vs. 26.6 ±1.5, $p < 0.001$), abnormal ECG (13.3% vs. 69.1%, $p < 0.001$), peak troponin level (median = 160 vs. 470 ng/L, $p < 0.001$), and ACEI/ARB (31.3% vs. 52.7%, $p = 0.03$) than those with non-improved diastolic dysfunction. In contrast, those with improved diastolic dysfunction demonstrated significantly higher TIMI frame count for LAD (46 ±3 vs. 44 ±3, $p =0.044$) and beta-blockers use (51.1% vs. 30.9%, $p =0.04$) than those with non-improved DD (Table, 1).

No significant differences were observed between those with improved and non-improved diastolic dysfunction regarding all the remaining parameters (Table, 1).

**Echocardiographic parameters:**

As displayed in **table 2**, significant increases were noted at three months in PWT ($p < 0.001$), E/A ratio ($p = 0.024$), Septal Em ($p < 0.001$), lateral EM ($p < 0.001$), average EM ($p < 0.001$), and average Em/Am ($p < 0.001$) compared to baseline measure.

Significant decreases were observed at three months regarding WMSI ($p < 0.001$), LA diameter ($p = < 0.001$), LAVI ($p < 0.001$), IVRT ($p = 0.026$), DT ($p = 0.003$), average E/Em ($p < 0.001$), and TR velocity ($p < 0.001$) as opposed to baseline ***(Table, 2).***

No significant variations (*p*.0.05) were noted at three months concerning LVEDD, LVESD, LVEDVI, LVESVI , LVEF, septal thickness, average Sm, average Am (Table 2).

**Diastolic dysfunction grade:**

Diastolic dysfunction grade significantly differed at three months, contrary to baseline ($p < 0.001$). At three months, 55% were normal compared to 24% at baseline. Grades I, II, and III represented 38%, 6%, and 1%, respectively, at three months, compared to 60%, 11%, and 5%, respectively, at baseline ***(Table 3 and figure 1).***

**Diastolic dysfunction parameters:**

At three months, there were significantly lower percentages of average E/Em > 14 (2% vs. 16%, $p < 0.001$), LAVI > 34 mL/m2 (46% vs. 76%, $p < 0.001$), lateral Em < 10 (61% vs. 76%, $p < 0.001$), and TR velocity (41% vs. 76%, $p < 0.001$) compared to baseline ***(Table 4, Figure 2).***

**MACE-free survival:**

Kaplan Meier analysis was performed to calculate MACE-free survival. It showed that at 1.5 months, the MACE-free survival was 97.8% and 92.7% in those with improved and non-improved diastolic dysfunction, respectively. At three months, the overall survival in the improved group remained the same, while in the non-improved group, it declined to 87.3%. The log-rank *p* -value showed a borderline significant variation ($p = 0.058$) ***(Figure 3).***

**Prediction of non-improvement of diastolic dysfunction:**

Multivariate logistic regression analysis was performed to predict non-improvement of diastolic dysfunction. All predictors were selected clinically, including age, gender, peak troponin level, hypertension, and mean TIMI frame count for all vessels. The model revealed that one unit increase in the peak troponin level was linked to a 3% higher risk of non-improvement of diastolic dysfunction (OR = 1.033, 95% CI = 1.018 – 1.049, $p < 0.001$).

