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# Angiographic No-Reflow Phenomenon as a Predictor of Adverse Long-Term Outcome in Patients Treated With Percutaneous Transluminal Coronary Angioplasty for First Acute Myocardial Infarction

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**OBJECTIVES** We sought to elucidate the long-term prognostic importance of angiographic no-reflow phenomenon after percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction (AMI).

**BACKGROUND** Angiographic no-reflow phenomenon, a reduced coronary antegrade flow (Thrombolysis in Myocardial Infarction [TIMI] flow grade ≤2) without mechanical obstruction after recanalization, predicts poor left ventricular (LV) functional recovery and survival in the early phase of AMI. We hypothesized that angiographic no-reflow phenomenon also predicts long-term clinical outcome.

**METHODS** We studied 120 consecutive patients with their first AMI treated by PTCA without flow-restricting lesions. The patients were classified as either no-reflow (n = 30) or reflow (TIMI-3) (n = 90) based on post-PTCA cineangiograms to follow up (5.8 ± 1.2 years) for cardiac death and nonfatal events.

**RESULTS** Patients with no-reflow had congestive heart failure ($p < 0.0001$), malignant arrhythmia ($p = 0.038$), and cardiac death ($p = 0.002$) more often than did those with reflow. Kaplan-Meier curves showed lower cardiac survival and cardiac event-free survival ($p < 0.0001$) in patients with no-reflow than in those with reflow. Multivariate analyses disclosed that no-reflow phenomenon was an independent predictor of long-term cardiac death (relative risk [RR] 5.25, 95% confidence interval [CI] 1.85 to 14.9, $p = 0.002$) and cardiac events (RR 3.71, 95% CI 1.79 to 7.69, $p = 0.0004$). At follow-up, survivors with no-reflow had higher end-diastolic and end-systolic LV volume indices and plasma brain natriuretic peptide levels, and lower LV ejection fractions ($p = 0.0002$, $p < 0.0001$, $p = 0.002$, $p < 0.0001$, respectively) than did those with reflow, indicating that no-reflow may be involved in LV remodeling.

**CONCLUSIONS** Angiographic no-reflow phenomenon strongly predicts long-term cardiac complications after AMI; these complications are possibly associated with LV remodeling. (J Am Coll Cardiol 2000;36:1202–9) © 2000 by the American College of Cardiology

It is well known that early restoration of coronary antegrade flow limits the progression of myocardial necrosis; such restoration is expected to enhance the functional recovery of postischemic dysfunctioning myocardium in patients with acute myocardial infarction (AMI) (1–3). However, recent studies have demonstrated that successful reopening of an occluded epicardial coronary artery does not necessarily lead to left ventricular (LV) functional recovery; in fact, the "no-reflow" phenomenon occurs in some cases (4,5). The "no-reflow" phenomenon refers to the absence of myocardial perfusion even after successful reopening of the infarct-related artery (IRA) (6,7). This phenomenon has been evaluated by various methods, including contrast echocardiography (5,8), scintigraphy (9,10), and cineangiography (4,11) in patients with AMI. On angiograms, the no-reflow phenomenon is defined as substantial coronary antegrade flow reduction (less than Thrombolysis in Myocardial Infarction [TIMI] flow grade 3) without mechanical obstruction (12).

We previously demonstrated that the "angiographic no-reflow" phenomenon after percutaneous transluminal coronary angioplasty (PTCA) predicts poor LV functional recovery and a higher risk of cardiac mortality during the early phase of disease in patients with AMI (4). Since that report was published, the clinical importance of angiographic no-reflow phenomenon has been well investigated and established as it relates to AMI (11,13–17). However, the long-term prognosis after AMI, which is strongly associated with progressive LV dilation (18–20), remains unexplored in patients with angiographic no-reflow. Consequently, we further investigated the long-term prognostic importance of the angiographic no-reflow phenomenon after successful PTCA for AMI in terms of cardiac death and nonfatal events, and LV function and remodeling in the surviving patients.

