Original Article

Clinical and procedural predictors of no-reflow in patients with acute myocardial infarction after primary percutaneous coronary intervention

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BACKGROUND: The treatment of acute myocardial infarction (AMI) is thought to restore antegrade blood flow in the infarct-related artery (IRA) and minimize ischemic damage to the myocardium as soon as possible. The present study aimed to identify possible clinical predictors for no-reflow in patients with AMI after primary percutaneous coronary intervention (PCI).

METHODS: A total of 312 consecutive patients with AMI who had been treated from January 2008 to December 2010 at the Cardiology Department of East Hospital, Tongji University School of Medicine were enrolled in this study. Inclusion criteria were: (i) patients underwent successfully primary PCI within 12 hours after the appearance of symptoms; or (ii) patients with ischemic chest pain for more than 12 hours after a successful primary PCI within 24 hours after appearance of symptoms. Exclusion criteria were: (i) coronary artery spasm; (ii) diameter stenosis of the culprit lesion was $\leq 50\%$ and coronary blood flow was normal; (iii) patients with severe left main coronary or multivessel disease, who had to require emergency revascularization. According to thrombolysis in myocardial infarction (TIMI), the patients were divided into a reflow group and a no-reflow group. The clinical data, angiography findings and surgical data were compared between the two groups. Univariate and multivariate logistic regressions were used to determine the predictors for no-reflow.

RESULTS: Fifty-four (17.3%) of the patients developed NR phenomenon after primary PCI. Univariate analysis showed that age, time from onset to reperfusion, systolic blood pressure (SBP) on admission, Killip class of myocardial infarction, intra-aortic balloon pump (IABP) use before primary PCI, TIMI flow grade before primary PCI, type of occlusion, thrombus burden on baseline angiography, target lesion length, reference luminal diameter and method of reperfusion were correlated with no-reflow ($P < 0.05$ for all). Multiple logistic regression analysis identified that age > 65 years [$OR = 1.470$, 95% confidence interval (CI) 1.460–1.490, $P = 0.007$], long time from onset to reperfusion > 6 hours ($OR = 1.270$, 95%CI 1.160–1.400, $P = 0.001$), low SBP on admission < 100 mmHg ($OR = 1.910$, 95%CI 1.018–3.896, $P = 0.004$), IABP use before PCI ($OR = 1.949$, 95%CI 1.168–3.253, $P = 0.011$), low (≤ 1) TIMI flow grade before primary PCI ($OR = 1.100$, 95%CI 1.080–1.250, $P < 0.001$), high thrombus burden ($OR = 1.600$, 95%CI 1.470–2.760, $P = 0.030$), and long target lesion ($OR = 1.948$, 95%CI 1.908–1.990, $P = 0.019$) on angiography were independent predictors of no-reflow.

CONCLUSION: The occurrence of no-reflow after primary PCI for acute myocardial infarction can predict clinical, angiographic and procedural features.

KEY WORDS: Acute myocardial infarction; No-reflow phenomenon; Percutaneous coronary intervention; Thrombus

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INTRODUCTION

The treatment of acute myocardial infarction (AMI) is thought to restore antegrade blood flow in the infarct-related artery (IRA) and minimize ischemic damage to the myocardium as soon as possible. Primary percutaneous coronary intervention (PCI) is the most efficient way to restore antegrade blood flow in the current management of ST-elevation AMI. Despite the recent progress in PCI, however, a proportion of patients develop epicardial coronary artery reperfusion but not myocardial reperfusion after primary PCI, known as no-reflow. Patients who have developed no-reflow are at an increased risk for left ventricular dysfunction and progressive myocardial damage. The present study was undertaken to identify clinical factors, angiographic findings and procedural features, which predict the no-reflow phenomenon in patients with AMI after primary PCI.

