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No-Reflow Phenomenon in Patients with ST-Elevation Acute Myocardial Infarction, Treated with Primary Percutaneous Coronary Intervention: A Study of Predictive Factors

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ABSTRACT

Introduction: No-reflow phenomenon in coronary vessels, manifested in some patients with reperfused acute myocardial infarction (MI), is associated with poor clinical and functional outcomes. Therefore, evaluation of predisposing risk factors can be helpful in risk assessment and identification of patients at higher risk. Herein, we aimed to study the predictive factors for the development of no-reflow phenomenon in patients with ST-elevation acute MI (STEMI), following primary percutaneous coronary intervention (PCI).

Materials and Methods: Overall, 141 patients with STEMI, treated with primary PCI, were enrolled in a cross sectional study. Angiographic data associated with no-reflow phenomenon including thrombolysis in MI (TIMI) were evaluated. Patients were divided into study and control (TIMI grade 3) groups. Demographic, clinical and laboratory (lab) data including cardiovascular risk factors (e.g., diabetes, hypertension, hyperlipidemia, smoking), door-to-balloon time, serum creatinine and glucose levels, white and red blood cell counts (WBC and RBC counts, respectively), mean platelet volume (MPV), and red cell distribution width (RDW) were evaluated in both groups.

Results: The mean age of the patients was 60.3±11.9 years. No-reflow was observed in 35 (24.8%) cases. WBC count, MPV, serum creatinine, BS, and high-density lipoprotein (HDL) levels were significantly correlated with TIMI flow <3.

Conclusion: Certain lab indices including MPV, WBC count, creatinine and HDL levels played significant independent roles in the no-reflow phenomenon. Thus, measuring such parameters might be helpful in predicting the risk of this condition in patients; however, further studies are required.

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Introduction

Primary percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI) has been used as an important therapeutic method since the last decade of the 20th century and has gradually become the method of choice in many medical centers. Various studies have shown that primary PCI is associated with lower rates of mortality, reinfarction and cerebral hemorrhage in comparison with thrombolytic treatments (1).

The no-reflow phenomenon is a serious complication during primary PCI for patients with MI. It is defined as reduced blood flow in coronary vessels, following a successful angioplasty and stenting procedure in which thrombolysis in MI (TIMI) flow grade reaches

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below 3, despite the absence of mechanical obstruction.

Persistent no-reflow phenomenon is associated with increased mortality rate and recurrent MI. Several studies have shown poor short- and long-term prognoses in such patients. The prevalence of this phenomenon has been reported as 0.2-30% in various studies (2-6).

The exact mechanism and associated risk factors have not been fully identified yet, although different pathophysiologies have been proposed mainly including plateletdisorders (7), endothelial dysfunction (8), plaque embolization or distal thrombosis (3) and local release of vasoconstrictors (9).

Considering the rapid development of angiography and angioplasty units in our country and the prominent role of primary PCI in the management of acute MI, evaluation of prognostic and risk factors, which contribute to the development of no-reflow phenomenon during primary PCI, can be effective in the prevention and treatment of this condition. The present study aimed to assess these contributing factors.

Materials and Methods

STEMI patients, referring to the emergency unit of Imam Reza Hospital Mashhad University of Medical Sciences, Mashhad, Iran, were enrolled in a cross sectional study. The subjects were candidates for primary PCI, based on the American College of Cardiology (ACC) criteria. A questionnaire including demographic data (e.g., age and sex) and cardiovascular risk factors (e.g., diabetes, hypertension, hyperlipidemia and smoking) was completed for all patients.

Data related to the interval between the manifestation of symptoms and primary PCI, obstructed coronary arteries and use of thrombectomy devices were recorded. TIMI flow was measured in all patients in the first angiographic view, following stenting. In addition, serum creatinine and glucose levels, *white blood cell* (WBC) *count*, red blood cell (RBC) count, platelet count, mean platelet volume (MPV) and red cell distribution width (RDW) were measured at admission.

