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Risk Factors for No-Reflow Phenomenon after Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome

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ABSTRACT

Background: To explore risk factors for no-reflow phenomenon after percutaneous coronary intervention in patients with acute coronary syndrome. **Methods:** A total of 733 acute myocardial infarction patients with persistent ischemic chest pain within 12 or 12-24 hours after onset received emergency percutaneous coronary intervention. Patients were divided into a normal reflow group and a no-reflow group, according to TIMI grading and myocardial blush grading after percutaneous coronary intervention. Related risk factors were analyzed. **Results:** The incidence of no-reflow phenomenon after percutaneous coronary intervention was 16.1%. Univariate analysis showed that, compared with the normal reflow group, the no-reflow group was older, reperfusion time was significantly longer, preoperative systolic pressure was lower, troponin peak was higher, and creatine kinase enzyme peak was higher ($p < 0.05$). The proportions of preoperative cardiac function Killip grade ≥ 2 and number of patients using preoperative intra-aortic balloon pump were significantly different ($p < 0.05$). Multivariate logistic regression analysis showed that age > 65 years (OR: 1.471; 95% CI: 1.462-1.492; p = 0.007), reperfusion time > 6 hours (OR: 1.274; 95% CI: 1.164-1.405; p = 0.001), low systolic pressure at admission (< 100 mmHg) (OR: 1.918; 95% CI: 1.017-3.897; p = 0.004), intra-aortic balloon pump use before percutaneous coronary intervention (OR: 1.949; 95% CI: 1.168-3.253; p = 0.011), low TIMI grade (≤ 1) before percutaneous coronary intervention (OR: 1.100; 95% CI: 1.086-1.257; p < 0.01), high thrombus load (OR: 1.274; 95% CI: 1.423-2.761; p = 0.030), and long target lesion (OR: 1.948; 95% CI: 1.908-1.990; p = 0.019) were independent risk factors. **Conclusions:** No-reflow phenomenon after percutaneous coronary intervention in patients with acute coronary syndrome was affected by complicated pathological factors. (REV INVES CLIN. 2017;69:139-45)

Key words: Myocardial infarction. No-reflow phenomenon. Percutaneous coronary intervention.

INTRODUCTION

Rapid opening of infarct-related artery (IRA) in emergency percutaneous coronary intervention (PCI), which can effectively recover the blood flow in infarcted areas, has been mainly used for the reperfusion of acute myocardial infarction (AMI) patients. However, for some patients, even if IRA is opened, the damaged myocardium still cannot receive effective perfusion, referred to as no-reflow phenomenon after PCI[1-3]. An

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epidemiological study showed that the annual incidence of no-reflow phenomenon after PCI was about 5-25%. The phenomenon is closely related to the clinical outcome of patients, and is also one of the leading causes of death after PCI[4]. It is of both theoretical and clinical value to analyze the risk factors associated with no-reflow phenomenon to improve the safety and therapeutic effects of PCI. Adequate measures can then be taken to improve the clinical outcome of patients[5,6]. In this study, we explored the risk factors for no-reflow phenomenon after PCI through univariate and multivariate analyses of clinical data.

MATERIALS AND METHODS

Baseline clinical data

Acute myocardial infarction patients with acute ST-segment elevation, who underwent emergency PCI in our hospital between January 2011 and December 2012, were selected. The study was approved by the ethics committee of our hospital, and written consent was obtained from all patients. Inclusion criteria were: severe chest pain lasting for over 30 min; ≥ 2 consecutive ST-segment elevations for > 1 minute in ECG leads or new left bundle branch block; myocardial enzyme level increased more than twice the normal value; presenting signs and symptoms of persistent ischemia within 12 or 12-24 hours after onset; successful PCI; with complete clinical data. A total of 733 patients were enrolled. Exclusion criteria were: coronary artery spasm or stenosis degree of culprit lesion ≤ 50% confirmed by coronary angiography; with normal coronary artery blood flow after receiving conservative drug treatment; severe lesion in the left main coronary artery or triple-vessel lesion that required emergency coronary artery bypass grafting; culprit lesion in the graft blood vessel or the left internal mammary artery; and failure to open the coronary artery in surgery.

