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The Predictors of No-Reflow Phenomenon after Primary Angioplasty for Acute Myocardial Infarction

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ABSTRACT

Background: No-reflow phenomenon is a serious complication of primary Percutaneous Coronary Intervention (PCI), which may increase the risk of progressive myocardial damage, profound left ventricular dysfunction, and death.

Objectives: This study aimed to investigate the incidence of no-reflow phenomenon and its clinical, para-clinical, and angiographic determinants in patients who underwent primary PCI for ST Elevation Myocardial Infarction (STEMI).

Patients and Methods: This non-randomized prospective cohort study was conducted on 397 patients in a cardiovascular tertiary care center in Tehran, Iran from April 2012 to April 2014. The inclusion criteria of the study were presenting with acute STEMI of ≤ 12 h duration or having admitted between 12 and 24 hours after onset with symptoms and signs of ongoing ischemia. The participants underwent standard coronary angiography. No-reflow phenomenon was defined as a Thrombolysis In Myocardial Infarction (TIMI) flow ≤ 2 and no presence of spasm, distal embolization, or dissection after completion of the procedure. The association between no-reflow and its determinants was assessed by chi-square, student's t-test, or Mann–Whitney U test. Logistic regression models were also used for multivariate analysis. P values < 0.05 were considered to be statistically significant.

Results: The participants' mean (SD) age was of 59 (12.2) years and female/male ratio was 83/314. The incidence of no-reflow phenomenon was 63 (15.9%). Besides, the results of multivariate analysis showed that only thrombus burden, lesion length, time to reperfusion, and type of occlusion had an adjusted association with this phenomenon.

Conclusions: The study results suggested that no-reflow phenomenon after primary PCI would be predictable. Thus, preventive measures, such as using distal protective devices or administration of platelet glycoprotein IIb/IIIa antagonists, are advised to be used in high-risk patients.

►*Implication for health policy/practice/research/medical education:*
Considering the results of this study, cardiologists may be able to predict the occurrence and apply suitable methods for prevention of no-reflow phenomenon in patients with STEMI after primary PCI.

1. Background

Nowadays, primary Percutaneous Coronary Intervention (PCI) is a gold standard treatment for patients with acute ST Elevation Myocardial Infarction (STEMI) (1). Although the full patency of the infarct-related artery is achieved by primary PCI most of the times, the success rate can be reduced if the no-reflow phenomenon occurs (2, 3). Thrombolysis In Myocardial Infarction (TIMI) flow grade is the most commonly used method for assessment of primary PCI success (4). No-reflow phenomenon is a serious complication of primary PCI defined as a TIMI

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flow ≤ 2 (2, 3). This phenomenon can occur after primary PCI in up to one fourths of cases and such patients are at an increased risk of progressive myocardial damage, profound left ventricular dysfunction, and higher morbidity and mortality rates (2, 3, 5-7). Up to now, many studies have investigated the pathogenesis and risk factors of no-reflow phenomenon (5-10).

2. Objectives

The present study aims to investigate the clinical, laboratory, and angiographic predictors of no-reflow phenomenon in patients who underwent primary PCI for acute STEMI in a tertiary referral cardiovascular center.

3. Patients and Methods

3.1. Study Participants

This non-randomized prospective cohort study was conducted in Rajaie Cardiovascular Medical and Research Center, the main cardiovascular tertiary care center in Tehran, Iran, from April 2012 to April 2014. Totally, 397 patients admitted in our center with a diagnosis of acute STEMI who underwent emergent coronary catheterization were consecutively enrolled into the study. According to the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, "STEMI is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent Electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis" (1). The inclusion criteria of the study were presenting with acute STEMI of ≤ 12 h duration or having admitted between 12 and 24 hours after onset with symptoms and signs of ongoing ischemia. After coronary angiography, the patients with coronary vasospasm, less than 50% diameter stenosis, and need for emergent/surgical revascularization, including left main coronary stenosis and any lesions leading to MI on the grafted vessels in the patients previously undergone CABG, patients who received platelet glycoprotein IIb/IIIa receptor antagonists before angiography, and those who were treated with thrombolytic therapy, were excluded from the study. The study protocol was approved by the research and ethics committee of Rajaie Cardiovascular Medical and Research Center.

