Predicting No-reflow Based on Angiographic Features of Lesions in Patients with Acute Myocardial Infarction

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Objectives: We tried to elucidate angiographical predictors of no-reflow and to determine a preferable recanalization therapy based on the morphology of lesions. Methods: Seventy-six patients were randomly assigned into groups to receive primary angioplasty (n = 41) or intracoronary thrombolysis (n = 35). Based on angiography, occlusive infarct-related lesions were divided into thrombus-rich and hard plaque lesions. The outcome of the two therapies used for each lesion was compared. Results: The incidence of no-reflow was higher in the thrombus-rich than hard plaque lesions (38 percent vs. 0 percent, p = 0.006); the left ventricular ejection fraction in the chronic phase was lower (46 ± 6 percent vs. 55 ± 5 percent, p < 0.001) for primary angioplasty than thrombolysis. No-reflow was not observed in the hard plaque lesions. However, the incidence of additional reperfusion therapy (88 percent vs. 8 percent, p < 0.001) was higher in the patients who underwent thrombolysis rather than primary angioplasty. Conclusions: We suggest that thrombus-rich lesions in primary angioplasty may predict no-reflow in acute myocardial infarction, and thrombolysis prior to angioplasty may be preferable for these lesions. We also suggest that primary angioplasty may be more effective than thrombolysis for hard plaque lesions. J Atheroscler Thromb, 2005; 12: 315–321.

Key words: Primary angioplasty, Thrombolysis, No-reflow phenomenon, Lesion morphology

Introduction

In acute myocardial infarction (AMI), reperfusion therapy is important for the preservation of cardiac function and improving prognosis. Interventional reperfusion therapies such as primary percutaneous transluminal coronary angioplasty (PTCA) and stenting for patients with AMI have become established in recent years (1). Such therapies help in salvaging the ischemic myocardium and contribute toward improving the prognosis. Previous studies (2–5) have reported that primary PTCA is superior to intracoronary thrombolysis (ICT) in AMI. However, recent studies have disclosed that no-reflow occurs frequently during interventional treatment for AMI and can lead to poor left ventricular function (6–9). This phenomenon may be attributed to coronary thrombus in certain cases. As a result, intracoronary thrombus aspiration therapy (10) and antecedent intravenous thrombolysis have recently received more attention than primary PTCA (11). Accordingly, these antithrombotic procedures have been regarded as important for successful interventional revascularization. However, few reports have elucidated the angiographical features that are frequently complicated by the occurrence of no-reflow.

To identify predictors of no-reflow in reperfusion therapy, we hypothesized that the occurrence of no-
reflow depends on the angiographic features of lesions. Given this viewpoint, at least two types of infarct-related lesions were observed in AMI, one mainly composed of thrombi and the other comprising hard plaques. We presumed that primary PTCA performed for the former type of lesion would be complicated by a high incidence of no-reflow. The purpose of this prospective study was to elucidate angiographical predictors of no-reflow and to determine the most appropriate recanalization therapy based on the morphology of lesions in patients with AMI.

Methods

Study design and patients

Between September 1993 and April 1995, 76 consecutive Japanese patients (56 men and 20 women) were prospectively enrolled for this study; they were admitted to the Health Insurance Nankai Hospital within 6 hours of the onset of symptoms. Prior to an emergency angiography, these patients were randomly assigned to groups to receive primary PTCA or ICT. The randomization of the assignment was achieved using the envelope method. Interventional reperfusion therapy was performed after coronary arteriography. Patients in whom angiography or thrombolysis was contraindicated, those without total coronary occlusion, and those with antecedent systemic thrombosis were excluded from the study. Patients with cardiogenic shock or left main trunk lesion were also excluded.

AMI was diagnosed based on a combination of ≥ 20 minutes of ischemic symptoms unrelieved by sublingual nitroglycerin (0.3 mg) and ST-segment elevation of ≥ 1 mV on the electrocardiogram in at least two contiguous leads. Upon admission, all patients or their families gave written informed consent to interventional therapies and to participate in the study. The study protocol was approved by the ethics committee of the Health Insurance Nankai Hospital.

