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# Evaluation of No-Reflow Phenomenon Using $^{201}$TlCl/$^{123}$I-BMIPP Dual-isotope Myocardial SPECT

Yasuhiro Shimizu[1], Shin-ichiro Kumita[1], Keiichi Cho[1], Masahiro Toba[1], Sunao Mizumura[1], Keiji Tanaka[2], Teruo Takano[2] and Tatsuo Kumazaki[1]

[1]Department of Clinical Radiology, Nippon Medical School Graduate School of Medicine
[2]Department of Functional Pathophysiology for Human Organs, Nippon Medical School Graduate School of Medicine

## Abstract

**Objectives:** We assessed the usefulness of $^{201}$thallous chloride (TlCl)/$^{123}$I-beta-methyl iodophenyl pentadecanoic acid (BMIPP) dual-isotope single-photon emission computed tomography (SPECT) to identify the "no-reflow phenomenon," defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction.

**Methods:** $^{201}$TlCl/$^{123}$I-BMIPP SPECT was performed in 73 patients within approximately 1 week of initial acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI). We divided the left ventricular myocardium into 17 segments on each SPECT image and scored tracer accumulation in each segment with a five-point scoring system according to the American Heart Association criteria. Total severity scores were calculated by summing the scores for all 17 segments. The mismatch ratio between myocardial perfusion and metabolism was derived from the $^{201}$TlCl and $^{123}$I-BMIPP total severity scores: mismatch ratio=($^{123}$I-BMIPP total severity score −$^{201}$TlCl total severity score)/$^{123}$I-BMIPP total severity score. Patients were classified according to Thrombolysis in Myocardial Infarction (TIMI) flow grade as having TIMI reflow grade 0-I (TIMI 0-I reflow group; n=11), II (TIMI II reflow group; n=17) and III (TIMI III reflow group; n=45). The TIMI III reflow group was subdivided into two groups with $^{201}$TlCl total severity scores of ≤13 (TIMI III (A) reflow group; n=36) and ≥14 (TIMI III (B) reflow group; n=9), respectively.

**Results:** The mismatch ratios in the TIMI II (0.4 ± 0.3) and TIMI III (0.4 ± 0.2) reflow groups were significantly higher than that in the TIMI 0-1 reflow group (0.1 ± 0.1, $p<0.05$). Although coronary angiography revealed TIMI III flow after reperfusion, the mismatch ratios in the TIMI III (B) reflow group (0.2 ± 0.1) and in the TIMI 0-I reflow group (0.1 ± 0.1) were significantly lower than that in the TIMI III (A) reflow group (0.4 ± 0.2, $p<0.01$), reflecting noneffective recanalization (so called no-reflow phenomenon).

**Conclusion:** $^{201}$TlCl/$^{123}$I-BMIPP dual-isotope myocardial SPECT reveals the biochemical degree of the no-reflow phenomenon, whereas coronary angiography shows recanalized vascular flow only. Dual-isotope myocardial SPECT might be useful for evaluating reperfusion therapy.

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**Key words:** no-reflow phenomenon, reperfusion therapy, dual-isotope SPECT, $^{201}$TlCl, $^{123}$I-BMIPP

Correspondence to Yasuhiro Shimizu, MD, Department of Radiology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: yasu-s@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

## Introduction

Early recanalization of an occluded infarct-related artery as a treatment for acute myocardial infarction (AMI) is thought to preserve left ventricular function and relieve ischemia[1–3]. Although drug-based (thrombolysis) or mechanical (percutaneous coronary intervention; PCI) approaches to recanalization have been applied as early strategies, PCI has become the initial treatment of choice because of its established advantages[4]. However, a recent report has shown that myocardial reperfused flow does not always resume even after an occluded infarct-related artery is recanalized during reperfusion therapy for AMI. This is referred to as the "no-reflow phenomenon"[5]. This phenomenon is being studied using various methods[2], such as coronary angiography (CAG)[6–8], myocardial scintigraphy[3,9,10], and myocardial contrast echography[11,12]. Previous study have shown a discrepancy between the results of nuclear imaging (functional and biochemical assessment) and those of CAG (morphological assessment) for the evaluation of the effectiveness of reperfusion therapy after AMI[2,3,9,10]. Therefore, we investigated the relationship between perfusion/metabolism mismatch and the degree of the reflow after reperfusion therapy for AMI to evaluate the usefulness of $^{201}$thallous chloride (TlCl)/$^{123}$I-beta-methyl iodophenyl pentadecanoic acid (BMIPP) dual-isotope single photon emission computed tomography (SPECT) for diagnosing the no-reflow phenomenon.

