CARDIAC IMAGING
Iran J Radiol. 2022 April; 19(2):e122423.
doi: 10.5812/iranjradiol-122423.
Published online 2022 June 16.
Research Article

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 [2], Keita Fujimoto [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

Received 2022 January 08; **Revised** 2022 May 18; **Accepted** 2022 May 21.

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}TlCl (Tl) 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}Tl 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). Moreover, previous research has investigated the mismatch of ^{201}Tl and ^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) dual SPECT (4). A mismatch defect between ^{201}Tl 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}Tl and requires the simultaneous administration of two nuclides, resulting in a high exposure dose.

In recent years, ^{99m}Tc-sestamibi myocardial perfusion imaging (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 $\pm$ 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 $\leq$ 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 $\leq$1 week after PCI, whereas stress ^{99m}Tc-MIBI MP-SPECT was performed in $\leq$ 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. 99mTc-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 $\times$ 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

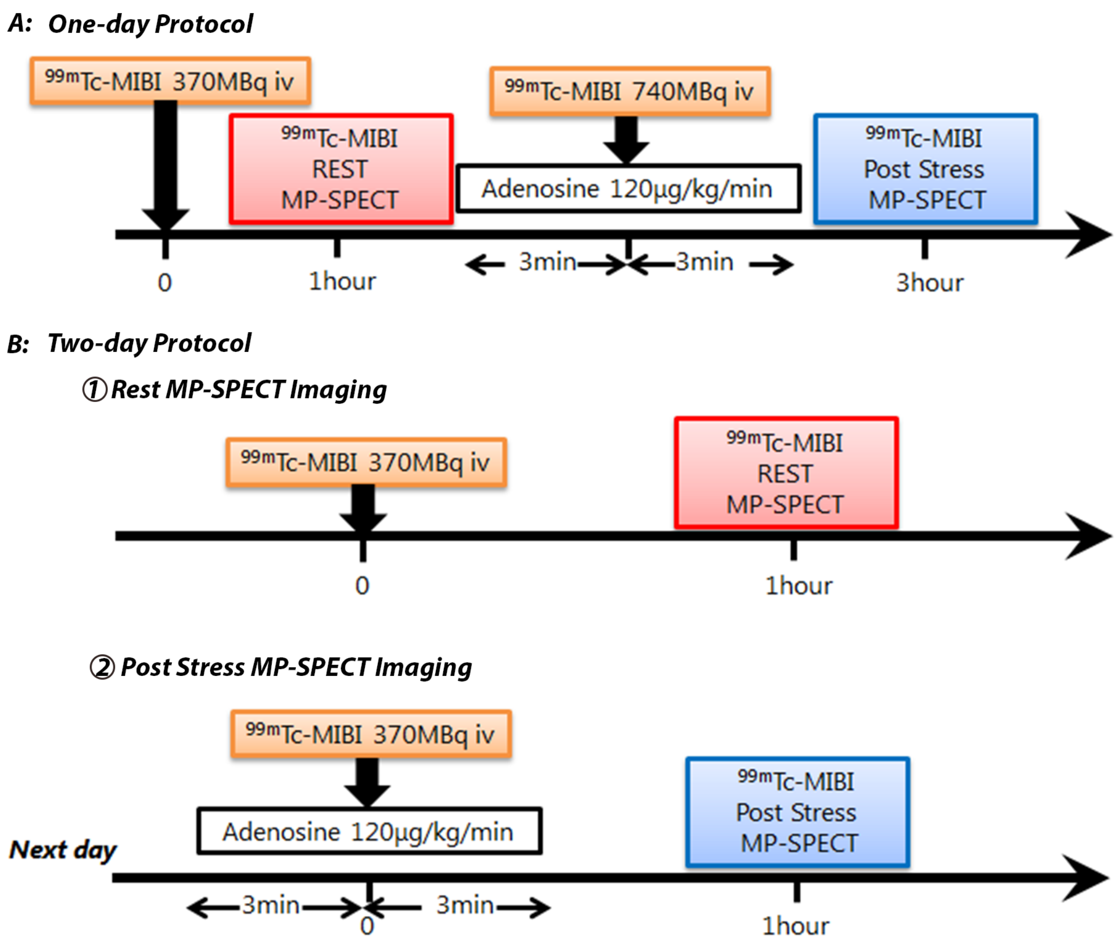

Figure 1. Standard rest-stress ^{99m}Tc-sestamibi myocardial perfusion imaging (MIBI) myocardial perfusion-single photon emission computed tomography (MP-SPECT) protocols. Rest-stress MP imaging with ^{99m}Tc-MIBI can be performed based on either a one-day protocol (A) or a two-day protocol (B). In the rest-stress one-day protocol, the dose of stress imaging should be higher than that of rest imaging.

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.

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.

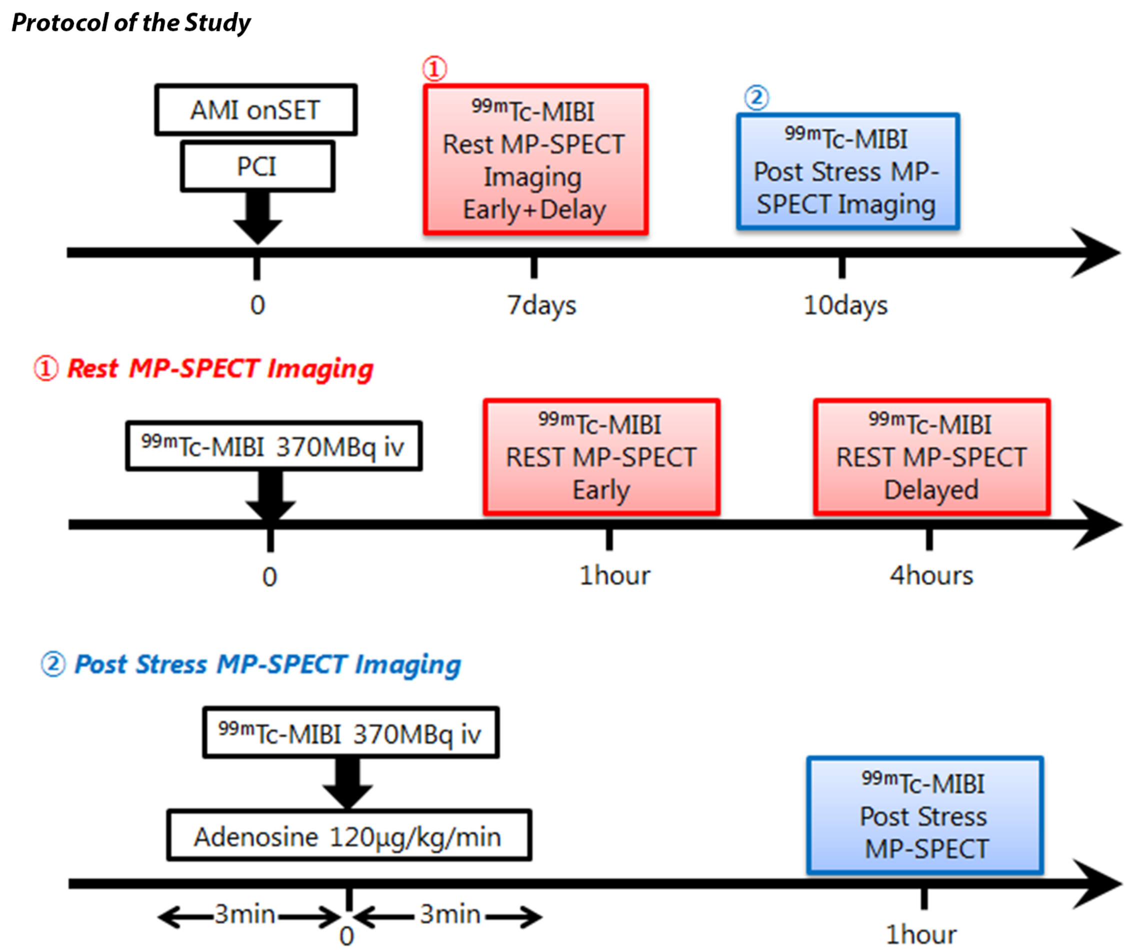

Figure 2. The study protocol. Rest myocardial perfusion (MP) imaging with ^{99m}Tc-sestamibi was performed within seven days after percutaneous coronary intervention (PCI). Stress MP imaging was performed within 10 days after rest imaging.

