Evolution of Diastolic Dysfunction in Patients with Coronary Slow Flow Phenomenon and Acute Non-ST Segment Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND: Diastolic function has been reported to be impaired in many patients with coronary slow flow phenomenon (CSFP). CSFP has broad spectrum of clinical presentations, including non-ST elevation myocardial infarction (NSTEMI). We sought to study the short-term evolution of diastolic function in CSFP patients presenting with NSTEMI.

METHODS: This study included 92 patients with CSFP and acute NSTEMI. Conventional echocardiography Doppler imaging and tissue Doppler echocardiography imaging were used to evaluate diastolic function during index NSTEMI and after 3 months.

RESULTS: Mean age of study patients was 45.7 ± 6.8 years. The prevalence of diastolic dysfunction (DD) at baseline was 69 patients (75%) and 28 patients (30.4%) at 3 months, p < 0.001. Various diastolic function indices showed significant improvement from baseline to 3 months follow-up. E/Em was 17.32 ± 3.41 at baseline compared to 12.41 ± 5.58 at 3 months, p = 0.039. Septal e' velocity was 5.67 ± 4.56 cm/s at baseline compared to 7.78 ± 3.22 cm/s at 3 months, p = 0.023. Medications used were not significantly different between those with improved versus unimproved DD.

CONCLUSIONS: Diastolic function seems to improve over short-term follow-up in patients with CSFP presenting with NSTEMI. This could reflect a transient worsening during acute NSTEMI.

Keywords: Coronary slow flow; Non-ST elevation myocardial infarction; Microvascular dysfunction; Diastolic dysfunction

INTRODUCTION

Initially reported by Tambe et al.,1) coronary slow flow phenomenon (CSFP) was described during coronary angiography as a delayed opacification of distal coronary arteries in the absence of significant obstructive coronary artery disease (CAD).

Pathophysiologic mechanisms involved in CSFP are not yet completely understood. CSFP has been linked to myocardial ischemia, acute myocardial infarction (MI), and sudden cardiac death.2) Many case-series studies have consistently shown CSFP to occur in a unique demographic group of patients,3) namely middle-aged males with mixed pattern angina that is frequently
characterized by remitting relapsing episodes, resulting in considerable impairment in quality of life. CSFP patients may present with chronic stable angina or acute coronary syndromes (ACS) with or without cardiac biomarkers rise, including unstable angina, non-ST elevation MI (NSTEMI) or ST elevation MI (STEMI).3)

Pathogenesis of CSFP is still unclear with microvascular reserve abnormalities, increased vasoconstrictor mediators, low nitric oxide levels and inflammation represent the major proposed underlying mechanisms.4-7)

Patients with CAD often have diastolic dysfunction (DD) which usually precedes left ventricular (LV) resting wall motion abnormalities and is a predictor of adverse outcome in patients with acute MI.5,9) Few studies have reported improvement of DD after revascularization in patients with ACS or ischemic cardiomyopathy.4,12) Gradual improvement of DD after MI has been also described following thrombolytic therapy and was mainly attributed to be secondary to gradually recovering stunned myocardium at the time of acute MI and to the effect of medications as beta blockers.13-14) Diastolic function has been studied in patients with CSFP4,5,6) and was reported to be impaired in the majority. On the other hand, description of DD in CSFP patients presenting with NSTEMI and its evolution over short term follow-up have not been previously reported. Unlike patients with obstructive epicardial CAD who present with MI where improvement of DD following revascularization could be predicted, pathophysiologic mechanisms involved in myocardial ischemia in CSFP are different and are not fully elucidated.4,7) The aim of this study was to clarify the short-term changes and the predictors of improvement of diastolic function in CSFP patients presenting with NSTEMI.

METHODS

Study population
Ninety-two patients, with previously established diagnosis of primary CSFP, who presented to cardiology department at Zagazig University Hospitals, Egypt, with chest pain and were subsequently diagnosed as NSTEMI. Patients were prospectively enrolled in the study in the period from January 2016 to March 2020. NSTEMI diagnosis was established by the detection of a rise and/or fall of cardiac troponin with at least one value above the 99th percentile and symptoms of acute myocardial ischemia with or without new ischemic electrocardiographic (ECG) changes, excluding ST segment elevation.5)

Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board and local ethical committee (ZU- IRB-med#1/2016). Exclusion criteria included patients with obstructive CAD; CSF secondary to other pathologic conditions as myocarditis or thromboembolic infarctions; coronary ectasia; atrial fibrillation; LV ejection fraction (LVEF) < 50%; pulmonary hypertension; pericardial disease; history of chronic inflammatory disease; paced rhythm; history of cardiac surgery or percutaneous coronary intervention; significant valvular heart disease, cardiomyopathy and poor echocardiographic window.