## Materials and Methods

### Patient Population

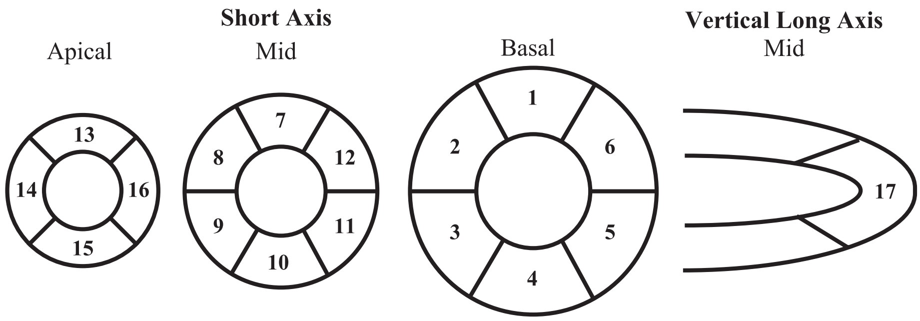
Seventy-three patients (50 men and 23 women; mean age, 66 ± 11 years; age range, 36 to 90 years) with AMI who underwent PCI in the coronary care unit were enrolled in this study. Infarction was diagnosed according to clinical, enzymatic, and electrocardiographic criteria. The left ventricular ejection fraction was determined with left ventriculography after hospitalization. All patients underwent $^{201}$TlCl/$^{123}$I-BMIPP SPECT within approximately 1 week (mean of 7.5 ± 4.9 days) of initial AMI. Informed consent was obtained from each patient.

### Myocardial SPECT Data Acquisition and Reconstruction

After the patient had fasted for at least 6 hours, $^{201}$TlCl (111 MBq) and $^{123}$I-BMIPP (111 MBq) were simultaneously injected at rest. Acquisition of dual-isotope myocardial SPECT data was started 30 min thereafter using a triple-headed gamma camera (PRISM 3000, Philips/Shimadzu, Kyoto) equipped with low-energy general-purpose collimators. The data were acquired over 360° in 72 (24 × 3) steps of 40 sec each in a 64 × 64 matrix. To separate the distribution of the isotopes, $^{201}$TlCl data were obtained using a symmetrical 70 keV window at 10% width (66.5 to 73.5 keV), and $^{123}$I data were captured using a symmetrical 159 keV window at 10% width (151.1 to 167 keV). We created three tomograms of vertical long, horizontal long, and short axis views and analyzed the obtained data using a ODYSSEY FX™ workstation (Philips/Shimadzu, Kyoto). Images were processed with a ramp back projection filter (order: 5, cut-off value: 0.25 cycles/cm in $^{201}$TlCl and $^{123}$I-BMIPP images).

### Assessment of Myocardial Distribution with Dual-Isotope SPECT

The left ventricular myocardium was divided into 17 segments on each SPECT image, and tracer accumulation in each segment was scored visually by using a five-point scoring system (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, absent) according to the American Heart Association (AHA) criteria by two experienced observers (**Fig. 1**)[13–17]. The total severity score was calculated by summing the scores for all 17 segments. The mismatch ratio was derived from the $^{201}$TlCl and $^{123}$I-BMIPP total severity scores: mismatch ratio=($^{123}$I-BMIPP total severity score −$^{201}$TlCl total severity score)/$^{123}$I-BMIPP total severity score. Patients were classified into three groups according to the Thrombolysis in Myocardial Infarction (TIMI) flow grade: the TIMI reflow grade 0-I (TIMI 0-I reflow group; n=11), II (TIMI II reflow group; n=17), and III (TIMI III reflow group; n=45) groups.




