

Association of Total Ischemia Time with No-Reflow Phenomenon in Patients Presenting with ST-Elevation Myocardial Infarction, Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

Objective: To find out the association of total ischemic time with no-reflow phenomenon, in terms of Thrombolysis in Myocardial Infarction (TIMI) flow grade, in patients presenting with ST-Elevation Myocardial Infarction and undergoing Primary Percutaneous Coronary Intervention (PPCI).

Study Design: Analytical Cross-Sectional study.

Place and Duration of Study: Armed Forces Institute of Cardiology/National Institute of Heart Diseases Rawalpindi Pakistan, from Nov, 2022 to Jan, 2023.

Methodology: This analytical cross-sectional study was conducted on n=184 patients, recruited through consecutive sampling technique to collect data prospectively. Patients were divided into no-reflow and normal flow group. Patients' total ischemic time was documented and pre & post-procedural TIMI flow was noted. SPSS version-24.00 was used to enter and analyze data. Chi-square, Fisher exact test and t-test were applied and p -value ≤ 0.05 was taken as statistically significant.

Results: Out of 184 study participants, 17(9.2%) were females as compared to 167(90.8%) males. The mean age was 60.23 ± 10.28 years. No-reflow phenomenon was observed in 20(10.9%) patients. The mean age was higher in the no-reflow group than that of the normal flow group (62.65 ± 11.61 vs 59.94 ± 10.12 years). Total ischemic time, pre & post-procedural TIMI flow were found to be significantly associated with no-reflow phenomenon ($p < 0.05$).

Conclusion: There exists a strong association between total ischemic time and the occurrence of no-reflow phenomenon. Patients with delayed reperfusion present with greater frequency of no-reflow and low TIMI grade and vice versa.

Keywords: No-Reflow Phenomenon, Primary Percutaneous Coronary Intervention, ST-Elevation Myocardial Infarction, Thrombolysis in Myocardial Infarction, Total Ischemic Time.

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INTRODUCTION

The highly recommended and efficient procedure to improve or restore the antegrade blood flow in stenosed coronary arteries is the Primary Percutaneous Coronary Intervention (PPCI). It is the currently known standard of care for the patients of acute ST-Segment Elevation Myocardial Infarction (STEMI) with improved outcomes.^{1,2} In spite of successful revascularization, non-perfusion of myocardium is still a big problem, encountered in up to 30% patients who undergo PPCI and is referred as no-reflow phenomenon.¹ No-reflow phenomenon can also be defined in terms of a complication linked with inadequate or improper perfusion of myocardial tissues with no evidence of angiographic epicardial vessel spasm, damage, dissection or obstruction.³

Pathologically, the no-reflow was categorized into two forms such as; structural no-reflow (necrotic

myocardial tissue containing micro vessels which can be due to the absence of capillary integrity because of endothelial inflammation and edema or can be due to microvascular obstruction depending upon ischemia duration) and functional no-reflow (compromised micro vasculature patency because of thrombo-embolization, spasm, ischemic damage, reperfusion injury and loading platelets and neutrophils as a result of neurohumoral system activation).^{2,4,5}

A number of past studies reported adverse clinical outcomes of PPCI due to no-reflow phenomenon such as; myocardial reinfarction, remodeling of Left Ventricle (LV), reduction in Left Ventricular Ejection Fraction (LVEF), malignant ventricular arrhythmias, cardiac rupture, Heart Failure (HF) and even mortality.^{3,6} As a consequence, identifying its predictors and detecting no-reflow is of prime importance. Thereby prevention from no-flow can be a step towards good clinical outcomes and improved patients' long-term prognosis.

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Multiple factors affecting no-reflow phenomenon, for example, stress hyperglycemia, thrombus burden, nisoldipine, streptokinase, door to balloon time, door to needle time, first medical contact to balloon were studied in a number of studies due to their prime importance in clinical setting while managing Acute Myocardial Infarction (AMI) patients as they effect prognosis.^{2,6-9} However, studies lacked in-depth knowledge pertaining total ischemic time (time from pain onset to reperfusion) which lead to no-reflow phenomenon.⁹ Hence, current study was aimed at determining the relevance of total ischemic time with no-reflow phenomenon as defined by Thrombolysis in Myocardial Infarction (TIMI) flow grade in STEMI patients who underwent PPCI. It will help to devise strategies to reduce the delay from symptom onset to actual revascularization.