Coronary angiography
Coronary angiography studies of all patients were retrieved. Diagnosis of CSFP was made using the TIMI frame count (TFC) method10) of cine frames, recording 30 frames/second.
TFC is the number that is required for the leading edge of the contrast to first reach standard distal coronary landmarks using the cine-viewer frame counter. The first counting frame is the image where the contrast fills at least 70% of the diameter of the arterial ostium. The last frame is the image where the contrast begins to fill the final landmark. Final landmarks for the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) were the mustache segment, the distal bifurcation segment and first branch of the posterolateral artery, respectively. TFC for the LAD artery was corrected by dividing by 1.7. Two interventional cardiologists independently assessed TFC in each patient. A third observer resolved any disagreements when present.

All participants with a corrected TFC greater than 2 standard deviation of the published range for the vessel were reported to have CSFP. For LAD, RCA, and LCX, TFC cutoff values of 41, 26 and 30 respectively were used to diagnose CSFP. Mean TFC was calculated by dividing the sum of TFC for each major epicardial coronary by 3.

**Transthoracic echocardiography**

Using 2.5–3.5 MHz transducer, GE vivid 7, Milwaukee, WI, every patient had 2 echocardiographic studies. First study was during index hospital admission with NSTEMI. Follow-up study was 3 months later. All parameters assessed were according to criteria of the American Society of Echocardiography. M-mode echocardiography was used to assess LV dimensions and wall thickness. LVEF was assessed by Simpson’s biplane rule in apical 2 and 4-chamber views at end systole and end diastole. For Doppler images, pulsed-wave sampling volume was placed between tips of mitral valve, then early diastolic flow (E), atrial contraction wave (A) and E deceleration time (DT) were assessed. Pulsed wave doppler was also used to assess isovolumic relaxation time (IVRT). Tissue Doppler imaging was then used to assess mitral annular velocities at septal and lateral mitral annulus. Peak systolic myocardial velocity (Sm), early (Em), late (Am) diastolic velocities were measured for the septal and lateral annular sides.

LVDD was said to be present if > 2 criteria of the following were present, (while presence of 2 or less criteria exclude or make DD diagnosis indeterminate).

1-Average E/Em > 14; 2-Septal Em velocity < 7 cm/s or lateral Em velocity < 10 cm/s; 3-Tricuspid regurgitation (TR) velocity > 2.8 m/s; 4-LA volume index > 34 mL/m².

If a parameter could not be assessed during the study (e.g., TR velocity), this was considered a negative value during assessment of DD.

Diastolic dysfunction was also graded as follows:

- Normal pattern: E/A > 0.8, DT = 160–240 msec, IVRT 70–90 msec and (E/Em) < 10.
- Grade I: E/A < 0.8, DT > 240 msec, IVRT > 100 msec and (E/Em) < 10.
- Grade II: E/A = 0.8–2, DT = 160–240 msec, IVRT 70–100 msec, E/Em 10–14,
- Grade III: E/A > 2, DT < 160 msec, IVRT < 70 msec and E/Em > 14.

Two experienced echocardiographers independently assessed echocardiographic studies in each patient. A third echocardiographer resolved any disagreements when present.
Course of hospital admission and after discharge
Patients' management during hospital stay and after discharge, medications' prescription and doses were as per current guidelines, and were left to the discretion of the treating physicians in coronary care unit and in the outpatient clinic.

Clinical outcome
Major adverse cardiac events (MACE) including cardiac death, reinfarction and heart failure were assessed in study patients after 3 months follow-up period.

Statistical analysis
Statistical analyses were performed using SPSS software (version 20.0; SPSS, Chicago, IL, USA). Quantitative variables were assessed as mean ± standard deviation, while qualitative ones as numbers and percentages.

The \( \chi^2 \) test was used to assess qualitative variables and t-test for quantitative variables. Paired sample t-test was used to compare values at baseline and at 3 months follow-up. Binary logistic regression analysis was used to assess different predictors of DD improvement. For interobserver and intra-observer variabilities, Bland Altman test was used to calculate mean difference and 95% confidence interval. A 2 tailed p-value < 0.05 was considered significant.

RESULTS
This study included 92 patients, 76 males (82.6%) and 16 females (17.4%), mean age was 45.7 ± 6.8 years. Smokers represented 60.8% of studied patients (Table 1).

Table 2 shows the comparison between conventional echocardiographic parameters that included LV dimensions and volumes, wall thickness, LVEF, left atrial diameter, and left atrial volume index at baseline and after 3 months.