**Table 1: Baseline characteristics & coronary angiographic findings according to diastolic dysfunction improvement**

| | | Improved DD at 3m | | |
|---|---|---|---|---|
| | **Total (n = 100)** | **Yes (n = 45)** | **No (n = 55)** | ***p*-value** |
| **Age (years)** | 46 ±4 | 46 ±5 | 46 ±4 | 0.589 |
| **Gender** | | | | |
| Males | 73 (73) | 33 (73.3) | 40 (72.7) | 0.946 |
| Females | 27 (27) | 12 (26.7) | 15 (27.3) | |
| **Hypertension** | 45 (45) | 9 (20.0) | 36 (65.5) | **<0.001*** |
| **Diabetes mellitus** | 36 (36) | 8 (17.8) | 28 (50.9) | **<0.001*** |
| **Dyslipidemia** | 40 (40.0) | 2 (4.4) | 38 (69.1) | **<0.001*** |
| **Body mass index (kg/m$^2$)** | 25.1 ±2 | 23.4 ±0.9 | 26.6 ±1.5 | **<0.001*** |
| **Abnormal ECG** | 44 (44.0) | 6 (13.3) | 38 (69.1) | **<0.001*** |
| **Peak Troponin level (ng/L)** | 280 (40 – 580) | 160 (40 – 270) | 470 (40 – 580) | **<0.001*** |
| **Heart rate (bpm)** | 82 ±8 | 84 ±8 | 81 ±8 | 0.085 |
| **Systolic blood pressure (mmHg)** | 132 ±13 | 130 ±14 | 133 ±13 | 0.221 |
| **Diastolic blood pressure (mmHg)** | 84 ±9 | 83 ±9 | 86 ±8 | 0.085 |
| **TIMI frame count (f/second)** | | | | |
| LAD (f/second) | 45 ±3 | 46 ±3 | 44 ±3 | **0.044*** |
| LCX (f/second) | 38 ±2 | 38 ±2 | 38 ±2 | 0.458 |
| RCA (f/second) | 34 ±4 | 33 ±4 | 34 ±4 | 0.272 |
| For all vessels (f/second) | 38.8 ±1.6 | 38.8 ±1.7 | 38.8 ±1.5 | 0.918 |
| **In-hospital medications** | | | | |
| ACEI/ARB | 43 (43) | 14 (31.3) | 29 (52.7) | **0.03*** |
| Statins | 78 (78) | 34 (75.6) | 44 (80.0) | 0.594 |
| DAPT | 89 (89) | 43 (95.6) | 46 (83.6) | 0.058 |
| Beta-blockers | 40 (40.0) | 23 (51.1) | 17 (30.9) | **0.04*** |
| CCB | 94 (94) | 44 (97.8) | 50 (90.9) | 0.219 |

*Statistically Significant ($p$ <0.05); DD: Diastolic dysfunction; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: Right coronary artery; ACEI: angiotensin-converting enzyme inhibitor; DAPT: dual antiplatelet therapy; CCB: calcium channel blocker; please add the statistical test used in this table to get the $p$ value.

**Table 2: Echocardiographic parameters of the studied patients at baseline and three months**

| | Baseline | At 3 months | *p*-value |
|---|---|---|---|
| **LVEDD (mm)** | 48.5 ±3.6 | 48.7 ±3.4 | 0.754 |
| **LVESD (mm)** | 32.6 ±3.1 | 33 ±2.9 | 0.830 |
| **LVEDVI (mL/m$^2$)** | 43.03 ±6.22 | 43.3 ±5.6 | 0.172 |
| **LVESVI (mL/m$^2$)** | 19 ±3 | 19 ±2.9 | 0.924 |
| **WMSI** | 1.24 ±0.19 | 1.22 ±0.17 | **<0.001*** |
| **LVEF (%)** | 61.5 ±2.8 | 61.2 ±2.6 | 0.852 |
| **Septal thickness (mm)** | 10.6 ±0.8 | 10.6 ±0.8 | 0.523 |
| **PWT (mm)** | 10.43 ±0.81 | 10.5 ±0.8 | **0.032*** |
| **LA diameter (mm)** | 36.7 ±4.5 | 34.7 ±3.7 | **<0.001*** |
| **LAVI (mL/m$^2$)** | 39.1 ±4.6 | 36.3 ±3.8 | **<0.001*** |
| **E/A** | 0.77 (0.58 - 2.45) | 1.1 (0.58 - 2.35) | **0.024*** |
| **IVRT (ms)** | 98 ±18 | 94 ±16 | **0.026*** |
| **DT (ms)** | 226 ±39 | 214 ±35 | **0.003*** |
| **Average E/Em** | 11.7 ±2.8 | 10.2 ±2 | **<0.001*** |
| **Septal Em (cm/s)** | 7.2 ±1.5 | 7.8 ±1.2 | **<0.001*** |
| **Lateral Em (cm/s)** | 8.9 ±1.3 | 9.4 ±1 | **<0.001*** |
| **Average Em (cm/s)** | 8.04 ±1.37 | 8.6 ±1.07 | **<0.001*** |
| **Average Sm (cm/s)** | 9.9 ±0.9 | 10 ±0.7 | 0.202 |
| **Average Am (cm/s)** | 10.6 ±1.2 | 10.6 ±1 | 0.812 |
| **Average Em/Am** | 0.76 ±0.11 | 0.82 ±0.1 | **<0.001*** |
| **TR velocity (m/s)** | 2.82 ±0.53 | 2.55 ±0.45 | **<0.001*** |

