Original Article

Clinical, Laboratory, and Procedural Predictors of No-Reflow in Patients Undergoing Primary Percutaneous Coronary Intervention

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Abstract

Background: *No-reflow is a major challenging issue in the management of patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). This study aimed to investigate the clinical, laboratory, and procedural predictors of no-reflow.*

Methods: *This study was conducted on 378 patients with STEMI admitted to Dr. Heshmat Educational and Remedial Center (a referral heart hospital in Rasht, Iran) between 2015 and 2017. The study population was divided based on the thrombolysis in myocardial infarction (TIMI) flow grade and the myocardial blush grade into no-reflow and reflow groups. The clinical, laboratory, and procedural characteristics at admission were compared between the 2 groups using the multivariate logistic regression analysis.*

Results: *The mean age of the participants was 58.57±11.49 years, and men comprised 74.1% of the study population. The no-reflow phenomenon was found in 77 patients. The no-reflow group was significantly older and more likely to be female; additionally, it had higher frequencies of hypertension, diabetes mellitus, hyperlipidemia, and a history of cardiovascular diseases. The multivariate logistic regression analysis showed that age >60 years (OR=1.05, 95% CI:1.00–1.09), hypertension (OR=2.91, 95% CI:1.35–6.27), diabetes (OR=4.18, 95% CI:1.89–9.22), a low systolic blood pressure (OR=3.53, 95% CI:1.02–12.2), a history of cardiovascular diseases (OR=4.29, 95% CI:1.88–9.77), chronic heart failure (OR=4.96, 95% CI:1.23–20), a low initial TIMI flow grade (OR=7.58, 95% CI:1.46–39.2), anemia (OR=3.42, 95% CI:1.33–8.77), and stenting vs. balloon angioplasty (OR=0.42, 95% CI:0.19–0.91) were the significant independent predictors of no-reflow.*

Conclusion: *This study revealed some clinical, laboratory, and procedural predictors of no-reflow for the prediction of high-risk patients and their appropriate management to reduce the risk of no-reflow.*

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Keywords: *ST elevation myocardial infarction; Percutaneous coronary intervention; No-reflow phenomenon*

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Introduction

Primary percutaneous coronary intervention (PPCI) is a nonsurgical treatment for the myocardial reperfusion of patients with ST-segment elevation myocardial infarction (STEMI). However, in a significant proportion of patients, myocardial perfusion is not successful, leading to the no-reflow phenomenon, which itself is an independent predictor of major adverse cardiovascular events.[1, 2] No-reflow, defined as the inability of the reperfusion of an ischemic region in a recanalized infarcted coronary artery,[3] is a major challenging issue in the management of patients undergoing PPCI and is associated with a worse outcome and a higher incidence of complications and mortality.[4-6] The reason behind no-reflow is not fully distinguished, and a combination of clinical and inflammatory mechanisms have been proposed.[7, 8] The present study aimed to identify the clinical, procedural, and laboratory predictors of no-reflow in patients with STEMI undergoing PPCI.

Methods

This study was performed on 378 consecutive patients diagnosed with STEMI who underwent PPCI within a 12-hour period from the onset of symptoms at Dr. Heshmat Educational and Remedial Center (a referral heart hospital in Rasht, Iran) between 2015 and 2017. Acute STEMI was diagnosed upon the presence of persistent anginal chest pains lasting for ≥20 minutes accompanied by >1 mm (0.1 mV) ST-segment elevation in 2 or more contiguous precordial leads or the presence of new left bundle branch block. The primary sample size was calculated based on a prior estimate of 25% for no-reflow. Assuming 5% precision and 10 extra cases for every 15 predictors, we estimated a total of 380 cases. Patients with cardiogenic shock at admission, active infection, a history of systemic inflammatory diseases, hemorrhagic disorders, liver disease, known malignancy, and kidney failure were excluded from the study. The study protocol was approved by the Review Board of Guilan University of Medical Sciences.

All the patients received 325 mg of aspirin orally and 600 mg of clopidogrel before PPCI. The PPCI procedures were performed via the standard femoral approach with Judkins catheters. The use of balloon angioplasty and thrombosuction was left to the operator's decision. Immediately after the decision to perform coronary intervention, 50–70 unit/kg of an intravenous bolus of unfractionated heparin was administered to the patients who were not treated with enoxaparin before coronary angiography. For the patients having received an initial enoxaparin dose of 1 mg/kg before angiography, no additional booster dose of enoxaparin was administered within 8 hours of the first dose. An additional booster of 0.3 mg/kg of enoxaparin was given intravenously between 8 and 12 hours after the first dose. The application of the thrombus aspiration catheter in the patients with high thrombus burden and the administration of eptifibatide (a glycoprotein IIb/IIIa inhibitor with a 180 mcg/kg IV bolus dose over 1–2 minutes, followed by a continuous infusion of 2 mcg/kg/min with another 180 mcg/kg IV bolus dose 10 minutes after the first one for at least 12 hours) were at the discretion of the interventional cardiologist.

