Predictors and Long-term Prognosis of Angiographic Slow/No-Reflow Phenomenon During Emergency Percutaneous Coronary Intervention for ST-Elevated Acute Myocardial Infarction

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ABSTRACT

Objective: Angiographic slow/no-reflow during emergency percutaneous coronary intervention (PCI) in patients with ST-elevated acute myocardial infarction (AMI) may result in unfavorable outcomes. The aim of our study was to investigate the clinical factors and angiographic findings that predict slow/no-reflow phenomenon and the long-term prognosis of AMI patients with angiographic slow/no-reflow.

Methods: A total of 210 consecutive AMI patients, who underwent primary PCI within 12 hours of symptom onset were divided into a normal flow group (thrombolysis in myocardial infarction [TIMI] flow grade 3, n = 169) and a slow/no-reflow group (≤TIMI flow grade 2, n = 41), based on cineangiograms performed during PCI.

Results: A total of 41 patients (19.5%) developed slow/no-reflow phenomenon. Univariate analysis showed that delayed reperfusion, high thrombus burden on baseline angiography, and acute hyperglycemia all correlated with slow/no-reflow ($P < 0.05$ for all). Multivariate analysis revealed that hyperglycemia on admission (≥10 mmol/L; odds ratio [OR]: 1.7, 95% confidence interval [CI]: 1.423–2.971, $P = 0.012$), reperfusion time (≥6 h; OR:1.4, 95% CI: 1.193–1.695, $P = 0.040$), and high thrombus burden (OR: 1.6, 95% CI: 1.026–2.825, $P = 0.031$) were significant and independent predictors of angiographic slow/no-reflow. The 6-month mortality and incidence of major adverse cardiac and cerebrovascular events (MACCE) were significantly higher in the slow/no-reflow group than in the normal flow group. Angiographic slow/no-reflow was independently predictive of MACCE (hazard ratio [HR]: 2.642, 95% CI: 1.304–5.932, $P = 0.028$).

Conclusion: Delayed reperfusion, high thrombus burden on baseline angiography, and blood glucose level on admission can be used to stratify AMI patients into a lower or higher risk for angiographic slow/no-reflow during PCI. In addition, angiographic slow/no-reflow predicts an adverse outcome in AMI patients.

Introduction

The aim of treatment for ST-elevation acute myocardial infarction (AMI) is to restore full antegrade blood flow into the infarct-related artery (IRA) and minimize ischemic damage to the myocardium. Thrombolytic therapy is an option, but primary emergency percutaneous coronary intervention (PCI) is the treatment of choice, based on lower rates of recurrent ischemia or infarction and good success rates in restoring antegrade blood flow in the IRA.[1,2] The beneficial effects of stents for patients with AMI have been reported,[3] but these effects have been limited because of a 14% to 25% incidence of slow/no-reflow phenomenon detected during angiography.[4,5] Several studies have demonstrated that AMI patients with angiographic slow/no-reflow have poor functional recovery and more frequently manifest post-AMI complications in comparison to those with good flow.[4,6–9]

Previous studies have shown that thrombus formation or large plaque burden and blood serum markers of inflammation, such as C-reactive protein, peripheral white blood cell count, or plasma glucose level could predict the development of angiographic slow/no-reflow in patients who have had an acute coronary event.[10–15]

Methods to predict effectively the development of angiographic slow/no-reflow have not yet been established. The purpose of this study was to investigate clinical and angiographic features that could effectively predict angiographic slow/no-reflow prior to PCI and also to predict the long-term prognosis for patients with AMI.