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**Abbreviations and Acronyms**

| | |
|---|---|
| AMI | = acute myocardial infarction |
| BNP | = brain natriuretic peptide |
| CHF | = congestive heart failure |
| CK | = creatine kinase |
| IRA | = infarct-related artery |
| LV | = left ventricular |
| LVEDVI | = left ventricular end-diastolic volume index |
| LVEF | = left ventricular ejection fraction |
| LVESVI | = left ventricular end-systolic volume index |
| MI | = myocardial infarction |
| NYHA | = New York Heart Association |
| PTCA | = percutaneous transluminal coronary angioplasty |
| TIMI | = Thrombolysis in Myocardial Infarction trial |

## METHODS

**Patient population.** Of 476 consecutive patients with AMI who were treated at the Department of Cardiology of Ogaki Municipal Hospital between January 1990 and June 1994, 120 patients (79 men and 41 women) age 35 to 89 years were admitted to the study. Criteria for inclusion were: 1) initial episode of AMI; 2) a single-culprit lesion; 3) the IRA was recanalized with direct or rescue-PTCA within 6 h of the disease onset or between 6 h and 24 h if evidence showed continuing ischemia; 4) residual stenosis not more than 50%; and 5) absence of apparent dissection or thrombosis that might restrict coronary flow despite multidirectional observations on cineangiograms. Patients excluded from the study were those with concomitant severe diseases such as chronic terminal renal failure and malignancy, those with significant valvular heart disease, and those with the culprit lesion in the left main trunk.

**Assessment of angiographic no-reflow phenomenon.** Coronary angiograms were carefully reviewed by three experienced investigators who were blinded to other parameters of the patients. The TIMI flow grades were determined by the consensus of the three investigators. Patients were diagnosed as having angiographic no-reflow if they developed substantial coronary flow reduction (TIMI flow grade $\leq$2) in cineangiograms obtained at the end of PTCA (No-Reflow group) (4,11,12). The Reflow group consisted of the remaining patients with restored good coronary flow (TIMI flow grade 3) after PTCA.

**In-hospital clinical course.** Adjunctive medical therapy followed the standards of the coronary care unit. The following data were obtained: age, gender, coronary risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking), serum peak creatine kinase (CK) level, cardiac complications, repeated PTCA, cardiac surgery, and LV ejection fraction (LVEF). The serum peak CK levels were determined among the serial samples obtained upon the patient's arrival and every 4 h following recanalization of the IRA. Cardiac complications included recurrent AMI, malignant arrhythmia (excluding reperfusion arrhythmia), cardiac rupture, pump failure, and death. Malignant arrhythmia included sustained ventricular tachycardia, ventricular fibrillation, or high degree atrioventricular block. Pump failure was defined as Killip class $\geq$II or Forrester subset $\geq$II. Follow-up coronary angiography was performed preceding patients' discharge; when necessary, the patients underwent additional PTCA or coronary artery bypass graft surgery. The LVEF was determined by the last available contrast left ventriculogram during index hospitalization period.

**Long-term follow-up.** Patients were seen every month at the outpatient clinic of Ogaki Municipal Hospital. Follow-up data and cardiac function of the patients were assessed in July 1998, by which time all patients had completed the minimal follow-up period of four years (mean 5.8 $\pm$ 1.2 years).

Follow-up data included information about recurrent AMI, malignant arrhythmia, congestive heart failure (CHF) and/or unstable angina pectoris requiring hospitalization, repeated PTCA, cardiac surgery, and death. Data were obtained from hospital charts and supplemented by the patient's general physicians as well as by a structured direct interview or by a telephone interview with the patient or with one of his or her immediate relatives; the interview was conducted by cardiologists who were blinded to the patient's initial angiographic data. Deaths were classified as either cardiac or noncardiac according to the diagnosis stated on the patient's death certificate. Diagnoses were further confirmed by information from hospital charts, patients' general physicians, or by immediate relatives of the patients. No patient was lost to follow-up.