3.2. Angiography and Primary PCI Procedure

All the patients were treated with 300 milligram (mg) aspirin, 600 mg clopidogrel, and 5000 - 10000 units unfractionated heparin before transmission to catheterization laboratory. Standard left and right coronary angiography was performed in all the patients via femoral approach using guiding catheter and at least 2 best projections were acquired for each patient. The angiograms were assessed and quantitative angiographic measurements were done by an expert interventional cardiologist and the following findings were recorded: Infarct Related Artery (IRA) and its luminal diameter, target lesion characteristics (lesion location, lesion length, type of occlusion, lesion type in subtotal occlusion, and thrombus burden), and initial and post procedural TIMI flow grade. Decision to perform primary PCI and to choose the optimal PCI technique in each patient was also made by the interventional cardiologist after coronary angiography. Depending on the lesion characteristics, one of the following techniques was used for primary PCI: balloon angioplasty, stenting with pre–dilation, and direct stenting with or without thrombus suction.

Occlusion was defined as total type if the lesion had an abrupt end without tapering and as subtotal if the lesion had a tapered end. If the most protruding margin of the lesion was located in the outer quarter of the vessel lumen, the lesion was defined as subtotal. Besides, the intraluminal filling defects that did not have calcification were defined as thrombus (9). The thrombus burden of the target lesion was assessed according to the TIMI thrombus classification (4). "Thrombus burden was classified as mild if consistent with TIMI thrombus class 0 and 1, moderate if consistent with TIMI thrombus class 2 and 3, and high if the greatest linear dimension of the thrombus was more than TIMI thrombus class 3" (9).

3.3. Definition of No-Reflow Phenomenon

If TIMI flow ≤ 2 was observed despite successful dilatation and there was no spasm, distal embolization, or dissection after completion of the procedure, the patient was considered to have no-reflow phenomenon.

3.4. Reperfusion Time

Time to reperfusion was defined as the time from the onset of symptoms to the first angioplasty balloon inflation. Additionally, door to balloon was defined as the time from patient's arrival to the emergency department to the first balloon inflation (1).

3.5. Study Variables and Data Collection

The primary outcome of the study was "no-reflow phenomenon". Other variables, including the predictors of the no-reflow phenomenon, were measured, as well. Besides, demographic data, risk factors of cardiovascular diseases, clinical and para-clinical findings, and characteristics of the recent MI were extracted from the patients' medical records. Also, angiographic findings, primary PCI findings, and characteristics of the target lesion were obtained during the angiographic procedure, as explained above.

3.6. Statistical Analysis

All the statistical analyses were performed using the IBM SPSS statistical software for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Firstly, Kolmogorov-Smirnov test was used to assess the normal distribution of the data. Categorical variables were expressed as number and percentage and quantitative ones as mean (standard deviation) or median (interquartile range) for the variables that did not follow normal distribution. Categorical variables were compared by chi-square, student t-test, or Mann–Whitney test, as appropriated. In addition, binary logistic regression analysis was used for multivariate analysis. P values < 0.05 were considered to be statistically significant.

4. Results

4.1. Baseline Characteristics

This study was conducted on 397 patients with the mean

age of 59 ± 12.2 years (female/male ratio = 83/314). No-reflow phenomenon was diagnosed in 63 patients (15.9%). The patients with and without the no-reflow phenomenon were compared regarding the background data, and the results have been presented in Table 1. Accordingly, the patients in the no-reflow group were older than other participants (P < 0.001). The history of MI was also higher among these patients (P = 0.001).

4.2. Characteristics of Myocardial Infarction

Some characteristics of MI in our study population have been presented in Table 2. Based on the results, there was no significant difference between the two groups regarding the risk factors of coronary artery disease, history of previous MI, and the infarction territory in the current MI and IRA. However, time to reperfusion and door to balloon time were longer in the no-reflow group (P < 0.001). Except for platelet count, inflammatory factors were also higher among the patients with the no-reflow phenomenon (P < 0.001) (Table 2).