METHODS

Patients

A total of 312 consecutive AMI patients who had undergone emergency PCI between January 2008 and December 2010 at the Cardiology Department of East Hospital, Tongji University School of Medicine were enrolled in the study. Inclusion criteria were: (i) patients underwent successfully primary PCI within 12 hours after appearance of symptoms; and (ii) patients with ischemic chest pain for more than 12 hours who underwent successfully primary PCI within 24 hours after appearance of symptoms. AMI was defined as typical chest pain for more than 30 minutes and either ST segment elevation of >1 mm in 2 consecutive leads or the onset of left bundle-branch block with 2-fold elevation of creatine kinase (CK) and creatine kinase-MB (CK-MB) fraction. Exclusion criteria were: patients who were treated conservatively for coronary artery spasm or $\leq 50\%$ diameter stenosis of the culprit lesion with normal coronary blood flow; those who required emergency revascularization for severe left main coronary artery or multivessel diseases; those with saphenous vein grafts or left internal mammary artery lesions; and those who did not achieve coronary artery patency.

Coronary angiography and primary PCI

All patients were subjected to oral aspirin (300 mg) and clopidogrel (300 mg), as well as intravenous 8 000–10 000 U unfractionated heparin. They received PCI through the femoral artery or the radial artery. Before the PCI,

standard left and right coronary angiograms with at least 2 best projections were obtained for each patient. Two experienced interventional cardiologists assessed a set of parameters for each angiogram and reached consensus on the findings. These parameters included: morphology of the IRA, Rentrop collateral flow, angiographic features of the target lesion, TIMI flow grades before and after primary PCI, culprit lesion stenosis degree, target lesion length, and luminal diameter. Angiographic data of the lesion responsible for the infarction were recorded: (i) thrombus burden (mild, moderate or high); (ii) types of total occlusion if present (tapered or cut-off lesion); (iii) types of lesion if subtotal occlusion is present (eccentric or concentric lesion); (iv) length of target lesion; and (v) lesion location (proximal, mid or distal lesion). Thrombus burden was scored in five degrees according to Gibson,^[1] it was classified as mild if the TIMI thrombus was class 0 and 1, moderate if the TIMI thrombus was class 2 and 3, and high if the TIMI thrombus was more than class 3. The reperfusion therapy (balloon angioplasty or stent placement) was determined by physician's discretion during primary PCI. Stent placement was strongly encouraged unless the IRA was heavily calcified or reference luminal diameter (RLD) <2.25 mm. Drug-eluting stents were used for all stenting procedures. Each patient was treated with clopidogrel for at least 1 year after PCI. Infarct size was estimated by the measurement of peak activity of serum creatine kinase (CK), and peak enzyme release was assessed using 5–6 serial measurements taken at the first 4 days after appearance of symptoms. ST-segment resolution was evaluated before and 1 hour after primary PCI.

All patients were divided into two groups based on the post-procedural TIMI flow in the IRA: TIMI flow ≤ 2 (no-reflow) and TIMI flow 3 (reflow). The patient was considered to exhibit a no-reflow phenomenon if blood flow in the IRA was a TIMI ≤ 2 flow despite successful dilatation and absence of mechanical complications such as dissection, spasm or angiographically evident distal embolization after completion of the procedure.^[2]

Statistical analysis

All variables were expressed as mean $\pm$ standard deviation. The Chi-square test was used to analyze categorical variables. Student's *t* test and analysis of variance were used for continuous variables. Univariate and multivariate analyses were performed to identify independent predictors of no-reflow phenomenon. Statistical analysis was made using SPSS 19.0. A *P* value <0.05 was considered statistically significant.

RESULTS

Baseline clinical characteristics

In the 312 patients who had undergone primary PCI, 54 (17.3%) showed an angiographic no-reflow phenomenon. The baseline clinical characteristics are shown in Table 1. There were no significant differences between the reflow group and the no-reflow group in sex distribution, hypertension, diabetes mellitus, hypercholesterolemia, current smoking, family history of coronary artery disease, primary MI, and infarct localization or pre-infarction angina ($P>0.05$ for all). Compared with the reflow group, the no-reflow group had a higher mean age (67.1 ± 14.9 vs. 61.1 ± 12.4 years for no-reflow and reflow, respectively), a longer mean reperfusion time (6.7 ± 3.2 vs. 5.4 ± 2.8 hours, respectively), a lower level of SBP in admission (101.2 ± 25.8 vs. 116.2 ± 22.4 , respectively), a higher level of CK (239 ± 205 vs. 160 ± 166 U/L, respectively) ($P<0.05$ for all). Moreover, there were significant differences between the reflow and no-reflow groups in respect to Killip classes before PCI and IABP use before PCI ($P<0.05$ for all).