Table 1. Demographic, clinical and coronary angiography findings in study patients

| Variable           | Values                  |
|--------------------|-------------------------|
| Age (years)        | 45.7 ± 6.8              |
| Sex (male)         | 76 (82.6)               |
| BMI (kg/m\(^2\))   | 25.1 ± 4.8              |
| Smoking            | 56 (60.8)               |
| Hypertension       | 24 (26)                 |
| DM                 | 22 (23.9)               |
| Abnormal ECG       | 28 (30.4)               |
| Peak troponin (ng/L) | 534.1 ± 115.5         |
| HR (baseline) (b/m) | 86.1 ± 15.3            |
| Systolic Bp (mmHg) | 129.1 ± 10.8            |
| Diastolic Bp (mmHg) | 79.7 ± 6.2             |
| TFCs (f/s)         |                        |
| LAD                | 47.1 ± 14.3             |
| LCX                | 38.3 ± 11.1             |
| RCA                | 32.8 ± 10.9             |
| Mean TFC (f/s)     | 38.3 ± 13.1             |

Data are shown as mean ± standard deviation or number (%).

BMI: body mass index, Bp: blood pressure, DM: diabetes mellitus, ECG: electrocardiographic, HR: heart rate, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, TFC: TIMI frame count.
Initial transthoracic echocardiography was done during hospitalization period of the index NSTEMI. All patients had preserved systolic function with EF > 50% (both at baseline and on follow-up studies). The prevalence of DD at baseline was 69 patients (75%) and 28 patients (30.4%) at 3 months, \( p < 0.001 \). Various diastolic function indices showed statistically significant improvement from baseline to 3 months follow-up as shown in Table 2.

TR velocity could not be obtained in 16 patients and TR as a DD parameter was considered negative for those patients. Other 3 parameters were obtainable in all patients.

Initially, 23 patients (25%) had normal/indeterminate diastolic function, while 69 (75%) patients had DD. After 3 months, 64 patients (69.6%) had normal/indeterminate diastolic function as shown in Table 3. It also shows the distribution of different diastolic function grades. There was significant improvement of different DD grades (\( p < 0.001 \)).

### Table 2. Echocardiographic data of study patients at baseline and after 3 months

| Variable                  | Baseline       | After 3 months | \( p \)-value |
|---------------------------|----------------|----------------|---------------|
| LVEDD (mm)                | 48.2 ± 5.5     | 47.9 ± 6.1     | 0.83          |
| LVESD (mm)                | 32.7 ± 3.4     | 33.2 ± 3.1     | 0.78          |
| LVEDVI (mL/m\(^2\))      | 55.43 ± 16.44  | 57.92 ± 12.56  | 0.45          |
| LVESVI (mL/m\(^2\))      | 29.72 ± 8.95   | 27.32 ± 7.81   | 0.65          |
| WMSI                      | 1.23 ± 0.35    | 1.17 ± 0.29    | 0.04          |
| LVEF (%)                  | 63.2 ± 1.5     | 101.1 ± 1.7    | 0.77          |
| Septal thickness (mm)     | 9.9 ± 2.2      | 9.7 ± 2.1      | 0.82          |
| PWT (mm)                  | 10.1 ± 4.2     | 38.1 ± 6.8     | 0.69          |
| LAVI (mL/m\(^2\))        | 39.3 ± 10.1    | 34.7 ± 8.9     | 0.59          |
| E/A                       | 1.23 ± 0.42    | 1.61 ± 0.32    | < 0.001       |
| IVRT (ms)                 | 93.73 ± 17.3   | 84.51 ± 16.2   | < 0.001       |
| DT (ms)                   | 198.33 ± 40.1  | 171.1 ± 38.3   | < 0.001       |
| Average E/Em              | 17.32 ± 3.41   | 12.41 ± 5.58   | 0.039         |
| Septal Em (cm/s)          | 5.67 ± 4.56    | 7.78 ± 3.22    | 0.023         |
| Lateral Em (cm/s)         | 9.38 ± 2.77    | 10.77 ± 3.12   | 0.035         |
| Average Em (cm/s)         | 7.23 ± 2.71    | 8.31 ± 2.55    | < 0.001       |
| Average Sm (cm/s)         | 8.32 ± 2.73    | 9.5 ± 2.79     | 0.002         |
| Average Am (cm/s)         | 10.2 ± 2.83    | 9.32 ± 2.98    | 0.001         |
| Average Em/Am             | 0.72 ± 0.23    | 0.84 ± 0.12    | < 0.001       |
| TR velocity (m/s)         | 2.21 ± 0.9     | 1.22 ± 0.43    | 0.042         |