If no-reflow phenomenon occurred during primary PCI (TIMI grade<3), the patient was allocated to the study group; on the other hand, patients with TIMI grade 3 were included in the control group. The two groups were matched in terms of stenting, stent type, stent size, prescription of glycoprotein IIb/IIIa inhibitors and use of predilection and thrombosuction before angioplasty.

Results

In total, 141 patients were evaluated in this study. The mean age of the subjects was 60.3±11.9 yrs. No-reflow was reported in 35 (24.8%) cases. Overall, 99 (70.2%) patients were male and no significant difference was observed between the two groups in terms of sex (P=0.301), smoking (P=0.142), diabetes (P=0.116), hypertension (P=0.585), dyslipidemia (P=0.173), culprit vessel (P=0.219), thrombosuction (P=0.388) or predilation (P=0.075) (Table 1 & 2).

In order to study the correlation between different variables, multivariate regression model was applied. The obtained results showed that WBC count, serum creatinine, Glucose, MPV and high-density lipoprotein (HDL) levels were significantly correlated with no-reflow phenomenon (Table 3).

Table 1. Socio-Demographic Data of the Patients

Socio-demographic variables	Number	Number of No-reflow	Number of NL flow	*P* value
		Sex		
Male	99	27	72	0.301
Female	42	8	34	0.301
Total	141	35	106	0.301
		Smoking		
smokers	33	5	28	0.142
Non- smoker	108	30	78	0.142
Total	141	35	106	0.142
		DM		
diabetic	49	16	33	0.116
Non-diabtic	92	19	73	0.116
Total	141	35	106	0.116
		HTN		
Hypertensive	62	14	48	0.585
Non-Hypertensive	79	21	58	0.585
Total	141	35	106	0.585
		Dyslipidemia		
Dyslipidemic	22	8	14	0.173
Non-Dyslipidemic	119	27	92	0.173
Total	141	35	106	0.173

Table2. Co variance analysis

Dependent Variable: Rank of TIMI Flow						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	120032.227[a]	22	5456.010	5.839	.000	.523
Intercept	403.003	1	403.003	.431	.513	.004
Sex	183.139	1	183.139	.196	.659	.002
smoking	.160	1	.160	.000	.990	.000
DM	1071.535	1	1071.535	1.147	.286	.010
HTN	2272.983	1	2272.983	2.433	.122	.020
Dyslipidemia	2837.576	1	2837.576	3.037	.084	.025
Thrombosuction	172.087	1	172.087	.184	.669	.002
Age	583.653	1	583.653	.625	.431	.005
doortobaloon	8999.684	1	8999.684	9.632	.002	.076
BS	4152.966	1	4152.966	4.445	.037	.037
Cr	439.552	1	439.552	.470	.494	.004
Chol	1805.940	1	1805.940	1.933	.167	.016
LDL	2430.774	1	2430.774	2.602	.109	.022
HDL	6531.677	1	6531.677	6.991	.009	.056
Hb	1307.082	1	1307.082	1.399	.239	.012
WBC	8615.084	1	8615.084	9.220	.003	.073
Error	109318.021	117	934.342			
Total	942993.250	140				
Corrected Total	229350.248	139				

a. R Squared = .523 (Adjusted R Squared = .434)

Table3. Correlation between different variables on a multivariate regression model based on Backward LR method