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.

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.

The rest-early phase ^{99m}Tc-MIBI MP-SPECT and delayed phase ^{99m}Tc-MIBI MP-SPECT imaging were performed at 6.5 ± 2.0 days after successful PCIs, and the post-adenosine stress ^{99m}Tc-MIBI MP-SPECT imaging was performed at 2.3 ± 1.9 days after the rest ^{99m}Tc-MIBI MP-SPECT imaging. The images of a 71-year-old woman who developed AMI and underwent ^{99m}Tc-MIBI MP-SPECT after PCI are presented in Figure 3. The left anterior descending coronary artery was almost occluded, and a successful coronary reflow was achieved through direct PCI. Perfusion defect areas were detected in the anterior and septal regions of the LV. These defect areas were larger on the delayed polar map compared to the post-stress polar map (Figure 3A). Moreover, accumulations in the anteroseptal and apical areas were

Table 1. Baseline Characteristics of the Patient Population [a]

Characteristics	All patients
Age (y)	71 ± 8.4
Sex	
Male	23
Female	6
From symptom onset to PCI time (h)	5.1 ± 3.6
From symptom onset to MIBI rest interval (d)	6.5 ± 2
From MIBI rest to MIBI stress interval (d)	2.3 ± 1.9
Peak CPK (IU/I)	737 ± 2116
Culprit arteries	
LAD	19
LCx	3
RCA	11
Diabetes mellitus	9 (31)
Hypertension	18 (62)
Hypercholesterolemia	27 (93)
Smoker	16 (55)
CKD (eGFR < 60 mL/min/1.73 m^2)	19 (66)

Abbreviations: PCI, percutaneous coronary intervention; MIBI, ^{99m}Tc-sestamibi myocardial perfusion imaging; CPK, creatine phosphokinase; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; CKD, chronic kidney disease; GFR, glomerular filtration rate.
[a] Data are expressed as No. (%) or mean ± SD, unless otherwise indicated.

fewer in the rest-delayed phase images compared to other images (Figure 3B).

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% ± 14.9% vs. 27.8% ± 14.0%; $P < 0.001$). Additionally, the TPD score of post-stress SPECT was significantly lower than that of rest-delayed phase SPECT (22.2% ± 14.3% vs. 27.8% ± 14.0%; $P < 0.001$) (Figure 4). The washout TPD score was significantly higher than the difference in the TPD score (6.24% ± 4.85% vs. 0.79% ± 4.76%; $P < 0.0001$) (Table 2).

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 ^{99m}Tc-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 ^{99m}Tc-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, Torrealba 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 ^{99m}Tc-MIBI decreased, and the ^{99m}Tc-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 ^{99m}Tc-MIBI was lost. Moreover, the ^{99m}Tc-MIBI washout region, identified by rest-delayed phase imaging, represented a myocardial tissue with normal oxygen supply through successful PCI reperfusion (20, 26); however, mi-

