# A Cross-Sectional Study of Microcirculatory Transit Time as a Risk Stratification Method in Cardiac Syndrome X Conducted in a Tertiary Hospital at Hyderabad, Telangana

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**ABSTRACT**

**BACKGROUND**

Cardiac syndrome X (CSX) is not benign, and it needs long-term follow up and risk factor modification. In this study, we wanted to calculate microcirculatory transit time on coronary angiography in patients with cardiac syndrome X (CSX), compare microcirculatory transit time in patients with and without CSX and to see whether microcirculatory transit time can be proposed as a risk stratification method in CSX.

**METHODS**

Cross sectional study of 52 patients. The angiogram was taken at 15 frames per second. The left coronary artery was injected with 7 ml of contrast approximately. Microcirculatory transit time (MCTT) was obtained offline. The microcirculatory transit time in seconds is calculated as last frame count minus first frame count/15. Microcirculatory transit time was compared and analysed in both groups.

**RESULTS**

A total of 52 subjects were analysed. There were 26 cases in the angina group with a mean age of 49.96 years and 26 cases in the control group with a mean age of 50.32 years. Dyslipidemia, smoking and statin use were more common in the angina group, which was statistically significant ($P < 0.05$). The mean MCTT of the group with angina and positive treadmill test (TMT) was 6.76 seconds, whereas the negative TMT group was 6.39 seconds. The mean frame count was 58.1, and the mean MCTT was 3.8 seconds in the control group, whereas the mean frame count and mean MCTT were 98.1 and 6.5 seconds in the angina group, which was statistically significant ($P < 0.001$).

**CONCLUSIONS**

CSX patients had longer MCTT than patients without chest pain and normal coronary arteries. MCTT can be used to assess the risks of CSX. Long-term follow-up studies with a large sample size should be conducted.

**KEYWORDS**

Cardiac Syndrome X, Angina, Coronary Artery Disease, Microcirculation

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## BACKGROUND

Normal coronary arteries have been observed in 20 % of diagnostic angiograms in patients referred for chest pain.[1] Cardiac syndrome X (CSX) comprises patients with typical angina, a positive exercise stress test, normal epicardial coronaries, and no angiographic evidence of coronary artery spasm.[2] Microcirculatory dysfunction may be responsible for persistent symptoms and an abnormal stress test.[3,4] Studies showed an increased risk of adverse cardiovascular outcomes.[5,6] CSX is associated with a two-fold increase in cardiovascular events, and patients should undergo studies of vascular function and risk factor modification.[7] The methods used for assessing microcirculation have been significantly conflicting, yet no simple method is available to assess coronary microcirculation.[8,9]

### Objectives

1. To calculate microcirculatory transit time on coronary angiography in patients with cardiac syndrome X (CSX).
2. To compare microcirculatory transit time in patients with and without CSX
3. To see whether microcirculatory transit time can be proposed as a risk stratification method in CSX.

## METHODS

A cross-sectional study was performed over six months in the hospital's Cardiology Department. A sample of 52 patients was studied. The following were included (1) Patients with definite angina with/without positive treadmill test; (2) Patients with probable angina and with a positive TMT; (3) Patients undergoing coronary angiogram for pre-operative cardiac risk stratification for non-cardiac surgery; (4) Patients undergoing coronary angiogram before the electrophysiological study (EPS); (5) Rheumatic valvular heart disease patients undergoing coronary angiography before valve surgery. Patients with abnormal coronaries were excluded from the study.

