Assessment of “Microvascular No-Reflow Phenomenon” Using Technetium-99m Macroaggregated Albumin Scintigraphy in Patients With Acute Myocardial Infarction

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Objectives. The aim of this study was the scintigraphic evaluation of clinical no-reflow phenomenon.

Background. In patients with acute myocardial infarction, the relationship of the severity of reduction of microvascular reflow to the ischemia time or to the secondary extension of myocardial necrosis is poorly understood, and we accordingly conducted a scintigraphic evaluation of clinical no-reflow phenomenon.

Methods. The group studied consisted of 25 consecutive patients with their first acute myocardial infarction. After recanalization, each patient received intracoronary injections of technetium-99m macroaggregated albumin (MAA).

Results. Eight patients (32%) had absent tracer uptake (scintigraphic no-reflow phenomenon). Fourteen patients showed absent or moderately reduced MAA uptake (group 1) and 11 showed slightly reduced or normal uptake (group 2). The time to recanalization was significantly longer in group 1 than in group 2 (290.4 ± 130.6 min vs. 177.3 ± 93.5 min; p = 0.0238). In chronic phase, the thallium-201 (TI-201) defect score index was significantly larger (p < 0.01) and regional ejection fraction was significantly lower (p < 0.01) in group 1 compared with corresponding values in group 2. No significant deterioration from acute phase to chronic phase in either TI-201 defect score index or regional ejection fraction was found in either group (two-way repeated measures analysis of variance).

Conclusions. These findings suggest that scintigraphic no-reflow phenomenon occurs in a subgroup of patients without angiographic no-reflow phenomenon, that the myocardial damage depends on the severity of microvascular damage and that prolonged ischemia time may increase the likelihood of “microvascular no-reflow phenomenon.”

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Early reperfusion is well known to reduce infarct size and improve survival. However, there are patients with successful early recanalization who do not show reduction of the infarct size in the chronic phase (1). One possible explanation for the failure of infarct size reduction is disturbance of microcirculation during epicardial coronary reperfusion (2–10). Kloner et al. (3) found that, after 90-min occlusion and reperfusion in experimental animals, the inner layer of the myocardium had little or no blood flow, despite removal of the epicardial coronary obstruction. This has been termed the “no-reflow phenomenon.” There are several unanswered questions about this phenomenon in humans, including the frequency, the relationship of its degree to the ischemia time to recanalization of an infarct-related artery and to myocardial damage, and whether secondary extension of infarcted segments occurs due to the disturbance of microcirculation during reperfusion.

The methods of assessment of microvascular circulation immediately after recanalization in clinical settings are limited (11–17). In this study we evaluated the reduction of microvascular reflow using intracoronary injection of technetium-99m macroaggregated albumin (MAA) after coronary recanalization. The objective of this study was the scintigraphic evaluation of the frequency of clinical no-reflow phenomenon, the relationship of the severity of disturbance of intramyocardial microcirculation to the ischemia time for successful recanalization and to the myocardial damage in the chronic phase and the presence or absence of secondary infarct extension.

Methods

Patients. The study population consisted of 25 consecutive patients with their first acute myocardial infarction. The acute myocardial infarction was verified on the basis of clinical, electrocardiographic (ECG) and enzymatic criteria. Inclusion criteria were one-vessel disease and grade 3 reflow according to the Thrombolysis In Myocardial Infarction (TIMI) (18) criteria. Informed consent was obtained from each patient.

Acute coronary arteriography and coronary angioplasty. Selective coronary arteriography (CAG) of both the left and right coronary systems was performed in several projections before percutaneous transluminal coronary angioplasty (PTCA). All patients were monitored continuously by three-lead ECG. Coronary arteriography of the infarct-related artery and standard 12-lead ECG were recorded at each occurrence of ST-segment changes, arrhythmias, chest pain or hypoten-
The collateral flow was graded by methods previously described (0 = no filling of collateral vessels; 1 = filling only of branches but no distal filling of the infarct-related artery; 2 = visualization of part of the vessel distal to the lesion; and 3 = ready visualization of most or all of the vessel distal to the lesion) (19). Collateral vessels graded 2 or 3 were considered to show good collateral circulation.

