Evaluation of the Clinical and Procedural Predictive Factors of no-Reflow Phenomenon Following Primary Percutaneous Coronary Intervention

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Background: The no-reflow phenomenon is an uncommon and critical occurrence which myocardial reperfusion does not restore to its optimal level. Several predisposing factors of the no-reflow phenomenon have been identified. However, at present we know little about clinical predictors of no-reflow after percutaneous coronary intervention (PCI).

Objectives: In this study, we evaluated clinical predictors of no-reflow phenomenon after PCI in patients with acute STEMI, to plan a better treatment of these patients.

Patients and Methods: During an 18-month period, from 2013 to 2014, 438 patients with acute myocardial infarction (AMI) presenting within the first 24 hours from symptoms onset were treated with primary PCI in the Rajaie Cardiovascular Medical and Research Center. Thrombolysis in myocardial infarction (TIMI) flow was measured in all patients on the first angiography, following stenting. A total of 49 patients were allocated to the case group, based on the no-reflow phenomenon occurred during primary PCI (TIMI grade 0 and 1) and 50 patients without the no-reflow phenomenon (TIMI grade ≥ 3) were randomly selected, as the control group. They were evaluated from the point of demographic variables and also infarction territory, pain duration, maximal ST-change, left ventricle (LV) function, laboratory data, coronary anatomy, culprit vessel, location of lesion, target vessel diameter, lesion length, eccentricity, thrombus grade, tortuosity, lesion angulation, bifurcation, predilation, postdilation, thrombus aspiration, number of stent, in stent thrombosis. Data were then analyzed with the SPSS statistical software.

Results: Mean age of patients was 59.47 (SD = 12.48) years, of which 75 (75.8%) were male and 24 (24.2%) were female. Based on univariable analysis, white blood cell (WBC) count, pain duration, LV function, maximal ST-change, thrombus grade and eccentricity were identified as predictors of the no-reflow phenomenon. After multivariable logistic regression: WBC count and thrombus grade remained the significant independent predictors of the no-reflow phenomenon (P < 0.05). In case group, slow-flow was seen in 42 (9.5%), while no-reflow was seen in seven (1.6%) patients.

Conclusions: The WBC count and thrombus grade are strong, independent predictive factors of developing the no-reflow phenomenon, in AMI patients undergoing primary PCI. There is also an association between the no-reflow phenomenon and pain duration, maximal ST-change, LV function, high sensitivity C-reactive protein (hs-CRP), bifurcation, eccentricity and coronary anatomy.

Keywords: No-Reflow Phenomenon; Acute Myocardial Infarction; Angiography; Percutaneous Coronary Intervention

1. Background

Primary percutaneous coronary intervention (PCI) is a reperfusion strategy used in patients with acute ST-segment elevation myocardial infarction (STEMI), to prevent progression of myocardial necrosis. Besides the advantages of this strategy, there are situations in which myocardial reperfusion does not restore to its optimal level (1-5). This condition, known as "no-reflow" phenomenon, happens in several cases (6). In those cases, even after reopening of infarct-related coronary artery, and while there is no angiographic evidence of mechanical obstruction, optimal myocardial reperfusion is not seen (7). The no-reflow phenomenon is an uncommon and critical occurrence and, if not reversed, causes a high rate of morbidity and mortality (8). A study demonstrated that the no-reflow phenomenon after primary PCI is a strong predictor of death extending to up to 5 years after the acute event in patients with STEMI (9). Several studies investigated predisposing factors of the no-reflow phenomenon. However, at present we know little about clinical predictors of no-reflow after PCI. Considering a steady increase in the use of primary PCI, improving in efficacy of coronary reperfusion after STEMI seems necessary (5).

2. Objectives

This study aims to evaluate clinical and procedural pre-

dictive factors of the no-reflow phenomenon, following primary PCI.

3. Patients and Methods

3.1. Study Population

During an 18-month period, from 2013 to 2014, 438 patients with acute myocardial infarction (AMI), presenting within the first 24 h from symptoms onset, were treated with primary PCI in Rajaie Cardiovascular Medical and Research Center, Tehran, Iran, a tertiary care center for cardiovascular patients. Coronary angiography and primary PCI was performed according to the standard criteria. The thrombolysis in myocardial infarction (TIMI) flow was measured in all patients during the first angiography, following stenting. The no-reflow phenomenon was diagnosed, based on two criteria: 1) reopening of occluded coronary artery and successful stent placement on angiography; 2) TIMI flow grade 0 and 1 on angiography. According to the no-reflow phenomenon definition, in this case-control study, 49 patients were allocated to the case group, based on the no-reflow phenomenon occurred during primary PCI (TIMI grade 0 and 1), and 50 patients without no-reflow phenomenon (TIMI grade ≥ 3) were randomly selected, as control group, who were matched in terms of stenting, stent type, stent size, prescription of glycoprotein IIb/IIIa inhibitors and use of predilation.