Data are shown as mean ± standard deviation.
A: mitral inflow contraction velocity; Am: atrial contraction wave using tissue Doppler imaging, DT: deceleration time, E: mitral velocity of early diastolic filling from transmitral flow, Em: early diastolic filling using tissue Doppler imaging, IVRT: isovolumic relaxation time, LA: left atrium, LAVI: left atrial volume index, LVEDD: left ventricular end-diastolic dimension, LVEF: left ventricular ejection fraction, LVEDVI: left ventricular end-diastolic volume index, LVESD: left ventricular end-systolic dimension, LVESVI: left ventricular end-systolic volume index, PWT: posterior wall thickness, Sm: systolic wave using tissue Doppler imaging, TR: tricuspid regurgitation, WMSI: wall motion score index.

### Table 3. Diastolic function assessment of study patients at baseline and after 3 months

| Diastolic function | Baseline      | After 3 months | \( p \)-value |
|--------------------|---------------|----------------|---------------|
| Normal/indeterminate | 23 (25)     | 64 (69.6)     | < 0.001       |
| DD                 | 69 (75)      | 28 (30.4)     | < 0.001       |
| Normal             | 28 (30.4)    | 64 (69.6)     | < 0.001       |
| Grade I            | 46 (50)      | 20 (21.7)     | < 0.001       |
| Grade II           | 10 (10.8)    | 6 (6.50)      | < 0.001       |
| Grade III          | 8 (8.8)      | 2 (2.2)       | < 0.001       |

Values are presented as number (%). DD: diastolic dysfunction.
Table 4 shows the distribution of the 4 different indices of DD at baseline and at 3 months. TR velocity > 2.8 m/s was the least prevalent (39.1% at baseline compared to 31.5% at 3 months).

Table 5 shows that there was no significant statistical difference regarding use of different medications during the 3 months post index NSTEMI between patients with improved diastolic function (41 patients, 44.6%) and those with absent improvement (28 patients, 30.4%), excluding those with initially normal/indeterminate diastolic function from analysis (23 patients). There was also no significant difference regarding peak troponin at baseline, baseline abnormal ECG or resting wall motion abnormality (RWMA) in the basal segments (inferobasal or basal-lateral). Regarding MACE, heart failure was more encountered in patients with unimproved DD (p < 0.001).

Table 6 shows binary logistic regression analysis for independent predictors of improvement of DD. Significant variables on univariate regression were further subjected to multivariate analysis. There was no independent significant predictor of improvement of DD following NSTEMI in CSFP on multivariate regression analysis.

For different parameters of diastolic function assessment, inter- and intra-observer variabilities of 35 (38%) randomly selected patients were assessed by 2 different observers for interobserver variability and on 2 occasions by same observer (at least 4 weeks apart). Inter- and intra-observer variabilities were nonsignificant for any of the 4 parameters (p = 0.34 and 0.74 respectively for average E/Em, p = 0.46 and 0.73 respectively for lateral Em velocity, p = 0.54 and 0.22 respectively for TR velocity and p = 0.59 and 0.66 respectively for LAVI).

Table 4. Parameters of diastolic function assessment in study patients at baseline and after 3 months

| Variable                     | Baseline | After 3 months | p-value |
|------------------------------|----------|----------------|---------|
| Average E/Em > 14           | 76 (82.6)| 44 (47.9)      | 0.027   |
| LAVI > 34 mL/m²              | 77 (83.7)| 48 (52.2)      | 0.032   |
| Lateral Em < 10              | 71 (77.2)| 37 (40.2)      | 0.012   |
| TR velocity > 2.8 m/s        | 36 (39.1)| 29 (31.5)      | 0.097   |

Values are presented as number (%).
E: mitral velocity of early diastolic filling from transmitral flow, Em: early diastolic filling using tissue Doppler imaging, LAVI: left atrial volume index, TR: tricuspid regurgitation.