Percutaneous coronary intervention method

The IRA lesion was repeatedly sucked by a thrombus suction catheter 3-5 times or more when necessary, aiming to effectively remove thrombus load and to open the blood flow forward. Then, the intracoronary thrombosis was mostly cleared, without floating thrombus, continuous retention of contrast agent, or residual of IRA distal thrombus fragments. Delayed angiography was conducted after intracoronary injection of 50-100 μg nitroglycerin. With respect to the vascular diameter, when the residual stenosis was < 70% or the stent could successfully pass, stent implantation was initiated. Alternatively, at a proper pressure using a balloon, pre-dilation was performed before implantation (5-14 atm). Before stent implantation or balloon pre-dilation, the amount of contrast agent was controlled, the number of angiographic procedures was reduced, and the interval between two angiographic examinations was prolonged during surgery.

Angiographic characteristics of target lesions

The following angiographic characteristics were recorded: (i) thrombus load (low, moderate or high); (ii) if the blood vessel with lesion was completely occluded, the characteristics of vascular morphology should be recorded; (iii) centrifugal or centripetal lesions should be recorded in case of a sub-occluded lesion; (iv) length of the target lesion; (v) position of the lesion (proximal, middle or distal). Thrombosis was scored according to the Gibson standard[7] and classified into TIMI grades 0-5. Grades 0-1, low thrombus load; grades 2-3, moderate thrombus load; ≥ 4, high thrombus load. During surgery, it was determined whether balloon dilation or stent implantation was conducted for the blood vessel with lesion. Unless the stent failed to pass due to serious lesion calcification or because the diameter of the normal control segment near the lesion was < 2.25 mm, stent implantation should be performed for all available ischemia-related blood vessels. Only drug-eluting stents were used. The patients took Plavix routinely after surgery. The range of infarction was evaluated according to the peak level of myocardial enzyme; the level was measured 5-6 times at regular intervals 96 hours after onset. The ST-segment depression was observed before and one hour after emergency PCI.

Grouping criteria

According to TIMI grading after PCI, the patients were divided into a no-reflow group (TIMI grade ≤ 2) and a normal reflow group (TIMI grade 3). No-reflow phenomenon was diagnosed if there was successful lesion dilation without mechanical complications such as dissection, spasm or obvious distal embolization, and TIMI

Table 1. Baseline clinical data of acute coronary syndrome patients with normal reflow and no-reflow after percutaneous coronary intervention

Variable	Normal reflow group	No-reflow group	t/χ^2	P
Age (years, x ± s)	61.1 ± 1.8	68.4 ± 15.3	28.932	< 0.01
Male (case, %)	366 (59.51)	78 (12.68)	1.687	0.38
Hypertension (case, %)	182 (29.59)	46 (7.47)	1.165	0.23
Diabetes mellitus (case, %)	102 (16.58)	18 (2.92)	0.337	0.67
Hyperlipidemia (case, %)	304 (49.43)	62 (10.08)	1.674	0.18
History of smoking (case, %)	183 (29.75)	42 (6.83)	1.124	0.29
Family history of coronary artery disease (case, %)	206 (33.49)	41 (6.67)	0.487	0.87
History of infarction (case, %)	32 (5.2)	6 (0.98)	0.043	0.57
Pre-infarction angina (case, %)	24 (3.9)	36 (5.85)	0.578	0.84
Position of infarction (case, %)			1.892	0.45
Anterior wall	347 (56.42)	77 (12.52)		
Inferior wall	201 (32.68)	28 (4.55)		
Others	55 (32.68)	10 (1.63)		
Preoperative systolic pressure (mmHg)	118.3 ± 21.8	102.3 ± 29.4	24.953	< 0.01
Preoperative diastolic pressure (mmHg)	72.8 ± 12.8	66.3 ± 18.4	10.287	0.04
Troponin peak (U/l)	18.4 ± 2.5	41.8 ± 2.9	10.238	0.02
Creatine kinase enzyme peak (U/l)	160.4 ± 1548.4	243.3 ± 209.0	11.879	0.02
Reperfusion time (hours)	5.5 ± 1.9	6.3 ± 4.3	5.879	0.01
Cardiac function Killip grade (case, %)			9.387	0.02
1	457 (74.31)	48 (7.8)		
2	162 (26.34)	41 (6.67)		
3	33 (5.37)	4 (0.65)		
4	14 (2.28)	16 (2.6)		
Preoperative IABP use (case, %)	55 (8.94)	28 (4.55)	43.3	< 0.01

