Investigation of the Clinical Efficacy of $^{99m}$Tc-Sestamibi Washout in Patients with Acute Myocardial Infarction and Comparison with Stress Myocardial Imaging with $^{99m}$Tc -Sestamibi Using a Two-Day Protocol

Mieko Ota 1, 2, Fuminori Hyodo 3, *, Shinro Matsuo 4, Takashi Kato 5, Nobuyuki Kawai 2, Fumihiko Nakamura 3, Keita Fujimori 2, Yo Kaneko 2, Hiroki Kato 2 and Masayuki Matsuo 2

1 Radiological Center, Gifu Prefectural General Medical Center, Gifu, Japan
2 Department of Radiology, School of Medicine, Gifu University, Gifu, Japan
3 Department of Radiology, Frontier Science for Imaging, School of Medicine, Gifu University, Gifu, Japan
4 Matsuo Medical Clinic, Hirakata, Japan
5 Department of Cardiology, Gifu Prefectural General Medical Center, Gifu, Japan

* Corresponding author: Department of Radiology, Frontier Science for Imaging, School of Medicine, Gifu University, Gifu, Japan. Email: hyodof@gifu-u.ac.jp

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Abstract

Background: $^{99m}$Tc-sestamibi myocardial perfusion imaging (MIBI) washout is associated with myocardial mitochondrial damage in patients with a successful percutaneous coronary intervention (PCI) following acute myocardial infarction (AMI) and may predict the functional improvement of the left ventricle in follow-ups.

Objectives: This study aimed to investigate the clinical efficacy of $^{99m}$Tc-MIBI washout in patients with AMI by measuring the mean defect area based on $^{99m}$Tc-MIBI myocardial perfusion-single photon emission computed tomography (MP-SPECT) rest imaging in early and delayed phases and comparing it with the defect area based on $^{99m}$Tc-MIBI MP-SPECT adenosine stress imaging based on a two-day rest/stress protocol.

Patients and Methods: This study was conducted on 29 consecutive patients with AMI (23 males and 6 females; mean age, 71 ± 8.4 years), who underwent MP-SPECT using a standard two-day rest/stress protocol. The rest $^{99m}$Tc-MIBI MP-SPECT images were acquired in the early phase at one hour after the injection of $^{99m}$Tc-MIBI and in the delayed phase at three hours after the early phase. The total perfusion deficit (TPD) score for SPECT was measured to compare the defect area between the rest-early phase, rest-delayed phase, and post-stress imaging conditions.

Results: Based on the results, the post-stress TPD score was significantly lower than the rest-delayed phase score (TPD: 22.2% ± 14.3% vs. 27.8% ± 14.0%; P < 0.001). Also, the rest-early phase score was significantly lower than the rest-delayed phase score (TPD: 21.5% ± 14.9% vs. 27.8% ± 14.0%; P < 0.001). However, no significant difference was observed between the post-stress score and the rest-early phase score.

Conclusion: The combination of rest-early phase, delayed phase, and post-stress $^{99m}$Tc-MIBI imaging using a two-day protocol after AMI reperfusion was a clinically useful method, which could identify residual ischemia and predict the left ventricular function improvement in the chronic phase of disease while reducing the exposure dose.

Keywords: $^{99m}$Tc-sestamibi (MIBI), Washout, Two-day Protocol

1. Background

The prognosis of acute myocardial infarction (AMI) mainly depends on the left ventricular (LV) function, infarct size, and the extent of myocardial ischemia in infarcted and non-infarcted areas. It is generally important to investigate the effects of treatment on AMI (1). Previously, dual single photon emission computed tomography (SPECT) using $^{201}$TI (TI) and $^{99m}$Tc-pyrophosphate (PYP) tracers was performed to determine the effects of acute treatment on AMI. $^{99m}$Tc-PYP, which depicts a necrotic myocardium, can quantify an infarcted myocardium. This agent, by capturing the overlap region between $^{201}$TI and $^{99m}$Tc-PYP on dual SPECT, can identify necrotic tissues in a re-inflated myocardium in the acute phase, and its usefulness has been reported in the literature (2, 3). More-
over, previous research has investigated the mismatch of $^{201}$TI and $^{123}$I-$\beta$-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) dual SPECT (4). A mismatch defect between $^{201}$TI and $^{123}$I-BMIPP dual SPECT has been reported following AMI reperfusion in patients with a blood flow deficit and a fatty acid metabolism disorder, with the cardiac function expected to recover in the mismatched area (4, 5). However, $^{99m}$Tc-PYP and $^{123}$I-BMIPP dual SPECT uses $^{201}$TI and requires the simultaneous administration of two nuclides, resulting in a high exposure dose.

