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Reversible defect of ^{123}I-15-(*p*-iodophenyl)-9-(*R,S*)-methylpentadecanoic acid indicates residual viability within infarct-related area

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To evaluate the relationship between the reversible defect of ^{123}I-15-(*p*-iodophenyl)-9-(*R,S*)-methylpentadecanoic acid (9MPA) and residual viability within an infarct-related area, we performed resting single photon emission computed tomography (SPECT) with 9MPA and positron emission tomography (PET) with ^{18}F-deoxyglucose (FDG) and ^{13}N-ammonia (NH_3) in 7 patients with prior myocardial infarction.

9MPA-SPECT was obtained 2 min (early) and 50 min (delayed) after tracer injection. Tomographic images of the left ventricle were divided into 13 segments to correlate the regional uptake of each tracer. Residual viability within an infarct-related segment was confirmed by NH_3- and FDG-PET. Twenty-six infarct-related segments, confirmed by NH_3-PET, showed reduced uptake of 9MPA on early images. In these 26 segments, 6 showed reversible defect of 9MPA and 20 showed fixed defect on delayed images. Residual viability was present in all segments exhibiting reversible 9MPA defect and 7 segments (35%) exhibiting fixed defect ($p < 0.05$). The sensitivity, specificity and accuracy of reversible 9MPA defect for the detection of myocardial viability were 46%, 100%, and 73%, respectively. Myocardial clearance of 9MPA was significantly slower in non-viable segments than in ischemic but viable segments ($4.9 \pm 5.1\%$ vs. $10.1 \pm 5.3\%$; $p < 0.05$).

These data suggest that a reversible 9MPA defect indicates residual viability within the infarct-related area.

Key words: ^{123}I-15-(*p*-iodophenyl)-9-(*R,S*)-methylpentadecanoic acid, reversible defect, myocardial infarction, myocardial viability

INTRODUCTION

RADIONUCLIDE IMAGING with fatty acid analogue is a sensitive indicator of metabolic alteration in ischemic myocardium. ^{123}I-15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP, Fig. 1) is now widely used for assessing myocardial fatty acid utilization.[1] BMIPP shows prolonged myocardial retention by introducing methyl-branch into the beta-3 position to inhibit beta-oxidation. A number of reports have described the usefulness of imaging with BMIPP for evaluating myocardial ischemia in patients with coronary artery disease. Furthermore, combined BMIPP and myocardial perfusion imaging has been shown to assess myocardial viability, namely reduced uptake of BMIPP relative to perfusion indicates the presence of ischemic (metabolically impaired) but viable myocardium (i.e. stunned or hibernating myocardium).[2,3] Nevertheless, as reduced accumulation of BMIPP is observed not only in ischemic but viable myocardium but also in scar tissue, imaging with BMIPP alone is not sufficient for assessing myocardial viability.

^{123}I-15-(*p*-iodophenyl)-9-(*R,S*)-methylpentadecanoic acid (9MPA, Fig. 1) has been designed to be washed out from myocardium by introducing the methyl-branch into the ninth carbon location of the fatty acid chain to undergo beta-oxidation three times,[4–7] so that its clearance is expected to reflect the beta-oxidation of fatty acids. In

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fact, a few reports have described how the clearance of 9MPA from myocardium was slower in an ischemic region than in a normal region.[4–6] Chouraqui et al. reported that differential myocardial clearance from normal and ischemic regions results in reversible 9MPA defect.[7] We therefore hypothesized that a reversible 9MPA defect indicates the presence of ischemic but viable myocardium. In this study we performed single photon emission computed tomography (SPECT) with 9MPA and positron emission tomography (PET) with ^{18}F-deoxyglucose (FDG) in patients with prior myocardial infarction to determine whether the reversible 9MPA defect indicates the presence of residual viability within an infarct-related area.

MATERIALS AND METHODS

Seven patients (4 men, 3 women; 54 to 73 years old, mean age 64 ± 6) with prior myocardial infarction (more than 1 month after onset) were recruited for our study. Patients with overt diabetes were excluded. In all subjects, myocardial SPECT imaging with 9MPA, coronary angiography, biplane left ventriculography, PET with FDG and ^{13}N-ammonia (NH_3) were performed. This study was performed as a part of the phase III clinical trial of 9MPA in Japan and was approved by the institutional review board of Fukui Medical University Hospital. Written informed consent was obtained from all patients.

Coronary angiography and biplane left ventriculography were performed within 2 weeks of a 9MPA study. Coronary stenosis was measured by the cross-sectional method and significant stenosis was defined as luminal narrowing > 50% after nitroglycerin administration. On left ventriculography, we calculated the left ventricular ejection fraction (EF) by the area-length method.