3.2. Data Collection, Angiographic Evaluation and Clinical Follow-up

Physical examination was performed at the time of admission, by the staff physicians. Duration of pain and a clinical history of risk factors, such as smoking, diabetes mellitus and hypertension were obtained. Laboratory data were gathered using white blood cell (WBC) count and high-sensitivity C-reactive protein (hs-CRP) tests. We did not include patients who had a history of myocardial infarction or received thrombolytic therapy. The exclusion criteria were: 1) presence of mechanical failure; 2) Severe bradycardia or 3rd-degree atrio-ventricular (AV)-block; 3) inadequate quality angiograms. Patients were diagnosed with STEMI if they had chest pain for more than 20 minutes and these changes in electrocardiographs (ECG): ST segment elevated ≥ 1 mm in the limb leads and ≥ 2 mm in the precordial leads in at least two anatomically contiguous leads. All patients underwent coronary angiography and the diagnosis of STEMI was confirmed. Diagnosis of the no-reflow phenomenon and slow-flow was made by reviewing coronary angiographic criteria of CTFC (corrected TIMI frame count). Each patient underwent a 12-lead ECG to investigate ST-changes and then a two-dimensional-echocardiography was performed to determine left ventricle (LV) function. Size of lesion and diameter of target vessel were also measured. With 30 minutes before coronary angiography, all patients received aspirin (325 mg) and clopidogrel (600 mg), orally. Then, all patients received

heparin (100 U/kg) and angiography was performed using the right femoral artery approach to investigate the culprit lesion. Bifurcation lesions, eccentricity and coronary anatomy were investigated and the presence of single vessel disease (SVD), two vessel disease (2VD) and three vessel disease (3VD) were recorded. Then, by using balloon catheters of appropriate size, percutaneous transluminal coronary angioplasty (PTCA) was performed. The TIMI thrombus grade, based on the Mehta Strategy for Thrombus Management (10) was defined as G0 = no thrombus, G1 = possible thrombus, G2 = small [greatest dimension $\leq 1/2$ vessel diameter (VD)], G3 = moderate ($> 1/2$ and < 2VD), G4 = large (≥ 2VD), G5: total occlusion (11).

3.3. Inter-Observer Reliability Study

The 20 cases of all patients were randomly selected and assessed for the inter-observer reliability study of TIMI flow before and after PCI. The TIMI flow was determined by the first physician and then repeated by a second observer. The operators were blinded to each other's examination results.

3.4. Statistics

Mean value, standard deviation (SD) and frequency were used in the descriptive analysis. For evaluation the distribution of data, one-sample Kolmogorov-Smirnov test was used. Qualitative data were compared with Chi-squared test. Mann Whitney U test was used to compare quantitative variables. Variables that had any relationship with the no-reflow phenomenon were entered into the multivariable logistic regression model, using the backward variable selection method, which was constructed based on significant variables (P < 0.05) that resulted from the univariate analysis. The Bland-Altman method was used for inter-observer reliability measurement between two observers. The mean determined TIMI flows of these two observers were also compared by paired sample t-test.

4. Results

4.1. Demographic and Baseline Characteristics Results

Mean age of study population was of 59.47 (SD = 12.48) years. From these patients, 75 (75.8%) were male and 24 (24.2%) were female. Smoking was seen in 20 (20.2%) patients. The case group included 60% (12 patients) of smokers. There were no significant differences between the two groups, according to smoking (P = 0.29). Forty patients (40.4%) had a history of diabetes mellitus, and among them, 20 (50%) patients were in case group. No significant difference was detected in these variables between the two groups (P = 0.93). A total of 27 (27.3%) of patients had hypertension, and 55.6% of them (15 patients) were in the case group. There were no significant differences between two groups, according to hypertension (P = 0.46).