**Assessment of cardiac function of the survivors.** Cardiac function of the survivors at the end of the study was also assessed by the New York Heart Association (NYHA) functional classification, echocardiography, and plasma brain natriuretic peptide (BNP) levels. The NYHA functional class was determined by direct interview or telephone interview with patients. A single investigator blinded to both clinical and angiographic data analyzed the echocardiograms. The LV volume was measured by the area-length method (21); the volume index (volume/body surface area) and LVEF were calculated to estimate LV remodeling. Observer variability for LV volume analysis was assessed in 20 patients. The mean interobserver variabilities, which were defined as the difference between two observers' measurements, were 5.2 $\pm$ 2.8% for LV end-diastolic volume index (LVEDVI) and 6.3 $\pm$ 4.2% for LV end-systolic volume index (LVESVI). The mean intraobserver variabilities, which were assessed by two independent measurements one week apart, were 6.8 $\pm$ 3.4% for LVEDVI and 8.1 $\pm$ 3.9% for LVESVI. Plasma BNP levels were determined by a specific immunoradiometric assay kit of Shiono RIA BNP (Shionogi, Osaka, Japan). The assay uses two monoclonal antibodies that recognize the carboxyterminal sequence and the ring structure of human BNP, respectively (22). Informed consent was obtained from each patient.

**Statistics.** Continuous baseline and outcome variables are expressed as mean ± SD, whereas discrete variables are given as absolute values, percentages, or both. Continuous variables were compared with the Student two-tailed *t* test. For comparison of rates of discrete outcome variables, the chi-square test or the Fisher exact test was used. Differences between subgroups in long-term cardiac survival and cardiac event-free survival after patients' discharge from the index hospitalization were examined with the Kaplan-Meier method and associated log-rank test. The composite outcomes of the following cardiac events were employed in the analyses: cardiac death, recurrent AMI, malignant arrhythmia, and CHF requiring hospitalization. Multivariate analyses of predictors of long-term cardiac and cardiac event-free survival were performed using a Cox proportional-hazards regression model. Forward-stepwise selection method was used with inclusion criteria of a p value $<0.05$ to identify the variables remaining as independent risk factors for long-term survival. Variables included in the analyses were age ≥70 years old, gender, multivessel disease, anterior infarction, Killip class ≥II, serum peak CK levels ≥3,000 IU/liter, LVEF ≤50%, and no-reflow. Among the survivors during the index hospitalization period, those with incomplete data were excluded from the multivariate models. Patients who had already had cardiac rupture and recurrent myocardial infarction (MI) during their index hospitalization period were also excluded from the analysis of cardiac event-free survival. Finally, 111 and 109 patients were included in the multivariate analyses of cardiac survival and cardiac event-free survival, respectively. Data analyses were performed by using the statistical software Stat View 5.0 (SAS Institute Inc., 1998). A p value of $<0.05$ was accepted as statistically significant.

## RESULTS

**Patient characteristics.** Of 120 patients studied, angiographic no-reflow phenomenon was present in 30 patients (25%). Baseline and angiographic characteristics of the patients are shown in Table 1. Compared with the patients in the Reflow group, those in the No-Reflow group presented more often Killip class ≥II ($p = 0.0003$) and anterior wall infarction ($p = 0.0003$). Age, ischemic time, collateral grade, initial TIMI flow grade, and residual stenosis were not different between the two groups. The similar proportions of the no-reflow and reflow patients received angiotensin-converting enzyme inhibitor (30% vs. 19%, $p = 0.201$) and beta-blocker (0% vs. 7%, $p = 0.335$).

**In-hospital clinical course.** Peak CK levels were significantly higher in the No-Reflow group than in the Reflow group ($p < 0.0001$) (Table 2). We observed more cardiac complications, including pump failure ($p < 0.0001$), malignant arrhythmia excluding reperfusion arrhythmia ($p = 0.048$), and cardiac rupture ($p = 0.015$) in the No-Reflow group than in the Reflow group. Cardiac ruptures included LV free-wall rupture in two patients and ventricular septal perforation in one patient; the diagnosis was proven in all cases during surgical closure of the ruptured site. The LVEF was significantly lower in the No-Reflow group than in the Reflow group ($p < 0.0001$). All patients who died during their hospital stay were in the No-Reflow group; causes of death were low output syndrome in two patients and unsuccessful closure of the ruptured free wall in one patient. Thus, cardiac mortality was significantly higher in the No-Reflow group than in the Reflow group ($p = 0.015$).