In the thrombolysis group, the patients initially underwent ICT, and rescue PTCA was performed when an optimal result (TIMI grade 3) was not obtained. Angioplasty was initially performed in patients in the primary PTCA group. Additional thrombolysis or stent implantation was performed when successful recanalization or optimal result was not obtained.

An emergency coronary angiography via the femoral approach was performed using a 6-French diagnostic catheter (Judkins or Amplatz type) with a non-ionic contrast medium. Prior to angiography, 162 mg of aspirin was administered orally and 3,000 units of heparin and 5 mg of isosorbide dinitrate were administered intravenously. Multi-directional cineangiograms (CAS-CP-4S; Toshiba, Inc., Tokyo) and digital subtraction angiograms (DSA; DFP-1000A, Toshiba, Inc., Tokyo) of the infarct-related artery were recorded.

Based on the angiography, the infarct-related lesions were divided into the following four types: filling defect, fade-out, tapered, and abrupt type closures (Fig. 1). We defined the former two as thrombus-rich lesions and the latter two as hard plaque lesions. Following interventional therapy, two cardiologists who were unaware of the study protocol separately classified the morphology of the lesions of study patients.

In the thrombolysis group, after the multi-directional coronary angiography, 20 ml of saline containing 1.6 × 10^6 units of tissue plasminogen activator (t-PA, Plasvata®, ASAHI CHEMICAL INDUSTRY CO., LTD., Tokyo) was administered intracoronarily through the diagnostic catheter positioned in the infarct-related artery every 10 minutes. A cineangiogram was obtained after each infusion of t-PA. The ICT was terminated when the total dose of t-PA reached 6.40 × 10^6 units or when successful recanalization was obtained prior to the maximum dose. Additionally, the patients with unsuccessful thrombolysis (TIMI 0, 1, and 2) were treated with rescue PTCA.

Primary PTCA was performed following the diagnostic coronary angiography with an additional intravenous injection of 5,000 units of heparin. The devices used during the procedure included an 8-French Judkins’ or Amplatz type guiding catheter, an intracoronary guide wire (0.014 inches in diameter), and 2.5 to 4.0 mm angioplasty balloons. Successful PTCA was defined as the achievement of a TIMI grade-3 flow and the absence of major coronary dissection. We evaluated the procedure time, which was defined as the time taken from the start of catheterization to successful reperfusion.

The outcome of the two therapies was compared based on the incidence of no-reflow, read for additional interventional therapies, procedure time, final angiographical success, incidence of congestive heart failure (CHF), left ventricular ejection fraction (LVEF) during the chronic phase, hemorrhagic complications, the incidence of reinfarction, and in-hospital mortality rate. The LVEF was assessed echocardiographically using a modified Simpson’s method four months after the onset of symptoms.

Definition

Coronary flow reduction was classified into slow flow and no-reflow. Based on the Thrombolysis in Myocardial Infarction (TIMI) trial (12), we defined a no-reflow event as being equal to TIMI grade 1, i.e., neither attributable to abrupt closure nor target lesion dissection or coronary spasm. A successful ICT is generally recognized as TIMI grade 2 or 3 (13). However, the determination of a successful ICT remains controversial. According to the TEAM-3 study (14), the clinical outcome including ejection fraction, enzyme peaks, ECG findings, and morbidity in TIMI grade-2 patients did not differ from that in grade-0 or grade-1 patients. In this study, we defined a
Lesion Morphology Predicts No-reflow

Numerical data were expressed as the mean ± standard deviation. Chi-square analysis and Fisher’s exact probability test were used to assess the difference among the categorical variables. Student’s t-test was used to assess differences in numerical data. In this study, p values less than 0.05 were considered to be statistically significant.

Results

The baseline clinical characteristics of the patients assigned to the primary PTCA and ICT groups are listed in Table 1. No significant differences were observed between the two groups in age, elapsed time from the onset of symptoms to hospitalization, underlying disease, number of diseased vessels, or infarct-related arteries. The percentage of male patients was significantly higher in the thrombolysis group than in the angioplasty group. The percentage of smokers was also significantly higher.