*statistically significant *(p*<0.001*);* LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDVI: left ventricular end-diastolic volume index; LVESVI: left ventricular end-systolic volume index; WMSI: Wall Motion Score Index; LVEF: left ventricular ejection fraction; PWT: Posterior Wall Thickness; LA: Left atrial; LAVI: Left Atrial Volume Index; IVRT: Isovolumic Relaxation Time; DT: Deceleration Time; TR: Tricuspid Regurgitation; please add the statistical test used in this table to get the *p* value.

**Table 3: Diastolic dysfunction grade at baseline and three months**

| DD grade | | Baseline | At 3 months | *p*-value |
|---|---|---|---|---|
| Normal | n (%) | 24 (24) | 55 (55) | **<0.001*** |
| G I | n (%) | 60 (60) | 38 (38) | |
| G II | n (%) | 11 (11) | 6 (6) | |
| G III | n (%) | 5 (5) | 1 (1) | |

*statistically significant (*p* <0.001); DD: Diastolic dysfunction

**Table 4: Diastolic dysfunction parameters at baseline and three months**

| | | Baseline | At 3 months | *p*-value |
|---|---|---|---|---|
| **Average E/Em > 14** | n (%) | 16 (16) | 2 (2) | **<0.001*** |
| **LAVI > 34 mL/m2** | n (%) | 76 (76) | 46 (46) | **<0.001*** |
| **Lateral Em < 10** | n (%) | 76 (76) | 61 (61) | **<0.001*** |
| **TR velocity > 2.8 m/s** | n (%) | 76 (76) | 41 (41) | **<0.001*** |

* statistically significant ($p$ <0.001; LAVI: Left Atrial Volume Index; TR: Tricuspid Regurgitation; please add the statistical test used in this table to get the $p$ value.

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**Table 5: Multivariate logistic regression analysis to predict non-improvement of diastolic dysfunction**

| | OR (95% CI) | *p*-value |
|---|---|---|
| **Age (years)** | 0.924 (0.755 - 1.132) | 0.447 |
| **Gender** | 0.898 (0.123 - 6.54) | 0.916 |
| **Peak Troponin level (ng/L)** | 1.033 (1.018 - 1.049) | **<0.001*** |
| **Hypertension** | 0.084 (0.006 - 1.142) | 0.063 |
| **Mean TIMI frame count for all vessels (f/second)** | 0.873 (0.484 - 1.574) | 0.652 |

* statistically significant ($p$ <0.001; OR: Odds ratio; 95% CI: 95% Confidence interval

## Discussion

In this study, we demonstrated that throughout a 3-months follow-up, DD appeared to improve in patients with CSFP who exhibit NSTEMI.

Patients eligible for inclusion in this study were those with NSTE-ACS, which includes unstable angina (UA) and NSTEMI. While we did not explicitly specify whether patients underwent PCI in our initial study. We would like to clarify that none of our patients had PCI, as we included patients with CSFP only without obstructive coronary artery disease.

During the 3-months follow-up period, patients received standard medical care in accordance with established clinical guidelines for the management of NSTE-ACS. The management strategies included medical therapies, lifestyle modifications, and patient education. These strategies aimed to optimize cardiovascular health and mitigate the risk of adverse cardiac events. However, we did not collect specific data on each patient's medication regimen and lifestyle modifications during the follow-up period.

The mean age of the participants in this research was 46 ± 4 years with a male domination (73%). The mean blood pressure was 132 ± 13 mmHg for the systolic component and 84 ± 9 mmHg for the diastolic component. The mean TIMI frame count was 45 ±3 for LAD, 38 ±2 for LCX, 34 ±4 for RCA, and 38.8 ±1.6 for all vessels.