**Segmental Scoring**
0 = Normal
1 = Mildly Reduced Uptake
2 = Moderately Reduced Uptake
3 = Severely Reduced Uptake
4 = Absent Uptake

Fig. 1 Assignment of 17 Myocardial segments. The left ventricular myocardium was divided into 17 segments on each SPECT image, and tracer accumulation in each segment was scored with a five-point scoring system. Total severity scores were calculated by summing the scores for all 17 segments.

Table 1 Patients Characteristics

| | TIMI 0-I reflow group (n=11) | TIMI II reflow group (n=17) | TIMI III reflow group (n=45) | p Value (ANOVA) |
|---|---|---|---|---|
| Age (yr) | 65 ± 10 | 68 ± 11 | 66 ± 12 | NS |
| Gender (M/F) | 7/4 | 12/5 | 31/14 | NS |
| IRA (LAD/RCA/LCX) | 4/3/4 | 9/3/5 | 24/16/5 | NS |
| Reperfusion Time (hr) | 139.2 ± 192.3** | 39.5 ± 64.5 | 26.1 ± 48.9 | p<0.01 |
| Interval to dual SPECT from the onset of AMI (day) | 8.7 ± 4.6 | 6.6 ± 4.3 | 7.5 ± 5.3 | NS |
| LVEF (%) | 43.3 ± 11.8 | 47.5 ± 11.1 | 51.1 ± 12.8 | NS |

**p<0.01 vs. TIMI II and III reflow groups (post hoc analysis)
IRA: infarct-related artery, LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery, LVEF: left ventricular ejection fraction, Data are means ± SD, NS: not significant.

Additionally, on the basis of the $^{201}$TlCl total severity score, the TIMI III reflow group was subdivided into two groups with $^{201}$TlCl total severity scores of ≤13 (TIMI III (A) reflow group; n=36) and ≥14 (TIMI III (B) reflow group; n=9) according to the AHA criteria for severely reduced myocardial blood flow[14–17]. The mismatch ratios in all groups were compared.

### Statistical Analysis

All data are expressed as means ± 1 standard deviation. Multiple comparisons were performed with a single-factor analysis of variance. For post hoc analysis, the Bonferroni correction was applied. Differences with a p value of <0.05 were considered significant.

## Results

**Table 1** shows the characteristics of patients in the three groups classified according to TIMI flow grade. Age, gender, distribution of the infarct-related artery, time until dual SPECT from the onset of AMI, and left ventricular ejection fraction did not significantly differ among the groups. Reperfusion time in the TIMI 0-I reflow group (139.2 ± 192.3 hr) was significantly longer than that in the TIMI II reflow group (39.5 ± 64.5 hr, p<0.01) or the TIMI III reflow group (26.1 ± 48.9 hr, p<0.01) (**Table 1**).

Table 2 Results of semiquantitative Analysis

| | TIMI 0-I reflow group (n=11) | TIMI Ⅱ reflow group ( n=17) | TIMI Ⅲ reflow group (n=45) | p Value (ANOVA) |
|---|---|---|---|---|
| $^{201}$TlCl Total Severity Score | 15.2 ± 6.6* | 9.2 ± 7.3 | 8.9 ± 6.3 | p<0.05 |
| $^{123}$I-BMIPP Total Severity Score | 17.3 ± 7.2 | 13.9 ± 6.6 | 13.5 ± 6.2 | NS |
| Myocardial perfusion/metabolism mismatch ratio | 0.1 ± 0.1* | 0.4 ± 0.3 | 0.4 ± 0.2 | p<0.05 |

*p<0.05 vs. TIMI II and III reflow groups (post hoc analysis)
Data are means ± SD, NS: not significant.