Table 5. Medications used in the 3-months follow-up period, peak troponin at baseline, abnormal ECG at baseline, basal segments RWMA at baseline and MACE encountered in patients with improved diastolic dysfunction vs. those with absent improvement

| Medications               | Improved (n = 41) | Absent improvement (n = 28) | p-value |
|---------------------------|-------------------|----------------------------|---------|
| Calcium channel blocker   | 41 (100)          | 28 (100)                   | 1.0     |
| ACEI/ARB                  | 10 (24.4)         | 8 (28.6)                   | 0.77    |
| Statins                   | 36 (87.8)         | 23 (82.1)                  | 0.87    |
| Dual antiplatelets        | 37 (90.2)         | 24 (85.7)                  | 0.79    |
| Peak troponin (baseline)  | 480.8 ± 99.6      | 552.3 ± 143.5              | 0.08    |
| Abnormal ECG (baseline)   | 13 (31.7)         | 11 (39.2)                  | 0.26    |
| Basal segments RWMA       | 5 (12.2)          | 3 (10.7)                   | 0.69    |

Data are shown as mean ± standard deviation or number (%).
ACEI/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers, ECG: electrocardiographic, MACE: major adverse cardiac events, RWMA: resting wall motion abnormality.
In this study, we showed that in patients with CSFP who present with NSTEMI, DD seems to improve over a follow-up period of 3 months. Moreover, this improvement in diastolic function indices seems to be spontaneous and independent from medications used during the acute NSTEMI or during the follow-up period.

It is well known that DD is associated with the development of heart failure and is predictive of all-cause mortality. Coronary artery obstruction results in DD and is followed by systolic dysfunction that varies in severity according to the mass of jeopardized myocardium. Timely reperfusion of the LV myocardium could revert these changes.

Clinical studies have been conducted to clarify the pathophysiologic basis of CSFP. Mangieri et al. hypothesized that functional obstruction of the microvascular system causes CSF. They showed that microvascular dysfunction partially normalizes after intracoronary infusion of dipyridamole. Similarly, Suner and Cetin reported DD to improve in patients with CSFP treated with dipyridamole for 2 months.

In our study, improvement of diastolic function in CSFP patients as shown by improvement in different DD indices seems to be spontaneous and independent from medications used, as concluded from the non-significant difference between those with improved DD and those...
with no improvement regarding medications used. On multivariate analysis, no significant independent predictor was found among different variables to predict improvement of DD. Moreover, many risk factors known to cause and/or worsen DD were present in the study cohort as diabetes mellitus, body mass index and hypertension. Yet, when we assessed DD in same patients (at baseline and after 3 months), the effects of such variables on the improvement of DD were not significant. There was no significant difference between baseline ECG abnormalities or peak troponin on comparison between improved and unimproved DD patients. This reflects that improvement in DD was not related to size of myocardial damage. We also found no significant difference between RWMA in basal LV segments between both groups. Basal hypokinesia could affect diastolic function assessment by affecting Em values, which may hinder the accurate assessment of LV diastolic function. However, in our study, there was no difference in the proportion of patients with regional wall motion abnormalities in the basal segments among those with improved and non-improved LVDD.

Mean peak hs-troponin level in our study patients was 534.1 ± 115.5 ng/L which reflects minimal myocardial injury in most cases and could explain such spontaneous recovery of DD on follow-up.

Our patients showed a preserved systolic function which could reflect mild muscle injury associated with NSTEMI in such cases.

In their work, Subramaniyan et al., 30 showed that DD in STEMI patients was more likely to improve after primary PCI with shorter total ischemic times. This means more salvaged myocardium by early reperfusion and hence less myocardial necrosis. Patients with absent improvement in DD in our study showed significant heart failure prevalence despite preserved LVEF and this suggests that DD in CSFP could be translated into clinical events and could affect prognosis.

NSTEMI in CSFP might be related to prolonged coronary microvascular constriction, as suggested by induction of typical angina and ST-segment changes, after intracoronary administration of acetylcholine or other vasoconstrictor stimuli. 31 We propose transient worsening of already impaired microvascular function at the level of coronary bed as a plausible pathophysiologic mechanism leading to NSTEMI in CSFP patients. Transient increases in microvascular dysfunction mediated by neurohormonal mediators precipitating ACS could possibly pave a road to understand possible reversibility and improvement of DD in CSFP patients. Yet, this has to be proved in a prospective study that aims at assessing microvascular resistance during acute coronary events and at follow-up. This could have potential therapeutic and preventive implications.

First, a major limitation of the study was the small number of patients with lack of longer-term follow-up. Our results need to be consolidated by larger multicenter studies. Second, our results could have been more accurate if compared against a gold standard diagnostic tool as LV end diastolic pressure during invasive coronary angiography. Third, coronary angiography data were retrieved retrospectively in our study. Fourth, the inherent limitation of echocardiography for assessment of different diastolic function parameters should be considered.

In patients with CSFP presenting with NSTEMI, diastolic function seems to improve over a period of 3 months. This could reflect a transient worsening during NSTEMI. Underlying pathophysiologic mechanisms of DD reversibility in that cohort of patients remain to be clarified.
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