If the infarct-related artery showed TIMI grade 0 to 2 or grade 3 with stenosis ≥90%, PTCA was attempted. The time to recanalization was defined as the interval from the onset of chest pain to the appearance of TIMI grade 3 reflow after PTCA, or to the first visualization on CAG in patients with spontaneous recanalization (TIMI grade 3). Four weeks after reperfusion, the patency of the infarct-related artery was confirmed in 23 of the 24 patients examined. One patient refused to undergo a repeat CAG. Ischemic event was not observed during the follow-up period in any patient.

Serial evaluation of left ventricular function was conducted using cineventriculograms obtained in 30° right anterior oblique projection before PTCA and 4 weeks after the onset of acute myocardial infarction. The regional ejection fraction of the infarcted area was determined by the area method described (0 = normal; 1 = slightly reduced; 2 = moderately reduced; 3 = absent uptake) (Fig. 1). The short-axis slices from apical to basal are displayed on the left and vertical long-axis slices on the right.

### Abbreviations and Acronyms

- CAG = coronary arteriography
- CK = creatine kinase
- ECG = electrocardiography
- MAA = macroaggregated albumin
- MCE = myocardial contrast echocardiography
- PTCA = percutaneous transluminal angioplasty
- SPECT = single-photon emission computed tomography
- TIMI = Thrombolysis In Myocardial Infarction
- TI-201 = thallium-201

### Figure 1.

The grading of technetium-99m macroaggregated albumin single-photon emission computed tomographic defect score in patients with anterior myocardial infarction. A four-point defect score system was employed (normal = 0, Panel A; slightly reduced = 1, Panel B; moderately reduced = 2, Panel C; and absent uptake = 3, Panel D). The short-axis slices from apical to basal are displayed on the left and vertical long-axis slices on the right.

### Scintigraphic examinations.

#### Intracoronary MAA scintigraphy.

After the angiographic diagnosis of reperfusion, each patient received intracoronary injections of MAA. To avoid the effects of hyperemic high flow due to the contrast medium, intracoronary MAA infusion was performed at least 20 min after the last injection of contrast medium (21). Each patient received a single hand-pressure injection of approximately 300,000 MAA particles (mean size per particle, 22.6 μm) labeled with 27 MBq (1.0 mCi) of technetium-99m pertechnetate into both coronary arteries (left coronary artery, 0.7 mCi; right coronary artery, 0.3 mCi) (21–24). The particles were added to the injections of contrast material (24). This procedure allows documentation of the actual flow of contrast material and particles in the proximal vessel with identification of subselective injections into the circumflex or left anterior descending coronary artery (24). The subselective injection was not documented in this study. Before and after the tracer injection, any new symptoms, ECG changes and arterial pressure were monitored. Following completion of the catheterization procedure, patients were taken directly to the Nuclear Medicine Laboratory; imaging was usually started within 1 h of the tracer injection. Single-photon emission computed tomography (SPECT) imaging was performed using a Toshiba GCA-602A digital gamma camera equipped with a high-resolution low-energy collimator (energy peak, 140 KeV; energy window, ±20%). Thirty images were acquired over a 180° arc from the 50° right anterior oblique position to the 40° left posterior oblique position, with each image being acquired over 30 s. All projection images were acquired into 64 × 64 image matrices. Prereconstruction filtering of the projection data sets was performed using a Butterworth filter (Tokyo, Japan). Filtered backprojection in conjunction with a ramp filter was used to reconstruct the transaxial tomograms, which were then reoriented into short-axis images perpendicular to the long axis of the left ventricle. The SPECT images were obtained with a 0% lower cut-off level. Attenuation correction was not performed. In the visual interpretation of the SPECT images, short-axis and vertical long-axis tomograms were used. As a measure of the myocardial perfusion defect depicted on the scintigrams, the radioisotope uptake was scored using a 20-segment analysis (6 basal, 6 middle and 6 apical segments identified on the short-axis tomograms and 2 apical segments on the vertical long-axis tomograms); a 4-point defect score was calculated for each segment (0 = normal; 1 = slightly reduced; 2 = moderately reduced; 3 = absent uptake) (Fig. 1). In addition, the MAA SPECT images were analyzed quantitatively. The count for the segment (noninfarcted segments) with the highest count was set at 100%, and the counts in the infarcted segments were normalized to that segment. The value (percent count) represents the percent maximal uptake of the tracer in the infarcted segments.
Serial thallium-201 (TI-201) scintigraphy. Each patient was injected intravenously with 111 MBq (3.0 mCi) of TI-201 at rest, in both the acute phase (within 30 h of the MAA SPECT imaging) and the chronic phase (24.5 ± 6.5 days after the MAA SPECT imaging). Ten minutes after injection, SPECT acquisition was performed through a 20% window centered on the 72-KeV X-ray peak of the tracer. As undertaken for MAA imaging, the TI-201 SPECT images were acquired over 180°. The data acquired at the TI-201 SPECT study were processed identically to the MAA SPECT study using the same filters. The images were obtained with a 30% lower cut-off level. Studies of MAA and TI-201 were aligned with each other and the same reorientation was used.