In recent years, $^{99m}$Tc-sestamibi (MIBI) washout has been associated with myocardial mitochondrial damage in patients with AMI after a successful percutaneous coronary intervention (PCI); it may also predict the functional improvement of LV during follow-ups (6-8). Overall, the myocardial uptake of MIBI depends on a large negative charge in mitochondrial membranes (9); this observation is associated with mitochondrial dysfunction and LV dysfunction in the myocardium (6-8).

Myocardial perfusion-SPECT (MP-SPECT) imaging is used to detect the residual ischemic myocardial mass after an AMI revascularization. $^{99m}$Tc-MIBI, as a myocardial perfusion imaging tracer, is commonly used to detect coronary artery disease (10, 11). $^{99m}$Tc-MIBI is taken up by the normal myocardium through passive transport depending on the blood flow. Accordingly, rest-stress $^{99m}$Tc-MIBI MP-SPECT examinations have been clinically performed to detect myocardial ischemia (Figure 1). Generally, a rest-stress $^{99m}$Tc-MIBI MP-SPECT examination requires two injections, that is, one injection for the rest condition and one injection for the stress condition to assess cardiac perfusion (Figure 1); consequently, this method has a disadvantage of higher exposure dose. Conversely, in the comparison of early and delayed phases, the region of $^{99m}$Tc-MIBI washout is known to be associated with mitochondrial dysfunction in the myocardium damaged by acute myocardial infarction (6). However, the clinical efficacy of $^{99m}$Tc-MIBI washout according to rest $^{99m}$Tc-MIBI MP-SPECT imaging for the evaluation of myocardial function has not been investigated or compared with rest-stress imaging. Based on a comparison of rest-early/delayed phase $^{99m}$Tc-MIBI MP-SPECT images and rest-stress $^{99m}$Tc-MIBI MP-SPECT images, if the results of these two MP-SPECT imaging conditions are consistent, only the rest-early/delayed phase $^{99m}$Tc-MIBI MP-SPECT imaging can be performed, which is a great advantage for patients.

2. Objectives

This study aimed to investigate the clinical efficacy of $^{99m}$Tc-MIBI washout in AMI patients by determining the mean defect area according to rest $^{99m}$Tc-MIBI MP-SPECT imaging in early and delayed phases and comparing it with the defect area according to $^{99m}$Tc-MIBI MP-SPECT adenosine stress imaging using a two-day rest-stress protocol.

3. Patients and Methods

3.1. Study Protocol

A total of 29 consecutive patients with AMI (23 males and 6 females), with a mean age of 71 ± 8.4 years, were evaluated in this study. All the patients were admitted within six hours after the onset of symptoms and successfully received direct PCI. On the other hand, patients with myocardial infarction associated with another culprit branch of coronary arteries in ≤ 1 month of PCI treatment were excluded from the study. Angioplasty was considered technically successful when residual stenosis of < 50% and Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 on angiography (12) were observed at the end of angioplasty. All patients underwent $^{99m}$Tc-MIBI MP-SPECT based on a standard two-day rest-stress protocol (Figure 1B). The rest MP-SPECT imaging with $^{99m}$Tc-MIBI was performed in ≤ 1 week after PCI, whereas stress $^{99m}$Tc-MIBI MP-SPECT was performed in ≤ 10 days after rest MP-SPECT (Figure 2).

The Institutional Review Board of Gifu Prefectural General Medical Center (Gifu, Japan) approved this study. This study was performed according to the ethical standards of the 1964 Declaration of Helsinki. The requirement to obtain informed consent was waived because of the retrospective design of the study.

3.2. $^{99m}$Tc-MIBI MP-SPECT Data Acquisition and Processing

The rest $^{99m}$Tc-MIBI MP-SPECT images were acquired in the early phase at one hour after the injection of 370-MBq of $^{99m}$Tc-MIBI and in the delayed phase at four hours post-injection. The stress $^{99m}$Tc-MIBI MP-SPECT images were acquired at one hour after adenosine stress (120 μg/kg/min infused for 6 min) (13) by injecting 370 MBq of $^{99m}$Tc-MIBI (Figure 2).