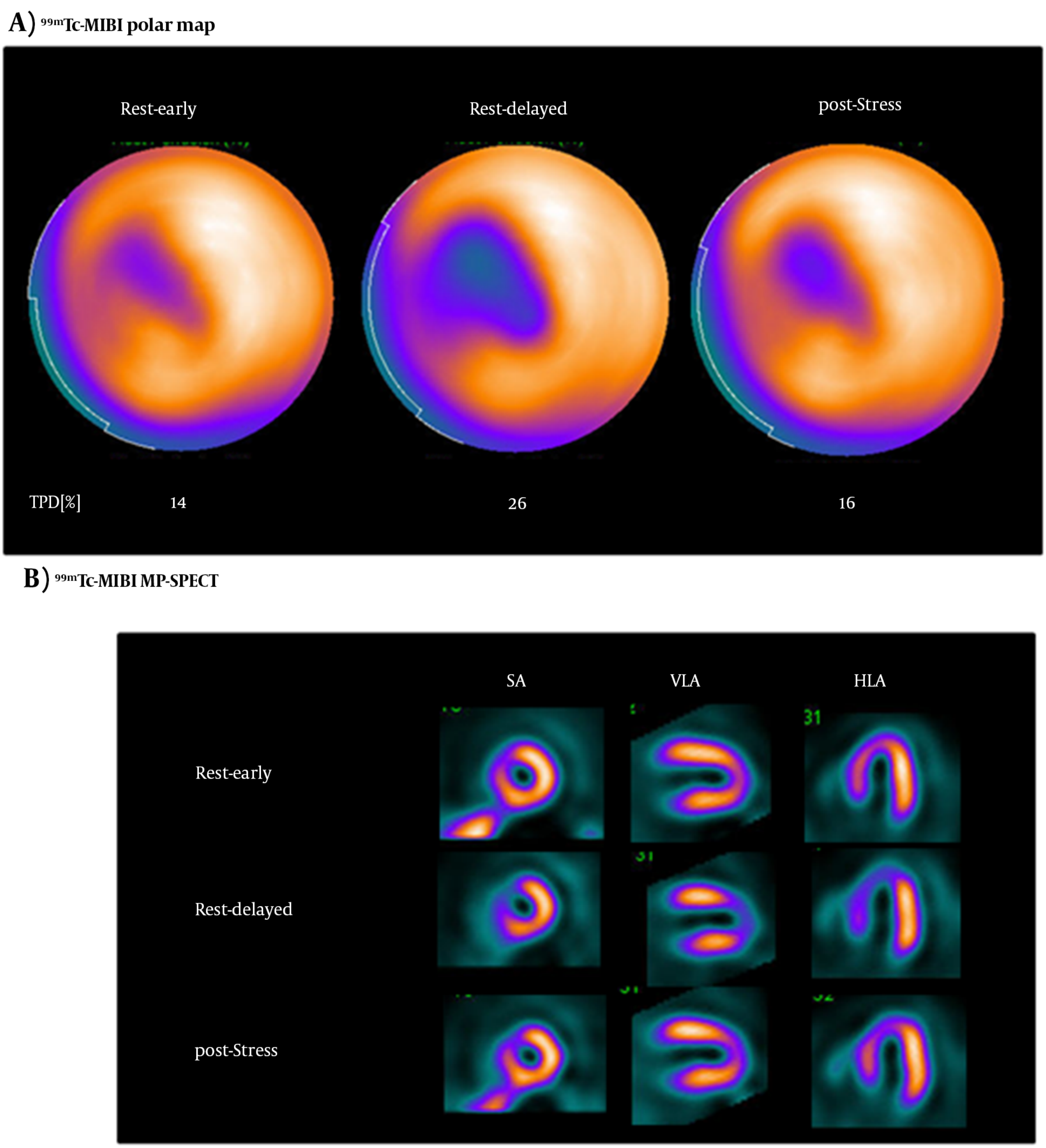

Figure 3. A typical serial imaging study (A and B). The myocardial images of a 71-year-old woman in early phase, delayed phase, and stress conditions using ^{99m}Tc-sestamibi myocardial perfusion imaging (MIBI) single photon emission computed tomography (SPECT). The delayed phase images show severe ^{99m}Tc-MIBI washout in the septal regions of the left ventricle (LV).

tochondrial damage caused by AMI remained unchanged, and ^{99m}Tc-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.