Angiographic findings and primary PCI characteristics

The angiographic data and procedural features

Table 1. Baseline clinical data in the reflow group and the no-reflow group (n, %)

Variables	Reflow (n=258)	No-reflow (n=54)	t/χ^2 value	P value
Age(yr)	61.1±12.4	67.1±14.9	24.703	<0.01
Male	160 (62.0)	38 (70.3)	1.682	0.324
Hypertension	94 (36.4)	23 (42.5)	1.152	0.224
Diabetes mellitus	41 (15.9)	10 (18.5)	0.438	0.635
Hypercholesterolemia	121 (46.9)	29 (53.7)	1.652	0.174
Current smoker	90 (34.8)	20 (37.0)	1.120	0.295
Family history of CAD	88 (34.1)	19 (35.2)	0.436	0.829
Previous MI	13 (5.0)	3 (5.6)	0.024	0.660
Pre-infarction angina	78 (30.3)	17 (31.4)	0.576	0.841
Infarct location				
Anterior	157 (60.8)	36 (66.7)	1.832	0.494
Inferior	79 (30.6)	14 (25.9)		
Other locations	22 (8.6)	4 (7.4)		
Physical findings on admission				
SBP (mmHg)	116.2±22.4	101.2±25.8	24.734	<0.001
DBP (mmHg)	71.4±13.4	66.1±16.8	9.973	0.050
Peak CK-MB (U/L)	160±166	239±205	11.762	0.014
Reperfusion time (h)	5.4±2.8	6.7±3.2	5.678	0.011
Killip classes (%)			9.653	0.02
1	176 (68.2)	24 (44.4)		
2	64 (24.8)	20 (37)		
3	13 (5.0)	2 (3.7)		
4	5 (2)	8 (14.9)		
IABP use before PCI (%)	20 (7.8)	14 (25.9)	42.8	<0.0001

Data were presented as mean±SD or number (%) of patients; CAD: coronary artery disease; MI: myocardial infarction; SBP: systolic blood pressure; DBP: diastolic blood pressure; CK: creatine kinase; IABP: intra-aortic balloon pump.

revealed that no-reflow was more frequent in patients who had a low (≤ 1) initial TIMI flow (92.6% vs. 69.8%), a total cut-off occlusion (42.6% vs. 29.1%), a long target lesion (21.6 ± 9.25 vs. 18 ± 6.48 mm), and a large vessel diameter (3.3 ± 0.4 vs. 3.0 ± 0.3 mm, respectively). Moreover, the no-reflow incidence was significantly higher in patients with a delayed reperfusion (>6 hours) and a high thrombus burden. Reperfusion had an influence on the incidence of no-reflow ($P<0.05$). However, IRA, the presence of multivessel diseases, locations of target lesions, types of lesions in subtotal occlusions, grades of collateral flows, number of implanted stents, maximal inflation pressures, and repeated balloon dilatations did not affect the incidence of no-reflow ($P>0.05$) (Table 2).

Table 2. Angiographic and surgical data in the reflow group and the no-reflow group (n, %)