Successful ICT as TIMI grade 3. Slow flow or TIMI grade 2 followed a successful PTCA with no-reflow.

**Statistical analysis**

Numerical data were expressed as the mean ± standard deviation. Chi-square analysis and Fisher’s exact probability test were used to assess the difference among the categorical variables. Student’s t-test was used to assess differences in numerical data. In this study, p values less than 0.05 were considered to be statistically significant.

**Fig. 1.** Angiographical Classifications of the Infarct-related AMI Lesions.

A: The defect type thrombus-rich occlusion. The right coronary artery was occluded in segment 1 associated with the crab claw-like filling defect.

B: The fade-out type thrombus-rich occlusion. The margin of the obstructive end of the right coronary artery was unclear.

C: The tapered, hard plaque type occlusion. The shape of the obstructive end was tapered like a wedge.

D: The abrupt, hard plaque type occlusion. The right coronary artery was abruptly occluded in segment 1. The margin of the vascular end was clear.
Based on angiography, the subjects were divided into two groups: a thrombus-rich group (34 patients) and a hard plaque group (42 patients). Table 2 shows a comparison of the clinical outcome of primary PTCA and ICT for thrombus-rich lesions. In the group with thrombus-rich lesions, the incidence of no-reflow was higher for angioplasty than thrombolysis and the LVEF during the chronic phase and final angiographical success rate were lower. The phenomenon of no-reflow occurred in two out of six patients following insertion of the guide wire. No differences were observed between the two groups in the incidence of additional interventional therapy, procedure time, angiographical success rate, hemorrhagic complications, or the incidence of reinfarction. Two out of 16 patients developed CHF, and one died during hospitalization. However, no statistical significance was observed in the incidence of CHF or in-hospital death rate.

A comparison of the clinical outcome of primary PTCA and ICT for the hard plaque lesions is shown in Table 3. In comparison to primary PTCA, ICT for the hard plaque lesions was more frequently followed by additional recanalization therapies. The procedure lasted significantly longer with ICT than with primary PTCA. Additionally,
thrombolysis for this type of lesion results in reduced LV function during the chronic phase.

**Discussion**

Several studies have reported the factors that may cause the no-reflow phenomenon. These include embolization of the destroyed plaque and thrombi from infarct-related lesions, microvascular spasms (15), neutrophil plugging in the microvessels (16), and free oxygen radicals (17).

It has been reported that the no-reflow phenomenon in elective PTCA for degenerated saphenous vein grafts is likely to be caused by distal embolization of the destroyed plaques and thrombi (18). Thus, a thromboembolic mechanism may play an important role in the no-reflow associated with reperfusion therapy in AMI. In this study, we reported that no-reflow could be predicted based on the angiographical features of lesions. Thrombus-rich lesions may indicate no-reflow following primary angioplasty. We also suggest that the hard plaque type closure should be treated with primary angioplasty without pretreatment for the thrombus because the incidence of no-reflow is low for this type of lesion. Furthermore, when compared with thrombolysis, primary PTCA for the thrombus-rich type of lesion may lead to poor left ventricular function in convalescents. On the other hand, thrombolysis was observed to be less effective for hard plaque lesions and rescue PTCA was frequently required. Thus, in comparison with primary angioplasty, thrombolysis for such lesions was observed to involve more time for the interventional procedure. In this study, there were significant differences in the percentage of male patients and smokers between the angioplasty and the thrombolysis group. The random assignment of the study subjects was done using the envelope method, however, there was an incidental gender imbalance.

One new finding of the present study is that two angiographical obstructive patterns of infarct-related arteries are present in AMI. Another is that the efficacy of reperfusion therapy appears to depend on these patterns. Two possible mechanisms are involved in the development of AMI: the formation of thrombus-rich lesions caused by the disruption of vulnerable plaques with injury to the endothelium or sustained coronary vasospasm (19), and the closure of an extremely severe stenotic coronary lesion of Ambrose type II or I (20). Primary angioplasty for the first type of lesion does not appear to be effective and may be harmful if the thrombus migrates into the distal coronary artery. The second type of lesion may develop into a hard plaque. The most appropriate revascularization therapy for this type of lesion appears to be primary angioplasty without thrombolytic therapy.