IABP: intra-aortic balloon pump

grade of the target blood vessel was ≤ 2[2]. Depending on the blood pressure, the no-reflow group was treated with intracoronary administration of 200-400 μg nitroglycerin and/or 1 mg verapamil; the patients with systolic pressure < 90 mmHg were intravenously given dopamine to increase the pressure and coronary perfusion. As a result, the patients were relieved from symptoms.

Statistical analysis

Numerical data were expressed as percentage, and categorical data were expressed as mean ± standard deviation. The continuous variables were analyzed using the Wilcoxon signed-rank test for comparison of two independent samples. The binary logistic regression analysis was used to analyze the correlations between the basic clinical data of AMI patients (gender, age, body mass index, smoking, diabetes, hypertension, hyperlipidemia history, myocardial infarction history, preoperative blood pressure, heart rate, time from onset to PCI, Killip grade, preoperative intra-aortic balloon pump [IABP] use, etc.), angiographic results, surgery-related data (number of blood vessels with lesions, IRA, preoperative TIMI grade, degree of thrombus compliance, length, diameter and position of lesions, method of reperfusion, number of implanted stents) and no-reflow phenomenon after emergency PCI. All data were analyzed by the SPSS 21.0 software. P < 0.05 was considered statistically significant.

RESULTS

Baseline clinical data

Of the 733 enrolled patients, 54 presented with the no-reflow phenomenon after PCI, with an incidence of 16.1%. The baseline clinical data are summarized in table 1. The normal reflow and no-reflow groups were similar with respect to gender, main risk factors for coronary artery disease (e.g. diabetes mellitus,

hypertension, hyperlipidemia, family history of coronary artery disease), history of infarction, location of infarction, and pre-infarction angina. Compared with the normal reflow group, the no-reflow group was older (68.4 ± 15.3 vs. 61.1 ± 1.8 years); the reperfusion time was significantly longer (6.3 ± 4.3 vs. 5.5 ± 1.9 hours); the preoperative systolic pressure was lower (102.3 ± 29.4 vs. 118.3 ± 21.8 mmHg); the troponin peak was significantly higher (18.4 ± 2.5 vs. 41.8 ± 2.9 U/l) ($p < 0.05$), and the CK enzyme peak was significantly higher (243.3 ± 209 vs. 160.4 ± 1,548.4 U/l) ($p < 0.05$). There were significant differences ($p < 0.05$) in the proportion of preoperative cardiac function Killip grade ≥ 2 and the number of patients using preoperative IABP between the two groups.

Angiography and emergency percutaneous coronary intervention

During angiography and emergency PCI, the normal reflow and no-reflow groups had significantly different patients of preoperative TIMI grade ≤ 1, discrete complete occlusion, long target lesion and reference vessel diameter ($p < 0.05$) (Table 2). The patients with reperfusion time > 6 hours and high thrombus load were more prone to no-reflow phenomenon, also with significant inter-group differences ($p < 0.05$). The two groups had similar IRA, number of blood vessels with lesion, position of target lesion, type of sub-occlusion and collateral blood flow ($p > 0.05$). The method of reperfusion also determined whether no-reflow phenomenon occurred in the two groups ($p < 0.05$). In contrast, the number of implanted stents, maximum distending pressure, or repeated balloon dilation did not affect such phenomenon ($p > 0.05$) (Table 2).