Table 2. Individual Characteristics of the Population [a]

Sex	Age (y)	Culprit arteries	TPD score				
			Rest early	Rest delayed	Post stress	Washout	Difference
M	63	LAD	16	31	22	15	6
M	74	LAD	7	22	11	15	4
M	74	LAD, RCA	7	22	7	15	0
F	71	LAD	14	26	16	12	2
M	90	RCA	20	32	15	12	-5
M	64	LAD, RCA	26	37	29	11	3
M	64	LAD	2	13	3	11	1
F	68	LAD	21	31	26	10	5
M	73	RCA	3	13	4	10	1
M	77	LAD	26	34	26	8	0
M	70	LAD	11	17	22	6	11
M	66	RCA	35	41	38	6	3
M	71	LAD	49	55	51	6	2
M	57	LAD, RCA	29	35	28	6	-1
M	83	RCA	9	14	11	5	2
M	71	LAD	34	39	34	5	0
F	77	LAD	34	39	21	5	-13
M	63	RCA	16	20	21	4	5
F	77	LAD	22	26	24	4	2
M	63	LCx	43	47	44	4	1
F	79	LAD	47	51	38	4	-9
M	57	LAD	0	3	1	3	1
M	63	LCx	11	14	10	3	-1
M	74	LAD	12	14	15	2	3
F	69	RCA	35	37	33	2	-2
M	73	LCx	19	20	16	1	-3
M	56	LAD	3	3	5	0	2
M	86	RCA	20	19	15	-1	-5
M	76	LAD, RCA	53	50	58	-3	8
Mean			21.5	27.8	22.2	6.24	0.79
SD			14.9	14.0	14.3	4.85	4.77

Abbreviations: M, male; F, female; TPD, total perfusion deficit; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; SD, standard deviation

[a] [Washout TPD score] = [rest-delayed TPD score] - [rest-early TPD score], and [Difference TPD score] = [post-stress TPD score] - [rest-early TPD score]

Investigation of treatment effects on AMI is important for predicting the AMI prognosis. The myocardium with ^{99m}Tc-MIBI washout in rest-early phase and delayed phase ^{99m}Tc-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