Variables	Reflow (n=258)	No-reflow (n=54)	t/χ^2 value	P value
Multivessel disease	138 (53.5)	32 (59.3)	0.873	0.326
IRA			1.743	0.568
LAD	152 (58.9)	36 (66.7)		
LCX	23 (8.9)	4 (7.4)		
RCA	83 (32.1)	14 (25.9)		
Initial TIMI flow			32.742	0.0007
0/1	180 (69.8)	50 (92.6)		
2/3	78 (30.2)	4 (7.4)		
Target lesion location			1.172	0.386
Proximal	93 (36.0)	21 (38.9)		
Mid	159 (61.6)	30 (55.6)		
Distal	6 (2.4)	3 (5.5)		
Type of occlusion				
Subtotal	103 (39.9)	11 (20.3)	9.763	0.024
Tapered	80 (31.0)	20 (37.1)		
Cut-off	75 (29.1)	23 (42.6)		
Lesion types in subtotal occlusion			1.362	0.428
Eccentric	23 (22.3)	4 (36.4)		
Concentric	80 (77.7)	7 (63.7)		
Target lesion length (mm)	18±6.48	21.6±9.25	8.324	<0.0001
Reference diameter (mm)	3.1±0.3	3.3±0.4	2.213	0.029
Thrombus burden			23.762	0.010
Low	70 (27.1)	9 (16.7)		
Moderate	75 (29)	12 (22.2)		
High	113 (43.9)	33 (61.1)		
Good collateral flow	16 (6.2)	4 (7.4)	0.532	0.635
Method of reperfusion			7.634	0.002
Balloon angioplasty	9 (3.4)	4 (7.4)		
Stenting after pre-dilation	163 (63.2)	44 (81.4)		
Direct stenting	86 (33.4)	6 (11.2)		
Repeated balloon dilatations (≥ 2)	79 (30.6)	23 (42.6)	2.384	0.054
Multiple stents (≥ 2)	43 (16.7)	15 (27.8)	2.765	0.051
Aspiration thrombectomy	164 (63.5)	32 (59.3)	0.876	0.628
Tirofiban use	180 (69.8)	40 (74)	0.435	0.644

Data were presented as mean±SD or the number of patients; IRA: infarct-related artery; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; TIMI: thrombolysis in myocardial infarction.

Independent predictors of no-reflow phenomenon

Univariate and multivariate analyses identified that age >65 years ($OR=1.470$, 95%CI 1.460–1.490, $P=0.007$), reperfusion time >6 hours ($OR=1.270$, 95%CI 1.160–1.400, $P=0.001$), SBP on admission ≤ 100 mmHg ($OR=1.910$, 95%CI 1.018–3.896, $P=0.004$), IABP use before PCI ($OR=1.949$, 95%CI 1.168–3.253, $P=0.011$), a low initial TIMI flow (≤ 1) ($OR=1.100$, 95%CI 1.080–1.250, $P<0.001$), a high thrombus burden ($OR=1.600$, 95%CI 1.470–2.760, $P=0.030$), and a long target lesion ($OR=1.948$, 95%CI 1.908–1.990, $P=0.019$) were the independent predictors of the no-flow phenomenon (Table 3).

DISCUSSION

The rate of no-reflow phenomenon after primary PCI in our study (17.3%) was similar to that (5%–25%) reported previously.^[3] The cause of no-reflow after primary PCI in patients with STEMI is complex. The possible mechanisms of no-reflow include endothelial dysfunction, microvascular disorders, spasm, embolization, and reperfusion injury. Advanced age, delayed reperfusion, a low TIMI flow to PCI, SBP on admission <100 mmHg, intra-aortic balloon pump (IABP) use before PCI, a long target lesion and a high thrombus burden were independent predictors of no-reflow. Wang et al^[4] showed that on admission plasma glucose >13 mmol/L was one of the no-reflow predictors.

In-hospital and long-term mortality rates are higher in elderly patients with AMI. The success rate of primary PCI in these patients is lower than in younger patients because of delayed hospitalization and increased co-morbidities. Diffuse coronary atherosclerosis, severe vascular calcification, distal microembolization

and microcirculation dysfunction are more common in the elderly patients. These pathological changes are related to advanced age, and absence of ischemic preconditioning and collateral circulation, and altered neurohormonal and autonomic influences. They may contribute to distal embolization during primary PCI, resulting in no-reflow.^[5,6]