Methods

Study Population

Between April 2007 and July 2008, 210 consecutive AMI patients, who were admitted within 12 hours after the onset

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of symptoms, underwent an emergency PCI at the Department of Cardiology, Xuanwu Hospital, Capital Medical University, Beijing China. Acute myocardial infarctions were defined by the following characteristics: chest pain consistent with any ongoing myocardial ischemia persisting longer than 30 minutes, ischemic electrocardiographic changes, and a greater than 3-fold increase in serum creatine kinase levels. This study excluded patients with a history of recent surgery or trauma within the preceding 2 months, renal insufficiency (creatinine >106 mmol/L), malignancy or liver cirrhosis, febrile disorders, acute or chronic inflammatory disease on study entry or history of recent infection, previous myocardial infarction, those with AMI onset >12 hours, those patients in whom antiplatelet agents had been used for more than 3 days before AMI, and cardiogenic shock patients.

Study Protocol

We performed coronary angiography using the right brachial or femoral approach to determine the culprit lesion. Percutaneous coronary intervention was performed as a reperfusion therapy in all AMI patients: coronary stents were used in 201 patients and conventional balloon angioplasty in 9 patients. During the study period, drug eluting stents were used in all patients. The IRA was the only target of the procedure. Angiographic slow/no-reflow during PCI was defined as thrombolysis in myocardial infarction (TIMI) flow grade ≤2 during the procedure without evidence of dissection, stenosis, or vasospasm. The TIMI flow grades were determined by the consensus of 3 investigators. Angiographic criteria of a <50% residual stenosis and TIMI flow grade 3 were used to determine the end of the interventional procedure.

Clopidogrel (300 mg preoperative loading dose, then 75 mg/d) was given for at least 1 year to patients. Aspirin (orally 100 mg/d) was given to each patient indefinitely. Low-molecule-weight heparin was injected subcutaneously to all patients for 7 days after PCI. Patients with angiographic slow/no-reflow phenomenon were injected with intracoronary nitroglycerin through a guiding catheter during the operation several times and were given, by drip IV, unfractionated heparin for 2 days continuously. Only 4 patients were given platelet glycoprotein IIb/IIIa inhibitor (tirofiban [Wuhan Grang Pharmaceutical Group, China]).

Blood samples for measuring white blood cell count, C-reactive protein (CRP), low-density lipoprotein cholesterol (LDL-C), and glucose were taken from a peripheral vessel in the cardiac intensive care unit before the administration of any medication. Left ventricular ejection fraction was measured with Doppler echocardiography during the 3 days after acute myocardial infarction. The angiographic morphologic features of the IRA that indicate high burden thrombus formation is defined as[16]: (1) an angiographic thrombus with its greatest linear dimension greater than 3-fold the reference lumen diameter (RLD); (2) a cut off pattern (ie, lesion morphology with an abrupt cut off without tapering before the occlusion); (3) the presence of accumulated thrombus (>5 mm of linear dimension) proximal to the occlusion; (4) the presence of floating thrombus proximal to the occlusion; (5) persistent dye stasis distal to the obstruction; and (6) RLD of the IRA ≥4.0 mm.

Clinical Follow-up

Patients in this study were followed up at 6 month intervals after the AMI event. Clinical information regarding major adverse cardiac and cerebrovascular events (MACCE), including any cardiac death, development of heart failure requiring hospitalization, or ischemic stroke, was obtained from telephone interviews or outpatient follow-up with patients and hospital records. Heart failure was defined as a hospital readmission for which heart failure was the primary reason. Ischemic stroke was defined as a new focal neurological deficit of sudden onset lasting ≥24 hours that was not caused by hemorrhage with corroborative imaging evidence by computed tomography or magnetic resonance imaging. Oral medication, such as aspirin, clopidogrel, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, β-blocker, statins, or nitrate esters were recorded in most of patients during the follow-up.

Statistical Analysis

Data are expressed as mean ± SD or frequency. The comparison of the data between the 2 groups was performed by an unpaired t test for continuous variables and by a χ^2 test or Fisher exact test for discrete variables. Multivariate logistic regression models were used to determine the predictors of angiographic slow/no-flow. Cox multivariate analysis was used to determine whether angiographic slow/no-reflow was related to outcomes. All $P < .05$ were considered statistically significant. Analyses were done using the statistical software SPSS 11.0 (SPSS, Inc., Chicago, IL).