Following the $^{99m}$Tc-MIBI injection, $^{99m}$Tc-MIBI MP-SPECT imaging was performed after the patient had eaten to accelerate the excretion of isotopes through the gallbladder into the bowel. The $^{99m}$Tc-MIBI MP-SPECT imaging was performed on a BrightView X SPECT system (Philips Healthcare, Eindhoven, Netherlands), equipped with a cardiac high-resolution collimator. A total of 36 images were acquired at 60 seconds per frame (matrix, 64 × 64; magnification, 1,46) under stress and rest conditions, using the “step-and-shoot” technique (90°/head). Images were acquired along an auto-proximity circular orbit in a range of 180° (from 45° right anterior oblique to 45° left posterior oblique). Energy discrimination was provided by a 20% window, centered over the 140-keV photon peak of $^{99m}$Tc.
Figure 1. Standard rest-stress $^{99m}$Tc-sestamibi (MIBI) myocardial perfusion single photon emission computed tomography (MP-SPECT) protocols. Rest-stress MP imaging with $^{99m}$Tc-MIBI can be performed based on either a one-day protocol (A) or a two-day protocol (B). In the rest-stress one-day protocol, the dose of stress imaging should be higher than that of rest imaging.

Additionally, transverse images were reconstructed using a filtered back projection with a Butterworth pre-filter (order, 8; cutoff frequency, 0.6 cycle/pixel) and a ramp post-filter for processing without attenuation correction. The transaxial images were then reformatted along the short axis, vertical long axis, and horizontal long axis of the LV.

3.3. Quantitative Analysis of 99mTc-MIBI MP-SPECT Images

The total perfusion deficit (TPD), proposed by Slomka et al. (14) as an objective parameter, was automatically calculated using the QPS quantitative perfusion SPECT software (Cedars-Sinai Medical Center, Los Angeles, CA, USA) (15) to represent both the defect severity and the defect extent. The TPD scores of SPECT were calculated as the percentage of the total surface area of LV below the predefined uniform average deviation threshold. A normal database, developed by the Japanese Society of Nuclear Medicine, was used for TPD scoring (16). This database is based on exercise-rest myocardial perfusion images, acquired from 80 Japanese individuals with a low likelihood of cardiac disease.

The TPD scores of SPECT were measured under rest-early phase, rest-delayed phase, and adenosine stress conditions. The TPD scores of $^{99m}$Tc-MIBI MP-SPECT imaging were compared between the rest-early phase, rest-delayed phase, and adenosine stress conditions. The $^{99m}$Tc-MIBI washout was accelerated if the TPD score on rest-delayed phase SPECT was higher than that of rest-early phase SPECT. The washout TPD score of $^{99m}$Tc-MIBI was defined as the difference between the rest-delayed phase and early phase TPD scores. Also, the TPD score difference was defined as the difference between the post-stress and rest-early phase TPD scores.
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Figure 2. The study protocol. Rest myocardial perfusion (MP) imaging with $^{99m}$Tc-sestamibi was performed within seven days after percutaneous coronary intervention (PCI). Stress MP imaging was performed within 10 days after rest imaging.

TPD scores.

3.4. Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Continuous variables were compared using Student’s paired t-test. A P-value less than 0.05 was considered statistically significant.

4. Results

A total of 29 consecutive patients with AMI (23 men and 6 women; mean age, 71 ± 8.4 years), who underwent successful PCI on admission, were examined in this study. A general summary of the total population characterlike is shown in Table 1.
In Table 2, the TPD scores are presented for the rest-early phase, rest-delayed phase, and poststress conditions, as well as the washout rates and differences between 29 patients. In the rest-stress study for the detection of myocardial ischemic areas, no significant difference was observed between the post-stress TPD score and the rest-early phase TPD score on SPECT. In the early and delayed phase studies for the detection of $^{99m}$Tc-MIBI washout area, the TPD score of rest-early phase SPECT was significantly lower than that of rest-delayed phase SPECT ($21.5\% \pm 14.9\%$ vs.
5. Discussion

The results of the present study showed that the TPD score of post-stress SPECT was significantly lower than that of rest-delayed phase SPECT. The significantly smaller ischemic area relative to the ⁹⁹mTc-MIBI washout area was the main finding of this study. TPD, which represents both the extent and severity of defect/abnormality on MP-SPECT images, was used to investigate the defect size. Previous studies on ⁹⁹mTc-MIBI washout have mostly employed visual segmental scoring systems to calculate the defect score, including the total stress and rest scores (6). However, these systems are semi-quantitative and require special skills or imaging interpretation knowledge, which can be only gained through training and experience. Alternatively, Yoda et al. (17) reported that TPD, automatically calculated by the QPS software (Cedars-Sinai Medical Center, USA) (15) on a normal Japanese database, is an objective quantitative index with high reproducibility, which is comparable to conventional visual segmental assessments by experienced interpreters; therefore, the TPD of SPECT was used in this study.