Delayed reperfusion (a long duration from onset to reperfusion) is related to no-reflow. Our study demonstrates that patients with a long duration of reperfusion (>6 hours) had a significantly greater thrombus burden and a 1.3-fold increase in no-reflow rate than patients with a short duration of reperfusion. Myocardial necrosis occurs in about 6 hours after the appearance of coronary occlusion. As reported, prolonged ischemia leads to edema of distal capillary beds, swelling of myocardial cells, neutrophil plugging, alterations of capillary integrity, and disruption of microvascular bed,^[7] which contribute to the pathogenesis of no-reflow.^[8] In the early stages of AMI, the thrombus is rich in thrombocytes and relatively easier to lyse adjunctive pharmacotherapy. With a longer duration to reperfusion, the thrombus takes on more erythrocytes and becomes more rigid. Such thrombi tend to fragment with balloon dilatation, which can lead to distal coronary embolization. Furthermore, delayed reperfusion results in an older well-organized intracoronary thrombus. This may increase the risk of distal embolization during primary PCI and reduce the likelihood of achieving TIMI 3 flow after the procedure.^[9] Yip et al^[10] demonstrated that in patients with AMI who had a high thrombus burden, the rate of no-reflow was lower than in those with reperfusion less than 4 hours. This indicates the possible correlation of a thrombus burden with the duration of reperfusion. In case of a long duration of reperfusion and a high thrombus burden, the use of a distal protection device

Table 3. Independent predictors of no-reflow phenomenon shown by univariate and multivariate analyses

Variables	Univariate analysis		Multivariate analysis	
	<i>P</i> value	<i>OR</i> (95%CI)	<i>P</i> value	<i>OR</i> (95%CI)
Age (>65 yr)	<0.0001	1.884 (1.830–1.980)	0.007	1.470 (1.460–1.490)
Reperfusion time (>6 hours)	0.005	1.564 (1.362–1.872)	0.001	1.270 (1.16–1.40)
SBP on admission <100 mmHg	0.005	1.570 (1.390–1.850)	0.004	1.910 (1.018–3.896)
IABP use before PCI	0.003	1.879 (1.152–3.172)	0.011	1.949 (1.160–3.253)
Initial TIMI flow (0–1)	0.002	1.112 (1.083–1.236)	<0.001	1.100 (1.080–1.250)
High thrombus burden	0.020	1.423 (1.062–1.854)	0.030	1.600 (1.470–2.760)
Long target lesion	0.027	1.269 (1.156–1.405)	0.019	1.948 (1.908–1.990)

OR: odds ratio; CI: confidence interval. Variables entered univariate analysis were age, reperfusion time, SBP on admission, Killip classes, IABP use before PCI, type of occlusion, target lesion length, thrombus burden, initial TIMI flow, reference diameter, and method of reperfusion. Killip classes, type of occlusion, reference diameter, and method of reperfusion were not included in multivariate analysis because they did not have a P value <0.05 in univariate analysis.

may improve myocardial reperfusion by alleviating the adverse effects of organized thrombus.^[26] In addition, no-reflow may occur even in patients with AMI who have a low thrombus burden and a long reperfusion time. In that case, the material potential to embolize is small, extended ischemia can disrupt the microvascular bed, and the degree of this disruption is known to be a key factor in the pathogenesis.^[11]

Patients who had a low (≤ 1) TIMI flow in the IRA prior to PCI had a higher rate of no-reflow than those with good (≥ 2) TIMI flow on baseline angiography. De Luca et al^[12] found that pre-PCI good TIMI flow was strongly related to post-procedural TIMI 3 flow, myocardial blush grade 2–3 and lower enzymatic infarct size. Good patency of the IRA prior to PCI suggests a lower thrombus burden, spontaneous endogenous lysis of the thrombus, resolution of vasospasm and smaller infarct size. Thus, treatment of AMI should focus on the patency of the IRA and achieving a sustained antegrade blood flow as soon as possible. Although primary PCI is superior to thrombolytic therapy in achieving a TIMI 3 flow, its main limitation is the time delay on transferring patients or social problem. If a delayed primary PCI is expected, platelet glycoprotein IIb/IIIa receptor antagonists or low dose thrombolytic drugs in the early phase of AMI should be administered to restore early IRA patency and increase the chances of achieving a post-procedural TIMI 3 flow.^[13]

Lee et al^[14] reported that a systolic BP (SBP) < 120 mmHg in patients with AMI was associated with a higher mortality than in those with SBP > 120 mmHg. A previous study showed that a low SBP < 120 mmHg decreased coronary blood flow (CBF), collateral blood flow, and increased infarct size.^[15] Their findings showed that low normal BP is associated with decreased CBF. Furthermore, the decreased CBF accelerates leukocyte accumulation, increases trapping leukocytes in capillaries, adhesion of leukocytes in venules, and no-reflow.^[16]