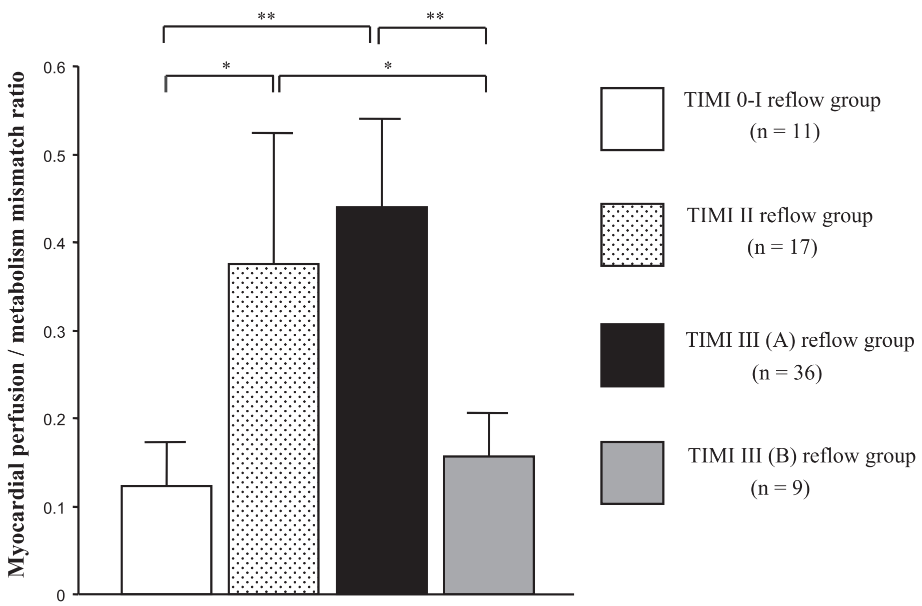



Fig. 2 Comparison of myocardial perfusion/metabolism mismatch ratio in the TIMI 0-I, Ⅱ, Ⅲ (A), and Ⅲ (B) reflow groups.
*p<0.05, **p<0.01 (post hoc analysis)

**Table 2** shows that the $^{201}$TlCl total severity score in the TIMI 0-I reflow group (15.2 ± 6.6) was significantly higher than that in the TIMI II reflow group (9.2 ± 7.3, p<0.05) or the TIMI III reflow group (8.9 ± 6.3, p<0.05). The $^{123}$I-BMIPP total severity score did not differ significantly among the groups. The mismatch ratios in the TIMI II (0.4 ± 0.3) and TIMI III (0.4 ± 0.2) reflow groups were significantly higher than that in the TIMI 0-1 reflow group (0.1 ± 0.1, p<0.05). The mismatch ratios did not differ significantly between the TIMI II and III reflow groups (**Table 2**).

**Figure 2** shows that the mismatch ratios in the TIMI 0-I (0.1 ± 0.1) and TIMI III (B) reflow groups (0.2 ± 0.1) were significantly lower than that in the TIMI II reflow group (0.4 ± 0.3, p<0.05). Although the mismatch ratios in the TIMI 0-I (0.1 ± 0.1) and TIMI III (B) reflow groups (0.2 ± 0.1) were significantly lower than that in the TIMI III (A) reflow group (0.4 ± 0.2, p<0.01), the mismatch ratios did not significantly differ between the TIMI 0-I and III (B) reflow groups **(Fig. 2)**.

Note the $^{201}$TlCl and $^{123}$I-BMIPP SPECT images of two AMI patients after PCI in **Figure 3** to demonstrate the differences in two SPECT image sets. A 79-year-old woman in the TIMI III (A) reflow group had a larger and more profound uptake abnormality of $^{123}$I-BMIPP than of $^{201}$TlCl in the inferoposterior region **(Fig. 3a)**. **Figure 3b** shows the $^{201}$TlCl and $^{123}$I-BMIPP image set of a 65-year-old man in the TIMI III (B) reflow group. Similar abnormalities were identified in the same regions

