

# Coronary Sinus Filling Time as a Predictor of Coronary Microvascular Obstruction and Future Cardiovascular Events after Elective Left Anterior Descending Artery Stenting

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## Abstract

**Objective** The main objective of this article is to study the usefulness of coronary sinus filling time (CSFT) as a predictor of coronary microvascular obstruction (CMVO) and future cardiovascular (CV) events after percutaneous coronary intervention (PCI) for left anterior descending (LAD) in stable coronary artery disease patients.

**Materials and Methods** We analyzed 50 patients with stable angina who underwent elective PCI for single LAD significant stenosis. After stent deployment, coronary sinus was visualized in left anterior oblique 40 degree cranial 30 degree views, CSFT, and corrected thrombolysis in myocardial infarction frame count (cTFC) calculated from frame count. Post-procedure electrocardiographic changes noted and cardiac biomarker creatine phosphokinase and creatine phosphokinase-myocardial band levels estimated, and follow-up was done for 6 months. Patients classified into two groups: Group 1 with major adverse cardiac events (MACE) and Group 2 (without MACE). CSFT and cTFC measurements were compared among the two groups.

**Results** Out of 50 patients who were recruited in the study, Group 1 comprises 20 patients, and Group 2 comprises 30 patients. Among the Group 1, 40% were females, while in Group 2, they were 16%. Group 1 showed high CSFT values compared to Group 2, and such are post-procedure ST, T changes (90% in Group 1, 20% in Group 2), cardiac biomarkers elevation (80% in Group 1, 23.3% in Group 2). At 6 months follow-up ejection fraction was lower in Group 1 ( $31.8 \pm 6.4\%$ ) compared with Group 2 ( $58.8 \pm 5.8\%$ ) at  $p < 0.0001$ , and angina (85%) versus (20%). Mean CSFT was significantly more in Group 1 ( $5.77 \pm 0.75s$ ) compared with Group 2 ( $4.61 \pm 0.55s$ ) at  $p < 0.0001$ . With respect to cTFC, no significant differences were seen between the two groups ( $p < 0.5628$ ). Receiver operating characteristic curve analysis showed CSFT of  $> 5.2s$  was the best cutoff value to differentiate the two groups.

**Conclusion** CSFT significantly prolonged in patients with adverse cardiac events, and it may be used as a simple and quantitative predictor of CMVO and future CV events after elective PCI.

## Keywords

- ▶ coronary sinus filling time
- ▶ coronary microvascular obstruction
- ▶ corrected TIMI frame count
- ▶ major adverse cardiac events



## Introduction

After percutaneous coronary interventions (PCI), even with the restoration of thrombolysis in myocardial infarction (TIMI 3) flow in the epicardial coronary circulation, there may be microvascular functional and structural obstruction, namely coronary microvascular obstruction (CMVO). This is due to the embolization of atherosclerotic material from the large epicardial vessel wall into the distal microvasculature. CMVO leads to myocardial tissue hypoperfusion, myocardial injury, and future cardiovascular (CV) adverse events. Many studies have shown that coronary microvascular dysfunction increases the risk of future CV events regardless of the epicardial vessel disease status.<sup>1</sup>

Sangareddi and Alagesan<sup>2</sup> proposed how to calculate the transit time through the microcirculation.<sup>2,3</sup> They proposed that coronary sinus filling time (CSFT) can be used as a marker of coronary microvascular function.<sup>4,5</sup> Perez de Prado *et al*<sup>14</sup> reported in a study that following primary angioplasty in acute MI coronary clearance frame count was a good predictor of myocardial reperfusion.<sup>6</sup> In the present study, we targeted to know CSFT as a simple, rapidly calculated parameter to evaluate coronary microvascular functional and structural obstruction in stable coronary artery disease (CAD) after elective PCI.

## Patients and Method

In the present prospective study, we recruited 50 patients with stable CAD who have undergone successful PCI for isolated left anterior descending (LAD) significant stenosis between July 2018 to December 2018 in the Department of Cardiology from our institute. Exclusion criteria include (1) patients with valvular heart disease; (2) left bundle branch block; (3) ejection fraction < 35%; (4) patients with diseases affecting CSFT such as hypothyroidism or hyperthyroidism, hepatic or renal failure, pulmonary diseases, and

malignancies, congenital heart disease; and (5) angiographic images that were inadequate for CSFT calculation. The institutional ethics committee approved the study protocol. Informed patient consent was taken. Epidemiological information (age, sex, occupation, and place), risk factor (smoking, alcohol, hypertension, diabetes mellitus, ischemic heart disease), clinical presentation (chest pain, dyspnea, pedal edema, etc.) and clinical signs were collected from patients in the study.