Univariate and multivariate logistic regression analysis results for risk factors related to no-reflow phenomenon after emergency percutaneous coronary intervention

Currently, the factors related to no-reflow phenomenon have not been widely studied. Here we performed univariate and multivariate logistic regression analyses for the factors with significant differences in the baseline clinical data of two groups as well as those with significant differences in angiographic and emergency PCI results. Age, time from appearance of symptoms to PCT (reperfusion time), systolic pressure upon hospitalization, cardiac function Killip grade, preoperative use of IABP, type of occlusion, length of target lesion, degree of thrombus load, preoperative TIMI grade, reference vessel diameter and reperfusion method were selected as the covariates. Finally, age > 65 years (OR: 1.471; 95% CI: 1.462-1.492; $p = 0.007$), reperfusion time > 6 hours (OR: 1.274; 95% CI: 1.164-1.405; $p = 0.001$), low systolic pressure at admission (< 100 mmHg, 1 mmHg = 0.133 kPa) (OR: 1.918; 95% CI: 1.017-3.897; $p = 0.004$), IABP use before PCI (OR: 1.949; 95% CI: 1.168-3.253; $p = 0.011$), low TIMI grade (≤ 1) before PCI (OR: 1.100; 95% CI: 1.086-1.257; $p < 0.01$), high thrombus load (OR: 1.274; 95% CI: 1.423-2.761; $p = 0.030$) and long target lesion (OR: 1.948; 95% CI: 1.908-1.990; $p = 0.019$) were identified as independent risk factors for no-reflow phenomenon after PCI (Table 3).

DISCUSSION

No-reflow phenomenon is one of the common complications after emergency PCI, with incidence rates of 5-25%[8]. Its pathophysiological mechanisms mainly include endothelial dysfunction, microvascular dysfunction, microvascular spasm, reperfusion injury, and microvascular embolism, among others. Old age, delayed reperfusion (a relatively long time from the onset of symptoms to PCI), low TIMI grade before PCI, hypotension at admission (systolic pressure < 100 mmHg), preoperative IABP use, long target lesion, and high thrombus load are all independent predictive factors for no-reflow phenomenon. In this study, the incidence of no-reflow phenomenon after emergency PCI was approximately 16.1%, being consistent with that in previous literature[9-11].

Compared with young patients, elderly patients usually have higher mortality during admission after AMI and long-term mortality as well as lower success rate of emergency PCI, probably because they have more underlying diseases, atypical onset symptoms of myocardial infarction, delayed treatment, and more complications. In addition, they have limited understanding of myocardial infarction, so the therapeutic effect is usually poor and the incidence of postoperative no-reflow phenomenon is high[12,13]. Meanwhile, elderly patients commonly suffer from diffuse atherosclerotic lesions, severe calcification, distal microvascular