**Long-term follow-up.** The clinical complications that occurred in both groups during the follow-up period are shown in Table 3. We observed a significantly higher incidence of malignant arrhythmia (excluding sudden death) ($p = 0.038$) and CHF requiring hospitalization ($p <$

**Table 1.** Baseline Clinical and Angiographic Characteristics of Patients

| | No-Reflow (n = 30) | Reflow (n = 90) | p Value |
|---|---|---|---|
| Age (yr) | 68 ± 14 | 63 ± 12 | NS |
| Male | 20 (67%) | 59 (66%) | NS |
| Risk factors | | | |
| Hypertension | 16 (53%) | 42 (47%) | NS |
| Diabetes mellitus | 8 (27%) | 25 (28%) | NS |
| Hyperlipidemia | 8 (27%) | 19 (21%) | NS |
| Smoking | 10 (33%) | 52 (58%) | 0.020 |
| Ischemic time (hours) | 6.0 ± 4.7 | 5.7 ± 5.3 | NS |
| Killip class on admission (class ≥II) | 18 (60%) | 22 (24%) | 0.0003 |
| Anterior infarction | 25 (83%) | 41 (46%) | 0.0003 |
| Initial TIMI flow grade (grade 0) | 25 (83%) | 65 (72%) | NS |
| Collaterals (Rentrop grade ≤1)* | 19 (68%) | 43 (52%) | NS |
| Multivessel coronary artery disease | 10 (33%) | 27 (30%) | NS |
| Residual stenosis (%) | 36 ± 12 | 35 ± 15 | NS |

*Collaterals were not investigated before recanalization of infarct-related artery in two patients from the No-Reflow group and in seven from the Reflow group because of their critical condition. Data are presented as the number of patients (percent) or mean value ± SD.

NS = not significant; TIMI = Thrombolysis in Myocardial Infarction trial.

**Table 2.** In-Hospital Clinical Course

| | No-Reflow (n = 30) | Reflow (n = 90) | p Value |
|---|---|---|---|
| Peak CK (IU/liter)* | 4,271 ± 3,111 | 2,362 ± 1,595 | < 0.0001 |
| Recurrent AMI | 1 (3%) | 0 (0%) | NS |
| Malignant arrhythmia | 3 (10%) | 1 (1%) | 0.048 |
| Cardiac rupture | 3 (10%) | 0 (0%) | 0.015 |
| Pump failure | 24 (80%) | 31 (34%) | < 0.0001 |
| Repeated PTCA | 1 (3%) | 18 (20%) | 0.041 |
| LVEF (%) | 51.7 ± 15.1 | 64.4 ± 10.3 | < 0.0001 |
| Cardiac surgery | 3 (10%)† | 2 (2%)‡ | NS |
| Cardiac death | 3 (10%) | 0 (0%) | 0.015 |

*Data were excluded regarding patients who underwent cardioversion before identification of peak creatine kinase levels (three patients in each group). †Closure of cardiac rupture; ‡coronary artery bypass graft surgery. Data are presented as the number of patients (percent) or mean value ± SD.

AMI = acute myocardial infarction; CK = creatine kinase; LVEF = left ventricular ejection fraction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

**Table 3.** Cardiac Complications During Long-Term Follow-up

| | No-Reflow (n = 27) | Reflow (n = 90) | p Value |
|---|---|---|---|
| Recurrent AMI | 5 (19%) | 14 (16%) | NS |
| Malignant arrhythmia | 3 (11%) | 1 (1%) | 0.038 |
| Unstable angina pectoris | 9 (33%) | 15 (17%) | NS |
| Congestive heart failure | 11 (41%) | 6 (7%) | < 0.0001 |
| Repeated PTCA | 13 (48%) | 47 (52%) | NS |
| Cardiac surgery | 1 (4%)* | 2 (2%)† | NS |
| Overall death | 12 (44%) | 15 (17%) | 0.003 |
| Cardiac death | 10 (37%) | 9 (10%) | 0.002 |

*Reclosure of ventricular septal perforation; †coronary artery bypass graft surgery. Data are presented as the number of patients (percent).