The clinical and demographic information of the patients was obtained from their medical records. A history of cardiovascular diseases was defined as having a previous stroke and coronary and peripheral artery diseases. For all the patients, venous blood samples were drawn from the antecubital vein during emergency admission. Complete blood count parameters were measured using a Sysmex AutoAnalyzer within 5 minutes of sampling. Anemia was defined as a serum hemoglobin level <12 g/dL. The postprocedural thrombolysis in myocardial infarction (TIMI) flow grades were evaluated by 2 cardiologists blinded to the grouping of the study population. The myocardial blush grade (MBG) was assessed during angiography according to the Van't Hof and Gibson method.[9] The no-reflow group was defined as a TIMI flow grade of 0–2 with an MBG ≤1, and the reflow group was defined as a TIMI flow grade of 3 with an MBG ≥2.

The data were described as the mean and the standard deviation for the continuous variables and frequencies and percentages for the categorical variables. Normal distribution was assessed using the Kolmogorov–Smirnov test. The 2 groups were compared using the *t*-test or the Mann–Whitney test for the continuous variables and the χ^2 test for the categorical variables. To identify the independent predictors of no-reflow and estimate adjusted odds ratios with 95% confidence intervals, we employed multivariate logistic regression. Stepwise multivariate logistic regression was created using variables with P values <0.05. All the statistical analyses were performed in Stata, version 13 (StataCorp LP, College Station, Texas).

Results

Seventy-seven (20.3%) patients were in the no-reflow group and 301 (79.6%) in the normal reflow group. Table 1 illustrates the baseline characteristics of the patients. The no-reflow group was older and more likely to be women. The prevalence of smoking in the no-reflow group (25.0%) was significantly lower than that of the reflow group (39.0%). In contrast, the prevalence rates of hyperlipidemia, hypertension, diabetes mellitus, and a history of congestive heart failure and cardiovascular diseases in the no-reflow group were significantly higher than those in the reflow group (Table 1). There were no significant differences in the use of thrombus aspiration, antiplatelet medical treatment,

Table 1. Clinical, angiographic, and laboratory characteristics of the study groups at admission*

	Reflow Group (n=301)	No-Reflow Group (n=77)	P
Age (y)	57.07±11.16	64.46±1.24	0.001
Male gender	231 (76.7)	49 (63.6)	0.011
Smoking	118 (39.2)	19 (24.7)	0.018
Hyperlipidemia	68 (22.6)	37 (48.1)	0.001
Hypertension	104 (34.5)	57 (74.0)	0.001
Diabetes	60 (19.9)	38 (49.3)	0.001
History of CHF	4 (1.3)	21 (27.3)	0.001
History of CVA	4 (1.3)	6 (7.8)	0.002
Systolic blood pressure (mmHg)	136.57±23.77	124.44±29.72	0.001
Diastolic blood pressure (mmHg)	80.72±12.90	75.10±15.98	0.001
LVEF (%)	38.22±7.82	33.18±8.92	0.001
Creatinine (mg/dL)	1.02±0.19	1.19±0.62	0.001
Hemoglobin (g/dL)	13.97±3.72	12.96±1.83	0.021
Anemia	33 (11.9)	26 (38.2)	0.001
GFR	79.08±15.23	66.87±17.21	0.001
Initial TIMI flow grade			0.009
0-1	262 (87.1)	75 (97.4)	
2-3	39 (12.9)	2 (2.6)	
PCI type			0.001
Balloon angioplasty	64 (21.3)	33 (42.9)	
Stenting	237 (78.7)	44 (57.1)	
Stent length (mm)	26.88±7.49	27.48± 7.13	0.615
Lesion length (mm)	17.65±7.72	17.26±7.20	0.690
Antiplatelet use	197 (65.4)	53(68.8)	0.576
Thrombus aspiration use	102 (33.9)	25 (32.5)	0.814
Symptom onset to PPCI (min)	163.80±133.38	178.38±115.20	0.380
White blood cell count ($\times 10^9$/L)	11.95±3.83	12.26±3.64	0.541
Platelet count ($\times 10^9$/L)	240.85±70.39	250.39±84.16	0.336
Monocyte count ($\times 10^9$/L)	0.22±0.14	0.21±0.12	0.840
Lymphocyte count ($\times 10^9$/L)	2.67±1.18	2.35±0.79	0.050
Neutrophil count ($\times 10^9$/L)	8.91±3.90	9.48±3.78	0.297

