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Significance of ^{99m}Tc-Sestamibi myocardial scintigraphy after percutaneous coronary intervention in patients with acute myocardial infarction

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Yoshihiro J. Akashi[1ABCDEF], Kohei Ashikaga[1BCF], Makoto Takano[1B], Masaki Izumo[1B], Yuki Ishibashi[1B], Keisuke Kida[1B], Kihei Yoneyama[1BCD], Kengo Suzuki[1D], Fumihiko Miyake[1D], Maciej Banach[2E]

[1] Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan
[2] Department of Hypertension, Medical University of Lodz, Lodz, Poland

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Summary

Background: This study was designed to clarify the significance of washout rate (WR) determined from ^{99m}Tc-sestamibi myocardial scintigraphic images and the levels of cardiac enzymes in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI).

Material/Methods: A total of 56 consecutive patients with AMI (mean age 65.8±8.5 years), who underwent PCI on admission, were included. Cardiac enzyme, the MB isoenzyme of creatinine kinase (CK-MB), was measured every 3 h after admission. Two weeks after the onset of AMI, ^{99m}Tc-sestamibi myocardial scintigraphy was performed at early (30 min) and delayed (4 h) phases after tracer injection. The heart-to-mediastinum ratio (H/M) and WR were calculated from the planar images.

Results: PCI was performed at 9.4±6.0 h after the onset of AMI. In 26 patients the culprit lesion was located in the right coronary artery and in 24 patients it was located in the left anterior descending coronary artery. The peak CK-MB was 274.1±169.4 IU/L (13.5±3.9 h). The early and delayed H/Ms and WR of ^{99m}Tc-sestamibi were 2.74±0.58, 3.00±0.70, and 58.8±10.0%, respectively. The delayed H/M was significantly correlated with the peak CK-MB (r=–0.37, p=0.005). The WR of ^{99m}Tc-sestamibi was also significantly correlated with the peak CK-MB (r=–0.34, p=0.012).

Conclusions: These results suggest that the WR determined from ^{99m}Tc-sestamibi myocardial scintigraphic images reflects the extent of myocardial damage in AMI patients.

key words: acute myocardial infarction • creatinine kinase • ^{99m}Tc-sestamibi • washout rate

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Author's address: Yoshihiro J. Akashi, Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan, e-mail: johnny@marianna-u.ac.jp

Background

Creatinine kinase (CK) and cardiac troponin is used for diagnostic evaluation of myocardial damage in patients with acute myocardial infarction (AMI). CK is an established noninvasive measure of myocardial infarct size and severity [1] and has been accepted as a reliable prognostic marker in AMI patients undergoing primary percutaneous coronary intervention (PCI) [2]. Although early reperfusion phenomena strongly influence CK release [3], the peak values of cardiac biomarkers, including CK and the MB isoenzyme of CK (CK-MB), predict the prognosis of AMI patients after PCI [2,4]. In general, contrast-enhanced magnetic resonance imaging [5,6] and nuclear cardiology techniques [1,7,8] evaluate the association between cardiac biomarkers and myocardial damage.

Since 1990, single-photon emission computed tomography (SPECT) with technetium-99m hexakis 2-methoxyisobutyl-isonitrile (^{99m}Tc-sestamibi) has been widely used to assess myocardial damage at rest after the onset of AMI [9]. ^{99m}Tc-sestamibi is known to exhibit the phenomenon of reverse redistribution, so-called washout, in patients with AMI after PCI [10–12]. Myocardial scintigraphy with ^{123}I-metaiodobenzylguanidine is a standard method of rendering early and delayed images; nuclide tracer washout is the gold standard for evaluating cardiac function [13]. However, washout of ^{99m}Tc-sestamibi is still a matter of debate; the significance of washout has not been fully elucidated in AMI patients after primary PCI. No previous study has demonstrated the significance of cardiac biomarkers and washout of ^{99m}Tc-sestamibi for the evaluation of cardiac damage in AMI patients. Accordingly, the present study was designed to clarify the association between the washout rate (WR) of ^{99m}Tc-sestamibi determined from myocardial scintigraphic images and cardiac enzymes in AMI patients after PCI.