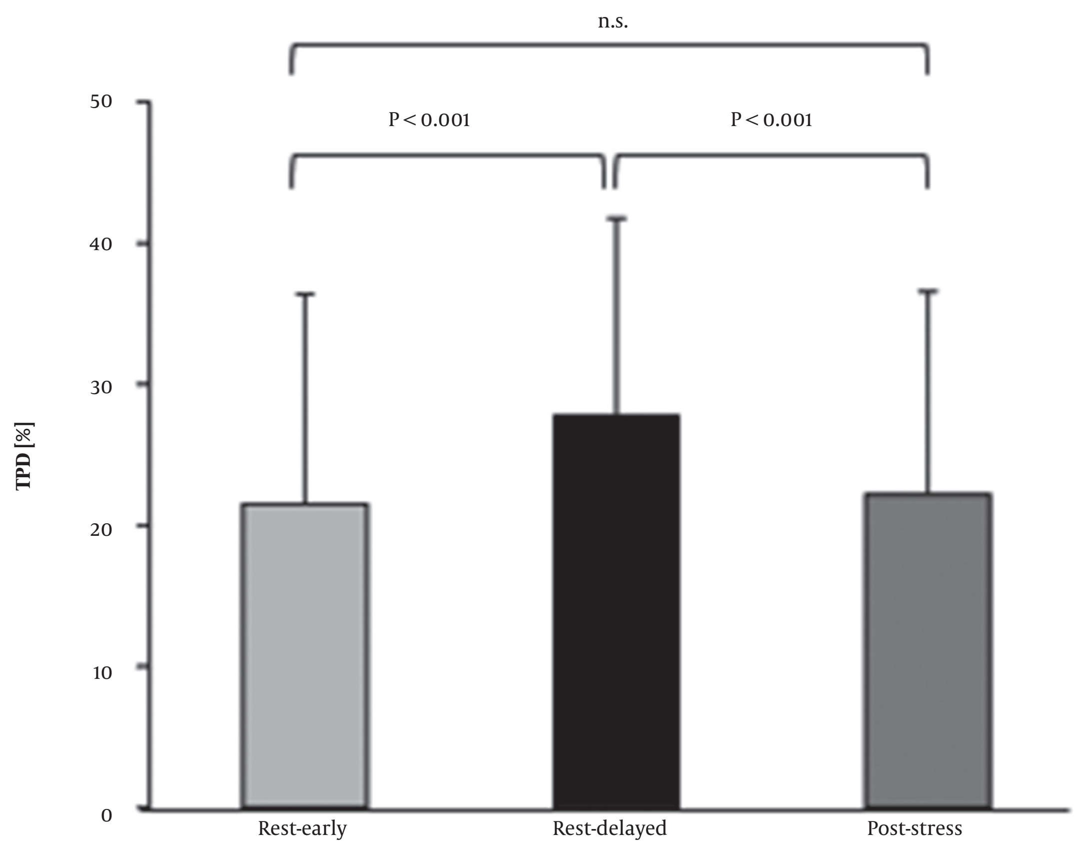

Figure 4. Comparison of the total perfusion deficit (TPD) scores between the rest-early phase, rest-delayed phase, and post-stress ^{99m}Tc-sestamibi myocardial perfusion-single photon emission computed tomography (MP-SPECT) images. The post-stress and rest-early phase TPD scores were significantly lower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

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 post-stress ^{99m}Tc-MIBI MP-SPECT imaging was found to be a clinically useful imaging method that could not only identify residual ischemia after AMI reperfusion, but also predict the LV function improvement in the chronic phase. In the current study, the rest-early/delayed phase ^{99m}Tc-MIBI MP-SPECT imaging on the first day and post-stress ^{99m}Tc-MIBI MP-SPECT imaging on the following day were performed (the so-called "two-day protocol"). Generally, the two-day protocol is less affected by shine-through defects compared to the one-day protocol, where rest-stress MP-SPECT imaging is performed on the same day. The dose of ^{99m}Tc-MIBI for the one-day protocol is 1,100 MBq in rest-stress MP-SPECT imaging, while it is 740 MBq for the two-day protocol in rest-stress MP-SPECT imaging (ie, 2/3 of the exposure dose at our hospital). Since this protocol uses a ^{99m}Tc tracer, the exposure dose can be significantly lower than that of dual SPECT with ^{201}Tl and ^{123}I-BMIPP, which is conventionally used to determine the effects of treatment on AMI (27).

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).

Funding/Support: We did not receive any funding from any profit or not-for-profit organizations for the research, authorship, or publication of this article.

Informed Consent: The requirement to obtain informed consent was waived because of the retrospective design of the study.