*Data are presented as mean±SD, n (%).
CHF, Chronic heart failure; LVEF, Left ventricular ejection fraction; GFR, Glomerular filtration rate; PPCI, Primary percutaneous coronary intervention; TIMI, Thrombolysis in myocardial infarction

and times from symptom onset to PPCI between the 2 groups. The no-reflow group had a significantly higher level of serum creatinine and lower hemoglobin, left ventricular ejection fraction, and glomerular filtration rate than the reflow group. The initial TIMI flow grade in the no-reflow group was significantly lower than that in the reflow group, and the no-reflow group was less likely to receive stenting during PPCI than the reflow group.

The results of the multivariate logistic regression are shown in Table 2. The model had good discrimination capability (area under the ROC curve=0.89) and goodness of fit (Hosmer–Lemeshow test=326; P=0.112). According to the multivariate adjusted logistic regression results, age, hypertension, diabetes mellitus, a history of cardiovascular diseases, chronic heart failure, systolic blood pressure (SBP), anemia, type of reperfusion, and the initial TIMI flow grade were the significant independent predictors of no-reflow. Advanced age was associated with 5% increases in the odds of no-reflow. The hypertensive patients were over twice as likely as the non-hypertensive patients to have no-reflow. A current SBP <100 mmHg increased the odds of no-reflow by 253.0%. The odds of no-reflow in the diabetic patients were 4.18 higher than those in the nondiabetic patients. A history of cardiovascular diseases and chronic heart failure were also associated with increased odds of no-reflow (OR=4.96 and 4.29, respectively). The odds of developing no-reflow in the patients with hemoglobin levels < 12 g/dL, defined as anemic patients, were 242.0% higher than those of the patients with normal levels of hemoglobin. Low initial TIMI flow grades were associated with increased odds of no-reflow

Table 2. Multivariate adjusted predictors of the no-reflow phenomenon using the logistic regression analysis

	Adjusted OR	95% CI	P
Age (y)	1.05	1.00-1.09	0.026
Sex (female)	0.90	0.37-2.18	0.817
Smoking	0.72	0.29-1.76	0.482
Hypertension	2.91	1.35-6.27	0.007
Diabetes mellitus	4.18	1.89-9.22	0.001
Hyperlipidemia	1.05	0.48-2.31	0.901
History of CHF	4.96	1.23-20.01	0.024
History of CVD	4.29	1.88-9.77	0.001
SBP <100 mmHg	3.53	1.02-12.17	0.046
DBP <50 mmHg	0.40	0.15-1.10	0.076
GFR	0.99	0.96-1.03	0.652
Creatinine mg/dL	0.91	0.18-4.56	0.910
Anemia	3.42	1.33-8.77	0.010
LVEF	0.98	0.94-1.03	0.513
PCI type (stenting vs. balloon angioplasty)	0.42	0.19-0.91	0.029
Initial TIMI flow grade (0-1)	7.58	1.46-39.25	0.016

CVD, Cardiovascular diseases, CHF, Chronic heart failure; DBP, Diastolic blood pressure; LVEF, Left ventricular ejection fraction PCI, Percutaneous coronary intervention; TIMI, Thrombolysis in myocardial infarction

(OR=7.58). Direct stenting as the method of reperfusion decreased the odds of no-reflow by 58.0%.

Discussion

The findings of the current study revealed some clinical, procedural, and laboratory predictors of the no-reflow phenomenon. No-reflow, a major limitation of infarcted artery recanalization, is prevalent among patients with STEMI undergoing PPCI.[5, 10, 11] In the current study, no-reflow was found in 20.0% of the patients, which is consistent with previous reports of no-reflow rates[12-14] and much higher than the 4.1% rate estimated by Ashraf et al.[15] We used recent comprehensive criteria to define no-reflow according to the TIMI flow grade and the MBG, which are the preferred methods to evaluate myocardial blood flow rather than the epicardial flow, which is estimated by the TIMI flow grade.[9, 16] The reason behind the development of no-reflow is multifactorial.