## CSFT Calculation

One best view chosen for proper delineation for LAD by coronary angiogram was left anterior oblique 40 degree, and cranial 20 degree. CSFT is calculated in seconds (last frame count–first frame count/15). CFST is calculated from the frame count the contrast appears at D1 or S1 (whichever was earlier taken as first frame count) to the time taken to pacify coronary sinus (junction of great cardiac vein to the post lateral vein – last frame count)<sup>7</sup> (►Fig. 1).

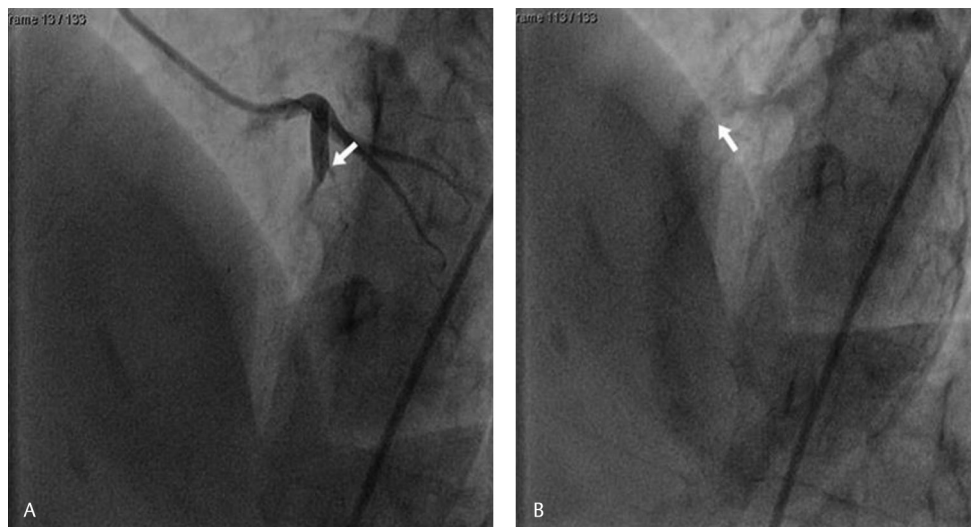
TIMI frame count is done as the number of the frames when the first contract appears in the ostium of the coronary to its distal-most portion. cTFC = frame count/ 1.7.

## Follow-Up

Post-procedure electrocardiographic (ECG) changes were noted, and cardiac biomarker creatine phosphokinase-(CPK) and creatine phosphokinase-myocardial band (CPK-MB) levels were measured 12 hours after PCI. Clinical and echocardiographic follow-up was done for the next 6 months following PCI.

## Analysis

Patients were classified into two groups. Group 1 (with major adverse cardiac event [MACE] like all-cause mortality, nonfatal MI, and hospitalization for heart failure and Group 2 (without MACE). Clinical, ECG parameters, CSFT, and



**Fig. 1** (A) Frame showing left anterior descending opacification at the origin of D1 (arrow). (B): Frame showing coronary sinus origin (arrow) at the confluence of the great cardiac vein with posterolateral vein.

corrected thrombolysis in myocardial infarction (cTFC), were compared within two groups.

### Statistical Analysis

Minitab 17 (Minitab, Ltd, United Kingdom) was used for means, and percentages calculation and Medcalc (Belgium) were used to calculate the receiving operating characteristic (ROC) curves. A *p*-value < 0.05 was considered statistically significant.

### Results

We analyzed 50 patients with a mean age of 59.8 years, with stable CAD who underwent successful PCI for isolated LAD significant stenosis. Thirteen females were there in this study population. Out of them, 19 (38%) were diabetics, and 23 (46%) were hypertensives. At 6 months, MACE (including in-hospital adverse cardiac events) occurred in 20 patients. The adverse events observed in-hospital were new ECG changes (24 patients—48%) with an increase in cardiac enzymes (23 patients—46%). At 6 months follow-up, MACE occurred were recurrence angina (23 patients—46%) and deterioration of left ventricular (LV) function.

Patients were divided into two groups depending on the occurrence of MACE: Group 1 comprises subjects with MACE, and Group 2 comprises subjects without MACE. There were 20 patients in Group 1 and 30 patients in Group 2. The baseline characteristics of patients in both groups are shown in ►Table 1. In Group 1, patients were more aged compared

**Table 1** Baseline characteristics

Parameter	Group 1 (n = 20)	Group 2 (n = 30)
Age (years)	66.65 ± 7.20	52.86 ± 10.12
Females (%)	8(40%)	5(16%)
Diabetes mellitus, n (%)	11 (55%)	8 (26.6%)
Hypertension, n (%)	10 (50%)	13 (43.3%)
Dyslipidemia, n (%)	9 (45%)	10 (33.3%)
Smoking, n (%)	12 (60%)	14 (46.6%)

Abbreviation: CV, cardiovascular.