After evaluating each patient, including reviewing medical history, relevant physical examination, and investigations, all patients underwent coronary angiogram within the same hospital stay. Patients with chest pain were categorized into having definite angina with/without positive TMT and probable angina with a positive TMT. Definite angina was defined as substernal chest pain of characteristic quality and duration relieved by rest or administration of sublingual nitrates. Probable angina was defined as those patients that have any two of the above characteristics. Coronary angiography was either performed using a radial or femoral approach. The normal coronary artery at angiography was defined as one without any wall irregularities, ectasia, or stenosis. 50 % or more significant reduction in the lumen area of the left main coronary artery, and 70 % or more significant reduction in the lumen area of any other coronary artery, is considered significant. Coronary angiography was conducted with a Philips Allura Xper FD20 at a rate of 15 frames per second. The TIG 5F catheter (Terumo) was used for diagnostic angiograms. The left coronary artery injection was taken with seven to ten ml of contrast approximately. Microcirculatory transit time[10] was defined as the time taken in seconds for the contrast agent to cross the coronary microvasculature and reach the origin of the coronary sinus. Frame count and MCTT were obtained offline. The MCTT was measured as the difference between the maximum left anterior descending artery system's opacification at first diagonal to the starting point of opacification of coronary sinus origin. The frame count noted at the first diagonal was noted as the first frame count, and the frame in which the origin of the coronary sinus is seen was noted as the last frame. With sufficient cranial angulation, the coronary sinus was assessed in the left anterior oblique (LAO). In seconds, the MCTT was computed as MCTT equal to last frame count minus first frame count/15. Microcirculatory transit time in both groups was compared and analysed.

### Statistical Analysis

All analyses were made using the Minitab 16 software package. Categorical data were expressed as frequencies and percentages. Comparison of categorical variables was performed by chi-square test. Fisher's exact test was applied for cell frequency < 5. Continuous variables were expressed as mean ± standard deviation, and analyses were done using a two-tailed t-test/ analysis of variance (ANOVA) F for equality of means. A P value of < 0.05 was accepted as statistically significant. The institutional ethics committee approved the research protocol. Written, informed consent was obtained from each patient.

## RESULTS

The total number of study cases and controls admitted to the hospital during the study period was 56. Out of 56 patients, two cases and two controls had an abnormal angiogram, and they were excluded from the data analysis. The data of 52 patients were analysed. There were 26 cases in the angina group and 26 cases in the control group. Baseline characteristics of both groups were given in Table - 1. The mean age of study cases and controls was 49.96 ± 9.65 years, 50.32 ± 5.04 years. 23 % of study cases were between 51 - 60 years of age group, and 92 % of the study controls were in the age group of 41 - 60 years. Patients in the angina group had significant risk factors when compared to patients in the control group. The incidence of diabetes mellitus (DM), hypertension, dyslipidaemia was more in the angina group even though the differences were not statistically significant except for dyslipidaemia, statin use and nitrate use.

The mean microcirculatory transit time in the angina group with TMT positive was 6.76 seconds and was more than TMT negative patients (6.39 s) and inconclusive patients (6.58 s) but the difference among different TMT groups was not statistically significant (P = 0.876) (Table - 2 & Fig - 1). Patients referred for pre-operative cardiac risk stratification for non-cardiac surgery were the most common

control population accounting for 69.23 %. (Table - 3 & Fig. - 2). The mean frame count and mean MCTT in the angina group were 98.1 ± 23.9 and 6.5 ± 1.61 seconds, respectively, compared to the control group, in which the mean frame count and the mean MCTT were 58.1 ± 9.48 and 3.86 ± 0.63 seconds (P - value < 0.001), which was highly statistically significant. (Table - 4 & Fig - 3)