Similar to previous studies,[15, 17-19] we found that advanced age is an important predictor of no-reflow. In addition to the existence of several comorbidities, some conditions such as severe vascular calcification and disrupted microvascularization are more common in older patients. These conditions predispose them to the development of no-reflow more frequently than younger patients.[13, 20]

In the present study, hypertension was a strong predictor of no-reflow and showed a 2.91-fold higher rate of no-reflow than that in the non-hypertensive patients. This finding is in agreement with previous reports.[21-23] The coronary flow reserve has been shown to be reduced in hypertensive patients through some mechanisms including endothelial dysfunction, abnormalities of left ventricular diastolic relaxation, functional changes of the intramyocardial coronary arteries, and increased afterload.[24-26] However, in the current study, a current SBP <100 mmHg was independently associated with a 4-fold increase in the odds of no-reflow. Likewise, some previous studies have demonstrated that a lower SBP is associated with the increased risk of no-reflow because of a decreased coronary and collateral blood flow.[20, 27, 28] Therefore, it can be inferred that both the long-term consequences of hypertension on the function and structure of the coronary arteries and a current low SBP through lowering the coronary blood flow can be considered mechanisms contributing to the development of no-reflow. Moreover, our subgroup analysis showed that a low SBP was significantly associated with the increased odds of no-reflow only among the hypertensive group. This finding emphasizes the importance of the hypotension risk for developing no-reflow in patients suffering from chronic hypertension. Still, this issue remains questionable and needs to be verified in further research.

We found anemia to be the independent predictor of no-reflow in that it increased the odds of no-reflow by 3.42-fold. Based on our latest literature review, no previous studies have found anemia as a determinant of no-reflow in multivariate adjusted models. However, the effect of anemia on reducing oxygen-carrying capacity and viscosity of the blood has been well introduced.[29] Anemia is also associated with decreased coronary reserve.[30] The effect of anemia and its mechanism on no-reflow need to be established in further prospective

research.

In accordance with previous reports,[15, 31] our study showed that diabetic patients were more likely to develop the no-reflow phenomenon independent of other clinical and laboratory characteristics. Because of the emergency situation of the STEMI patients, in the current study, it was not possible to measure fasting blood glucose. Nonetheless, some previous studies have shown that hyperglycemia is the strongest predictive factor of no-reflow.[32, 33] In line with this finding, Malmberg et al.[34] demonstrated that optimal blood sugar control before the PCI procedure improved long-term prognosis in diabetic patients with acute myocardial infarction. It has also been demonstrated that pretreatment with metformin can reduce the incidence of no-reflow in diabetic patients.[35]

Low initial TIMI flow grades have been consistently reported as a major risk factor for no-reflow.[18, 20, 36] Similarly, we found higher odds of developing no-reflow in our patients with lower TIMI flow grades at admission. Higher initial TIMI grades suggest smaller infarct size and higher thrombus burden.

Although some studies have found an association between delayed reperfusion and the no-reflow phenomenon,[19, 37, 38] there is still controversy regarding the harmful and beneficial effects of prompt vs. deferred stenting on no-reflow and other major adverse outcomes following PCI.[37] In the current study, chiming in with some previous studies, there was no significant association between the time of symptom onset to PPCI and the no-reflow phenomenon.[4, 22, 39] In the present study, all the patients underwent PCI in a range of 10 to 700 minutes following the onset of symptoms.

Direct stenting as the method of reperfusion without pre-dilatation has been shown to reduce the risk of no-reflow compared with ballooning.[13] Our study confirms this finding in that it showed a 58% decrease in the risk of no-reflow in stenting relative to balloon angioplasty. The complete and direct scaffolding of the mural thrombus and the diminished likelihood of thrombus dislodgment and further distal embolization have been explained as the possible mechanisms of the reduced risk in direct stenting in comparison with balloon angiography.[13]

In a previous investigation, blood indices such as the white blood count were found to be the strong predictors of no-reflow.[40] In contrast, we did not find inflammatory markers and renal dysfunction[41, 42] to be the independent predictors of no-reflow. Additionally, similar to a previous investigation in Iran,[43] we did not find an independent association between smoking status and the no-reflow phenomenon.

This study suffered from some limitations. Firstly, we could not measure some other confounding variables including high-sensitivity C-reactive protein (as a specific inflammatory marker), the syntax score (for the severity of atherosclerosis), troponin and CK-MB levels (to detect infarct size as a potential confounding variable), and some other laboratory markers such as albumin that have been previously found to be the important predictors of no-reflow.[39, 44, 45] Secondly, our study was performed in a single center on a relatively small sample size. Thirdly, due to the emergency and acute condition of STEMI patients, the blood sample could not be taken from a small group of the patients before PPCI.

Conclusion

This study found some clinical, laboratory, and procedural predictors of the no-reflow phenomenon. The results of this study can be used for the identification of high-risk patients and their appropriate management to reduce the no-reflow phenomenon in STEMI patients undergoing PPCI.

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