The results of the present study did not show a significant close relationship between the TPD scores of post-stress and rest-early phase SPECT, indicating that all patients enrolled in this study underwent a successful PCI for AMI. Therefore, no residual ischemic area was detected in most patients, and the infarction area was only observed in few patients. Generally, the defect area size on rest-delayed phase images is related to tissue salvage and is a predictor of late functional recovery (6, 18). The main finding of the present study is that the defect area was significantly larger under rest-delayed phase conditions compared to the post-stress condition. Early interventions to protect the mitochondrial function may be also important for myocyte protection (19, 20). Also, accurate detection of mitochondrial dysfunction in patients with AMI can be considered useful (6).

The adenosine triphosphate (ATP) level in the myocardium with a blood flow-blocked AMI significantly decreased, as oxygen is required to produce ATP in the myocardium (21-24). Another study reported that the ATP concentration in cardiomyocytes depends on the extent and duration of damage to cardiac function (25). Besides, Torealba et al. found that when the oxygen supply decreased due to reduced myocardial blood flow, the mitochondrial membrane potential became abnormal, the ability to retain ⁹⁹mTc-MIBI decreased, and the ⁹⁹mTc-MIBI washout rate increased (20, 26). The residual ischemic region indicated by post-stress imaging represented a myocardial tissue, with increased mitochondrial damage due to a lack of oxygen. Consequently, the ability of myocardial tissue to retain ⁹⁹mTc-MIBI was lost. Moreover, the ⁹⁹mTc-MIBI washout region, identified by rest-delayed phase imaging, represented a myocardial tissue with normal oxygen supply through successful PCI reperfusion (20, 26); however, mitochondrial damage caused by AMI remained unchanged, and ⁹⁹mTc-MIBI was retained. The TPD scores of post-stress and rest-delayed phase SPECT were significantly different considering the difference between the degree of myocardial perfusion injury and the level of mitochondrial damage (Figure 4). The TPD score of delayed-phase SPECT was significantly higher, suggesting that delayed-phase imaging could sensitively detect mitochondrial damage.

Investigation of treatment effects on AMI is important for predicting the AMI prognosis. The myocardium with ⁹⁹mTc-MIBI washout in rest-early phase and delayed phase ⁹⁹mTc-MIBI MP-SPECT can be identified as the myocardium...
which is exposed to ischemia, but is expected to recover (6-8, 18). The current study showed that the extent of washed-out myocardium did not match the residual ischemic myocardial area and that the washout area was significantly larger than the residual ischemic area. Therefore, ischemia assessment using rest-stress $^{99m}$Tc-MIBI MP-SPECT imaging alone insufficiently evaluates the recovery of cardiac function after revascularization. Besides, rest-early phase and delayed phase $^{99m}$Tc-MIBI MP-SPECT imaging, which provides information on intramyocardial mitochondrial damage, is also necessary.

The combination of rest-early phase/delayed phase and
Figure 4. Comparison of the total perfusion deficit (TPD) scores between the rest-early phase, rest-delayed phase, and post-stress $^{99m}$Tc-sestamibi myocardial perfusion-single photon emission computed tomography (MP-SPECT) images. The post-stress and rest-early phase TPD scores were significantly lower than the rest-delayed phase score; however, the post-stress score and the rest-early phase score were not significantly different.

This study had some limitations. First, the acquisition interval of rest-early phase images and rest-delayed phase images was three hours. This could be influential through not only changes in the defective area due to $^{99m}$Tc-MIBI washout, but also the effects of count decrease considering the decay time of $^{99m}$Tc. Second, since the sample size was small, the reliability of statistical analysis may be insufficient.

In conclusion, in patients with AMI, after a successful PCI, rest-delayed phase $^{99m}$Tc-MIBI MP-SPECT imaging was more sensitive than post-stress $^{99m}$Tc-MIBI MP-SPECT for the detection of mitochondrial damage. Overall, the $^{99m}$Tc-MIBI washout rate can provide useful information for physicians. Based on the results, the combination of rest-early/delayed phase and post-stress $^{99m}$Tc-MIBI MP-SPECT imaging using a two-day protocol can reduce the exposure dose and provide a more accurate diagnosis method for patients with acute myocardial infarction.
Footnotes

Authors’ Contributions: Study concept and design: M.O., F.H., and S.M.; Analysis and interpretation of data: T.K., N.K., F.M., and S.B.; Drafting of the manuscript: M.O.; Critical revision of the manuscript for important intellectual content: H.K., Y.K., and M.M.; and statistical analysis: M.O.

Conflict of Interests: None.

Data Reproducibility: It was not declared by the authors.

Ethical Approval: This study was carried out according to the ethical standards and principles of the Declaration of Helsinki and approved by Gifu Prefectural General Medical Center, Gifu, Japan (approval code: 2019/442). It was also approved by the ethics committee of this hospital (approval number: 442) (www.gifu-hp.jp/wp-content/uploads/442.pdf).

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