Table 1. Comparison of Laboratory Data in Two Groups [a]

Laboratory Data	Case	Control	P Value
WBC-count	1298.45 (4635.82)	11223.40 (3413.16)	0.05
Hb-level, g/dL	14.52 (1.63)	13.94 (1.87)	0.12
Plt-count	224336.73 (72888.85)	229740 (58141.21)	0.65
Hs-CRP level	51.35 (57.48)	12 (23.94)	0.04
Creatinine, mg/dL	1.15 (.66)	1.13 (.99)	0.39
GFR, mL/min	76.24 (23.54)	77.20 (24.22)	0.69
FBS, mg/dL	161.82 (84.61)	163.96 (100.03)	0.60
BS-at admission	182.24 (93.78)	191.88 (112.39)	0.98
TG, mg/dL	130.39 (63.49)	116.05 (46.81)	0.53
LDL, mg/dL	100.18 (33.93)	107.07 (34.07)	0.39
HDL, mg/dL	43.30 (9.84)	42.28 (7.58)	0.96

[a] Abbreviations: BS, Blood sugar; FBS, fasting blood glucose; GFR, glomerular filtration rate; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high sensitivity-CRP; LDL-C, low-density lipoprotein cholesterol; Plt, platelet; TG, triglyceride; and WBC, white blood cell.

4.2. Laboratory Data Results

Laboratory data of the study sample are shown in Table 1. As can be seen in Table 1, there was a significant difference in WBC count and also hs-CRP level between the two groups of our study, while the WBC count and hs-CRP levels were 12982.45 (4635.821) and 51.357 (57.4866), respectively, in case group, and 11223.40 (3413.166) and 12.000 (23.9409), in the control group.

4.3. Examination and Angiographic Data Results

Mean duration of pain was 2.96 (SD = 1.84) hours and mean of maximal ST-change was 3.23 (SD = 1.07) millimeters. Left ventricle function was determined at 35.71% (SD = 10.20) by echocardiography. The mean length of the lesions, which were observed in patients, was 26.31 (SD = 9.99) millimeters and the target vessel diameter was 3.12 (SD = 0.44) millimeters. Table 2 shows that pain duration and LV function were statistically lower in the case group, while maximal ST-change was higher. Angiography data are depicted in Table 3. Thrombus grade was 3.73 (1.35) in cases and 2.70 (1.52) in controls, which was significantly different (P = 0.001). Bifurcation was higher in the case group (six (12.2%)) compared to control group (one (2%)) (P = 0.04). Lesions in 14 (28.6%) cases and five (10%) controls were eccentric (P = 0.01). There were statistically significant differences between the two groups in coronary anatomy (P = 0.001). Most of patients in the case group had 3VD (10 (20.4%)) or 2VD (15 (30.6%)), while 40 patients (80%) in the control group had SVD. Two vessel diseases were seen in 10 (20%) members of the control group. We used multivariable logistic regression test to determine predictors of no-reflow following primary PCI. Based on univariable analysis, WBC count, pain duration, LV function, maximal ST-change, thrombus graded and eccentricity

Table 2. Differences in Pain-Duration, Maximal ST-Change, LV-Function, Lesion Length and Target Vessel Diameter Between the two Groups of our Study [a]

Group	Mean ± SD	P Value
Pain-duration, h		< 0.001
Case	2.31 ± 1.37	
Control	3.60 ± 2.02	
Maximal ST-change, mm		0.004
Case	3.55 ± 1.15	
Control	2.92 ± 0.90	
LV-function, %		0.005
Case	32.65 ± 10.26	
Control	38.70 ± 9.30	
Lesion length, mm		0.52
Case	26.43 ± 9.19	
Control	26.20 ± 10.81	
Target vessel diameter, mm		0.41
Case	3.16 ± 0.48	
Control	3.09 ± 0.40	

[a] Abbreviation: LV, left ventricle.

were identified as predictors of the no-reflow phenomenon. After multivariable logistic regression, using backward variable selection method analysis, WBC count and thrombus grade remained as significant independent predictors of the no-reflow phenomenon (P < 0.05) (Table 4).

Table 3. Comparison of Angiographic Characteristics Between the two Groups [a,b]