Group 1, with CV events; group 2, without CV events.

with Group 1. Female preponderance is high in Group 1 (40%) compared with Group 2 (16%). Risk factors such as diabetes mellitus, hypertension, dyslipidemia, and smoking were significantly higher in Group 1.

Angiographic characteristics, ECG changes, and cardiac biomarkers of patients in both groups were shown in ►Table 2. CSFT was more prolonged in Group 1 patients than in Group 2, when though there was no difference in cTFC between both groups. In-hospital group, one patient had new ECG changes and elevation of cardiac markers. At 6 months, Group 1 patients showed the deterioration of LV function and recurrence of angina. All these parameters were statistically significant, as mentioned in ►Table 2.

ROC curve analysis (►Fig. 2) was performed to find out the best cutoff value of CSFT to discriminate between the two groups. The best cutoff value from the ROC curve for CSFT was derived as >5.2s with 85% sensitivity and 83.3% specificity.

### Discussion

TIMI 3 flow in the epicardial coronaries, which was taken as an endpoint after coronary PCI, is a poor predictor for tissue perfusion because microvascular obstruction and dysfunction occur much more commonly than it is recognized. Even after an otherwise successful elective PCI, a rise in serum cardiac biomarkers such as troponin is seen in more than 70% of patients.<sup>8</sup> It reflects myocardial necrosis secondary to tissue hypoperfusion and ischemia.

Myocardial hypoperfusion usually occurs when >50% of coronary capillary obstruction occurs by atherosclerotic microspheres.<sup>9</sup> Impaired microvascular perfusion may result in elevation of a serum marker of myocardial ischemia such as CPK, and the MB isoenzyme of CPK-MB, troponins and ischemic ST, T changes in ECG after PCI. Myocardial ischemia may manifest as LV regional wall motion abnormalities and LV dysfunction in the long term.<sup>10</sup> This myocardial malperfusion is associated with higher cardiac events, high risk of progression to heart failure and CV mortality.<sup>8</sup>

Conventional angiography cannot visualize the very small vessels that are involved in the coronary microcirculation. TIMI score grading describes the rate of blood flow only in the epicardial coronary vessels.<sup>11</sup> Even with

**Table 2** Angiographic characteristics, ECG changes, and cardiac biomarkers of patients in both groups

Parameter after PCI in-hospital	Group 1 (n = 20)	Group 2 (n = 30)	<i>p</i> -Value
cTFC	40.69 ± 13.03	38.91 ± 8.61	0.5628
CSFT second (SD)	5.77 ± 0.75	4.61 ± 0.55	< 0.0001
ECG changes	18(90%)	6(20%)	0.000
Cardiac biomarker CPK and CPK-MB elevated <sup>a</sup>	16 patients (80%)	7 patients (23.3%)	0.000
At 6 months follow-up			
LVEF (SD) (%)	31.8 ± 6.4	58.5 ± 5.8	< 0.0001
Number of patients presenting with recurrent angina	17(85%)	6(20%)	0.000

Abbreviations: CPK-MB, creatine phosphokinase-myocardial band; CSFT, coronary sinus filling time; cTFC, corrected TIMI frame count; CV, cardiovascular; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SD, standard deviation.

Group 1, with CV events; Group 2, without CV events.

<sup>a</sup>Normal reference values for serum CK-MB took like 5 to 25 IU/L.