Table 2. Angiographic findings and emergency percutaneous coronary intervention

Variable	Normal reflow group	No-reflow group	t/χ^2	P
Multi-vessel lesion (case, %)	338 (54.95)	64 (54.24)	0.879	0.387
Infarct-related artery (case, %)			1.782	0.587
Anterior descending artery	266 (43.25)	72 (61.02)		
Circumflex artery	146 (23.74)	8 (6.78)		
Right coronary artery	203 (33.01)	28 (23.73)		
Initial TIMI grade (case, %)			32.891	0.0006
0/1	423 (68.78)	100 (84.75)		
2/3	192 (31.21)	18 (15.25)		
Position of lesion (case, %)			1.178	0.382
Proximal segment	234 (38.04)	42 (35.59)		
Middle segment	366 (59.51)	60 (50.84)		
Distal segment	15 (2.439)	6 (3.38)		
Occlusion (case, %)			9.478	0.026
Sub-occlusion	222 (36.10)	22 (18.6)		
Conical	204 (33.17)	40 (33.90)		
Discrete	189 (30.73)	58 (49.15)		
Type of sub-occlusion (case, %)			1.369	0.498
Centrifugal	57 (9.26)	8 (1.3)		
Centripetal	208 (33.82)	14 (2.28)		
Length of target lesion (mm)	18.3 ± 6.2	21.7 ± 9.4	8.323	< 0.01
Reference vessel diameter (mm)	3.1 ± 0.4	3.3 ± 0.4	2.189	0.028
Degree of thrombus load			24.8	0.011
Low	175 (28.45)	39		
Moderate	157 (25.53)	24		
High	283 (46.02)	55		
Good collateral circulation (case, %)	40 (6.5)	8	0.576	0.645
Reperfusion method (case, %)			7.687	0.001
Balloon dilation	28 (4.55)	15 (12.71)		
Balloon pre-dilation + stent implantation	372 (60.48)	89 (75.42)		
Stent implantation	215 (34.95)	14 (11.86)		
Post-dilation ≥ twice	198 (32.19)	47 (39.83)	2.476	0.026
≥ 2 stents (case, %)	108 (17.56)	32 (27.11)	2.718	0.046
Thrombus aspiration (case, %)	410 (66.67)	65 (55.08)	0.879	0.627
Use of tirofiban (case, %)	452 (73.49)	81 (68.64)	0.481	0.062

Table 3. Univariate and multivariate logistic regression analysis results for risk factors related to no-reflow phenomenon after emergency percutaneous coronary intervention

Variable	Univariate logistic regression		Multivariate logistic regression	
	P	OR (95% CI)	P	OR (95% CI)
Age > 65 years	< 0.010	1.884 (1.830-1.980)	0.007	1.471 (1.462-1.492)
Low systolic pressure at admission (< 100 mmHg)	0.005	1.570 (1.390-1.850)	0.004	1.918 (1.017-3.897)
Initial TIMI grade (0-1)	0.020	1.423 (1.062-1.854)	0.030	1.600 (1.473-2.764)
IABP use before PCI	0.003	1.879 (1.152-3.172)	< 0.01	1.100 (1.086-1.257)
High thrombus load	0.020	1.423 (1.062-1.854)	0.030	1.948 (1.908-1.990)
Reperfusion event > 6 hours	0.005	1.564 (1.362-1.872)	0.001	1.274 (1.423-2.761)
Long target lesion	0.027	1.268 (1.156-1.405)	0.019	1.948 (1.908-1.990)

IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention.

embolism, and microcirculation disorders. These pathological changes are associated with age and the lack of ischemic preconditioning, collateral circulation, and neurohumoral changes, which easily lead to distal embolization of coronary artery during emergency PCI and then to no-reflow phenomenon[14-16]. In our study, univariate analysis showed that the no-reflow group was older (68.4 ± 15.3 vs. 61.1 ± 1.8 years old) than the normal reflow group, like in previous studies.