Conforming our results, a 2021 study was conducted to determine how quickly diastolic function changes in CSFP patients with NSTEMI. The average age of the 92 patients was 45.7 ± 6.8 years, with 76 men

(82.6%) and 16 women (17.4%). The mean systolic and diastolic blood pressure were 129.1 ± 10.8 and 79.7 ± 6.2 mmHg, respectively. The mean TIMI frame count was 47.1 ± 14.3 for LAD, 38.3 ± 11.1 for LCX, 32.8 ± 10.9for RCA, and 38.3 ± 13.1 for all vessels (2).

In contrast, another study reported that patients with CSFP had significantly greater values of TFC for cLAD (42.6 ± 15.8 vs. 21.8 ± 3.1, $p$ <0.001), LCx (36.9 ± 17.1 vs. 21.6 ± 3.9, $p$ <0.001), and RCA (36.4 ± 19.3 vs. 21.2 ± 4.1, $p$ <0.001), as well as mean TFC (38.6 ± 13.5 vs. 21.5 ± 2.3, $p$ <0.001) than those with normal coronary flow. This might be because of their study's smaller sample size and the fact that they used 2D speckle-tracking echocardiography to measure the diastolic and systolic functions of both the left (LV) and right (RV) ventricles (17).

Regarding the echocardiographic parameters, significant increase was observed at three months in PWT, E/A ratio, septal Em, lateral EM, average EM, and average Em/Am compared to the baseline measure.

The observed significant increase in PWT at three months in our study can be attributed to several factors. These include the physiological adaptation and myocardial remodeling following the initial acute coronary syndrome event, potential medical interventions such as ACE inhibitors or ARBs, successful reperfusion effects, recovery of myocardial function, and inherent physiological variability in echocardiographic measurements. These combined factors likely contributed to the observed PWT changes, reflecting the complex dynamics of cardiac response and recovery following NSTEMI in our patient population.

Significant decrease was observed at three months regarding WMSI, LA diameter, LAVI, IVRT, DT, average E/Em, and TR velocity contrary to baseline. No significant difference was observed at three months regarding LVESVI, septal thickness, average Sm, and average Am.

In another study, significant decrease was observed in WMSI, IVRT, DT, average E/Em, average Am, and TR velocity. Significant increase was observed in septal Em, lateral Em, average Em, average Sm, and average Em/Am. However, no significant variations were noted in LVEDD, LVESD, and LA diameter (2). The observed significant decreases in E/A ratio, IVRT, and DT at three months in the current study and the previous one indicated improvements in diastolic function.

According to a previous study, mitral E/A was substantially reduced in CSFP patients ($p$ = 0.003) (17), and according to another study, the E/A ratio was one of the most important factors to consider when analyzing diastolic dysfunction (18). Other studies indicated that the mean LVEF had improved to the baseline and within the period of the follow-up ($p$ -value < 0.001) (19-21).

**Regarding diastolic dysfunction grade, it** significantly differed at three months, contrary to baseline ($p$ < 0.001). At three

months, 55% were normal compared to 24% at baseline. Grades I, II, and III represented 38%, 6%, and 1%, respectively, at three months, compared to 60%, 11%, and 5%, respectively, at baseline.

The notably high percentage of normal diastolic function observed at three months, despite all patients being over 40, can be attributed to the unique interplay of individual patient characteristics, and the multifaceted nature of cardiac recovery. Diastolic function recovery patterns can vary, and in this specific patient cohort, favorable baseline characteristics and effective management of coronary slow flow phenomenon may have contributed to the observed improvement.

Our findings are consistent with the findings of another study regarding diastolic dysfunction, which indicated that initially, 23 patients (or 25%) had normal/indeterminate diastolic function, and 69 (or 75%) had DD. Sixty-four individuals (69.6%) exhibited normal/indeterminate diastolic function at three months. Additionally, it displayed the distribution of various diastolic function grades. The subgroups of the DD group demonstrated enhanced diastolic performance, as indicated by a decline in the proportion of patients falling into the grade I, II, and III categories. The various DD grades improved significantly ($p < 0.001$) (2).

