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No-reflow phenomenon after primary percutaneous coronary intervention.

Nguyen Thuong Nghia[1*], Tran Nguyen Phương Hai[1], Nguyen Thi Anh Nga[2], Châu Thuan Thanh[3]

[1]Department of Interventional Cardiology, 201 B Nguyen Chi Thanh Ward 12, District 5, HCMC Ho Chi Minh City, Vietnam
[2]Cardiovascular Research, Methodist Hospital, Merrillville, IN 200 E 89th Ave, Merrillville, IN 46410, United States
[3]Cardiology Department, Kien Giang Hospital, Vietnam

Abstract

Background: No-reflow phenomenon is one of the major complications and may be associated with adverse outcomes of patients with ST-segment Elevation Myocardial Infarction (STEMI) undergoing Primary Percutaneous Coronary Intervention (PPCI).

Objective: To detect the prevalence and predictive factors of the no-reflow phenomenon in patients with STEMI undergoing PPCI.

Result: The prevalence of no-reflow is 17.6%. Predictors of the no-reflow phenomenon are thrombus burden ≥ 4(OR=10.37, CI 95% 3.27-32.83, p<0.001), Killip 3-4 at admission (OR=8.17, CI 95% 1.3-51.5, p=0.025), time from symptom onset to PPCI (OR=4.37, CI 95% 1.54-12.37, p=0.005), lesion length (OR=1.12, CI 95% 1.02-1.22, P=0.016).

Conclusion: No-reflow phenomenon after PPCI can be predicted with clinical and angiographic features.

Keywords: No-reflow phenomenon, Primary percutaneous coronary intervention, Coronary artery.
Abbreviations: STEMI: ST Elevation Myocardial Ìnarction; PCI: Percutaneous Coronary Intervention; LVEF: Left Ventricular Ejection Fraction

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Introduction

Reperfusion treatment in acute ST myocardial infarction plays a vital role in restoring flow in the blocked Coronary Artery Disease (CAD), helping to improve the prognosis and mortality of patients. Compared to fibrinolysis, Percutaneous Coronary Intervention (PCI) is preferred due to its significant reduction in stroke, re-infarction, and death. However, not all patients following Percutaneous Coronary Intervention (PCI) have myocardial reperfusion return to normal. "No-reflow" is defined as myocardial perfusion that is not fully restored despite the absence of mechanical blockage in the epicardial coronary artery. This phenomenon can occur after percutaneous coronary intervention with a frequency ranging from 5 to 50%. We conducted this study with the following objectives: To determine the prevalence and predictors of the "no-reflow" phenomenon in patients with Primary Percutaneous Coronary Intervention (PPCI).

Materials and Methods

Selection criteria

Patients with acute ST-Elevation Myocardial Infarction (STEMI) underwent the primary percutaneous coronary intervention procedure at Cho Ray Hospital's Interventional Cardiology Department between September 2021 and September 2022.

Exclusion criteria

Patients undergoing complications affecting the flow

• Coronary dissection

• Residual thrombosis in the culprit artery is visible on angiography

• Perforation of coronary artery

• Residual stenosis >70% of the coronary diameter after the stent.

BN did not agree to participate in the study.

Design of study

Descriptive, cross-sectional trial with analysis.

Data collection method

Post-intervention "no-reflow" is evaluated with coronary angiogram and interventions stored in the cardiac

catheterization room. The "no-reflow" phenomenon is defined when the TIMI flow grade ≤ 2. Clinical and subclinical parameters are obtained through examination and medical records.

Statistical processing procedures

Data is entered and analyzed by using Stata statistical software version 14.0.

Medical ethics

It has been approved by the Ethics Council in Biomedical Research of the University of Medicine and Pharmacology, HCMC.

Results

There were 238 STEMI patients admitted to the study. After the primary percutaneous coronary intervention, 42 patients were recorded with TIMI flow ≤ 2 ("no-reflow" phenomenon), accounting for 17.6%.

Clinical and subclinical factors of the patient

Compared to patients with the normal flow (TIMI ≥ 3) after the percutaneous coronary intervention, "no-reflow" patients have the following characteristics: Older age, longer duration of STEMI, lower heart rate, lower hemoglobin levels, higher blood sugar, lower glomerular filtration (Table 1).