Material and Methods

Subjects

This study population comprised 56 consecutive patients (mean age 65.8 years) who had suffered their first AMI. On arrival at the emergency department, venous blood was withdrawn from the cubital vein. AMI was diagnosed by cardiologists on the basis of the symptoms, electrocardiographic changes, echocardiograms, detection of human heart fatty acid binding protein by immunochromatography, and by hematological findings, including CK and CK-MB. In order to determine the actual onset time, cardiologists conducted interviews with the patients and family members.

Table 1 shows detailed patient characteristics. After the diagnosis of AMI, the patients were immediately transferred to the cardiac catheter laboratory for emergent cardiac catheterization. In 26 patients, the culprit lesion was located in the right coronary artery (RCA); in 24 in the left anterior descending coronary artery (LAD); and in 6 patients in the left circumflex coronary artery (LCx). Thrombus aspiration catheters were used to cross the occluding lesions; follow-up coronary angiography was performed during PCI. Blood samples were collected every 3 h after PCI to determine the peak values of cardiac enzymes. Those patients with AMI, who received PCI followed with conventional drugs, experienced no worsening of symptoms and required no hospitalization due to AMI-related complications, either before or after the scintigraphic examinations.

The Human Investigation Committee of St. Marianna University School of Medicine approved the study protocol. Written informed consent was obtained from each patient before the study.

Radionuclide studies

All study patients underwent SPECT 2 weeks after the onset of AMI. ^{99m}Tc-sestamibi (740 MBq; FUJI FILM RI Pharma Co. Ltd., Tokyo, Japan) was injected into the left antecubital vein, and thereafter SPECT was performed twice-initially at 30 min after injection (early ^{99m}Tc-sestamibi uptake) and subsequently at 4 h after injection (delayed uptake).

Before performing SPECT, anterior and lateral planar images were acquired for 300 s using a gamma camera equipped with a low-/medium-energy general-purpose collimator and a 512×512 matrix. ^{99m}Tc-sestamibi images were obtained using a double-headed gamma camera (Symbia E; Siemens-Asahi Medical Technologies Ltd., Tokyo, Japan) equipped with a low-/medium-energy general-purpose collimator. Two detectors (2×180°) were used to acquire 64 views for 25 s in 5.6° steps using a 64×64 matrix. The energy window of ^{99m}Tc was centered at 140 keV ±15%.

Raw imaging data were reconstructed using Butterworth-filtered (order, 8; cut-off frequency, 0.20 cycles/pixel) back-projection. Transaxial slices were reconstructed and reoriented to represent coronal slices, and then horizontal long- and short-axis slices were produced by axis shift.

Standard electrocardiographically gated images were acquired in 64 steps at 19 s per step, using the step acquisition mode in RR interval, and divided into 16 frames. Tracer uptake was assessed by non-gated early images created from the sums of all of the gated images obtained in standard acquisition mode.

Data analysis

Regions of interest (ROIs) were drawn over the entire heart and upper mediastinum depicted in the planar images. The H/M ratio and global WR of ^{99m}Tc-sestamibi were calculated from the pixel counts in the ROIs using the following equations: H/M = mean pixel count of cardiac ROI/mean pixel count of mediastinal ROI; and WR (%) = [(mean early cardiac pixel count – mean delayed cardiac pixel count)/mean early cardiac pixel count] × 100. Backgrounds and time-decay corrections were not applied to the calculation of WR.

Once a SPECT image was acquired and reconstructed from an early image, quantitative gated SPECT (QGS) software (Cedars-Sinai Medical Center, Los Angeles, CA) was used to calculate the ventricular edges and evaluate the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) [14].

Statistical analysis

The results are expressed as the means ±SD. The significance of differences among different coronary territories was assessed by one-way analysis of variance (ANOVA). Parameters

Table 1. Patients' characteristics, laboratory findings, and medications.