4.3. Coronary Angiography Findings

The associations between the incidence of no-reflow phenomenon and its determinants evaluated by coronary angiography have been presented in Table 3. Except for the culprit artery, all the measured factors were significantly associated with the no-reflow phenomenon. In the no-reflow patients, the target lesion was mainly located in the proximal segment of the arteries and occlusion was mainly total and with greater lesion length. Thrombosuction was a frequent method for reperfusion in these patients. Prescription of GP IIb/IIIa inhibitor was also more frequent in the patients with no-reflow phenomenon (all P values < 0.001).

4.4. Multivariable Analysis

For assessment of the adjusted associations between the no-reflow phenomenon and other predictors detected in bivariate analysis, a logistic regression model with backward elimination method was applied and the results have been presented in Table 4. The results indicated that among the several predictors previously mentioned, only

Table 1. Comparison of the Two Groups Regarding the Baseline Data

	Normal Reflow, (n = 334)	No-Reflow, (n = 63)	P value
Age, years	64 (13.8)	58 (11.6)	< 0.001
Gender (F/M)	15/48	68/266	0.3
Hypertension	22 (34.9%)	115 (34.3%)	0.5
Diabetes mellitus	12 (19%)	65 (19.5%)	0.7
Smoking	7 (11.1%)	39 (12%)	0.3
Hyperlipidemia	21 (33.3%)	109 (32.6%)	0.1
Family history	3 (4.7%)	17 (5%)	0.2
History of MI	30 (47.6%)	55 (16.5%)	0.001

Abbreviations: MI, myocardial infarction

* Data presented as mean (SD) and count (%)

Table 2. Myocardial Infarction Characteristics in the Study Groups

	No-Reflow, (n = 63)	Normal Reflow, (n = 334)	P value
MI territory			
Anterior	15(23.8%)	62(18.6%)	
Inferior	47(74.6%)	253(75.7%)	0.2
Posterior	1(1.6%)	19(5.7%)	
Time to reperfusion			
≤ 2 hours	0(0)	89(26.6)	
2 - 4 hours	2(3.2)	157(47)	< 0.001
≤ 4 hours	61(96.8)	88(26.3)	
Door to balloon			
< 30 min	1(1.6%)	129(38.6%)	
30 - 60 min	19(30.2%)	161(48.2%)	< 0.001
≥ 60 min	43(68.3%)	44(13.2%)	
ST segment resolution			
≥ 70%	22(34.9%)	264(79%)	< 0.001
< 70%	41(65.1%)	70(21%)	
CTnI	33.7(21)	1.8(3)	< 0.001
CK-MB	218(106)	45(25.3)	< 0.001
WBC count	15800(400)	10300(3023)	< 0.001
Platelet count	219000(3000)	219000(66250)	0.3
ESR	63(36)	17(9)	< 0.001
hs CRP	29(26)	4(4)	< 0.001

Abbreviations: MI, myocardial infarction; CTnI, cardiac troponin I; CK-MB, creatine kinase-MB; WBC, white blood cell; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein

* Data presented as mean ± SD and count (%)

Table 3. Angiographic Findings in the No-Reflow Patients Compared to the Normal Reflow Group