Table 1. *Clinical and para-clinical feature.*

Characteristics	No-reflow (n=42) n(%)	Flow TIMI 3 (n=196) n(%)	P
Cardiovascular risk factors			
Male ≥ 45 years old or female ≥ 55 years old	40 (95.24)	175 (89.29)	0.386 (Fisher)
Dyslipidemia	35 (83.33)	179 (91.33)	0.154 (Fisher)
Hypertension	36 (85.71)	174 (88.78)	0.599 (Fisher)
Smoking	24 (57.14)	131 (66.84)	0.232
Overweight	28 (66.67)	118 (60.2)	0.435
Diabetes mellitus	16 (38.1)	52 (26.53)	0.132
History of coronary heart disease	2 (4.76)	11 (5.61)	1 (Fisher)
Chronic kidney disease	4 (9.52)	7 (3.57)	0.108 (Fisher)
Clinical features			
Age (years)	66.9 ± 12.9	62.4 ± 12.49	0.04
Male	26 (61.9)	147 (75.0)	0.084
Time from chest pain (hours)	15.36 ± 11.63	9.74 ± 7.69	0.004
STEMI ≥ 12 hours	23 (54.76)	44 (22.45)	<0.001
Antiplatelet P2Y12 strong	24 (57.14)	132 (67.35)	0.207
Heart rate	72.31 ± 24.05	79.75 ± 20.51	0.039
Killip 3-4	10 (23.81)	17 (8.67)	0.012 (Fisher)
Systolic blood press	116.3 ± 38.0	120.9 ± 31.8	0.415
Para-clinical features			
Hemoglobin(g/L)	127.4 ± 21.4	136.6 ± 17.5	0.004
Anemia	17 (40.5)	42 (21.4)	0.009
Platelet (G/L)	254.6 ± 94.0	272.7 ± 84.2	0.217
Neutrophil (WBC)	11.6 ± 5.56	10.34 ± 3.87	0.08
Serum Glucose (mg/dL)	196.3 ± 101.5	160.2 ± 76.5	0.01
Blood sugar ≥ 200 mg/dL	14 (33.33)	33 (16.84)	0.015
Serum Creatinine (mg/dL)	1.37 ± 0.74	1.04 ± 0.51	0.008
eGFR<60 ml/min/1.73 m^2	21 (50)	48 (24.49)	0.001
LVEF(%)	41.7 ± 10.8	42.8 ± 10.2	0.54
LVEF<40%	17 (40.48)	68 (34.69)	0.478

Note: eGFR: estimated Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction.

Factors related and affected in the percutaneous coronary intervention procedures

Compared to patients with the normal flow (TIMI ≥ 3) after the intervention, patients without flow (No reflow phenomenon) have the following characteristics related intervention procedures: The culprit artery branch is mainly the right coronary artery branch, having a longer lesion length, a higher rate of a diffuse lesion, a higher rate of TIMI flow 0-1 before the intervention, the incidence of large thrombus burden TIMI ≥ 4 is more elevated (Table 2).

Table 2. *Factors affected in percutaneous coronary intervention procedures.*

Characteristics		No-reflow (n=42) n(%)	Normal flow TIMI ≥ (n=196) n(%)	p
Culprit coronary artery	LMCA	0 (0)	7 (3.75)	0.018 (Fisher)
	LAD	10 (23.81)	89 (45.41)	
	LCx	2 (4.76)	5 (2.55)	
	RCA	30 (71.43)	95 (48.47)	
Multivessel coronary artery		24 (57.14)	111 (56.63)	0.952
Proximal segment		24 (57.14)	88 (44.9)	0.149
Collaterals		5 (11.9)	33 (16.84)	0.428
Reference vessel diameter		3.1 ± 0.3	3.1 ± 0.4	0.89

Diffuse lesion	36 (85.7)	131 (66.8)	0.015
Length of lesion	30.7 ± 11.9	23.0 ± 8.0	<0.001
TIMI flow pre-intervention: 0-1	39 (92.86)	119 (60.71)	<0.001
Large thrombus burden TIMI ≥ 4	36 (85.71)	42 (21.43)	<0.001
Direct stenting	15 (35.71)	82 (41.84)	0.464
Post-stenting dilatation	6 (14.29)	51 (26.02)	0.106

Note: LAD: Left Anterior Descending Artery; LCx: Left Circumflex Coronary Artery; LMCA: Left Main Coronary Artery; RCA: Right Coronary Artery

Prognostic factors for the "No reflow" phenomenon post-PCI

Performing multivariate regression, the prognostic factors capable of predicting the occurrence of the "No-reflow" phenomenon are large thrombus burden TIMI ≥ 4, Killip 3-4 at admission, duration of STEMI>12 hours, length of the lesion (Table 3).

Table 3. *Multivariate regression of prognostic factors for "No flow" phenomenon.*

Factors	OR	CI 95%	p
Thrombotic burden TIMI ≥ 4	10.37	3.27-32.83	<0.001
Killip 3-4 at admission	8.17	1.3-51.5	0.025
The duration of STEMI >12 hours	4.37	1.54-12.37	0.005
Lesion Length (for every millimeter increased)	1.12	1.02-1.22	0.016

Discussion

Percentage of "no-reflow" phenomenon

In our study, the incidence of this "no-reflow" phenomenon occurred at 17.6%. This was higher than that in studies of O. Tasar (10.1%) and N. Rajesh (15.4%) [1,2]. The first conceivable reason is that the study of O. Tasar and N. Rajesh only selected the study population of STEMI with duration of <12 hours. In our study, there are only 71.85% of patients with STEMI with a duration of <12 hours. Indeed, in 2018 in the study of H. Li in China that enrolled STEMI patients with a duration >12-hour the "no-reflow" phenomenon was 18.7%, comparable to that of our study [3]. However, the "no-reflow" phenomenon could be caused by several mechanisms, and many factors could get involved. So, we conducted this study to determine the factors that can predict the occurrence of the "no-reflow" phenomenon.