In the current study, at three months, there were significantly lower ($p<0.001$) percentages of average E/Em > 14 (2% vs. 16%), LAVI > 34 mL/m$^2$ (46% vs. 76%), lateral Em < 10 (61% vs. 76%), and TR velocity (41% vs. 76%) compared to baseline.

Supporting our findings, a study observed significant improvements ($p<0.05$) in average E/Em > 14 (82.6% to 47.9%) and LAVI > 34 mL/m$^2$ (83.7% to 52.2%) and lateral Em < 10 (77.2% to 40.2%) reflecting better diastolic function at three months. However, in our study, TR velocity decreased significantly at three months, while in the previous study, there was no significant change (2).

In the present work, Kaplan Meier analysis was performed to estimate MACE-free survival. It indicated that at 1.5 months, the MACE-free survival was 97.8% and 92.7% in those with improved and non-improved diastolic dysfunction, respectively.

Regarding MACE, a study reported that patients with unimproved DD had a greater incidence of HF ($p < 0.001$) (2).

It is generally recognized that DD predicts all-cause mortality and is linked to the onset of HF. DD is caused by coronary artery obstruction, and the degree of the following systolic dysfunction depends on how much myocardium is at risk. These modifications might be undone by prompt reperfusion of the LV myocardium. After PCI following ACS, several prospective studies revealed an improvement in DD grade (7, 22).

Myocardial ischemia has been detected in about 28% to 75% of patients with CSFP during myocardial perfusion investigations (23, 24). CSFP may result in ischemia events like ACS and angina (25).

Clinical research has been done to better understand the pathophysiology of CSFP. According to a study, CSF results from the microvascular system's functional blockage. The study demonstrated that dipyridamole intracoronary infusion partially normalizes microvascular dysfunction (26). Similarly, research found that patients with CSFP who took dipyridamole for two months saw an improvement in their DD (19).

In another work (19), shorter overall ischemia periods increased the likelihood that DD in STEMI patients will improve following the first PCI. As a result, there will be less myocardial necrosis and more myocardium that can be saved by early reperfusion.

Multivariate logistic regression analysis was conducted to predict non-improvement of diastolic dysfunction. The model revealed that one unit increase in the peak troponin level correlated with a 3 % higher risk of non-improvement of diastolic dysfunction (OR = 1.033, 95% CI = 1.018 – 1.049, $p < 0.001$).

In a different study, multivariate regression analysis revealed no independent substantial predictor of enhancement of DD after NSTEMI (2).

This study had some restrictions, mainly the small sample number of patients with limited follow-up. Additionally, the fundamental processes by which CSFP may affect diastolic function are not discussed in this work. More extensive multicenter investigations are necessary to validate our conclusions.

## Conclusion

The diastolic function appears to improve over three months in CSF patients with NSTEMI as their first symptom. This can signify a momentary deterioration during NSTEMI. It is still unclear what pathophysiologic mechanisms underlie the reversibility of DD in that patient population.

## References

1. Alvarez C, Siu H. Coronary Slow-Flow Phenomenon as an Underrecognized and Treatable Source of Chest Pain: Case Series and Literature Review. J Investig Med High Impact Case Rep. 2018;6:2324709618789194.
2. Zayat AE, Abdelaziz M, Yousry A, Ibrahim I. Evolution of Diastolic Dysfunction in Patients with Coronary Slow Flow Phenomenon and Acute Non-ST Segment Elevation Myocardial Infarction. J Cardiovasc Imaging. 2021;29:347-56.
3. Turner SP. The pathophysiology of the coronary slow flow phenomenon. Research Theses: School of Medical Sciences; 2006.
4. Sarkees ML, Bavry AA. Acute coronary syndrome (unstable angina and non-ST elevation MI). BMJ Clin Evid. 2009;2009.
5. D'Amario D, Migliaro S, Borovac JA, Restivo A, Vergallo R, Galli M, et al. Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction. Front Physiol. 2019;10:1347.
6. Nikolajević Starčević J, Janić M, Šabovič M. Molecular Mechanisms Responsible for Diastolic Dysfunction in Diabetes Mellitus Patients. Int J Mol Sci. 2019;20.
7. Hashemi SR, Motamedi M, Khani M, Hekmat M, Gachkar L, Rezaeefar A. Evaluation of the effect of elective percutaneous coronary intervention as a treatment method on the left ventricular diastolic dysfunction in patients with coronary artery disease. J Tehran Heart Cent. 2010;5:194-8.
8. Tanaka H, Kawai H, Tatsumi K, Kataoka T, Onishi T, Nose T, et al. Improved regional