Results

Patient Characteristics

Among the 210 patients who underwent PCI, angiographic slow/no-reflow during PCI occurred in 41 patients (19.5%) and did not occur in 192 (80.5%). The baseline clinical and angiographic characteristics are shown in Table 1. The plasma glucose level and LDL-C on admission and age were higher in the patients with angiographic slow/no-reflow than in those without (12.4 ± 7.5 mmol/L vs 8.7 ± 4.1 mmol/L, $P = .012$; 3.5 ± 1.1 mmol/L vs 2.9 ± 0.9 mmol/L, $P = .016$; 67.1 ± 14.9 y vs 61.1 ± 12.3 y, $P = .031$, respectively). Time to reperfusion in the patients with angiographic slow/no-reflow was longer than in the patients with normal flow (6.7 ± 3.2 h vs 5.4 ± 2.8 h, $P = .037$). There were more patients with high thrombus burden in angiographic slow/no-reflow than in those without (73.3% vs 35.2%). Left ventricular ejection fraction in the

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Table 1. Baseline Clinical and Angiographic Characteristic

	Normal Flow Group (n = 169)	Slow/No-Reflow Group (n = 41)	*P* Value
Age (yrs)	61.1 ± 12.4	67.1 ± 14.9	0.031
Male sex	103 (60.8%)	29 (70.0%)	0.494
Hypertension	79 (46.7%)	25 (60.5%)	0.968
Hyperlipidemia	80 (47.2%)	23 (55.4%)	0.174
Current smoker	95 (56.3%)	25 (61.5%)	0.711
Diabetes mellitus	26 (15.6%)	8 (19.5%)	0.635
Left ventricular ejection fraction (%)	56.9 ± 8.1	45.5 ± 7.2	0.025
Time to reperfusion (h)	5.4 ± 2.8	6.7 ± 3.2	0.037
WBC count on admission (/mm^3)	10 484 ± 2716	10 562 ± 3075	0.901
CRP on admission (mmol/L)	5.7 ± 4.3	5.9 ± 5.4	0.861
Glucose on admission (mmol/L)	8.7 ± 4.1	12.4 ± 7.5	0.012
Peak creatine kinase levels (IU/L)	320.2 ± 2570	408.9 ± 2117	0.582
LDL-C (mmol/L)	2.9 ± 0.9	3.5 ± 1.1	0.016
In-hospital medication			
Aspirin	161 (95.2%)	40 (97.3%)	0.404
ACEI or ARB	129 (76.4%)	27 (65.6%)	0.105
Clopidogrel	161 (95.4%)	40 (98.2%)	0.334
Statins	160 (94.5%)	40 (98.2%)	0.662
β-Blockers	155 (91.5%)	36 (86.6%)	0.434
Infarct vessel			
LAD	92 (54.4%)	19 (46.7%)	0.773
LCX	19 (11.2%)	5 (13.3%)	0.984
RCA	58 (34.4%)	16 (40.0%)	0.907
TIMI flow grade 0 at baseline	114 (67.2%)	31 (76.7%)	0.314
Multivessel coronary disease	52 (31.1%)	10 (25.2%)	0.623
Stent implantation	161 (95.2%)	40 (97.3%)	0.944
Inflation pressure (atm)	11.2 ± 2.8	10.8 ± 1.2	0.607
High thrombus burden	59 (35.2%)	30 (73.3%)	0.001
MACCE	9 (5.6%)	7 (16.7%)	0.039

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CRP, C-reactive protein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular events; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction, WBC, white blood count.

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patients with angiographic slow/no-reflow was lower than in patients with normal flow (45.5 ± 7.2 vs 56.9 ± 8.1). However, there were no significant differences between the 2 groups with regard to white blood cell count, C-reactive protein values on admission, peak serum creatine kinase levels, or TIMI flow grade 0 at baseline.