METHODOLOGY

This Analytical Cross-sectional study was conducted from November 2022 till January 2023. It targeted the STEMI patients who underwent PPCI. Patients for data collection were selected via non-probability consecutive sampling technique. Prior to data collection ethical approval was taken from Institutional Ethical Review Board (IERB) of Armed Forces Institute of Cardiology, National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi, (IERB Ltr#9/2/ R&D/2022/216).

WHO calculator was used to calculate sample size by using 13.9% prevalence of post-PPCI no-reflow in STEMI patients.² Confidence level and margin of error was kept at 95% and 5% respectively. Resultant sample size was n=184.

Inclusion Criteria: Both male and female patients within age bracket of 18-80 years, who presented with STEMI and underwent primary PCI, were selected for the study.

Exclusion Criteria: Patients presenting with cardiogenic shock, unstable angina, NSTEMI, thrombophilia, pulmonary embolism or Deep Vein Thrombosis (DVT), malignancy, coagulation disorder, prior Coronary Artery Bypass Graft (CABG) procedure, stroke, Chronic Obstructive Pulmonary Disease (COPD), asthma, chronic renal failure, chronically ill patients and who had undergone thrombolysis were excluded.

Patients were evaluated by taking complete history and clinical examination at the time of presentation in emergency department. Legal formalities were done by taking informed consent from all study

participants. Standard right and left coronary angiograms with minimum two-projections were done for every patient. Two highly qualified and experienced cardiologists assessed study's required parameters such as; angiographic features of lesion, culprit artery and TIMI flow grade pre and post PCI. Primary PCI was done through trans-radial artery or trans-femoral approach according to operator's preference. Total ischemia time and TIMI flow grade were noted. Patients' data was documented in pre-designed proforma.

Patients were partitioned into two groups based upon no-reflow phenomenon such as; group-I: TIMI grade 0-2 (no-flow group), group-II: TIMI flow grade-3 (normal flow group). Score of TIMI flow was determined by using degree of blood flow in epicardial coronary arteries and it was graded as.²

Grade-0=totally no flow beyond the point of obstruction.

Grade-1=contrast material flow to some extent distal to obstruction point but no achievement of full arterial visualization. Grade-2=delayed opacification of complete artery. Grade-3=normal flow and complete prompt visualization of whole artery.

Statistical package for social sciences (SPSS); version-24:00 was utilized for data entry and analysis. Descriptive as well as inferential statistics were applied to compute the results. Qualitative and quantitative data was analyzed by frequency & percentage and mean & standard deviations respectively. Chi-square test, Fischer Exact test were applied to find the association of total ischemic time with no-reflow phenomenon. *p*-value of <0.05 was taken statistically significant.

RESULTS

The statistical findings on n=184 STEMI patients who underwent PPCI revealed mean age of 60.23±10.28 years of study participants. Frequency of males was 167(90.8%) and of females was 17(9.2%). Almost half of the patients presented with diabetes 97(52.7%), majority were hypertensive 107(58.2%) and 75(40.8%) were smokers. Patients with Single Vessel Coronary Artery Disease (SVCAD) were 74(40.2%) and those having Double Vessel Coronary Artery Disease (DVCAD) and Triple Vessel Coronary Artery Disease (TVCAD) were fewer [63(34.2%) and 47(25.5%)] respectively. LMS involvement was found in only single 1(0.5%) participant. Almost half were diagnosed with IWMI 94(51.1%) (Table-I).

Total Ischemia Time with No-Reflow in NSTEMI Patients

Table-I: Demographics and Clinical Characteristics of Study Participants (n=184)

Variables		Frequency(%) (n=184)	No-Reflow Group Frequency(%) (n=20)	Normal Flow Group Frequency(%) (n=164)	p-value
Age (years) (Mean±SD)		60.20±10.20	62.65±11.61	59.94±10.12	0.32
Gender	Male	167(90.8)	19(95.0)	148(90.2)	0.77
	Female	17(9.2)	1(5.0)	16(9.8)	
Diabetes Mellitus	Yes	97(52.7)	9(45.0)	88(53.7)	0.62
	No	87(47.3)	11(55.0)	76(46.3)	
Hypertension	Yes	107(58.2)	8(40.0)	99(60.4)	0.13
	No	77(41.8)	12(60.0)	65(39.6)	
Smoker	Yes	75(40.8)	11(55.0)	65(39.6)	0.37
	No	109(59.2)	9(45.0)	99(60.4)	
Coronary Artery Disease	SVCAD	74(40.2)	5(25.0)	69(42.1)	0.20
	DVCAD	63(34.2)	7(35.0)	56(34.1)	
	TVCAD	47(25.5)	8(40.0)	39(23.8)	
Left Main Stem Disease	Yes	1(0.54)	1(5.0)	0(0.0)	0.20
	No	183(99.5)	19(95.0)	164(100)	
ECG Diagnosis	AWMI	82(44.6)	11(55.0)	71(43.3)	0.18
	IWMI	94(51.1)	7(35.0)	87(53.0)	
	LWMI	8(4.35)	2(10.0)	6(3.7)	