Culprit lesion	Total	LAD	LCx	RCA	*p* value
Patients' number	56	24	6	26	
STEMI (n)	53	24	3	26	
Male/Female (n)	45/11	21/3	4/2	20/6	
Age (ys)	65.8±8.5	67.0±11.2	67.5±9.5	64.7±9.5	n.s.
Height (cm)	161.7±8.6	162.7±9.4	159.5±8.0	161.3±8.0	n.s.
Body weight (kg)	61.9±10.2	63.0±12.1	59.0±7.1	61.8±8.9	n.s.
Initial cardiac enzyme					
CK (IU/L)	410.7±1318.0	525.5±604.9	223.5±278.9	341.5±502.5	n.s.
CK-MB (IU/L)	39.8±198.1	57.8±91.0	24.9±49.1	26.8±51.6	0.15
Time to revascularlization from the onset (hr)	9.4±6.0	10.8±17.1	9.9±7.6	8.0±8.3	n.s.
Peak CK (IU/L)	2689.6±1167.4	3024.7±2438.5	2725.2±2961.5	2333.1±1500.7	n.s.
Sampling time	15.3±4.6	17.5±17.6	15.7±10.1	13.3±7.0	n.s.
Peak CK-MB (IU/L)	274.1±169.4	342.5±327.7	245.6±154.2	218.0±122.4	0.08
Sampling time	13.5±3.9	14.2±16.0	15.7±10.1	12.4±7.2	n.s.
Medications					
Aspirin (n)	56	24	6	26	
ACE-I or ARB (n)	55	24	6	25	
β-blocker (n)	48	22	6	20	
Calcium channel blocker (n)	21	13	2	6	
Statin (n)	49	22	5	22	
Diuretics (n)	4	3	0	1	

Values were expressed as mean ±S.D. LAD – left anterior descending coronary artery; LCx – left circumflex coronary artery; RCA – right coronary artery; STEMI – ST elevated myocardial infarction; CK – creatinine kinase; CK-MB – MB isoenzyme of CK; ACE-I – angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker. The actual onset time was interviewed.The peak sampling time was calculated based on the time of the onset.

in the early and delayed phases in the same patient were compared using a paired *t* test. Liner regression analysis was used to evaluate the significance of peak values of cardiac enzymes and the values obtained from ^{99m}Tc-sestamibi myocardial scintigraphic images. P value of less than 0.05 was considered to indicate statistical significance.

Results

Patients' characteristics and laboratory findings

PCI was performed 9.4±6.0 h after the actual onset of AMI. All patients received an appropriate PCI; in 51 (91%) patients, aspiration catheters successfully penetrated the occluding lesions and were followed by conventional PCI. The remaining 5 patients received PCI without aspiration catheters. Thrombolysis in myocardial infarction (TIMI) [15] grade 3 flow was observed in all patients after PCI.

There were no differences in the age, BMI, cardiac enzymes on admission, time from the onset to revascularization, and peak cardiac enzymes, even though the patients had culprit lesions located in different arteries (Table 1). The CK and CK-MB levels on admission were 410.6±1318.0 IU/L and 39.8±198.1 IU/L, and the peak CK and CK-MB levels were 2689.6±1167.4 IU/L (15.3±4.6 h) and 274.1±169.4 IU/L (13.5±3.9 h), respectively.

After 200mg of acetylsalicylic acid and 300 mg of clopidgrel sulfate administration as a loading dose, all patients received 100 mg of acetylsalicylic acid and 75 mg of clopidogrel sulfate after PCI as a maintenance dose. Most of the patients were treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, or some type of statin in order to prevent secondary cardiac events and deterioration of cardiac function. Seven patients who received statin were not able to continue the administration due to muscle ache.

Scintigraphic study

The early and delayed H/Ms and WR of ^{99m}Tc-sestamibi were 2.74±0.58, 3.00±0.70, and 58.7±10.0%, respectively. The early and delayed H/Ms were significantly lower in the patients with an LAD culprit lesion (2.59±0.36 and 2.70±0.41, respectively) than in those with an LCx culprit lesion (2.96±0.42,

Table 2. The results from ^{99m}Tc-Sestamibi myocardial scintigraphic study.

Culprit lesion	Total	LAD	LCx	RCA	p value
Early H/M	2.74±0.58	2.59±0.36	2.96±0.42	2.84±0.43	0,04
Delayed H/M	3.00±0.70	2.70±0.41	3.27±0.64	3.21±0.49	<0.01
WR (%)	58.8±10.0	61.1±6.6	59.4±3.8	56.4±4.5	<0.01
Corrected WR (%)	31.3±9.4	35.3±10.5	32.3±6.3	27.2±7.1	<0.01
EDV (ml)	97.9±27.2	96.2±27.4	98.3±28.8	98.6±27.5	n.s.
ESV (ml)	51.9±22.0	51.6±23.1	51.3±29.6	51.7±19.8	n.s.
EF (%)	48.8±10.0	48.2±10.1	51.0±16.0	49.0±8.6	n.s.