Predictors of Angiographic Slow/No-Reflow

The independent predictors of angiographic slow/no-reflow are shown in Table 2. Multivariate logistic regression analysis revealed that hyperglycemia on admission (≥10 mmol/L; odds ratio [OR]: 1.7, 95% confidence interval [CI]: 1.423–2.971, $P = .012$), reperfusion time (≥6 h; OR: 1.4, 95% CI: 1.193–1.695, $P = .040$), and high thrombus burden (OR: 1.6, 95% CI: 1.026–2.825, $P = .031$) were significant and independent predictors of angiographic slow/no-reflow.

Long-term Outcomes and Predictors of MACCE

The 6-month follow-up was completed in all the patients, and during this time, MACCE occurred in 15 patients; 7 patients died of cardiogenic events (cardiac rupture, severe heart failure, sudden cardiac death, or myocardial reinfarction), 3 developed heart failure requiring hospitalization, and 5 had ischemic strokes. The incidence of MACCE during the 6-month follow-up period was significantly higher in the slow/no-reflow group compared with the normal flow group. Table 3 lists the results of the multivariate Cox analysis. The only parameters associated with MACCE were age, left ventricular ejection fraction, and angiographic slow/no-reflow.

Discussion

The results of the present study suggest that the rate of no-reflow phenomenon after primary PCI was 19.5%, which was consistent with previously published no-reflow rates of 5% to 25%[8,17] and angiographic slow/no-reflow phenomenon is a marker of cardiac risk in AMI patients. In the results of the multivariate analysis, the independent predictors of angiographic slow/no-reflow were plasma glucose on admission, reperfusion time, and high thrombus burden. We found no relationship between white blood cell count, CRP level, age, plasma LDL-C level, or TIMI flow grade 0 at baseline with angiographic slow/no-reflow.

Several previous reports have suggested that hyperglycemia is associated with an impairment of microvascular function and can cause angiographic slow/no-reflow.[14,15,18] In this study, we found angiographic slow/no-reflow occurred more frequently in patients with acute hyperglycemia on admission. Several mechanisms could explain the association between hyperglycemia and angiographic slow/no-reflow. Acute hyperglycemia aggravates platelet dependent thrombus formation,[19] attenuates endothelium dependent vasodilatation,[20] and reduces collateral blood flow by adversely affecting nitric oxide availability.[21] These changes are associated with impairment in microvascular function before reperfusion and are related to angiographic slow/no-reflow.

In our study, patients with a long reperfusion time (≥6 h) had a significantly greater thrombus burden and a 1.4-fold increase in no-reflow rates than patients with short reperfusion times. It is well established that prolonged ischemia leads to edema of distal capillary beds, swelling of myocardial cells, neutrophil plugging, and alterations of capillary integrity.[22,23] Furthermore, delayed reperfusion can result in an older, more organized intracoronary thrombus,[24] which may increase the risk of distal embolization during primary PCI and reduce the likelihood of achieving TIMI flow grade 3 after the procedure. Yip et al[16] demonstrated that among patients with high thrombus burden, the rate of no-reflow phenomenon was lower in the subgroup with reperfusion time <4 hours.[25] In the early stages of AMI, the thrombus is rich in thrombocytes and relatively easier to treat with adjunctive pharmacotherapy. With a longer time to reperfusion, the thrombus takes on more and more erythrocytes and becomes more firm. Such thrombi tend to fragment with balloon dilatation, which can lead to distal embolization and

Table 2. Independent Predictors of Slow/No-Reflow Phenomenon in Multivariate Analysis