Characteristic	Case	Control	P Value
Thrombus grade	3.73 (1.35)	2.70 (1.52)	0.001
TIMI-flow before PCI	0.57 (0.86)	0.30 (0.64)	0.89
TIMI-flow after PCI	1.86 (.35)	3 (0)	< 0.001
CTFC	34.94 (10.32)	18.28 (4.03)	< 0.001
Infarction territory			0.80
Ant-MI	31 (63.3)	30 (60)	
Inf-MI	14 (28.6)	17 (34)	
Lat-MI	4 (8.2)	3 (6)	
Culprit vessel			0.52
LAD	30 (61.2)	30 (60)	
LCX	4 (8.2)	5 (10)	
RCA	13 (26.5)	15 (30)	
Graft	2 (4.1)	0 (0)	
Bifurcation lesion			0.04
No	43 (87.8)	49 (98)	
Yes	6 (12.2)	1 (2)	
Pre dilation			0.36
No	23 (46.9)	28 (56)	
Yes	26 (53.1)	22 (44)	
Post dilation			0.23
No	40 (81.6)	45 (90)	
Yes	9 (18.4)	5 (10)	
Thrombus aspiration			0.55
No	25 (52.1)	29 (58)	
Yes	23 (47.9)	21 (42)	
Lesion eccentricity			0.01
Concentric	35 (71.4)	45 (90)	
Eccentric	14 (28.6)	5 (10)	
Lesion angulation			0.55
Straight	32 (65.3)	34 (69)	
Angulated	17 (34.7)	16 (32)	
Location of lesion			0.44
Proximal	26 (53.1)	30 (60)	
Mid part	15 (30.6)	16 (32)	
Distal	8 (16.3)	4 (8)	
Coronary anatomy			0.001
SVD	24 (49)	40 (80)	
2VD	15 (30.6)	10 (20)	
3VD	10 (20.4)	0 (0)	
Tortuosity			0.59
Mild	45 (91.8)	47 (94)	
Moderate	3 (6.1)	3 (6)	
Sever	1 (2)	0 (0)	
Number of stent			0.11
0	3 (6.1)	1 (2)	
1	43 (87.8)	42 (84)	
2	3 (6.1)	7 (14)	
In-stent thrombosis			0.67
No	45 (91.8)	47 (94)	
Yes	4 (8.2)	3 (6)	

[a] Abbreviations: Ant-MI, anterior myocardial infarction; Inf-MI, inferior myocardial infarction; LAD, left anterior descending coronary artery; Lat-MI, lateral myocardial infarction; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; CTFC, corrected TIMI frame count; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.
[b] data are presented as No. (%).

Table 4. Multivariable Logistic Regression Based on Backward Logistic Regression Method [a]

Variables	Coefficient	P Value	OR (CI 95%)
WBC	0.517	0.003	1.67 (1.19 - 2.35)
Thrombus graded	- 0.46	0.01	0.67 (0.43 - 0.89)
Eccentricity	- 1.16	0.10	0.10 (0.07 - 1.26)
Maximal ST-Change	- 0.425	0.08	0.65 (0.40 - 1.05)

[a] Abbreviations: OR: Odds Ratio; WBC, white blood cell count.

4.4. Inter Observer Reliability

Bland and Altman method showed there were no statistically significant differences between determined TIMI flow before PCI (P = 0.57) and after PCI (P = 0.57) by two observers. Mean of differences of TIMI flow for two observers before PCI was -0.5 ± 0.39 (mean of differences ± 2, SD = -1.28 - 0.28). Mean of differences between two observed flows after PCI was 0.5 ± 0.39 (mean of differences ± 2, SD was -0.28 - 1.28).

5. Discussion

We found that the predictive factors of the no-reflow phenomenon in AMI patients undergoing primary PCI are: WBC count and thrombus grade. Also, there is an association between developing the no-reflow phenomenon and pain duration, maximal ST-changes, LV function, hs-CRP, bifurcation, eccentricity and coronary anatomy. Pain duration was shorter in the case group. The shorter pain duration, the fresher the clot in the artery would be. Therefore, fresh clot increases the risk of occurrence of the no-reflow phenomenon in AMI patients after PCI. Zalewski et al. (12) demonstrated that altered clot properties may characterize patients with the no-reflow phenomenon and might help identify subjects at increased risk of such a complication. Iwakura et al. (13) reported that a short duration pain before the onset of AMI, translates into attenuation of the size of the infarction area, which results in better cardiac function recovery after PCI. Komamura et al. (14) studied the changes in coronary vein flow in AMI patients and concluded that pre-infarction angina reduces the decrease in coronary flow, which helps the reperfusion after thrombolysis. Left ventricle ejection fraction (LVEF) was lower in patients with no-reflow phenomenon. This can be explained by the severity of coronary lesion and occlusion, and subsequently, more damage to the myocardium in case group. Ndrepepa et al. (5) reported worse LVEF at 6 months, in patients with the no-reflow phenomenon, in comparison with the control group. Other studies also demonstrated that, based on follow up studies, no-reflow phenomenon causes malignant arrhythmias, reduced ejection fraction, and increases risk of cardiac death (11, 15). The WBC count was higher in patients with the no-reflow phenomenon, which may be due to increased inflammation and aggregation of WBC in artery and myocardium. This