| | | | Angina Group (%) | Control Group (%) | Chi – Square / t test / Fischer's Exact | P - Value |
|---|---|---|---|---|---|---|
| Total No. | | | 26 | 26 | | |
| Demographic variables | Sex | Male<br>Female | 13 (50 %)<br>13 (50 %) | 12 (46.2 %)<br>14 (53.8 %) | 0.077 | 0.78 |
| | | Age (Yrs.) Mean ± SD | 49.96 ± 9.65 | 50.32 ± 5.04 | 0.17 | 0.87 |
| Non - communicable disease variables | Diabetes mellitus | YES<br>NO | 7 (26.9 %)<br>19 (73.1 %) | 2 (7.6 %)<br>24 (92.4 %) | 3.36 | 0.067 |
| | Hypertension | YES<br>NO | 8 (30.7 %)<br>18 (69.3 %) | 2 (7.6 %)<br>24 (92.4 %) | 4.46 | 0.035 |
| | Dyslipidemia | YES<br>NO | 11 (42.30 %)<br>15 (47.7 %) | 3 (11.58 %)<br>23 (88.42 %) | 6.26 | 0.012 |
| | Smoking | YES<br>NO | 7 (26.9 %)<br>19 (73.1 %) | 1 (3.8 %)<br>25 (96.2 %) | 5.32 | 0.05 |
| | Alcoholism | YES<br>NO | 6 (23.1 %)<br>20 (76.9 %) | 3 (11.5 %)<br>23 (88.5 %) | 1.21 | 0.27 |
| | Family history of CAD | YES<br>NO | 3 (3.8 %)<br>23 (96.2 %) | 0 (0 %)<br>26 (100 %) | 3.18 | 0.24 |
| Drugs | Beta blockers | YES<br>NO | 13 (50 %)<br>13 (50 %) | 7 (26.9 %)<br>19 (73.1 %) | 2.93 | 0.09 |
| | CCB | YES<br>NO | 10 (38.4 %)<br>16 (61.6 %) | 8 (30.7 %)<br>18 (69.3 %) | 0.34 | 0.56 |
| | Statins | YES<br>NO | 15 (57.7 %)<br>11 (42.3 %) | 2 (7.6 %)<br>24 (92.4 %) | 14.97 | 0.001 |
| | Nitrates | YES<br>NO | 18 (69.23 %)<br>8 (30.73 %) | 0 (0 %)<br>26 (100 %) | 27.53 | 0.001 |
| | ACEI/ARB | YES<br>NO | 12 (46.2 %)<br>14 (53.8 %) | 3 (11.5 %)<br>23 (88.5 %) | 7.59 | 0.006 |
| | Aspirin | YES<br>NO | 13 (50 %)<br>13 (50 %) | 6 (23.1 %)<br>20 (76.9 %) | 2.31 | 0.069 |

***Table 1. Baseline Characteristics of the Study Population***

*CCB : Calcium channel blockers † ACEI : angiotensin - converting enzyme inhibitor § ARB : angiotensin receptor blocker || CAD : coronary artery disease

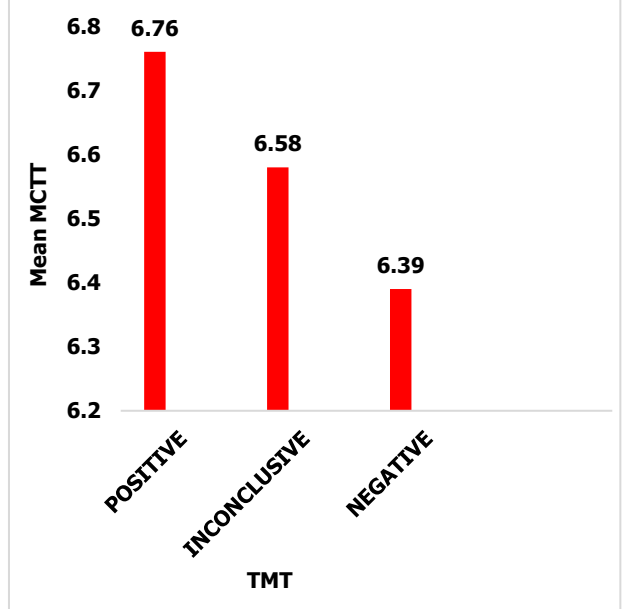


***Figure 1. Correlation of TMT and Mean MCTT***

TMT: treadmill test † MCTT: microcirculatory transit time

| TMT | Mean MCTT (Seconds) | ANOVA F Value | P - Value |
|---|---|---|---|
| Positive | 6.76 | 0.133 | 0.876 |
| Inconclusive | 6.58 | | |
| Negative | 6.39 | | |

***Table 2. Correlation of TMT and Mean MCTT in Angina Group***

*TMT: treadmill test † MCTT: mean circulatory transit time

| Control Group | Number Enrolled |
|---|---|
| Rheumatic valvular heart disease | 5 (19.23 %) |
| Pre-operative cardiac risk stratification | 18 (69.23 %) |
| EPS & RFA for PSVT | 3 (11.53 %) |

***Table 3. Subcategories in the Control Group***

EPS: Electrophysiological study † RFA: Radiofrequency ablation ‡PSVT: paroxysmal supraventricular tachycardia
*PSVT: Paroxysmal supraventricular tachycardia † EPS: Electrophysiological study ‡ RFA: Radiofrequency ablation