AMI patients with cardiogenic shock and Killip class 3 on admission generally needed IABP supported primary PCI, and these patients had a higher no-reflow rate after the procedure. Killip class ≥ 3 on admission may be resulted from a larger infarction caused by severe damage to the microvascular bed as well as decreased coronary perfusion pressure. This explains why the patients using IABP had a higher no-reflow rate. A study^[17] demonstrated that cardiac cells in the no-reflow area were swollen and that the capillary endothelium was damaged and exhibited regional swelling with large intraluminal

protrusions. Thus we consider that cellular edema and cell contracture compressing the capillaries may contribute to microvascular compression. A higher rate of distal embolization was found in patients with advanced Killip class, which may partially explain no-reflow in these patients.^[18]

Acute coronary syndromes result from plaque rupture or fissuring with superimposed thrombus formation. Microvascular embolization of plaque material and thrombus can be seen spontaneously or iatrogenically during PCI.^[19] Claeys et al^[20] reported if the distal embolism of thrombus plugging the capillary lumen was $> 50\%$, decreased irreversible myocardial perfusion developed. The diameter of thrombi related to microvascular malfunction did not exceed $200 \mu\text{m}$. Apart from distal embolism, thrombus can lead to impairment of autoregulation and be accompanied by local release of vasoconstrictors and cardiac sympathetic reflexes with microvascular dysfunction. These changes are related to angiographic no-reflow. Watanabe et al^[21] investigated preinterventional intravascular ultrasound (IVUS) findings, and they suggested a possible relationship between lipid-rich plaque and no-reflow. Tanaka et al^[22] used IVUS to examine plaque burden and identified a higher lipid content in the plaque inner core and width of the external elastic membrane as independent markers for the no-reflow phenomenon. Our study demonstrates that large lesioned vessels, especially those with the IRA diameter above 4 mm , increased the occurrence of no-reflow. Patients with a lesion larger than 20 mm were more likely to develop no-reflow after primary PCI than those with a lesion larger than $< 20 \text{ mm}$. Large vessels are able to contain large amounts of plaque lipid or thrombus. The larger the lesioned vessels, the slower the flow velocity. The longer the target lesion, the larger amount of thrombus and plaque burden. This would explain the high risk for slow/no-reflow observed in these patients after primary PCI.^[23,24]

In summary, the pathogenesis of no-reflow is complex and multifactorial. The possible mechanisms associated with no-reflow include swelling of myocardial cells compressing microvascular vessels, swelling of capillary endothelium with large intraluminal protrusions to plug the capillary lumen, contracture of myocardial cells compressing the capillaries, accumulation of neutrophils plugging in the microvasculature, embolization of capillaries caused by platelet aggregation, microthrombi, plaque lipid fragment, microvascular bed disruption, capillary spasm and dysfunction, and reperfusion injury. Patients

with advanced age, delayed reperfusion, low SBP on admission, IABP use before PCI, low TIMI flow and/or high thrombus burden on baseline angiography and long target lesions are at an increased risk for no-reflow development. Pharmacologic agents i.e., adenosine, verapamil, platelet glycoprotein IIa/IIIb antagonists, nitroglycerin, sodium nitroprusside have favorable effects on microvasculature, and they may be of value for no-reflow development. In patients, the use of a distal protection device or aspiration thrombectomy has favorable effects. In our study, we achieved TIMI 3 flow in the IRA after predilation, yet the same patients developed no-reflow after stent implantation. So, it is important to avoid or minimize trauma to the vessel, avoid repetitive balloon dilatations and use the shortest stent if possible. In recent years, it has been shown that coronary stent implantation without predilation is feasible and can be performed safely in selected patients with AMI.^[25] Because most patients with AMI have a combination of these factors, combined treatment strategies should be preferred.

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Conflicts of interest: The authors declare that there is no conflict of interest.

Contributors: Zhou H proposed the study, analyzed the data and wrote the first draft. All authors contributed to the design and interpretation of the study and to further drafts.

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