CAD=Coronary Artery Disease; SVCAD=Single vessel CAD, DVCAD=Double Vessel CAD; TVCAD=Triple Vessel CAD;TIMI=Thrombolysis in Myocardial Infarction

Mean of total ischemic time was calculated to be 619.0±355.67 min in no-reflow group which is almost double as compared to normal flow group (321±292.40 min). The Pre-PCI TIMI flow ≤II, implying the no-reflow phenomenon was observed in 20(10.9%) patients. However, the final TIMI flow achieved after thrombus resolution and intracoronary drug treatment for no-reflow was grade-III in 175 (95.1%) patients, with good clinical outcome.

Descriptive analysis mentioned in Figure has demonstrated highest frequency of LAD 79(42.9%), as culprit artery in our study sample, compared to RCA 73(39.7%) and LCX 25(13.6%).

Cross-tabulation was done to find out the association of study's variables with no-reflow phenomenon and statistically significant association was found in total ischemic time, pre-procedural and post-procedural TIMI-flow with no-reflow phenomenon ($p<0.01$). Majority of the patients had total

ischemic time more than 180 minutes 112(60.9%) with highest percentage in no-reflow group (90.0% vs 57.3%). Mean difference of total ischemic time also significantly varied in no-reflow and normal flow group (619.0±355.67 vs 321±292.4; $p=0.002$) (Table-II).

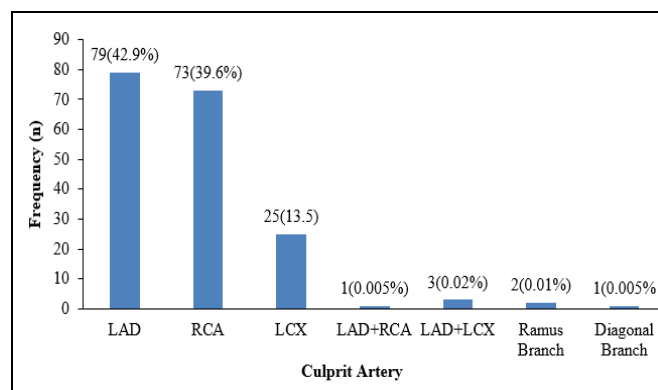


Figure: Frequency distribution of culprit artery (n=184)

LAD= Left anterior Descending; RCA=Right Coronary Artery; LCX=Left Circumflex

Table-II: Association of Total Ischemic Time and TIMI Flow with No-Reflow Phenomenon (n=184)

		Frequency(%) (n=184)	No-Reflow Group Frequency(%) (n=20)	Normal Flow Group Frequency(%) (n=164)	p-value
Total Ischemic Time (minutes) (Mean±SD)		353.70±312.91	619.00±355.60	321.00±292.40	0.002
Total Ischemic Time (min)	≤180	72(39.1)	2(10.0)	70(42.7)	0.006
	>180	112(60.9)	18(90.0)	94(57.3)	
Pre-procedural TIMI flow	TIMI≤II	20(10.9)	20(100.0)	0(0.0)	<0.001
	TIMI=III	164(89.1)	0(0.0)	164(100)	
Post-procedural TIMI flow	TIMI=I	1(0.5)	1(5.0)	0(0.0)	<0.001
	TIMI=II	8(4.3)	7(35.0)	1(0.6)	
	TIMI=III	175(95.1)	12(60.0)	163(99.4)	

TIMI=Thrombolysis in Myocardial Infarction

DISCUSSION

No-reflow phenomenon is common as entire restoration of coronary perfusion followed by myocardial may not always occur adequate post-revascularization of infarct related arteries.^{10,11} Past literatures showed that no-reflow phenomenon can occur in approximately one-third of patients who undergo PPCI.^{11,12} However, current study's findings showed no-reflow phenomenon in 10.9% of study participants and association of total ischemic time with no-reflow phenomenon was found to be statistically significant ($p < 0.01$). Cross tabulation has also demonstrated significant relationship TIMI flow grades with no-reflow phenomenon ($p < 0.01$).