AMI = acute myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

0.0001) in the No-Reflow group than in the Reflow group. Of 27 patients who died during the follow-up period, 12 (44%) were in the No-Reflow group, and 15 (17%) were in the Reflow group ($p = 0.003$). Incidence of cardiac death was also significantly higher in the No-Reflow group (37%) than in the Reflow group (10%) ($p = 0.002$); cardiac death included three sudden deaths (one in the No-Reflow group and two in the Reflow group). The prevalence of other complications (recurrent AMI, unstable angina pectoris requiring hospitalization, repeated PTCA, cardiac surgery) was not significantly different between the two groups.

**Long-term cardiac survival.** Kaplan-Meier survival analysis revealed that the patients in the No-Reflow group had a significantly higher incidence of cardiac death (log-rank $p < 0.0001$) (Fig. 1). The other univariate significant predictors of cardiac survival were LVEF ≤50% ($p = 0.0008$), age ≥70 ($p = 0.0008$), Killip class ≥II ($p = 0.0009$), and anterior infarction ($p = 0.023$). Peak CK levels ≥3,000 IU/liter ($p = 0.058$), multivessel disease ($p = 0.187$) and gender ($p = 0.933$) were not significant predictors. Multiple stepwise Cox regression analysis identified no-reflow ($p = 0.002$) as an independent predictor followed by age ≥70 years old ($p = 0.049$) (Table 4).

**Long-term cardiac event-free survival.** Patients in the No-Reflow group also had a significantly higher incidence of cardiac events (log-rank $p < 0.0001$) (Fig. 2). The other univariate significant predictors of cardiac event-free survival were Killip class ≥II ($p = 0.0001$), LVEF ≤50% ($p = 0.0004$), age ≥70 ($p = 0.037$). Multivessel disease ($p = 0.063$), anterior infarction ($p = 0.102$), peak CK levels ≥3,000 IU/liter ($p = 0.147$), and gender ($p = 0.887$) were not significant predictors. Multivariate analysis also disclosed no-reflow as an independent predictor ($p = 0.0004$) followed by Killip class ≥II ($p = 0.020$) (Table 4).

**Cardiac function of the survivors at follow-up.** At the end of the follow-up period, 80 patients among 90 survivors (89% of the survivors) continued to visit the outpatient clinic of Ogaki Municipal Hospital. To assess the NYHA functional class, we interviewed 84 patients (93%) directly and 6 patients (7%) by telephone. We performed echocardiogram and measured plasma BNP levels in 83 patients (92%); 13 of these patients were in the No-Reflow group (88%); 70 of them were in the Reflow group (93%). Clinical status of the survivors at follow-up is summarized in Table 5. One patient in the Reflow group was excluded from the echocardiographic study because of inadequate image quality. Four patients in the Reflow group were not available for NYHA classification, because they were bedridden due to brain infarction (two patients), multiple vertebral metastasis of prostate cancer (one patient), and severe spinal canal stenosis (one patient). The prevalence of NYHA functional class ≥III was significantly higher in the No-Reflow group than in the Reflow group ($p = 0.0005$). Both LVEDVI and LVESVI were significantly higher in the No-Reflow group than in the Reflow group ($p = 0.0002$ and $p < 0.0001$, respectively), indicating more advanced LV remodeling in the former group. The LVEF was significantly lower in the No-Reflow group than in the Reflow group ($p < 0.0001$). Plasma BNP levels were significantly higher in the No-Reflow group than in the Reflow group ($p = 0.002$). When the data concerning the patients who had experienced recurrent AMI or cardiac rupture were excluded, significant differences still existed between the two groups in relation to LVEDVI, LVESVI, LVEF, and plasma BNP levels (data not shown).

## DISCUSSION

The results of the present study clearly demonstrated for the first time the long-term prognostic value of the angiographic no-reflow phenomenon after successful reopening of the IRA in patients with AMI. Patients with no-reflow more commonly experienced malignant arrhythmia, CHF, and cardiac death than did those with reflow. They also had more advanced LV remodeling, as shown on the echocardiographic findings. Angiographic no-reflow phenomenon strongly predicts cardiac complications independent of other well-known early predictors of long-term outcome after AMI, such as age, Killip class, and LVEF.