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Age	-.068	.072	.910	1	.340	.934
	Sex(1)	-1.482	1.682	.776	1	.378	.227
	Smoking	-.406	1.590	.065	1	.798	.666
	DM	-2.148	3.033	.501	1	.479	.117
	HTN	-2.239	2.004	1.248	1	.264	.107
	Dyslipidemia	.781	1.790	.191	1	.662	2.184
	doortobaloon	.058	.032	3.290	1	.070	1.059
	BS	.028	.017	2.944	1	.046	1.029
	Cr	8.761	3.958	4.900	1	.027	6378.447
	Chol	-.022	.031	.540	1	.462	.978
	LDL	-.039	.045	.750	1	.386	.962
	HDL	-.448	.174	6.639	1	.010	.639
	Hb	.737	.520	2.006	1	.157	2.090
	WBC	.001	.001	6.816	1	.009	1.001
	RDW	-1.004	.704	2.031	1	.154	.367
	PDW	.698	.558	1.562	1	.211	2.010
	MPV	-3.054	1.332	5.258	1	.022	.047
	Thrombosuction(1)	1.556	1.661	.877	1	.349	4.741
	predilation(1)	-3.005	1.842	2.661	1	.103	.050
	Constant	16.166	14.726	1.205	1	.272	1.049E7
Step 18[a]	Cr	3.944	1.287	9.394	1	.002	51.612
	HDL	-.161	.051	10.110	1	.001	.851
	WBC	.001	.000	17.309	1	.000	1.001
	MPV	-.972	.418	5.394	1	.020	.378
	Constant	4.343	4.547	.912	1	.340	76.956

a. Variable(s) entered on step 1:Age,sex,DM,HTN,DLP, door to balloon, BS, Cr, Chol, LDL, HDL, Hb, WBC, RDW, PDW, MPV, Culpritvessel, Thrombosuction, predilation.

Discussion

Recent studies have shown that no-reflow phenomenon can occur in up to one third of patients, treated successfully by primary PCI, following MI (5). Moreover, the short- and long term survival rates of such patients are not favorable (4). Therefore, preventing this condition is accompanied by a reduced risk of subsequent complications such as arrhythmia and chest pain and would improve the long-term prognosis of patients with acute MI. Hence, from the clinical point of view, preventing the no-reflow phenomenon is important given its long-term clinical outcomes and its effects on left ventricular function during the chronic phase.

In the present descriptive study, 35 (24.8%) patients had an abnormal coronary flow, which indicates the higher rate of abnormal TIMI in comparison with many previous studies; however, some studies have reported an abnormal TIMI in up to 30% of cases (10). The reason behind the higher prevalence of no-reflow in our patients might be the fact that TIMI grades 0, 1 and 2 were considered abnormal, whereas in some studies, TIMI grade 2 was not regarded as no-reflow.

Nonetheless, most no-reflow cases in our study (23 patients) were in the TIMI grade 2 group. In fact, by excluding such patients from the study and considering only TIMI grades 0 and 1 as no-reflow, the prevalence of no-reflow in the current study would be similar to previously conducted research.

Another reason for the high no-reflow rate in our study was that there was no preference for either thrombolytic management or primary PCI in patients referring within the first 3 hours of symptom initiation. In our center, many such patients underwent thrombolytic treatment and were basically excluded from the study. Therefore, most patients with a higher risk and longer door-to-balloon time underwent primary PCI in our unit; in fact, both factors can affect the final outcomes.

Other possible etiologies might be the sample size, characteristics of the studied population and the availability of certain devices. In fact, the rate of no-reflow incidence in the current study can by itself be a challenging issue considering our study population and the number of MI patients in case of an epidemic of primary PCI application.

In the current study, a significant difference was observed in serum creatinine, HDL cholesterol and blood leukocyte levels between the two groups, based on the logistic regression model. Certain cardiovascular risk factors including hyperlipidemia, hypertension and smoking were similar to other studies with no significant difference between the two groups. Therefore, although such risk factors can affect the incidence of MI and atherosclerotic process, they do not influence the probable physiopathology of no-reflow phenomenon, which mostly includes small-vessel disorders, generalized vasoconstriction and microthrombosis.

Similarly, in a study by Iwakura, hypertension was not identified as an independent factor for no-reflow (11). Based on the logistic regression model, among all probable risk factors, only serum HDL level showed a significant difference between the two groups, being significantly lower in the no-reflow group (P=0.001). Moreover, no meaningful difference was observed in other aspects of dyslipidemia.