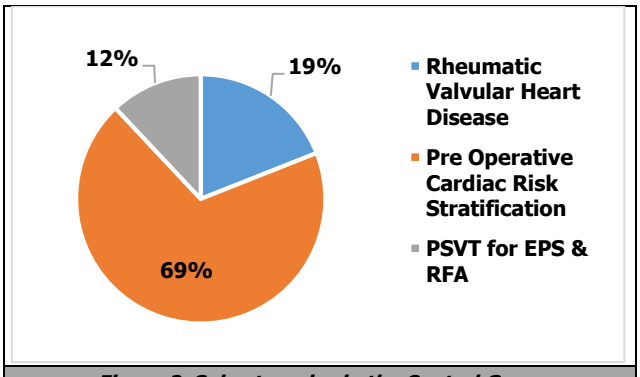


***Figure 2. Subcategories in the Control Group***

* PSVT: paroxysmal supraventricular Tachycardia † EPS: Electrophysiological Study; ‡ RFA; radio frequency ablation

| Parameter | Angina Group (Mean ± SD) | Control Group (Mean ± SD) | t - Test | P - Value |
|---|---|---|---|---|
| Mean frame count | 98.1 ± 23.9 | 58.1 ± 9.48 | 7.93 | < 0.001 |
| MCTT (Seconds) | 6.50 ± 1.61 | 3.86 ± 0.63 | 7.79 | < 0.001 |

***Table 4. Comparison of Mean Frame Count and Mean MCTT***

* MCTT: Microcirculatory transit time

## DISCUSSION

Our study showed a delay in coronary microcirculatory transit time in patients with Cardiac syndrome X. Coronary microcirculatory transit time is a sign of microvascular dysfunction in patients with cardiac syndrome X. CSX was defined by typical angina pectoris with a positive exercise test and a normal coronary angiogram.[7] Researchers have reported a heightened risk of myocardial infarction and cardiac death in patients with a positive stress test.[8,11]

Because no current imaging techniques can visualize the coronary microvasculature, new non-invasive imaging indices of this syndrome must be investigated. The doppler wire was previously reported to be a reliable method for evaluating microvascular dysfunction.[12] A less invasive diagnostic method is to assess myocardial perfusion reserve index using cardiac magnetic resonance imaging following adenosine administration. A study revealed that low MPRI scores in women might be associated with microvascular dysfunction.[13] However, they are not suitable for wide use because they require greater resources and technical knowledge. With this in mind, coronary angiography parameters derived from total frame count (TFC) such as coronary clearance frame count (CCFC) and coronary sinus filling time (CSFT) have gained popularity in recent years.

Sangareddi et al.[10] concluded that the time delay between the left anterior descending artery (LAD) opacification and the coronary sinus (CS) filling would indicate the microcirculatory time. CSFT was defined as the difference in frame counts between the maximum LAD opacification and the coronary sinus's maximum opacification. Coronary sinus emptying time and coronary sinus emptying velocity are also calculated as parameters for assessing microcirculatory transit. Since coronary sinus emptying time and velocity depend on the coronary sinus's drainage characteristics rather than coronary microcirculation, only MCTT was included in our study. The definition of MCTT has been changed as the difference in frame counts between the maximum opacification of LAD at the 1st diagonal level to the beginning of coronary sinus origin filling. The coronary sinus is a venous conduit, which preferentially drains between 80 percent to 85 percent of the left ventricle's unsaturated blood flow.[14] Studies have revealed a dynamic variation of the coronary sinus lumen during the normal cardiac cycle, and it is classified into passive response, normal response, and hyperactive.[1] An exaggerated response to this mechanism could render one vulnerable to the slow flow phenomena. Modulation of the normal canine heart's coronary sinus outflow affects myocardial tissue pressure. It has been shown to reduce subepicardial tissue blood flow independently of coronary arterial pressure.[4]

Due to the coronary sinus's maximal opacification being dependent on multiple factors other than microcirculation, we assessed the filling at the coronary sinus's origin. Our study supports the previous research that demonstrates that the transit time of coronary microcirculation in angina with normal coronaries is delayed.

In Ragab A. Mahfouz et al.[15] study, the total number of controls included was 15 (n = 15), and the total number of cases included was 64 (n = 64). Our study has included an equal number of study cases and controls for a better comparison of data. TIMI frame count measured the coronary blood flow in all three major coronary arteries in their study, but we calculated the TIMI frame count for LAD only in our study.