myocardial diastolic function assessed by strain rate imaging in patients with coronary artery disease undergoing percutaneous coronary intervention. J Am Soc Echocardiogr. 2006;19:756-62.

9. Kloner RA. Stunned and Hibernating Myocardium: Where Are We Nearly 4 Decades Later? J Am Heart Assoc. 2020;9:e015502.
10. Wang Y, Li J, Liu S, Mu L, Li G, Yu H, et al. Value of exercise stress electrocardiography for stratification of exercise capacity and left ventricular systolic and diastolic function on coronary slow flow: case-control study. BMC Cardiovascular Disorders. 2019;19:288.
11. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e139-e228.
12. Ford TJ, Berry C. Angina: contemporary diagnosis and management. Heart. 2020;106:387-98.
13. Gibson CM, Cannon CP, Daley WL, Dodge JT, Jr., Alexander B, Jr., Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996;93:879-88.
14. Sezgin AT, Topal E, Barutcu I, Ozdemir R, Gullu H, Bariskaner E, et al. Impaired left ventricle filling in slow coronary flow phenomenon: an echo-Doppler study. Angiology. 2005;56:397-401.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440-63.
16. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29:277-314.
17. Wang Y, Ma C, Zhang Y, Guan Z, Liu S, Li Y, et al. Assessment of left and right ventricular diastolic and systolic functions using two-dimensional speckle-tracking echocardiography in patients with coronary slow-flow phenomenon. PLoS One. 2015;10:e0117979.
18. Cosson S, Kevorkian JP. Left ventricular diastolic dysfunction: an early sign of diabetic cardiomyopathy? Diabetes Metab. 2003;29:455-66.
19. Subramaniyan S, Pandit N, Kumar Nath R, Raj A, Kamal A, Vatsa D. Acute effect of primary PCI on diastolic dysfunction recovery in anterior wall STEMI - A non-invasive evaluation by echocardiography. Egypt Heart J. 2018;70:427-32.
20. Remmelink M, Sjauw KD, Henriques JP, Vis MM, van der Schaaf RJ, Koch KT, et al. Acute left ventricular dynamic effects of primary percutaneous coronary intervention from occlusion to reperfusion. J Am Coll Cardiol. 2009;53:1498-502.
21. Scholz KH, Friede T, Meyer T, Jacobshagen C, Lengenfelder B, Jung J, et al. Prognostic significance of emergency department bypass in stable and unstable patients with ST-segment elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2020;9:34-44.
22. Misztal M, Stopyra K, Gackowski A, Zmudka K, Piwowarska W. Assessment of left ventricle diastolic function in myocardial infarction patients treated with primary angioplasty. Cardiol J. 2009;16:440-6.
23. Demirkol MO, Yaymaci B, Mutlu B. Dipyridamole myocardial perfusion single photon emission computed tomography in patients with slow coronary flow. Coron Artery Dis. 2002;13:223-9.
24. César LA, Ramires JA, Serrano Júnior CV, Meneghetti JC, Antonelli RH, da-Luz PL, et al. Slow coronary run-off in patients with angina pectoris: clinical significance and thallium-201

scintigraphic study. Braz J Med Biol Res. 1996;29:605-13.
25. Sen T. Coronary Slow Flow Phenomenon Leads to ST Elevation Myocardial Infarction. Korean Circ J. 2013;43:196-8.
26. Mangieri E, Macchiarelli G, Ciavolella M, Barillà F, Avella A, Martinotti A, et al. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn. 1996;37:375-81.

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