Prognostic factors for the "no-reflow" phenomenon

There are four main mechanisms for the "no-reflow" phenomenon: Microvascular embolism, ischemia, reperfusion injuries, and susceptibility of coronary micro vascular bed [4].

In our study, after performing a multivariate logistic regression method, we noted four factors that can independently predict the occurrence of the "no-reflow" phenomenon: TIMI large thrombus burden TIMI ≥ 4 (OR=10.37), Killip 3-4 at hospitalization (OR=8.17), duration of STEMI >12 hours (OR=4.37), lesion length (OR=1.12). We found these four factors related to the critical problems of patients with STEMI: Time that myocardium is ischemic, clinical hemodynamic status, and anatomical features of coronary lesions. However, the technical-related factors during the procedure, such as direct stenting or balloon dilation after stenting, are not prognostic factors for the "no-reflow" phenomenon.

Thrombotic burden

A coronary micro vascular embolism occurs possibly due to plaque debris or thrombosis from the epicardial culprit lesion, which is the most common cause of the "no-reflow" phenomenon in primary PCI. Microparticles with a diameter of >200 μm can block arterioles. Observations of many llaboratory research suggest that myocardial perfusion flow is irreversibly reduced if microparticles block more than 50% of coronary capillaries [4].

Therefore, the greater the large thrombus burden, the higher the risk of the "no-reflow" phenomenon. In addition, coronary micro vascular embolism also causes coronary spasms, increases sympathetic reflexes, and increases the secretion of substances that reduce coronary micro vascular function [5]. The authors M. Alidoosti, H. Refaat, and C. Kirma found that the large thrombus burden of TIMI ≥ 4 is an independent predictor of the "no-reflow" phenomenon after primary PCI [6-8].

Killip classification at admission

In our study, the proportion of hospitalized patients with clinical status Killip ≥ 3 in the "no-reflow" group was higher than in the normal flow group (23.81% *vs.* 8.67%); the difference was statistically significant, p=0.012; H. Li's study produced similar results (31.6% *vs.* 16.4%, p=0.032) [3]. The higher the Killip Classification at admission, the more disturbed hemodynamic status reflects the large volume of the damaged heart muscle. The more the microvascular coronary bed is damaged, the higher the risk of the "no-reflow" phenomenon.

The study by O. Tasar showed similar results to our study. When performing the multivariate regression method, Killip Classification at admission ≥ 2 was an independent factor to predict the "no-reflow" phenomenon (OR=1.99, p=0.002) [2].

Duration of STEMI

The longer the duration of STEMI, the more cellular changes will occur in endothelial cells, manifested by edema and protrusion into the lumen of the coronary vessels, causing a capillary blockage. In addition, a prolonged lack of oxygen supply reduces the ability of red blood cells to change shape, contributing to the

microvascular bed's blockage. Moreover, ischemic heart muscle cells and interstitial tissue will also be edematous, causing compression and reduced microvascular flow. At the same time, the longer the duration of STEMI, the greater the large thrombus burden, increasing the risk of the "no-reflow" phenomenon [4].

Most studies have shown the relation between the duration of STEMI and the "no-reflow" phenomenon, regardless of whether the study's criteria for selecting STEMI patients are less than 12 hours or more than 12 hours. The timeline chosen for comparison between the two groups of no-reflow and normal flow in the studies was 4 hours (study by C. Kirma and O. Tasar) or 8 hours (study by H. Li) [2,3,8]. However, the patients in our study had a later hospitalization time than the foreign studies, so we chose a timeline of 12 hours for comparison; the more the results also tried to conclude that the longer the heart attack, the greater the risk of no-reflow.

Lesion length

Many studies show a relation between the length of the lesion and the "no-reflow" phenomenon. Author O. Tasar based on multivariate analysis showed that coronary lesion more than 15 mm in length is an independent predictor of the "no-reflow" phenomenon (OR=4.31, 95% CI 2.89-6.41, p<0.001) [2].

The longer the lesion, the more significant the plaque burden and the larger the thrombus burden. These are the two main factors in the microvascular embolism mechanism of the "no-reflow" phenomenon. In addition, with a long diffuse lesion, when performing the PCI procedure. If it is necessary to dilate with the balloon, it must be dilated several times; it could further break the atheroma and thrombosis, causing a coronary microvascular embolism.

Conclusion

Across 238 primary percutaneous coronary intervention cases, we noted the "No-reflow" phenomenon prevalence of 17.6%. The "No-reflow" phenomenon can be related and predicted after primary PCI by the patient's clinical features and characteristics of coronary artery lesions such as: Large thrombus burden (TIMI ≥ 4) (OR=10.37), Killip 3-4 at admission (OR=8.17), duration of STEMI>12 hours (OR=4.37), long diffuse lesion length (OR=1.12).

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***Correspondence to:**

Nguyen Thuong Nghia

Department of Interventional Cardiology

201 B Nguyen Chi Thanh Ward 12

HCMC Ho Chi Minh City

Vietnam