	No-Reflow, (n = 63)	Normal Reflow, (n = 334)	P value
Infarct-related artery			
LAD	46 (73%)	254 (76%)	
RCA	15 (23.8%)	62 (18.6%)	0.5
LCx	2 (3.2%)	18 (5.4%)	
Initial TIMI flow			
0	56 (88.9%)	72 (21.6%)	
1	7 (11.1%)	161 (48.2%)	< 0.001
2	0	101 (30.2%)	
Target lesion location			
Proximal	59 (93.7%)	119 (35.6%)	
Medial	4 (603%)	169 (50.6%)	< 0.001
Distal	0	46 (13.8%)	
Type of occlusion			
Subtotal	1 (1.6%)	225 (6704%)	< 0.001
Total	62 (98.4%)	109 (32.6%)	0.004
Lesion type in subtotal occlusion			
Concentric	32 (50.8%)	105 (31.4%)	
Eccentric	31 (49.2%)	229 (68.9%)	< 0.001
Lesion length, mm	16 (14 - 18)	8 (6 - 10)	
Thrombus burden			
Low	0	135 (40.4%)	
Moderate	1 (1.6%)	185 (55.4%)	< 0.001
High	62 (98.4%)	14 (4.2%)	
Method of reperfusion			
Balloon angioplasty	0	88 (26.3%)	
Direct stenting	1 (1.6%)	138 (41.3%)	
Stenting + predilation	0	82 (24.6%)	
Thrombosuction	22 (34.9%)	12 (3.6%)	< 0.001
Direct stenting + thrombosuction	10 (15.9%)	2 (0.6%)	
Stenting + predilation + thrombosuction	18 (28.6%)	9 (2.7%)	
Angioplasty + thrombosuction	12 (19%)	3 (0.9%)	
GP IIb/IIIa inhibitor	45 (71.4%)	113 (33.8%)	< 0.001

Abbreviations: LAD, left anterior descending; RCA, right coronary artery; LCx, left circumflex artery; GP IIb/IIIa, glycoprotein IIb/IIIa

* Data presented as mean (SD) and count (%)

Table 4. Multivariable Analysis to Investigate the Adjusted Associations between No-Reflow Phenomenon and some Predictors

	Coefficient (β)	P value	Odds ratio (CI 95%)
Thrombus burden	-5.751	0.003	0.003 (0.001 - 0.135)
Lesion length	-0.900	0.021	0.407 (0.189 - 0.875)
Time to reperfusion	-4.062	0.046	0.017 (0.001 - 0.931)
Type of occlusion	-6.294	0.029	0.002 (0.001 - 0.519)

thrombus burden, lesion length, time to reperfusion, and type of occlusion were independently associated with the primary endpoint of the study (Table 4).

5. Discussion

The incidence of no-reflow phenomenon has been reported to be 5 - 24% in different studies (5-10). In the present study, the rate of no-reflow phenomenon following the primary PCI was 15.9%, which was similar to other studies. This rate was 24.8% in the study by Kirma et al. (9) and 9.5% in the one by Du et al. (11).

The results of univariate analysis showed that certain factors, such as age, WBC count, hs-CRP level, time to reperfusion, door to balloon time, type of occlusion (total, subtotal), type of lesion in subtotal occlusions (eccentric, concentric), lesion length, lesion location (proximal, medial, and distal), thrombus burden, and angioplasty technique, could be related to development of no-reflow phenomenon. However, time to reperfusion, type of occlusion, lesion length, and thrombus burden were identified as the independent predictors of no-reflow phenomenon in multivariate analysis.

Generally, prompt restoration of antegrade blood flow of the coronary artery is critical in treatment of Acute MI (AMI). Therefore, primary PCI is superior to thrombolytic therapy (1). One of the most important factors related to no-reflow phenomenon is the reperfusion time (6-10). In the current study, 96.8% of the patients with no-reflow phenomenon had a reperfusion time more than 4 hours. Previous studies showed that the patients with delayed

reperfusion time (more than 4 hours) had a 1.4 fold increase in the rate of no-reflow phenomenon (6-10). These patients also had a greater thrombus burden because delayed reperfusion causes the thrombus to be more organized and these organized intracoronary thrombi are very vulnerable to distal embolization during primary PCI. In the early stages of AMI, the main structural component of thrombus is thrombocyte that lyses more easily. With a delayed time to reperfusion, erythrocytes are entrapped within the thrombus and make it firmer. Fragmentation of these thrombi following balloon dilatation can lead to distal embolization. Furthermore, prolonged ischemia can lead to alteration in capillary integrity, edema in capillary bed and myocardial cells, and polymorphonuclear cell plugging (2, 3, 8-10). Although the thrombus burden is a very important issue in the occurrence of no-reflow phenomenon, this phenomenon can occur even in patients with lower burden of thrombus if they have a prolonged reperfusion time. Prolonged ischemia can destroy the capillary bed and it is known that the disruption of the vascular bed is one of the key elements in the pathogenesis of the no-reflow phenomenon (2, 3, 6, 8-11).