Current study revealed no-reflow phenomenon occurrence was relatively higher in older patients (62.65 ± 11.61 vs 59.94 ± 10.12 years) for those without no-reflow) which was in agreement to a study done by Khalfallah M and his companions. The mean age (62.8 ± 10.49 years) was found in no-flow group while in normal flow group, it was (59.9 ± 10.94 years) and the mean difference was also statistically significant ($p = 0.033$). Similarly, another study has reported (57 ± 11.2 years vs 63.1 ± 11.5 years respectively) with p -value < 0.001 .¹³ With increase in age, risk of coronary calcification, distal micro embolization, diffused atherosclerosis, atrial fibrillation and abnormal microcirculation increase which may progress to higher hemodynamic compromise along with comorbidities being the promoting factors to no-reflow phenomenon.^{2,14,15}

No-reflow phenomenon was also more prevalent in non-diabetic patients as compared to diabetics (45% vs 53.7% and $p = 0.62$) and it was in line with past studies (18% vs 51% & $p = 0.033$),¹³ (25.2% vs 36.8% & $p = 0.001$) respectively.² In diabetic patients lumen of vessels is already compromised and narrowed, thereby there is an increased risk of no-reflow post primary PCI.^{16,17} However, hypertension & dyslipidemia were also significantly associated with the occurrence of no-reflow phenomenon according to Khalfallah *et al.*²

Literature has reported the incidence of no-reflow phenomenon ranging from 4.1-25.7% in patients undergoing primary PCI.^{2,12,13,18,19} However, our study's analysis revealed 10.9% occurrence which is in the range found by past studies. Our study found that total ischemic time was significantly higher in no-reflow group relative to normal flow group (619.0 ± 355.67 vs 321 ± 292.40 min & $p = 0.002$). It was similar to the results reported by Khalfallah *et al.*, in

which total ischemic time was noted in hours with mean values in no-reflow and normal flow group as (8.17 ± 4.02 vs 4.54 ± 3.24 hours & $p = 0.01$).² Comparatively in a study conducted by Mirbolouk *et al.*, there was found insignificant difference pain onset to primary PCI time in normal and no-reflow group patients ($p > 0.05$).¹³

Kirma *et al.*, studied a sample of $n = 382$ patients who underwent primary PCI, stated that delay of more than 6 hours in reperfusion was correlated significantly with no-reflow ($p < 0.05$)¹⁰ which is supporting our study's findings in which 18(90%)/20 patient were having > 6 hours of total ischemic time and showed no-reflow phenomenon with statistically significant results ($p = 0.006$). Delayed reperfusion boosts the early stages of AMI due to thrombocyte rich thrombus. However it is easy to treat in early stages with adjunctive pharmacotherapy. Nevertheless, the increase in ischemia gives an ample time to thrombus to become rigid followed by fragmentation due to balloon dilatation leading to embolization. Moreover, it also leads to well-organized intracoronary thrombus formation which plays significant obstruction in achieving TIMI-III flow.^{14,20,21} This description is in agreement with statistical findings of current research work which has found a decreasing trend of TIMI flow with increase in total ischemic time and vice versa. Some studies also followed-up the patients to measure outcomes such as mortality and revealed high mortality rate in patients with delayed reperfusion and belonging to no-reflow group.^{9,13,22} However, this study lacked to follow-up of the patients. The patient group having delayed ischemic time can be followed to assess long-term clinical outcomes. In addition, the patients undergoing thrombolysis initially and then having facilitated PCI can be followed for occurrence of no-reflow phenomenon in relation to the time from chest pain onset to thrombolysis.

LIMITATIONS OF STUDY

This was a single centered and cross-sectional study with low sample size therefore, findings are not generalizable. Short and long-term follow-up of patients was not done to find in-hospital and long-term outcomes due to limited time availability. Mortality was also not considered. Thereby, longitudinal and follow-up studies are recommended.

CONCLUSION

There exists a strong association of total ischemic time with occurrence of no-reflow phenomenon. Patients

with delayed reperfusion presents with greater frequency of no-reflow and low TIMI grade and vice versa.

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Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript:

WA, SSK, & MNK: Study Design, Critical Review, Manuscript drafting, approval of the final version to be published.

AN, & BU: Intellectual Contribution, Proof Reading, Editing, Approval of the Final Version to be Published.

AS, JK, & MY: Critical review, Data Analysis, Editing, Intellectual Contribution, Final Approval.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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