Visual interpretation of the TI-201 SPECT images was performed by employing the 20-segment analysis with a 4-point defect score as used in the MAA SPECT image interpretation. The changes of the TI-201 defect score index (total defect score/number of infarct-related segments) from the acute to the chronic phase were evaluated.

All MAA and TI-201 SPECT images were visually interpreted by three experienced physicians without knowledge of data for any of the patients. A perfusion defect score was assigned when at least two of the observers agreed on the score. If conflicting results between physicians occurred, disagreements were resolved by consensus.

Cardiac enzyme measurements. Blood samples were collected on admission, every 4 h for the first 24 h and every 6 h for the next 24 h. Serum creatine kinase (CK) activity was measured by the technique of Rosalki (25), and CK-MB isoenzyme was measured with a radioimmunoassay. The peak levels of both CK and CK-MB were estimated for each patient.

Statistical analysis (26). Values are expressed as the mean ± SD. Demographic variables were compared between groups using Student’s t-test or chi-square testing, as appropriate. The correlation of the time to recanalization with percent count as a measure of MAA uptake in infarct segments was assessed with Spearman’s rank correlation, and linear regression analysis was done. For comparison of serial changes from acute phase to chronic phase in TI-201 defect score index and regional ejection fraction, two-way (group—phase) repeated analysis was done. For comparison of serial changes from acute phase to chronic phase in TI-201 defect score index and regional ejection fraction, two-way (group—phase) repeated analysis was done. For comparison of serial changes from acute phase to chronic phase in TI-201 defect score index and regional ejection fraction, two-way (group—phase) repeated analysis was done. For comparison of serial changes from acute phase to chronic phase in TI-201 defect score index and regional ejection fraction, two-way (group—phase) repeated analysis was done. For comparison of serial changes from acute phase to chronic phase in TI-201 defect score index and regional ejection fraction, two-way (group—phase) repeated analysis was done.

Results

MAA SPECT findings. In all 25 patients, images of sufficient quality to be analyzed were obtained. Before and after the tracer injection, new symptoms, ischemic ECG changes and hypotension (≥20 mm Hg) were not observed. Eight (32%) of the 25 patients had absent tracer uptake scores assessed visually. This group was considered to show scintigraphic no-reflow phenomenon. Table 1 lists the baseline characteristics in the two groups divided by the grading of the MAA defect score. Group 1 consisted of 14 patients who showed MAA defect scores of 3 (8 patients) or 2 (6 patients), and group 2 consisted of 11 patients who showed defect scores of 1 (7 patients) or 0 (4 patients). There were no statistical differences between the two groups in terms of age, gender or the distribution of the infarct-related vessels. The differences were not significant for the frequencies of either the spontaneous recanalization (TIMI grade 3 reflow) or the good collateral vessels at first visualization by CAG. However, the time to recanalization was significantly longer in group 1 than in group 2 (290.4 ± 130.6 min vs. 177.3 ± 93.5 min; p = 0.0238). The ischemia time to successful recanalization was correlated with the percent count, as a measure of MAA uptake, in the infarct-related segments (Fig. 2).