Values were expressed as mean ±S.D. H/M – heart to mediastinum ratio; WR – washout rate; EDV – end-diastolic volume; ESV – end-systolic volume; EF – ejection fraction. Other abbreviations are shown in Table 1.

p=0.037; and 3.27±0.64, p=0.01) or an RCA culprit lesion (2.84±0.43, p=0.040; and 3.21±0.49, p<0.01). The global WR of ^{99m}Tc-sestamibi was significantly accelerated in the patients with an LAD culprit lesion compared with those with an RCA culprit lesion (61.1±6.6% *vs.* 56.4±4.5%, p<0.01). A significant difference in the corrected WR was found between the patients with an LAD culprit lesion and those with an RCA culprit lesion (p<0.01; Table 2).

The Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular End Systolic Volume (LVESV), and Left Ventricular Ejection Fraction (LVEF) were 97.9±27.2 ml, 51.9±22.0 ml, and 48.8±10.0%, respectively (Table 2). No significant difference was observed among the patients with regard to the occluded artery.

Parameters from ^{99m}Tc-sestamibi images and peak cardiac enzymes

Figure 1 shows the association between the parameters obtained from the ^{99m}Tc-sestamibi planar images and cardiac enzymes. Although the early H/M was not correlated with the peak CK or peak CK-MB, the delayed H/M was correlated with the peak CK (r=–0.32, p=0.015) and peak CK-MB (r=–0.37, p=0.005). The WR of ^{99m}Tc-sestamibi was also correlated with the peak CK (r=–0.32, p=0.017) and peak CK-MB (r=–0.34, p=0.012).

Discussion

The present study demonstrated several significant aspects of ^{99m}Tc-sestamibi planar imaging for the assessment of cardiac damage in AMI patients after primary PCI. Firstly, the delayed uptake was negatively correlated with the peak values of CK and CK-MB. Secondly, the WR was positively correlated with the peak values of these cardiac enzymes. These results suggest that ^{99m}Tc-sestamibi imaging reflects injured myocardium. Since ^{99m}Tc-sestamibi WR indicates injured but viable myocardium, ^{99m}Tc-sestamibi imaging in the subacute phase of AMI may provide additional clinical information.

The association among peak CK, infarct size, and mortality was demonstrated in the 1970s [16,17]. After the importance of measuring CK in AMI patients was recognized, various studies were conducted to confirm the efficacy of peak CK. One study reported that CK-MB elevation without concomitant CK elevation is associated with a worse prognosis [18]. Although it has been suggested that CK-MB overestimates infarct size after reperfusion [19], a recent study has reported that peak CK and CK-MB are still related to mortality and infarct size in AMI patients with TIMI grade 3 flow after PCI. According to the guidelines described by Alpert et al [20], cardiac troponin is considered the sensitive marker of choice, and is more sensitive than CK and CK-MB. However, Tzivoni et al. [8] have demonstrated that peak troponin T is as accurate as peak CK, and CK-MB are as accurate as troponin T in estimating infarct size. Thus, in the present study, we determined peak CK and CK-MB and conducted a serological study for detecting cardiac damage.

^{99m}Tc-sestamibi is widely used as a myocardial perfusion tracer. The myocardial uptake mechanism of ^{99m}Tc-sestamibi depends on the passive distribution across the plasma and mitochondrial membranes in response to a transmembrane electrochemical gradient [21,22]; approximately 90% of its activity *in vivo* is associated with mitochondria [23]. Fundamental studies have reported a close relationship between mitochondrial function and retention of ^{99m}Tc-sestamibi in the myocardium. Crane et al. [24] have demonstrated that loss of mitochondrial metabolic function is related to ^{99m}Tc-sestamibi release from the myocardium. Another study reported that ^{99m}Tc-sestamibi uptake and retention are inhibited in a cultured chick myocyte model when mitochondrial membrane potential is depolarized [25]. Under ischemic conditions and during reperfusion, reactive oxygen species produced by endothelial cells induce the release of phagocytes in the myocardium, which leads to mitochondrial dysfunction [26]. Mitochondrial dysfunction may alter the mitochondrial membrane potential and impair myocardial retention of ^{99m}Tc-sestamibi.