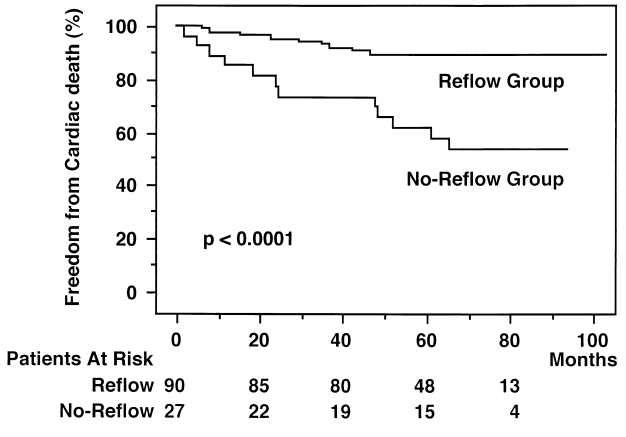


**Figure 1.** Kaplan-Meier cardiac survival curves following the index hospitalization; a comparison of patients with no-reflow versus reflow.

**Table 4.** Independent Predictors of Long-Term Event-Free Survival

| | Variables | Relative Risk | 95% CI | p Value |
|---|---|---|---|---|
| Cardiac death | No-Reflow | 5.25 | 1.85–14.9 | 0.002 |
| | Age ≥70 years | 2.85 | 1.01–8.08 | 0.049 |
| Cardiac death + events | No-Reflow | 3.71 | 1.79–7.69 | 0.0004 |
| | Killip class ≥II | 2.45 | 1.15–5.22 | 0.020 |

CI = confidence interval.

**Pathophysiology and clinical background of the angiographic no-reflow phenomenon.** The no-reflow phenomenon is defined as the occurrence of areas with heterogeneous or extremely low tissue flow after reopening the occluded artery (6,7). The no-reflow phenomenon may be a multifactorial condition reflecting damage to microvascular integrity established both during ischemia and at the time of reperfusion. Possible factors related include damage to endothelial cells, tissue edema (7), neutrophil plugging of the microvessels (23,24), and microvascular spasm (12,13). Myocardial contrast echocardiography (i.e., echocardiographic assessment of myocardial perfusion after intracoronary injections of sonicated microbubbles) is a valid technique that has been used to describe myocardial reperfusion after reopening the IRA in patients with AMI. The consensus seems to have been reached that no-reflow detected by myocardial contrast echocardiography is a predictor of poor LV functional recovery and remodeling in the early phase of AMI (5,8,25). Myocardial contrast echocardiography, however, can be performed only in limited investigational settings, mainly because of procedural complexity.

The TIMI flow grade is the simplest alternative available that assesses the no-reflow phenomenon, because neither additional techniques nor extra time is required, other than the cineangiograms obtained during PTCA. The TIMI flow grade ≤2 without obstructive lesion of the vessel has been generally regarded as the "angiographic no-reflow" phenomenon (4,11,12); increased microvascular impedance in the no-reflow zone may reduce epicardial coronary antegrade flow. Recently, studies with a Doppler guide wire demonstrated the distinctive altered flow pattern, possibly reflecting increased downstream microvascular impedance, in coronary arteries showing angiographic no-reflow phenomenon (14,15). Further, Ito et al. (16) elucidated the link between angiographic epicardial coronary flow and myocardial contrast echocardiographic findings of myocardial perfusion at the microvascular level. They found that all patients with TIMI flow grade 2 without obstruction after successful PTCA showed defects in myocardial perfusion (no-reflow). They concluded that TIMI flow grade 2 after successful PTCA reflects advanced microvascular damage and is a highly specific modality that can be used to detect the no-reflow phenomenon (16). However, TIMI flow grade 2 after thrombolytic therapy may not necessarily indicate such microvascular damage. Inadequate coronary patency may cause flow reduction even though downstream vascular or muscle injury is less severe and microvasculature is intact. Therefore, TIMI flow grade ≤2 after successful PTCA without obstructive lesions, which we dealt with in this study, should be regarded as an entity different from that after thrombolytic therapy with probable residual stenosis.