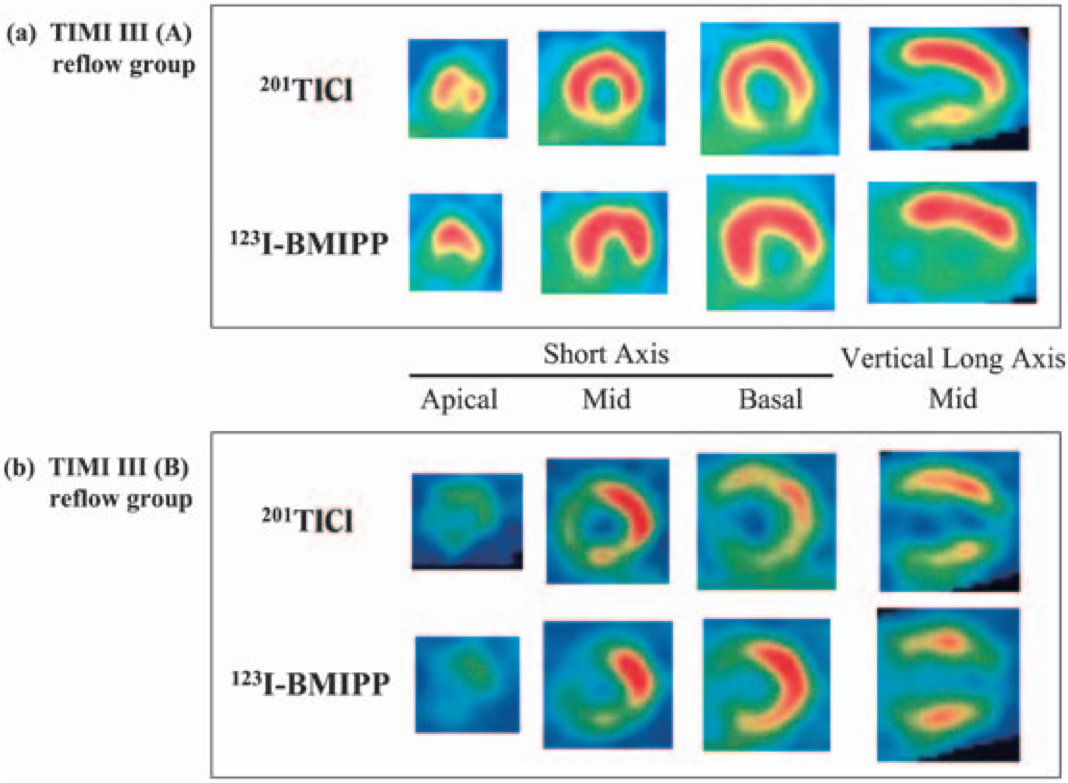



Fig. 3 Vertical long axis and short axis SPECT images of $^{201}$TlCl and $^{123}$I-BMIPP in two patients with AMI who underwent PCI.
(a) A 79-year-old woman in the TIMI III (A) reflow group; The extent and severity of $^{123}$I-BMIPP in SPECT images were larger and greater than those of $^{201}$TlCl in the inferoposterior region. $^{201}$TlCl total severity score, 4; $^{123}$I-BMIPP total severity score, 11; mismatch ratio, 0.64.
(b) A 65-year-old man in the TIMI III (B) reflow group; Similar abnormalities were identified in the same regions (anteroseptal and apical regions) by both the $^{201}$TlCl and $^{123}$I-BMIPP images (i.e., no-reflow phenomenon). $^{201}$TlCl total severity score, 20; $^{123}$I-BMIPP total severity score, 25; mismatch ratio, 0.2.

(anteroseptal and apical regions) by both images, indicating the no-reflow phenomenon.

## Discussion

With CAG, the angiographic no-reflow phenomenon is defined as decreased coronary blood flow above a specific level (less than TIMI III flow) without mechanical occlusion[6-8]. Kondo et al. have demonstrated that a reduction in microvascular reflow was recognized using intracoronary injection of $^{99m}$Tc macroaggregated albumin after coronary recanalization (scintigraphic evidence of no-reflow phenomenon) in 32% of patients without the “angiographic no-reflow phenomenon”[10]. $^{201}$TlCl/$^{123}$I-BMIPP dual-isotope myocardial SPECT reflects the myocardial flow, while CAG shows recanalized vascular flow only. This ability suggests that dual-isotope myocardial SPECT would be useful for evaluating reperfusion therapy.