In the present study, the delayed H/M and WR were correlated with the peak CK and CK-MB. A ^{99m}Tc-sestamibi kinetics study [27] has demonstrated a significant correlation between ^{99m}Tc-sestamibi activity after reperfusion and peak CK release in ischemic-reperfused rat heart models, which is consistent with the results of our study. Since peak CK represents the extent of myocardial injury, ^{99m}Tc-sestamibi-delayed H/M and WR are probably good markers of ischemic-damaged myocardium. In contrast, the early H/M of ^{99m}Tc-sestamibi was uncorrelated with peak CK and peak CK-MB. Weinstein et al. [28] reported that the initial uptake of

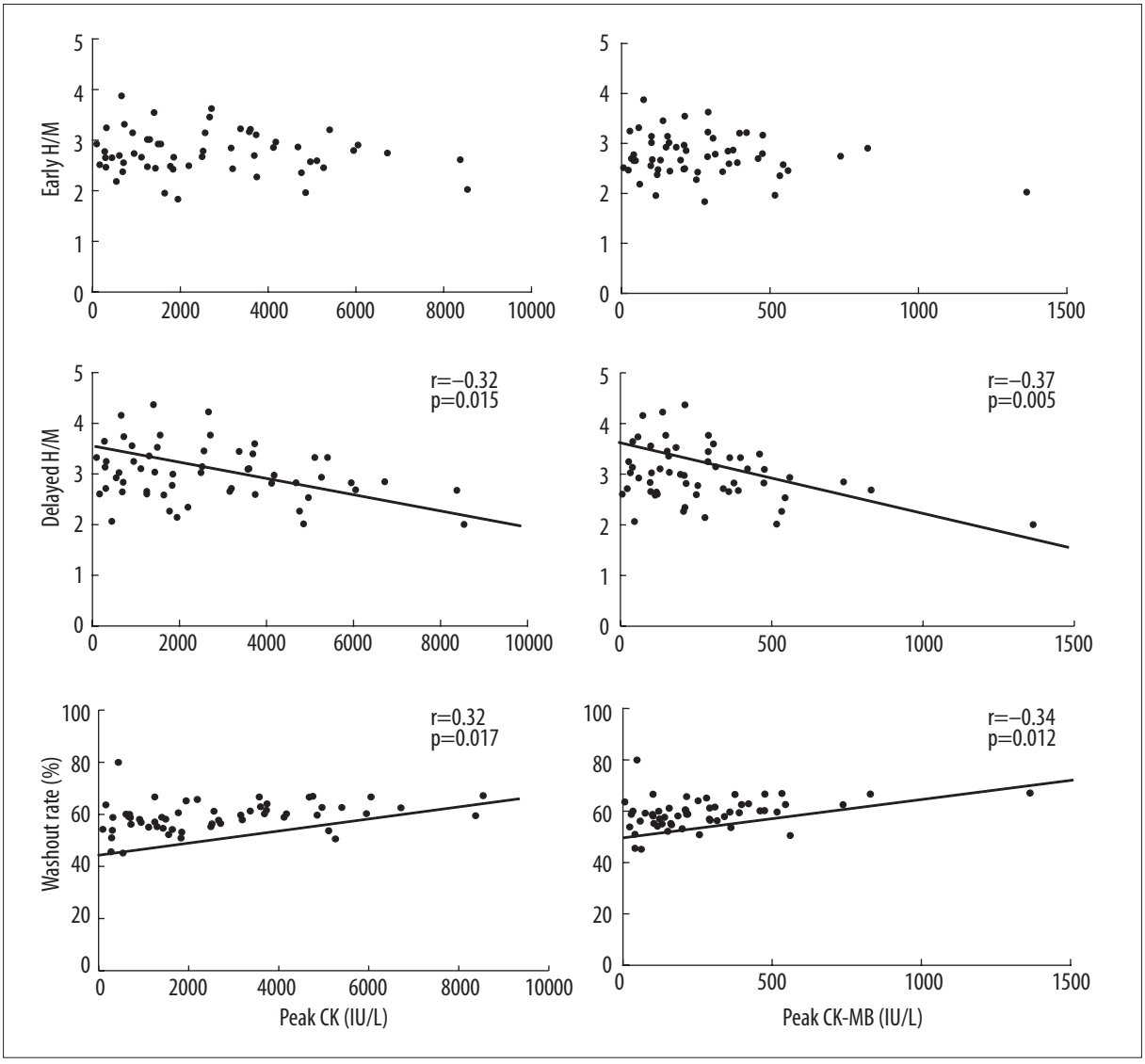

Figure 1. Association between the radionuclide parameters obtained from MIBI planar images and the peak values of cardiac enzymes. The delayed H/M is correlated with the peak CK (r=–0.32, p=0.015) and peak CK-MB (r=–0.37, p=0.005). The WR of ^{99m}Tc-sestamibi is also correlated with the peak CK (r=–0.32, p=0.017) and peak CK-MB (r=–0.34, p=0.012).

^{99m}Tc-sestamibi predominantly reflects coronary blood flow in a rabbit heart model of coronary occlusion. The early H/M of ^{99m}Tc-sestamibi reflects reperfused myocardial perfusion caused by primary PCI, which suggests that the early H/M of ^{99m}Tc-sestamibi is uncorrelated with peak CK and CK-MB. In studies conducted on ischemic patients, Takeishi et al. [10] reported that the WR of ^{99m}Tc-sestamibi after direct percutaneous transluminal coronary angioplasty was associated with infarct-related area and preserved left ventricular function. Fujiwara et al. [12] compared the WR of ^{99m}Tc-sestamibi with contractile reserve wall motion evaluated by low-dose dobutamine echocardiography. They concluded that the enhancement of ^{99m}Tc-sestamibi WR was related to the reversible functional abnormalities indicated by the dobutamine-responsive contractile reserve. These results suggest that the WR of ^{99m}Tc-sestamibi is associated with an ischemic-damaged but viable myocardium. In non-ischemic patients, Kumita et al. [29] reported that the WR of ^{99m}Tc-sestamibi, which was related to left ventricular function, was higher in patients with chronic heart failure than in controls. Matsuo et al. [30] analyzed left ventricular systolic and diastolic