Variables of myocardial damage. The peak CK and CK-MB isoenzyme activities were significantly higher in group 1 compared with group 2 (Table 2). The frequency of ST-segment re-elevation immediately after recanalization (19) by PTCA was higher in group 1 than in group 2 (7 of 14 vs. 1 of 7; p = 0.0421). Since four patients in group 2 showed TIMI grade 3 at first visualization by CAG, they were excluded from the evaluation of ST-segment re-elevation immediately after recanalization by the intervention.

Thallium-201 SPECT was performed in the acute phase (between 24 and 30 h after the intracoronary MAA injections)

<table>
<thead>
<tr>
<th>Clinical and Angiographic Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>65.1 ± 8.9</td>
<td>62.4 ± 16.2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>93</td>
<td>82</td>
<td>NS</td>
</tr>
<tr>
<td>Infarct-related vessel (% LAD)</td>
<td>79</td>
<td>45</td>
<td>NS</td>
</tr>
<tr>
<td>First visualization on CAG</td>
<td>5 (36)</td>
<td>7 (64)</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI 3 or with good collaterals (n [%])</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean time (min)</td>
<td></td>
<td></td>
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<tr>
<td>Symptoms to CAG</td>
<td>261.1 ± 131.4</td>
<td>160.0 ± 73.4</td>
<td>0.0229</td>
</tr>
<tr>
<td>Symptoms to recanalization</td>
<td>290.4 ± 130.6</td>
<td>173.3 ± 93.5</td>
<td>0.0092</td>
</tr>
</tbody>
</table>

Data are mean ± SD or percentage. CAG = coronary arteriography; LAD = left anterior descending artery; NS = not significant; TIMI = Thrombolysis In Myocardial Infarction trial.

Figure 2. Correlation of the time to recanalization from the onset of symptoms of acute myocardial infarction with the percent count as a measure of technetium-99m macroaggregated albumin uptake in the infarct-related segments.
and in the chronic phase in both groups (Table 3). Two-way repeated measures ANOVA revealed that the TI-201 defect score index was significantly larger in the acute phase than in the chronic phase (phase effect, p < 0.001) in both groups and in group 1 than in group 2 (group effect, p < 0.001) in both phases, to a similar extent (phase—group interaction, p = NS).

In each patient, the MAA and TI-201 defect segments correlated with the coronary ananomies. The correlation of the extent of perfusion defect segments in each SPECT image was 1) TI-201 > MAA in 9 patients, 2) TI-201 = MAA in 10 patients and 3) TI-201 < MAA in 6 patients.

Left cineventriculogram of adequate quality was obtained before and 4 weeks after PTCA in 11 of the 14 patients in group 1 and in 9 of the 11 patients in group 2. For the regional ejection fraction of the infarcted area, two-way repeated measures ANOVA showed two main effects of the phase (p = 0.0076) and the group (p < 0.001), and a significant interaction (p = 0.0356). Scheffe’s test revealed that the regional ejection fraction significantly increased in group 2 from the acute to the chronic phases (p = 0.0200), whereas the change in group 1 was not significant (Table 3). Although there was no significant difference between the groups in the regional ejection fraction in the acute phase, the regional ejection fraction in the chronic phase in group 1 was significantly smaller than that in group 2 (p < 0.01) (Table 3). Although significant deterioration was not found in either group, two patients in group 1 showed diminution of regional ejection fraction of ≥9% from the acute to the chronic phase. These two patients did not show deterioration of the TI-201 defect score index.