In the Mahfouz et al. analysis for the angina group and control group, the TIMI frame count for LAD was 37 ± 19, 23 ± 7, while in our study, the TIMI frame count for LAD in the angina group and control group was 98.1 ± 23, 58.1 ± 9.48, respectively. Patients who developed obstructive CAD and cardiomyopathy during follow-up had a more substantial increase in TIMI frame count than any other group in this Egyptian follow-up study. The South Indian population was studied in our research; both controls and study groups had a very high frame count in LAD compared to Egypt's study population. In the South Indian population, this increased frame count may suggest even more poor outcomes.

In a study conducted by Haridasan et al.[16] both TIMI frame count and CSFT were calculated. In their analysis, the mean TIMI frame count and CSFT were 63.76 ± 10.7 and 4.24 ± 0.72 among the cases tested, respectively, and 52.06 ± 5.0 and 3.45 ± 0.99 among the controls, respectively, which were statistically significant. In our sample, the mean TIMI frame count and mean MCTT among study patients were 98.1 ± 23.94; 6.5 ± 1.57, and 58.1 ± 9.48, 3.45 ± 0.99 among study controls respectively. ($P < 0.001$), which was statistically significant. Both the mean TIMI frame count and CSFT results in the study were longer than in the study by Haridasan et al. Our study had a larger study population (N = 52) than the previous study (N = 41). This study's control population was patients with structural heart disease.[3] However, in contrast to the previous study, our study recruited patients with structurally normal hearts and patients with structural heart diseases as controls. They compared the other parameters of perfusion, cTIMI frame count, and TMP. These two variables were not significantly different in the control and angina groups as in other studies.[4,17,18] We did not compare TMP in our study. We were unable to find any research addressing the importance of MCTT in the long-term. The usefulness of MCTT on long term outcomes in patients with angina and normal coronaries merits further study.

In a study conducted by Kadermuneer et al.[19] from Kerala, India, a greater number of patients were included (N = 88: study group = 72, control group = 16) when compared to our study (N = 52: angina group = 26, control group = 26). The mean CSFT values of this study (angina group: 5.91 ± 1.12, control group: 5.12 ± 0.91) were closely correlated with our study (angina group: 6.5 ± 1.57, control group: 3.86 ± 0.62).

Both these studies from South India have found increased TIMI frame count compared to the Egyptian population, indicating the more prevalent microvascular dysfunction in the South Indian population but this conclusion cannot be made as ours was not an epidemiological study and study's sample size was small. There is a need to conduct a multi-center study with large sample size before drawing any such conclusions.

Erkan Yildirim et al.[20] study from Turkey employed a nuclear imaging study as a stress study, while in our study, we have used TMT as a stress test. Coronary clearance frame count was used to assess microvascular dysfunction in their study. In contrast, we have used MCTT to assess microvascular dysfunction. CCFC in LAD territory was 43.82 ± 8.50 seconds in the CSX group, and 39.21 ± 7.95 seconds in the control group was statistically significant (P - 0.002). The mean frame counts of both study patients and study controls were significantly prolonged in our study compared to Erkan Yildirim et al. study (TIMI frame count in CSX group was 40.69 ± 13.03 and in the control group it was 38.91 ± 8.61). This study also clearly demonstrated the greater extent of microvascular dysfunction in the south Indian population.

## CONCLUSIONS

Microcirculatory transit time in patients with definite angina irrespective of the treadmill stress test and patients with probable angina with positive treadmill test are prolonged compared with patients without chest pain and normal coronaries. Microcirculatory transit time in patients with angina and normal coronaries can be proposed as a method to risk-stratify patients with angina and normal coronaries.

Patients with angina and normal coronaries should be followed over the long term, risk factor modification should be instituted, and therapies aimed at increasing microvascular function should be offered. Long-term follow-up studies with a multicentre design and a larger study population should be conducted in the future.

### Limitations

The current study had several shortcomings. The study was small, and the results could not be generalized. There was no standardization of hand injection; therefore, this may have biased the results. We did not consider inter-observer variability while calculating microcirculatory transit time. The microcirculatory transit time was not corrected for the heart rate. A stress test was not performed in the control group.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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