Lesion characteristics have also been considered to be an important issue in the no-reflow phenomenon (12). The findings of the present study revealed that type of occlusion, lesion length, and the thrombus burden were independently related to the no-reflow phenomenon. Total occlusion may be a sign of prolonged ischemia and a fully developed thrombus, and causes lower TIMI flow before primary PCI. The TIMI flow before the procedure is one of the key factors implicated in the no-reflow phenomenon (6-11). In our study, all the patients with the no-reflow phenomenon had a TIMI flow < 1 before the procedure and 89% showed no antegrade flow (TIMI flow = 0). De Luca et al. (8) and Kirma et al. (9) showed in their studies that the procedural success for primary PCI was better and catheterization complications were lower in the presence of higher TIMI flows prior to PCI. In general, good TIMI flow prior to PCI is a sign of good patency of the infarct-related artery and suggests spontaneous lysis of the thrombus and smaller thrombus burden.

Lesion length could show the plaque burden in an atherosclerotic artery. Kirma et al. (9) reported that the no-reflow phenomenon was 5.4 folds higher in the patients with lesion lengths above 13.5 millimeters. In our study, 84.1% of the patients with no-reflow phenomenon had lesion lengths above 13.5 millimeters, which was significantly higher compared to those without the no-reflow phenomenon.

Thrombus burden is one of the most important factors related to the no-reflow phenomenon. By Intra-Vessel Ultrasound (IVUS) studies, Tanaka et al. (12) and Watanabe et al. (13) demonstrated a marked relationship between the lipid rich plaques and the occurrence of the no-reflow phenomenon. In our study, 98.4% of the patients with the no-reflow phenomenon had a high thrombus burden, which was more prevalent among the patients with prolonged reperfusion time. According to Ndrepepa G et al. (10) and Zhao et al. (14), thrombus burden is the most important predictor of the no-reflow phenomenon. As discussed earlier, lesions with higher thrombus burdens are vulnerable to distal embolization following balloon predilation.

Generally, AMI can be more complicated and primary PCI may be less successful in the elderly mainly because of their numerous comorbidities and delay in hospitalization (15). In the present study, the patients who had the no-reflow phenomenon were almost 10 years older than those without this phenomenon. Advance age was also an independent predictor of the no-reflow phenomenon in the research by Kirma et al. (9). They stated that there was an increased tendency for distal microembolization during primary PCI in the elderly because of their more severe and diffuse coronary atherosclerosis and calcification. However, we found no independent relationships between age and occurrence of the no-reflow phenomenon.

Although the role of inflammatory factors in the no-reflow phenomenon has been investigated in many studies, there is no consensus in this regard. In the study by Du et al. (11), both WBC count and hs-CRP were independent predictors of the no-reflow phenomenon. However, the results of multivariate analysis in our study showed no relationships between WBC count and hs-CRP, and no-reflow phenomenon.

In conclusion, the findings of the present study indicated that the no-reflow phenomenon after primary PCI would be predictable. Accordingly, the patients with delayed reperfusion, higher thrombus burden, and longer and totally occluded target lesions were more likely to develop the no-reflow phenomenon. Thus, preventive measures, such as using distal protective devices or administration of platelet glycoprotein IIb/IIIa antagonists, are advised to be used in high-risk patients (16, 17). Overall, the study results indicated the necessity to perform primary PCI as soon as possible and to reduce the reperfusion time as the most important preventive measures that should be considered in administrative programming for AMI patients.

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Authors' Contribution

Ata Firouzi was the project supervisor and participated in developing the research idea, study design, data collection, and writing the manuscript. Kamran Aeinfar contributed to study design, data collection, and writing the manuscript. Hamidreza Sanati, Reza Kiani, and Hossein Shahsavari cooperated in data collection and p reparation of the manuscript.

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