	OR (95% CI)	*P* Value
High thrombus burden	1.6 (1.026–2.825)	0.031
Reperfusion time (≥6 h)	1.4 (1.193–1.695)	0.040
Plasma glucose on admission (≥10 mmol/L)	1.7 (1.423–2.971)	0.012
Low-density lipoprotein cholesterol (≥2.6 mmol/L)	1.1 (0.923–1.246)	0.079

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3. Cox Proportional Hazards Analyses of Independent Predictors for MACCE

	Hazard Ratio (95% CI)	*P* Value
Age (yrs)	1.090 (1.010–12.340)	0.032
Angiographic slow/no-reflow	2.642 (1.304–5.932)	0.028
Left ventricular ejection fraction (%)	1.924 (1.324–2.125)	0.030
High thrombus burden	2.359 (2.032–9.324)	0.075
Plasma glucose on admission (mmol/L)	1.005 (0.984–1.120)	0.322
Time to reperfusion (hr)	0.93 (1.823-1.132)	0.554

Abbreviations: CI, confidence interval.

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could explain why the no-reflow phenomenon occurs less frequently in cases of early reperfusion.

Previous studies have shown that the use of intravascular ultrasound before PCI allowed the detection of thrombus formation or large plaque burden that could predict the development of angiographic slow/no-reflow in patients who have had an acute coronary event.[10,11] It is well-known that acute coronary syndromes almost always result from plaque rupture or fissuring with superimposed thrombus formation. Microvascular embolization of plaque material and thrombus content can occur spontaneously or iatrogenically during the PCI procedure.[26] Watanabe et al investigated preinterventional intravascular ultrasound (IVUS) findings and their results suggest a possible relationship between lipid-rich plaque and the no-reflow phenomenon.[27] Also, Tanaka et alused IVUS to examine plaque burden and identified higher lipid content in the plaque inner core and width of the external elastic membrane as independent markers for the no-reflow phenomenon.[10] Those studies indicate that not only thrombus burden but also plaque material determines the development of slow/no-reflow phenomenon.

The clinical presentation of angiographic slow/no-reflow during the short-term intervention in myocardial infarction patients is often sudden and dynamic. Angiographic slow/no-reflow has also been linked to ventricular arrhythmias,[28] early congestive heart failure, left ventricular remodeling,[9] and even cardiac rupture.[29] Patients who develop heart failure after surviving AMI have a markedly increased risk of death compared with patients who do not develop heart failure.[30] The Cholesterol And Recurrent Events (CARE) study[31] reported several factors that are important independent predictors of heart failure development in long-term myocardial infarction survivors, including age, history of hypertension, history of myocardial infarction, diabetes mellitus, and left ventricular ejection fraction. Our study found that age and left ventricular ejection fraction is the predictor of MACCE which is related to heart failure. We also showed that MACCE in the slow/no-reflow group was higher than that in the normal flow group during the 6-month follow-up.

There were several limitations to our study. First, this was a single-center, nonrandomized, and retrospective study with a relatively small number of patients. We did not perform a glucose tolerance test in patients without any history of diabetes mellitus or a high HbA_{1c} value, nor did we analyze serum insulin, catecholamine, or free fatty acid levels which may have provided important additional information. Second, myocardial contrast echocardiography, ST-segment resolution, and angiographic "blushing" scores may provide a more meaningful assessment of reperfusion efficacy than the TIMI flow grade, using the TIMI flow grade to analyze this was still the most common assessment for reperfusion. Third, we did not use IVUS to quantitatively evaluate thrombus burden and plaque content. However, IVUS can prolong a PCI procedure and is more expensive than conventional primary PCI. Fourth, because the study is retrospective, there was only 1 follow-up done, mainly by telephone in January 2009. No accurate times of MACCE were recorded, so a Kaplan-Meier survival analyses was not performed.

In conclusion, patients with delayed reperfusion, high thrombus burden on baseline angiography, and high blood glucose level on admission are at increased risk for slow/no-reflow development. In addition, angiographic slow/no-reflow predicts an adverse outcome in AMI patients.

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