In consistence with our findings, Jeong showed that serum HDL level in the no-reflow group was significantly lower than that observed in the control group. However, LDL level was higher than that of the control group, which was inconsistent with our results (12). In our study, serum creatinine and glucose levels were significantly higher in the no-reflow group (P=0.002), which was in congruence with the results of previous studies (11, 12).

Different mechanisms can verify the correlation between hyperglycemia and no-reflow phenomenon. In large infarcts, there is a greater possibility for catecholamine secretion which affects the hemostasis of fatty acids and glucose (13). Acute hyperglycemia also increases the level of intercellular adhesion molecule-1 (ICAM-1) and P-selectin and subsequently increases the adhesion of leukocytes to capillaries (14).

Adherence of leukocytes to capillaries and coronary venules immediately after reperfusion was more common in diabetic mice in comparison with non-diabetic ones (15). The entrapment of such leukocytes in microcirculation can be accompanied by subsequent no-reflow phenomenon (15). In addition, hyperglycemia can also reduce the ischemic preconditioning effect which is itself an independent predictor of no-reflow phenomenon.

In the present study, a significant association was found between WBC count and the no-reflow phenomenon (P=0.000). In fact, a high WBC count can be a predictor of inflammation. In recent studies, the key role of inflammation in the atherothrombotic process has been well identified (16). In Jeong's study, similar to the current research, WBC count was significantly higher in the no-reflow group (12).

Inflammation can influence the no-reflow phenomenon and reduce the coronary blood flow given its effect on vascular microcirculation (due to its influence on inflammatory cytokines, immune responses and vascular endothelial injury). Use of anti-inflammatory medications such as aspirin can reduce the incidence of this phenomenon; still, further research is highly recommended in this regard.

Some studies consider the interval between the onset of MI symptoms and reflow during angioplasty as an influencing factor in the extent of infarction and its prognosis (17), while other studies have found no correlation (18). Our findings, similar to those of Brosh et al. (19), showed a remarkable difference in door-to-balloon time for maintaining the blood flow in patients with and without the no-reflow phenomenon (P=0.000).

MPV measurement is a simple and useful technique for the indirect study of platelet activity in different situations (20). In Jeong's study, it was concluded that platelets play a significant role in the pathophysiology of the no-reflow phenomenon. It was suggested that MPV might be considered a significant independent marker in the early diagnosis of patients at high risk of impaired reperfusion, following primary PCI. Based on the logistic regression model in our study, MPV was higher in the no-reflow group in comparison with the controls (P=0.02).

In a similar study, patients with higher MPV at admission were at a greater risk of thrombosis and no-reflow incidence (21). It has been shown that the phospholipids of the platelet membrane, platelet granules and microparticles are higher in such patients. On the other hand, the role of platelets in the rise of unfavorable complications has been attributed to increased inflammatory stimuli; it should be mentioned that platelets are among the acute phase proteins (21).

One of the major limitations of this research was its small sample size. In addition, regarding the limited number of no-reflow patients, the contributing factors cannot be introduced as definite predictive factors for this phenomenon; this fact highlights the need for further large-scaled studies to better clarify this phenomenon.

Conclusion

The no-reflow phenomenon, following coronary reperfusion, is associated with poor clinical outcomes and impaired cardiac function. Determination of predisposing risk factors is essential for identifying patients at high risk. Prolonged door-to-balloon time, lowered serum HDL level and high serum glucose level, creatinine level, leukocyte count and MPV can predict a higher incidence of no-reflow phenomenon. Therefore, considering the fact that the no-reflow phenomenon may have a higher prevalence in diabetic and uremic patients, more attention should be paid before, during and after angiography in these cases. The present study once again emphasizes the importance of more precise management of underlying diseases in order to prevent the incidence of these conditions and cardiovascular complications.

Conflict of Interest

Authors declare no conflict of interest.

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