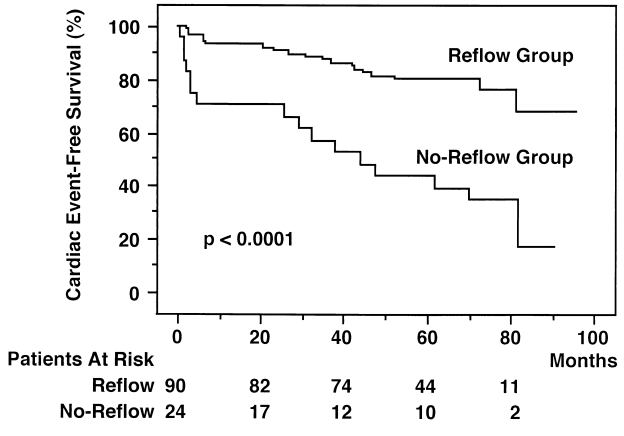


**Figure 2.** Kaplan-Meier cardiac event-free survival curves following the index hospitalization; a comparison of patients with no-reflow versus reflow. Cardiac events include cardiac death, recurrent acute myocardial infarction, malignant arrhythmia, and congestive heart failure.

**Relation of no-reflow phenomenon to LV remodeling and cardiac complications.** Progressive LV dilation after AMI, an important feature of LV remodeling, is strongly associated with adverse cardiovascular events, and it plays a particularly important role in the development of CHF (18–20). During the long-term follow-up period of the present study, patients with no-reflow experienced CHF more often than did those with reflow, rendering their cardiac mortality much higher than those with reflow. Moreover, even among the survivors, those with no-reflow showed significantly higher LVEDVI and LVESVI, and lower LVEF, than did those with reflow. These observations strongly suggest a link between no-reflow phenomenon and LV remodeling.

Various factors have been considered as influential in LV remodeling. These factors include infarct size, the perfusional status of the IRA (19), asynergy (26), and increased wall stress (18). In addition, Bolognese et al. (27) recently contended that the transmural extent of myocardial necrosis is necessary for LV expansion. In our previous study (4) comparing patients with no-reflow and reflow, those with no-reflow showed more extended transmural MI, which was detected by scintigraphy, as well as more severely depressed regional wall motion at three weeks after disease onset.

**Table 5.** Cardiac Function of the Survivors at Follow-up

| | No-Reflow (n = 15) | Reflow (n = 75) | p Value |
|---|---|---|---|
| NYHA class | | | |
| Class I | 9 (60%) | 58 (77%) | NS |
| Class II | 2 (13%) | 13 (17%) | NS |
| Class III | 4 (27%) | 0 (0%) | 0.0005 |
| Not evaluable | 0 (0%) | 4 (6%) | NS |
| Echocardiographic findings | | | |
| LVEDVI (ml/m$^2$) | 74.0 ± 31.5 | 52.3 ± 14.7 | 0.0002 |
| LVESVI (ml/m$^2$) | 44.4 ± 23.3 | 23.7 ± 11.1 | < 0.0001 |
| LVEF (%) | 41.8 ± 7.8 | 55.5 ± 11.2 | < 0.0001 |
| Plasma BNP (pg/ml) | 286.8 ± 512.9 | 73.3 ± 97.6 | 0.002 |

Data are presented as the number of patients (percent) or mean value ± SD.
BNP = brain natriuretic peptide; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NS = not significant; NYHA = New York Heart Association.

These findings may provide support for the hypothesis that the angiographic no-reflow phenomenon can be a predictor of LV remodeling. These results also confirm and expand on previous observations made by Ito et al. (25), who discovered that no-reflow, as detected by myocardial contrast echocardiography, is associated with LV remodeling one month after the onset of disease.

More recently, attention has been paid to injuries of the myocardial collagen matrix in association with LV expansion after AMI (28). Collagen forms an architectural scaffold for the myocytes; in addition, it provides strength and stiffness to the myocardium. The collagen is degraded by extracellular matrix metalloproteases, enzymes normally present in their latent form in the myocardium, but which are activated by ischemia (29). Animal experiments have demonstrated that reperfusion significantly attenuates increased activity of matrix metalloproteases induced by ischemia in the infarct zone (30). Thus, theoretically, no-reflow phenomenon, which indicates reperfusion failure, may lead to extensive damage to the myocardial collagen matrix and decrease myocardial strength and stiffness, resulting in cardiac rupture and LV expansion.