function in patients with dilated cardiomyopathy and demonstrated a positive correlation between the WR of ^{99m}Tc-sestamibi and the plasma BNP level. They also suggested that the WR of ^{99m}Tc-sestamibi might provide prognostic information in chronic heart failure patients because the incidence of cardiac events was higher in such patients with higher ^{99m}Tc-sestamibi WR. These non-ischemic heart disease studies also suggest that the WR of ^{99m}Tc-sestamibi might be a reliable marker of myocardial damage.

Study limitation

In the present study we did not evaluate regional WR of ^{99m}Tc-sestamibi in association with culprit region. Furthermore, this study was not a controlled trial. AMI patients who did not receive PCI should be included as controls in future studies. In the study with non-ischemic patients,

it was reported that WR of ^{99m}Tc-sestamibi might provide prognostic information. However, the prognostic values of H/M and WR in patients with ischemic cardiac disease remain unknown. Further investigations with larger numbers of patients should be conducted to evaluate the potential use of ^{99m}Tc-sestamibi as a prognostic incremental indicator.

Clinical implications

^{99m}Tc-sestamibi imaging is an objective tool for assessing myocardial damage and viability. The present study showed that ^{99m}Tc-sestamibi planar imaging may be useful for the assessment of cardiac damage in AMI patients. Since WR of ^{99m}Tc-sestamibi (after PCI) is associated with infarcted myocardium (but with preserved left ventricular function), increased WR might predict the improvement of left ventricular wall motion in chronic phase. Thus, ^{99m}Tc-sestamibi imaging after PCI may provide additional clinical information. Follow-up studies with larger number of patients are needed to confirm the usefulness of ^{99m}Tc-sestamibi images in AMI patients.

Conclusions

These results suggest that the WR determined from ^{99m}Tc-sestamibi myocardial scintigraphic images could reflect the extent of myocardial damage in AMI patients after PCI. This study also demonstrates the significance of taking ^{99m}Tc-sestamibi myocardial scintigraphic images at 2 different time points. Further studies are necessary to confirm these results.

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