The morphology of infarct-related lesions prior to the onset of myocardial infarction is an interesting issue because it is deeply concerned with the mechanisms of acute coronary syndrome. Ambrose et al. (21) reported that myocardial infarction frequently develops from non-severe lesions. One of the most important mechanisms of myocardial infarction is the disruption of vulnerable plaque (22). Vulnerable plaques break easily before they grow into severely stenotic lesions, and the arteries are subsequently occluded by the plaques and thrombi. In the present study, we suggest that the thrombus-rich lesions can be attributed to vulnerable plaques. On the other hand, following thrombolysis, advanced residual stenoses may often exist in hard plaque lesions. The lesions in the hard plaque group may be attributable to highly advanced organic plaques.

Recent reports (23, 24) showed that the findings of

<table>
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<th>Variable</th>
<th>Angioplasty (n = 25)</th>
<th>Thrombolysis (n = 17)</th>
<th>p value</th>
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<td>No-reflow phenomenon (%)</td>
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<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Additional interventional therapy (%)</td>
<td>Stent 2 (8)</td>
<td>r-PTCA 15 (88)</td>
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<td>Procedure time (min)</td>
<td>81 ± 17</td>
<td>135 ± 25</td>
<td>&lt; 0.001</td>
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<td>Final angiographical success (%)</td>
<td>24 (96)</td>
<td>17 (100)</td>
<td>0.99</td>
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<td>CHF (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>LVEF(chronic phase) (%)</td>
<td>54 ± 3</td>
<td>52 ± 5</td>
<td>0.04</td>
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<td>Hemorrhagic complications (%)</td>
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<td>0.99</td>
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<td>Reinfarction (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.99</td>
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<tr>
<td>In-hospital death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.99</td>
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Angioplasty represents primary PTCA; Thrombolysis represents intracoronary thrombolysis

Some values are means ± standard deviations

r-PTCA: rescue PTCA, CHF: congestive heart failure, LVEF: Left ventricular ejection fraction
travascular ultrasound (IVUS) might be predictive of coronary no-reflow in AMI. Remodeled large vessels and plaques with an abundant lipid pool were reported to be predictors of no-reflow. These results support our data. In our study, the thrombus-rich lesions may consist of a vulnerable lipid core and thrombi that may be easily embolized to the coronary microvessels during angioplasty.

It is suggested that disruption of the intracoronary thrombus and plaque content using a guide wire and angioplasty balloons frequently induces thromboembolic no-flow. In the thrombus-rich group in our study, six patients developed no-reflow due to angioplasty, and one of the patients died of congestive heart failure. They subsequently received ICT; however, the final angiographical success rate was lower than that for the thrombolysis group. This appeared to be due to the poor delivery of the thrombolytic agent to the peripheral coronary bed upon occurrence of the no-reflow phenomenon. Therefore, distal embolic protection devices (25, 26) have received more attention recently.

**Study limitation**

The present study was performed several years ago and the strategy for PCI in AMI is now somewhat different. The number of patients enrolled was not so large. However, interventional cardiologists work out a strategy for treating with ACS taking into account findings similar to those in the present paper. Namely, their strategy is based on the accumulated data together with their own experience, information mostly not published in scientific journals. Thus the significance of the present paper resides in the fact that it summarizes our understanding of PCI in patients with ACS and lends support to interventional cardiologists. The present study also holds meaning from a historical aspect, filling a void in the history of interventional cardiology.

In conclusion, based on angiography, thrombus-rich lesions in primary angioplasty may predict the occurrence of no-reflow in patients with AMI. In such lesions, thrombolysis prior to angioplasty may be preferable. Pre-hospital intravenous coronary thrombolysis appears reasonable. Thrombus aspiration therapy and distal embolic protection devices are also useful for treating those lesions. On the other hand, primary angioplasty may be more effective than thrombolysis in the case of hard plaque lesions. Further investigation is required to elucidate the type of lesion in AMI that may require other interventional procedures such as the use of a distal protection device.

**References**