**Discussion**

**Scintigraphic no-reflow phenomenon.** Macroaggregated albumin microspheres technique is considered to be an indicator of blood flow at the precapillary or capillary level (23,27). This indicates that the scintigraphic distribution of intracoronary MAA imaging is related to the degree of disturbance of intramyocardial microvascular flow after epicardial coronary reperfusion. Schofer et al. (12) presented scintigraphic evidence of no-reflow phenomenon acquired in human subjects using intracoronary TI-201 and MAA scintigraphy. They reported that the residual MAA perfusion defect reflects the area of no-reflow in the presence of normal filling and runoff of the contrast medium in the epicardial infarct-related vessel. However, they did not report the frequency of scintigraphic no-reflow phenomenon or the relationship of the severity of disturbance of MAA uptake to either the ischemia time or myocardial damage. In addition, in their evaluation they employed planar imaging. Recently, Morishima et al. (13) examined the frequency of angiographic no-reflow phenomenon. Severe disturbance of filling and runoff of the contrast medium was seen in 14% of patients with successful recanalization. In the present study, scintigraphic no-reflow phenomenon was recognized in 32% (8 of 25) of the patients without angiographic no-reflow phenomenon. The disturbance of MAA uptake showed variable degrees, and normally distributed MAA uptake was seen in only four patients (16%).

**Relation between ischemia time and no-reflow phenomenon.** The time to CAG or successful recanalization from the onset of symptoms of acute myocardial infarction was significantly longer in patients with completely absent or moderately reduced MAA uptake compared with those showing normal or slightly reduced uptake. In addition, we found a negative correlation between the ischemia time to successful recanalization and the percent count for MAA uptake in the infarct-related segments. Longer ischemia time to reflow promoted the “microvascular no-reflow phenomenon.” This suggests that the duration of ischemia is an important factor for determination of the degree of microvascular damage in human subjects (28). In contrast, two clinical studies employing myocardial contrast echocardiography (MCE) in patients with acute myocardial infarction within 6 h of the onset revealed no significant difference in time to recanalization between the groups with and without no-reflow (16,29). This difference may be related to the differences in the methods used for the evaluation of the microvascular flow pattern. In these two studies qualitative analysis was used to evaluate the grade of enhancement in risk segments. The present study revealed the correlation between ischemia time and the severity of reduction of intramyocardial MAA uptake both qualitatively and quantitatively. We believe that this is the first report of a correlation between ischemia time and the severity of reduction of intramyocardial microcirculation in patients with acute myocardial infarction.

**Relationship between disturbance of MAA uptake and myocardial damage.** Although the degree of disturbance of MAA uptake in the left ventricular wall was variable, the values of the myocardial damage parameters depended on the severity of the disturbance of MAA uptake immediately after successful recanalization. Furthermore, patients with completely absent or moderately reduced MAA uptake (group 1)

### Table 2. Results for Variables of Myocardial Damage

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
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<tbody>
<tr>
<td>Mean peak enzyme (IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase (CK)</td>
<td>4107.5 ± 2224.3</td>
<td>1137.8 ± 660.9</td>
<td>0.0008</td>
</tr>
<tr>
<td>CK-MB isozyme</td>
<td>454.1 ± 292.4</td>
<td>109.4 ± 58.1</td>
<td>0.0005</td>
</tr>
<tr>
<td>ST re-elevation (n°)</td>
<td>7/14</td>
<td>1/7</td>
<td>0.0421</td>
</tr>
</tbody>
</table>

*Numbers indicate the number of patients showing ST-segment re-elevation immediately after successful recanalization among patients with TIMI grade 0 to 2 at first visualization by CAG. Abbreviations as in Table 1.