increases the possibility of the no-reflow phenomenon. The existence of more bifurcations in the no-reflow phenomenon patients indicates more complex lesions, and therefore requires complex procedures (6). Thrombus grade was another predictive factor of the no-reflow phenomenon, which was higher in the case group. An increased clot volume causes higher thrombus grade and subsequently increases the possibility of no-reflow phenomenon (16). Logistic regression in this study shows that WBC count and thrombus grade are independent predictive factors of developing no-reflow phenomenon. It seems that more factors that were not investigated in our study can predict the development of the no-reflow phenomenon in AMI. Iwakura et al. (13) reported the number of abnormal Q-waves and the wall motion score as independent predictive factors. Larger infarct size is another predictive factor, which was evaluated in different studies (5, 9, 17). We had limitations while performing the study. The presence of pre-infarction angina was checked only through patients' records of clinical history, where silent ischemia could not be evaluated. We did not assess the effect of drugs that patients received during pre-infarction period. The WBC count and thrombus grade are strong, independent predictive factors of developing the no-reflow phenomenon in AMI patients undergoing primary PCI. There is also an association between the no-reflow phenomenon and pain duration, maximal ST-change, LV function, hs-CRP, bifurcation, eccentricity and coronary anatomy. Better prediction of no-reflow phenomenon would help us to conduct measures to prevent this phenomenon and reduce the subsequent complications. Further studies, focusing on the effect of drugs received during the pre-infarction period, and follow up of the patients are suggested.

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Authors' Contributions

Hoseinali Basiri, conduction of the project, clinical study and management; Omid Rafizadeh, collection of

References

1. Morishima I, Sone T, Mokuno S, Taga S, Shimauchi A, Oki Y, et al. Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. *Am Heart J.* 1995;**130**(2):239–43.
2. D'Onofrio G, Bernstein E, Bernstein J, Woolard RH, Brewer PA, Craig SA, et al. Patients with alcohol problems in the emergency department, part 1: improving detection. SAEM Substance Abuse Task Force. Society for Academic Emergency Medicine. *Acad Emerg Med.* 1998;**5**(12):1200–9.
3. Ambrosio G, Weisman HF, Mannisi JA, Becker LC. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. *Circulation.* 1989;**80**(6):1846–61.
4. Reffelmann T, Hale SL, Li G, Kloner RA. Relationship between no reflow and infarct size as influenced by the duration of ischemia and reperfusion. *Am J Physiol Heart Circ Physiol.* 2002;**282**(2):H766–72.
5. Ndrepepa G, Tiroch K, Keta D, Fusaro M, Seyfarth M, Pache J, et al. Predictive factors and impact of no reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. *Circ Cardiovasc Interv.* 2010;**3**(1):27–33.
6. Ito H, Tomooka T, Sakai N, Yu H, Higashino Y, Fujii K, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation.* 1992;**85**(5):1699–705.
7. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest.* 1974;**54**(6):1496–508.
8. Esteves Filho A, Garcia DP, Martinez Filho EE. The no reflow phenomenon in the coronary arteries. *Arq Bras Cardiol.* 1999;**72**(1):99–108.
9. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol.* 2010;**55**(21):2383–9.
10. Mehta S, Ishmael A, Oliveros E, Pena C, Raup-Da-Rosa P, Alfonso C. Selective Strategy for Thrombus Management in STEMI Interventions: Abridged from the Textbook of STEMI Interventions. *Cath lab digest.* 2011;**19**(2)
11. Taylor AJ, Al-Saadi N, Abdel-Aty H, Schulz-Menger J, Messroghli DR, Friedrich MG. Detection of acutely impaired microvascular reperfusion after infarct angioplasty with magnetic resonance imaging. *Circulation.* 2004;**109**(17):2080–5.
12. Zalewski J, Undas A, Godlewski J, Stepien E, Zmudka K. No-reflow phenomenon after acute myocardial infarction is associated with reduced clot permeability and susceptibility to lysis. *Arterioscler Thromb Vasc Biol.* 2007;**27**(10):2258–65.
13. Iwakura K, Ito H, Kawano S, Shintani Y, Yamamoto K, Kato A, et al. Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. *J Am Coll Cardiol.* 2001;**38**(2):472–7.
14. Komamura K, Kitakaze M, Nishida K, Naka M, Tamai J, Uematsu M, et al. Progressive decreases in coronary vein flow during reperfusion in acute myocardial infarction: clinical documentation of the no reflow phenomenon after successful thrombolysis. *J Am Coll Cardiol.* 1994;**24**(2):370–7.
15. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation.* 1998;**97**(8):765–72.
16. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, et al. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation.* 1996;**93**(2):223–8.
17. Ito H. No-reflow phenomenon and prognosis in patients with acute myocardial infarction. *Nat Clin Pract Cardiovasc Med.* 2006;**3**(9):499–506.