The NYHA functional class was significantly higher in the No-Reflow group than in the Reflow group among the survivors at this study's end point. Furthermore, plasma BNP levels were also higher in the No-Reflow group than in the Reflow group. The BNP has been established as a very sensitive marker of LV dysfunction. Plasma BNP concentrations have been shown to increase in proportion to the degree of LV dysfunction in patients with chronic heart failure (31) and with AMI (32). A decreased LVEF, higher NYHA functional class, and elevated BNP levels indicate severe LV dysfunction in patients with no-reflow in the chronic stage.

Plasma BNP levels might have prognostic implications. Recent studies have demonstrated that increased plasma BNP levels in the early phase of AMI predicts long-term poor cardiovascular mortality independent of well-known predictors (33,34). It is not fully elucidated that plasma BNP levels measured in the chronic phase of MI is also of prognostic value. One study did demonstrate that increased plasma BNP levels predict poor prognosis of patients with old MI and a low LVEF (<45%) (35). The BNP is released in increased amounts throughout the ventricular myocardium, especially from the infarct zone, in patients with old MI, presumably in response to increased regional wall stress (36). Again, increased regional wall stress is believed to be associated with adverse ventricular remodeling and poor prognosis following AMI (18). Thus, the potential association between plasma BNP levels and LV remodeling may contribute to the independent prognostic value of plasma BNP. Years after the onset of AMI, LV remodeling is still progressive (19,20); patients with increased BNP levels in the chronic phase of MI, as seen in the No-Reflow group, may be at risk of progressing LV remodeling and may consequently have a poor prognosis.

Recently, GUSTO-I investigators also reported clearly the adverse effects of TIMI flow grade ≤2 after thrombolytic therapy on the two-year survival based on the large cohort (37). The results in the present study support those in the GUSTO-I report. However, our study differs from the GUSTO-I report in the following aspects. We investigated patients recanalized by PTCA without obstructive lesions to narrow the argument down to severe microvascular damage (no-reflow). Our follow-up period was much longer. We studied not only mortality but also cardiac complications in detail. We also managed to follow up cardiac function of survivors.

**Study limitations.** The limitations of this study need to be addressed. 1) The study population represents only 25% of the patients treated for AMI at our center during the study period, because of the strict inclusion criteria employed in the present study. 2) The study population is relatively small, which may limit the statistical power to detect the predictor of long-term survival such as LVEF. 3) The TIMI frame count was not assessed in analyzing cineangiograms. 4) Echocardiographic study was performed only at the end of the study. Serial echocardiography would provide more accurate evaluation of LV remodeling. In addition to no-reflow, several factors may have contributed to advanced LV remodeling observed in the No-Reflow group; those include age, Killip class, enzymatic infarct size, and infarct

location. 5) We collected the long-term follow-up data retrospectively; however, nearly 90% of the survivors continued visiting Ogaki Municipal Hospital at least four years after disease onset. Thus, we obtained most of the data by reviewing the hospital charts and by direct interview with the patients. This enabled us to obtain the correct data in detail and also to reduce to a minimum any bias produced by interhospital discrepancy, such as differences in clinical decision and treatment. Thus, we believe that the quality of the data is sufficiently high. 6) Finally, this study represents no-reflow in a population in the era before coronary stenting, platelet glycoprotein IIb/IIIa receptor inhibitors, and pharmacological treatment of no-reflow with intracoronary verapamil (12,13).

**Conclusions.** Angiographic no-reflow phenomenon after PTCA predicts adverse long-term outcome in patients with AMI. Patients with no-reflow may be at risk of LV remodeling, which leads to progressive heart failure and cardiac death. The angiographic no-reflow phenomenon, the simplest clinical diagnostic tool to assess myocardial reperfusion, is therefore indispensable in early clinical decision making in treating patients with AMI.

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