Additionally, the reperfusion time was significantly prolonged in the patients with no-reflow after PCI (6.3 ± 4.3 vs. 5.5 ± 1.9 hours). The thrombus load was significantly elevated in the patients with reperfusion time > 6 hours, and the no-reflow incidence was increased about 1.3-fold compared with that of the patients with shorter reperfusion time. Pathophysiologically speaking, myocardial cells in the infarcted region become completely necrotic owing to the loss of effective blood supply six hours after the onset of myocardial infarction, so recanalization within six hours can exert evident preventive effects. In the case of no-reflow phenomenon after PCI, the ischemic time of myocardial cells in the infarcted region is prolonged, which can also lead to edema of the distal capillary bed, swelling of myocardial cells, neutrophil chemotaxis, alteration of the integrity of capillaries, and microvascular bed damage. Microvascular bed damage can further promote the occurrence of no-reflow phenomenon after PCI. In the early stages of AMI, using thrombolytic drugs to reduce small thrombus in the infarcted region has an obvious effect, and thrombolysis is also relatively easy. However, the no-reflow phenomenon prolongs the duration of infarction in the infarcted region, and many red blood cells are recruited in micro-thrombi of small arteries, so the thrombi become more compact and firmer from being dissolved. During balloon dilation, the thrombi easily fracture and flow to downstream smaller arteries with the recanalization of blood flow, resulting in adverse events such as distal coronary embolization and secondary embolism after recanalization. Moreover, prolonged reperfusion time can also lead to organization of a large number of intracoronary thrombi and form fibrous tissues, further increasing the difficulty of recanalization as well as the risk of PCI distal embolization[17-20].

Yip, et al.[21] reported that the subgroup of reperfusion time < 4 hours had a lower incidence of no-reflow phenomenon among AMI patients with high thrombus load, suggesting that reperfusion time was of great clinical significance to the incidence of no-reflow and correlated with thrombus load. In myocardial infarction patients with long reperfusion time and high thrombus load, using a distal protection device during PCI can effectively relieve thrombosis and other adverse reactions as well as obviously improve the perfusion of myocardial tissues in the infarcted region. However, the no-reflow phenomenon also endangers patients with long reperfusion time and moderate thrombus load, possibly because small particles such as thrombus fragments destroy the integrity of the microvascular bed, inducing the no-reflow phenomenon. Before PCI, the incidence of no-reflow phenomenon in the patients with TIMI grade of IRA ≤ 1 is 1.1 times that of the patients with TIMI grade ≥ 2. De Luea, et al.[22] found that before emergency PCI, high TIMI grade was closely related to whether postoperative grade could reach 3 and myocardial perfusion grade could reach 2-3, small infarct area, etc. It is generally believed that TIMI blood flow before PCI indicates good IRA patency, low thrombus load, spontaneous thrombus dissolution, and apparent release of vascular spasm, so the myocardial infarction area decreases. The main purpose of AMI treatment is to open IRAs as much as possible, thereby promoting the recovery of normal forward blood flow.

Ishikura, et al.[23] found that arterial systolic pressure < 120 mmHg could reduce both coronary and collateral blood flows to enlarge the myocardial infarction area. Thus, blood pressure reduction in AMI patients decreases coronary blood flow and promotes leukocyte accumulation, thereby increasing the incidence of no-reflow phenomenon. The AMI patients with Killip grade ≥ 3 need IABP that also facilitates the occurrence of no-reflow phenomenon. Such patients have large infarct area, severe microvascular bed damage, and decreased coronary perfusion pressure, resulting in the raised incidence of no-reflow phenomenon. When Killip grade prompts the occurrence of heart failure, patients have severe peripheral vascular embolization, accompanied by elevated incidence of no-reflow phenomenon after PCI[24]. Over 50% thrombosis of capillaries in distal coronary arteries can cause irreversible reduction of myocardial perfusion and coronary thrombosis, destruct the self-regulation of blood vessels, and promote the release of vasoconstrictors, together with a variety of neurohumoral fluids. The resulting damaged microvascular function leads to

no-reflow phenomenon. In terms of blood hydrodynamics, a larger diameter means a slower blood flow. Hence, a longer infarcted target lesion indicates a larger plaque volume in the lesion, more thrombi in blood vessels, a higher thrombus load, and slow blood flow or no-reflow phenomenon after PCI.

In summary, complex pathological factors affect the occurrence of no-reflow phenomenon after PCI, and these factors, with their combined action, can increase the incidence. However, this study has some limitations. Since some patients with incomplete clinical data upon hospitalization were excluded, there may be biases that led to a small sample size, thus giving non-significant results. Furthermore, we could not include all possible indices, so there may be other independent risk factors for no-reflow phenomenon.

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