References

1. Selker HP, Udelson JE, Ruthazer R, D'Agostino RB, Nichols M, Ben-Yehuda O, et al. Relationship between therapeutic effects on infarct size in acute myocardial infarction and therapeutic effects on 1-year outcomes: A patient-level analysis of randomized clinical trials. *Am Heart J*. 2017;**188**:18–25. doi: 10.1016/j.ahj.2017.02.028. [PubMed: 28577674].
2. Onishi T, Kobayashi I, Onishi Y, Kawashima T, Muramoto H, Nakamura H, et al. Evaluating microvascular obstruction after acute myocardial infarction using cardiac magnetic resonance imaging and 201-thallium and 99m-technetium pyrophosphate scintigraphy. *Circ J*. 2010;**74**(12):2633–40. doi: 10.1253/circj.cj-10-0532. [PubMed: 20975233].
3. Akutsu Y, Kaneko K, Kodama Y, Li HL, Nishimura H, Hamazaki Y, et al. Technetium-99m pyrophosphate/thallium-201 dual-isotope SPECT imaging predicts reperfusion injury in patients with acute myocardial infarction after reperfusion. *Eur J Nucl Med Mol Imaging*. 2009;**36**(2):230–6. doi: 10.1007/s00259-008-0922-y. [PubMed: 18787823].
4. Biswas SK, Sarai M, Hishida H, Ozaki Y. 123I-BMIPP fatty acid analogue imaging is a novel diagnostic and prognostic approach following acute myocardial infarction. *Singapore Med J*. 2009;**50**(10):943–8. [PubMed: 19907882].
5. Iwado H, Iwado Y, Ohmori K, Mizushige K, Yukiiri K, Takagi Y, et al. Latent abnormal fatty acid metabolism in apparently normal perfusion during stress in patients with restenosis after coronary angioplasty: assessment by exercise stress thallium-201 and iodine-123-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid-dual myocardial single-photon emission computed tomography. *Am J Cardiol*. 2004;**93**(6):685–8. doi: 10.1016/j.amjcard.2003.12.003. [PubMed: 15019869].
6. Masuda A, Yoshinaga K, Naya M, Manabe O, Yamada S, Iwano H, et al. Accelerated (99m)Tc-sestamibi clearance associated with mitochondrial dysfunction and regional left ventricular dysfunction in reperfused myocardium in patients with acute coronary syndrome. *EJNMMI Res*. 2016;**6**(1):41. doi: 10.1186/s13550-016-0196-5. [PubMed: 27169534]. [PubMed Central: PMC4864798].
7. Hayashi D, Ohshima S, Isobe S, Cheng XW, Unno K, Funahashi H, et al. Increased (99m)Tc-sestamibi washout reflects impaired myocardial contractile and relaxation reserve during dobutamine stress due to mitochondrial dysfunction in dilated cardiomyopathy patients. *J Am Coll Cardiol*. 2013;**61**(19):2007–17. doi: 10.1016/j.jacc.2013.01.074. [PubMed: 23501381].
8. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. *J Nucl Cardiol*. 2007;**14**(2):215–20. doi: 10.1016/j.nuclcard.2006.10.022. [PubMed: 17386384].
9. Norton M, Ng AC, Baird S, Dumoulin A, Shutt T, Mah N, et al. ROMO1 is an essential redox-dependent regulator of mitochondrial dynamics. *Sci Signal*. 2014;**7**(310):ra10. doi: 10.1126/scisignal.2004374. [PubMed: 24473195].
10. Matsuo S, Nakajima K, Kinuya S. Evaluation of Cardiac Mitochondrial Function by a Nuclear Imaging Technique using Technetium-99m-MIBI Uptake Kinetics. *Asia Ocean J Nucl Med Biol*. 2013;**1**(1):39–43. doi: 10.7508/aojnmb.2013.01.008. [PubMed: 27408841]. [PubMed Central: PMC4937671].
11. Nakajima K, Matsumoto N, Kasai T, Matsuo S, Kiso K, Okuda K. Normal values and standardization of parameters in nuclear cardiology: Japanese Society of Nuclear Medicine working group database. *Ann Nucl Med*. 2016;**30**(3):188–99. doi: 10.1007/s12149-016-1065-z. [PubMed: 26897008]. [PubMed Central: PMC4819542].
12. Morrow DA, Antman EM, Parsons L, de Lemos JA, Cannon CP, Giugliano RP, et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA*. 2001;**286**(11):1356–9. doi: 10.1001/jama.286.11.1356. [PubMed: 11560541].
13. Henzlova MJ, Cerqueira MD, Mahmarian JJ, Yao SS, Quality Assurance Committee of the American Society of Nuclear C. Stress protocols and tracers. *J Nucl Cardiol*. 2006;**13**(6):e80–90. doi: 10.1016/j.nuclcard.2006.08.011. [PubMed: 17174798].
14. Slomka PJ, Nishina H, Berman DS, Akincioglu C, Abidov A, Friedman JD, et al. Automated quantification of myocardial perfusion SPECT using simplified normal limits. *J Nucl Cardiol*. 2005;**12**(1):66–77. doi: 10.1016/j.nuclcard.2004.10.006. [PubMed: 15682367].
15. Germano G, Kavanagh PB, Waechter P, Areeda J, Van Kriekinge S, Sharir T, et al. A new algorithm for the quantitation of myocardial perfusion SPECT. I: technical principles and reproducibility. *J Nucl Med*. 2000;**41**(4):712–9. [PubMed: 10768574].
16. Nakajima K. Normal values for nuclear cardiology: Japanese databases for myocardial perfusion, fatty acid and sympathetic imaging and left ventricular function. *Ann Nucl Med*. 2010;**24**(3):125–35. doi: 10.1007/s12149-009-0337-2. [PubMed: 20108130]. [PubMed Central: PMC2855806].
17. Yoda S, Nakanishi K, Tano A, Hori Y, Suzuki Y, Matsumoto N, et al. Validation of automated quantification of nuclear cardiology in Japanese patients using total perfusion deficits: Comparison with visual assessment. *J Cardiol*. 2014;**63**(5):350–7. doi: 10.1016/j.jjcc.2013.10.004. [PubMed: 24262645].
18. Matsuo S, Nakajima K, Takeishi Y, Nishimura T. Prognostic value of normal stress myocardial perfusion imaging and ventricular function in Japanese patients with chronic kidney disease: a study based on the J-ACCESS-3 database. *Eur J Nucl Med Mol Imaging*. 2018;**45**(7):1101–7. doi: 10.1007/s00259-018-3956-9. [PubMed: 29502312].