$^{123}$I-BMIPP is used to visualize myocardial fatty acid metabolism, reflecting the memory at the onset of myocardial infarction. The discrepancy between blood flow and metabolism after PCI indicates the volume of reperfused myocardium and enables severe myocardial damage without decreased flow to be identified on CAG (i.e., no-reflow phenomenon)[3,18-21]. Therefore, to evaluate the usefulness of $^{201}$TlCl / $^{123}$I-BMIPP dual-isotope myocardial SPECT for identifying the no-reflow phenomenon, we investigated the relationship between perfusion/metabolism mismatch and the degree of reflow after PCI.

The “no-reflow phenomenon” was originally identified during an animal experiment conducted by Kloner et al., in which the coronary artery was occluded for 90 minutes and then reperfusion therapy was started. The myocardial blood flow in the inner half of the damaged myocardium was only slightly or not at all improved, although the occlusion of an epicardial coronary artery was relieved[5]. In a study of human coronary arteries conducted by Schofer et al. based on nuclear cardiology, myocardial reperfusion immediately after intracoronary thrombolysis could be estimated by performing intacoronary scintigraphy with technetium microalbumin aggregates before and after coronary intervention; the absence of technetium uptake was considered to reflect a lack of capillary reperfusion[3,9].

We found that the $^{201}$TlCl total severity score in the TIMI 0-I reflow group was significantly higher than that in the other groups, indicating that myocardial damage was extensive in the TIMI 0-I reflow group. The reperfusion time in the TIMI 0-I reflow group was significantly longer than that in the other groups. Therefore, reperfusion time seems to be a key factor in the appearance of the no-reflow phenomenon in the clinical setting[10,22].

Dual-isotope myocardial SPECT identified a significantly lower mismatch ratio in the TIMI 0-I reflow group than in the TIMI III reflow group. However, the mismatch ratio was similarly low in the TIMI III (B) and TIMI 0-I reflow groups, with no statistically significant difference. This finding indicates that the TIMI III (B) reflow group included many patients with myocardial damage that was as extensive as that in the TIMI 0-I reflow group with damage to endothelial cells, tissue edema[5,6], neutrophil plugging of the microvessels[6,23], and microvascular spasm[6,8], for which reperfusion therapy is not effective (i.e. no-reflow phenomenon). These results suggest that CAG cannot always identify a patient with no-reflow phenomenon. Such patients might be correctly identified with $^{201}$TlCl/$^{123}$I-BMIPP dual-isotope myocardial SPECT, even when CAG shows TIMI III reflow.

The present study used a 17-segment model, which provided the best agreement with available anatomic data for assessing the myocardium according to AHA criteria. The 20-segment model overrepresents the apex when compared with the anatomic data[13].

Other studies have used a difference in mismatch as an index for comparing $^{201}$TlCl and $^{123}$I-BMIPP images[18–21,24], whereas we used a comparison of mismatch ratios as an index to eliminate the influence of the size of myocardial infarction.

Although our protocol differed from those in previous studies (for example, at rest vs. stress[14–17]), the TIMI III reflow group was subdivided into (A) or (B) groups with $^{201}$TlCl total severity scores of $\leq$ 13 and $\geq$14, respectively. We were able to divide the TIMI III patients into two groups on the basis of the severity in myocardial perfusion. However, further studies are required to confirm our data in a larger group of patients with AMI.

## Conclusion

The TIMI III reflow group included some patients with severe myocardial damage; therefore, CAG might overestimate the degree of myocardial salvage after reperfusion therapy for AMI. Evaluation based on $^{201}$TlCl/$^{123}$I-BMIPP dual-isotope myocardial SPECT images is useful for judging myocardial damage for which reperfusion therapy is not effective.

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