### Table 3. Changes in TI-201 DSI and r-EF

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Chronic</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>TI-20 DSI</td>
<td>1.98 ± 0.66*</td>
<td>1.47 ± 0.88*</td>
<td>0.82 ± 0.76</td>
<td>0.12 ± 0.19†</td>
</tr>
<tr>
<td>r-EF (%)</td>
<td>22.25 ± 5.10</td>
<td>24.45 ± 12.63</td>
<td>27.01 ± 8.43</td>
<td>42.92 ± 9.40§</td>
</tr>
</tbody>
</table>

*p < 0.01 vs. group 2; †p = 0.053 vs. acute phase; ‡p = 0.0105 vs. acute phase; §p = 0.0200 vs. acute phase. r-EF = regional ejection fraction; TI-201 DSI = thallium-201 defect score index.
had more marked myocardial damage despite patent infarct-related arteries as they had higher peak CK and CK-MB activity and larger TI-201 defect score indexes compared with patients showing normal or slightly reduced MAA uptake (group 2). In addition, group 1 showed lower regional ejection fraction of the infarct area compared with group 2 in the chronic phase. These results seem to indicate that the myocardial damage in the chronic phase is closely related to the severity of scintigraphic disturbance of microcirculation immediately after recanalization. Thrombolytic therapy or PTCA is now an established treatment for acute myocardial infarction (30). In some patients, however, these therapies fail to produce limitation of infarct size or preservation of left ventricular function, even if early epicardial coronary reperfusion is successful (1). The present study reveals a discrepancy between the angiographic and scintigraphic assessments for myocardial blood flow and the results may explain, in part, the failure to limit the infarct size in patients with successful recanalization.

Recently, Ito et al. (14–17) found that the presence of no-reflow phenomenon revealed by MCE is a predictor of poor recovery of left ventricular function. However, it is difficult to grade the disturbance of microcirculation with the MCE method. In contrast, the present study revealed that the preservation of left ventricular function depended on the severity of the MAA defect score immediately after successful recanalization. In addition, the MAA defect score corresponded to the percent maximal uptake of the tracer in our patients. Thus, MAA techniques seems to offer an advantage in the assessment of microcirculation compared with MCE.

Limitations. Ambrosio et al. (31) examined the concept of the delayed no-reflow phenomenon experimentally. They described that the phenomenon might occur during the course of reperfusion and be an additional impairment to the “immediate no-reflow” at the time of reperfusion caused by microvascular damage. They postulated the existence of progressive impairment of blood flow of myocardium which was initially well reperfused, and myocardial infarct extension. The present study, however, did not reveal significant deterioration at the chronic phase compared to the acute phase of either TI-201 defect score index or regional ejection fraction in either group. However, the TI-201 SPECT at the acute phase was performed between 24 and 30 h after the intracoronary MAA injections. Therefore, the images acquired in the acute phase may not be adequate for the evaluation of progressive myocardial infarct extension by no-reflow phenomenon during reperfusion. We employed serial cineventriculography as an additional source of information to evaluate the changes of regional ejection fraction. No patient showed deterioration as assessed by both methods. Furthermore, histopathologic animal experiments have shown that microvascular damage was not a primary cause of the development of irreversible ischemic myocardial cell damage (32). Therefore, no-reflow itself would not cause additional tissue necrosis within the risk area. Thus, no-reflow would be a marker of severely damaged myocardium and microvasculature, but would not be a cause of additional myocardial damage. The evaluation of the serial changes of risk area from prerecanalization to the chronic phase in patients with or without no-reflow phenomenon may confirm the presence or absence of secondary infarct extension due to continued postreperfusion ischemia in a clinical setting (6,10).

Conclusions. This prospective study demonstrated that scintigraphic no-reflow phenomenon occurs in 52% (8 of 25) of patients without angiographic no-reflow phenomenon, and that the myocardial damage in the chronic phase depends on the severity of the MAA defect score immediately after recanalization. The ischemia time to reflow affects the severity of microvascular damage as assessed using MAA scintigraphy. In addition, there was no evidence of progressive infarct extension due to disturbance of microvascular reflow in our patients.

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