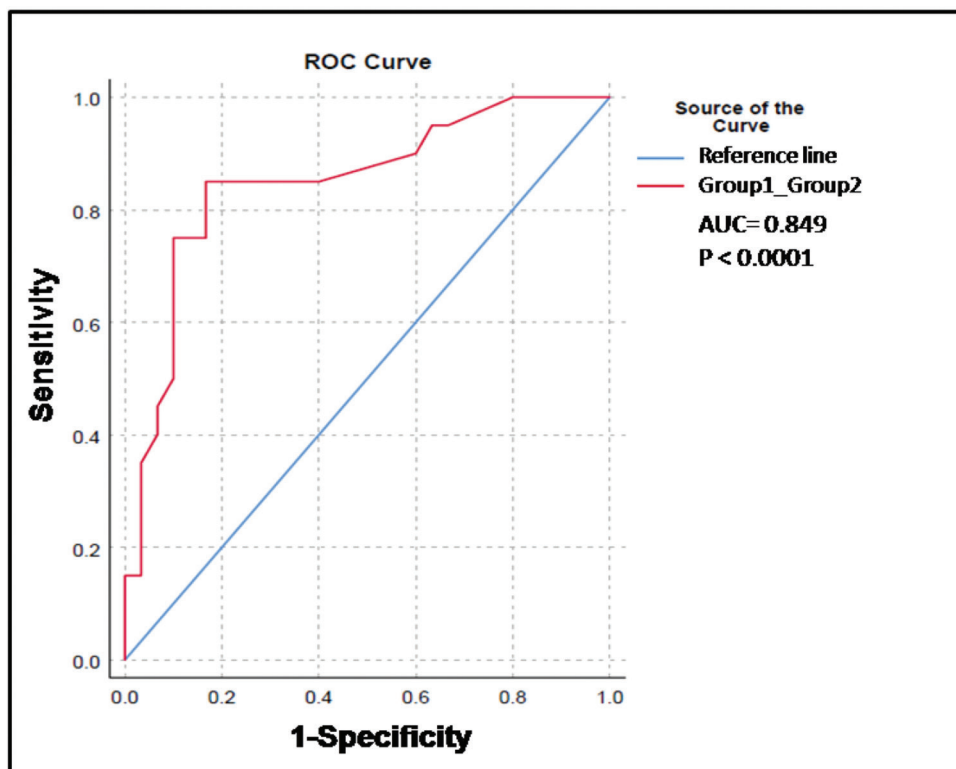


Fig. 2 Receiver operating characteristic (ROC) curve analysis. AUC, area under curve.

TIMI 3 flow after PCI, CMVO may be seen in nearly 50% of patients.<sup>12</sup> Other angiographic methods used to assess myocardial perfusion such as TFC (TIMI frame count), and myocardial blush grade) and TIMI myocardial perfusion grade may have reproducibility concern.<sup>13</sup> Direct measurement of coronary blood flow velocity using an intracoronary Doppler wire is the gold standard method for assessing coronary microvascular function.<sup>14</sup> However, it is complex and time-consuming and requires skill and specialized equipment. The most promising methods for noninvasive assessment of coronary microvascular function such as cardiac magnetic resonance, single-photon emission computed tomography, and positron-emission tomography are too expensive and complex techniques to use in routine practice.<sup>15</sup>

In our study, despite TIMI 3 flow angiographically, 90% of patients had ischemic ST-T changes post-PCI, and 80% had elevation cardiac biomarkers, which can be due to microvascular obstruction causing myocardial injury in Group 1. In a study by de Waha et al, CMVO was present in 56.9% of patients, which was calculated by the cardiac magnetic resonance imaging in primary PCI patients. They showed that the extent of MVO was determinant for mortality in graded response.<sup>16</sup>

In our study on 6 months follow-up, ejection fraction was lower in Group 1 and the incidence of angina was also more, even though there was no difference in the cTFC, but statistically significant difference in CSFT. This implies

that MVO may be contributing factors for these MACE at 6 months.

In a similar study by Mostafa and Mahfouz, CSFT was significantly delayed in patients with unfavorable outcome after elective PCI and proposed that CSFT of >5.0s was the best cutoff value in predicting unfavorable outcome after PCI for LAD.<sup>17</sup> Our study was compared with Mostafa and Mahfouz's study in ►Table 3. In our study, high CSFT remained significantly associated with CV events at 6 months follow-up, supporting the previous study. In our study, ROC analysis showed CSFT of >5.2s was the best cutoff value to differentiate the two groups with 85% sensitivity and 83.3% specificity.

## Limitations

Following are the limitations:

- (1). Short period of follow-up of only 6 months. Future studies with a longer follow-up may be needed.
- (2) Single-center design with a smaller number of patients.
- (3) Injection speed was not standardized, and
- (4) CSFT was not compared with any standard method used to assess CMVO.

## Conclusion

CSFT was significantly prolonged in patients with adverse cardiac events following PCI. It may be used as a simple and quantitative predictor of CMVO and future CV outcomes after elective PCI.

**Table 3** Comparison of study by Mostafa and Mahfouz<sup>17</sup>, with our study

Parameter	Mostafa and Mahfouz's <sup>17</sup> study, 78 patients			Our study, 50 patients		
	UF Group (n = 36)	F Group (n = 52)	p-Value	Group 1 (n = 20)	Group 2 (n = 30)	p-Value
Gender (females)	69.4%	44.6%	–	65%	46.6%	–
Angina	32(91.6%)	11(21%)	–	17(85%)	7(23.3%)	–
EF (SD)	32.3 ± 6.1%	59.5 ± 5.7%	p < 0.001	31.8 ± 6.4%	58.5 ± 5.8%	<0.0001
CSFT second (SD)	6.21 ± 0.45s	3.32 ± 0.74s	p < 0.001	5.77 ± 0.75s	4.61 ± 0.55s	< 0.0001
cTFC (SD)	–	–	–	40.69 ± 13.03	38.91 ± 8.61	0.5628

Abbreviations: CSFT, coronary sinus filling time; cTFC, corrected TIMI frame count; F Group, favorable group; SD, standard deviation, UF Group, unfavorable group.

Group 1, with CV events; Group 2, without CV events.

### Conflicts of Interest

None.

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