19. Hausenloy DJ, Duchen MR, Yellon DM. Inhibiting mitochondrial permeability transition pore opening at reperfusion protects against ischaemia-reperfusion injury. *Cardiovasc Res*. 2003;**60**(3):617–25. doi: 10.1016/j.cardiores.2003.09.025. [PubMed: 14659807].
20. Torrealba N, Aranguiz P, Alonso C, Rothermel BA, Lavandero S. Mitochondria in Structural and Functional Cardiac Remodeling. *Adv Exp Med Biol*. 2017;**982**:277–306. doi: 10.1007/978-3-319-55330-6_15. [PubMed: 28551793].
21. Tune JD. Control of coronary blood flow during hypoxemia. *Adv Exp Med Biol*. 2007;**618**:25–39. doi: 10.1007/978-0-387-75434-5_3. [PubMed: 18269186].
22. Richardson KJ, Kuck L, Simmonds MJ. Beyond oxygen transport: active role of erythrocytes in the regulation of blood flow. *Am J Physiol Heart Circ Physiol*. 2020;**319**(4):H866–72. doi: 10.1152/ajpheart.00441.2020. [PubMed: 32857630].
23. Matsuo S. Editorial: Regadenoson: An adenosine A2A receptor agonist for pharmacological myocardial perfusion imaging. *J Cardiol Cases*. 2014;**10**(2):46–7. doi: 10.1016/j.jccase.2014.03.004. [PubMed: 30546502]. [PubMed Central: PMC6281723].
24. Mustafa SJ, Morrison RR, Teng B, Pelleg A. Adenosine receptors and the heart: role in regulation of coronary blood flow and cardiac electrophysiology. *Handb Exp Pharmacol*. 2009;(193):161–88. doi: 10.1007/978-3-540-89615-9_6. [PubMed: 19639282]. [PubMed Central: PMC2913612].
25. Chimura M, Ohtani T, Sera F, Nakamoto K, Konishi S, Miyawaki H, et al. Focal severe decrease in myocardial technetium-99 m sestamibi uptake indicates ventricular irreversibility in patients with dilated cardiomyopathy. *Ann Nucl Med*. 2021;**35**(8):881–8. doi: 10.1007/s12149-021-01625-4. [PubMed: 34003458].
26. Yamanaka M, Takao S, Otsuka H, Yoichi O, Irahara S, Kunikane Y, et al. The Utility of a Combination of ^{99m}Tc-MIBI Washout Imaging and Cardiac Magnetic Resonance Imaging in the Evaluation of Cardiomyopathy. *Ann Nucl Cardiol*. 2021;**7**(1):8–16. doi: 10.17996/anc.21-00124.
27. Desiderio MC, Lundbye JB, Baker WL, Farrell MB, Jerome SD, Heller GV. Current Status of Patient Radiation Exposure of Cardiac Positron Emission Tomography and Single-Photon Emission Computed Tomographic Myocardial Perfusion Imaging. *Circ Cardiovasc Imaging*. 2018;**11**(12). e007565. doi: 10.1161/CIRCIMAGING.118.007565. [PubMed: 30558499].