9MPA (= 160 MBq) was injected at rest after overnight fasting, followed by SPECT acquisition 2 min (early) and 50 min later (delayed). The images were acquired in continuous rotational motion composed of 90 angular samples framed into 4° intervals with a 64 × 64 matrix for a total imaging time of 15 min. The photopeak and main window used for data acquisition in imaging were 160 keV and 26%, respectively. The projection images acquired by means of the main window were first smoothed with a Butterworth filter of order 8, and the cut-off frequency was 0.3 cycles/pixel. Image reconstruction was based on filtered backprojection with a ramp filter. Reconstructed transverse slices covered the left ventricular myocardium. These images were further processed to obtain vertical long axial and short axial slices.

All subjects underwent PET with FDG and NH_3 after an overnight fast within 2 weeks of 9MPA-SPECT with a whole-body tomograph (ADVANCE, GE, Milwaukee). Before the emission scan was performed, a 10-min transmission scan was performed with 2 rotating ^{68}Ge pin sources for attenuation correction. Static PET images were acquired over 10 minutes beginning 10 min after an intravenous bolus injection of NH_3 (= 740 MBq). FDG (= 370 MBq) was then injected intravenously, and static images were acquired over 10 minutes beginning 60 min after the injection.[8,9]

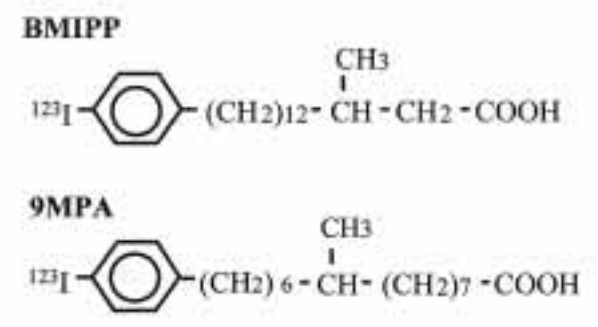

Fig. 1 Chemical structure of BMIPP and 9MPA.

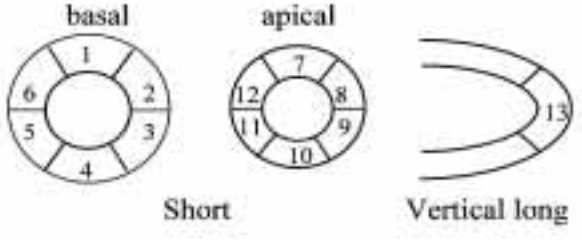

Fig. 2 Schematic representation of tomographic images.

Reconstructed images of the left ventricle (short axial slices and vertical long axial slices) were created. The reconstructed SPECT and PET images of the left ventricular slice (1 vertical long axial slice and 2 short axial slices) were divided into 13 segments to correlate the regional uptake of each tracer (Fig. 2). The myocardial accumulation of 9MPA was assessed visually by 2 independent observers who were unaware of the patient's data with a 4-point defect score (0; normal, 1; mild reduced, 2; moderate reduced, 3; severe reduced). The reduced tracer accumulation was defined as a 2 or 3 defect score, and normal was defined as 0 or 1. According to the findings of early and delayed 9MPA-SPECT, we defined the changes in tracer accumulation in each segment as follows: normal, normal accumulation of 9MPA is observed in both early and delayed images; reversible defect, reduced accumulation of 9MPA on early images altered normal accumulation in delayed images; fixed defect, reduced accumulation of 9MPA is observed in both early and delayed images. Then a circular region of interest (ROI), 10 mm diameter in size, was placed on each segment, and segmental clearance of 9MPA (washout rate; WR) was calculated by using the mean counts in the ROIs in the following equation:

$$WR\ (\%) = [1 - (Cd/Ce \times 0.5^{-Te-d/13})^{1/Te-d}] \times 100$$

Ce and Cd are the mean counts in the ROI on early and

delayed images, respectively, and Te–d is denote time (hours) between early and delayed images. We determined that the physical half life of ^{123}I is 13 hours.

For analysis of NH_3- and FDG-PET images, the myocardial tissue activity per pixel of both tracers (CT; cpm/m*l*) was measured in each 13 segments. Infarct-related segments (IRS) were defined as those showing less than 70% of the maximal NH_3 uptake.[8] The FDG uptake in each segment was quantified as the FDG Uptake Index, a percent dose per unit volume of the myocardium (% dose/100 m*l*) in relation to the total injected dose of FDG, described previously.[8,9] According to our previous report, the upper limit of normal FDG Uptake Index is 0.575.[8] An increase in the FDG Uptake Index above 0.575 in infarct-related segments was classified as ischemic but viable tissue, whereas segments with no increase in FDG uptake were classified as non-viable tissue. All data are presented as the mean value ± SD. The unpaired Student's t test was used to assess differences in mean values between groups. The Fisher exact test was used to compare proportions. A p value < 0.05 was considered significant.

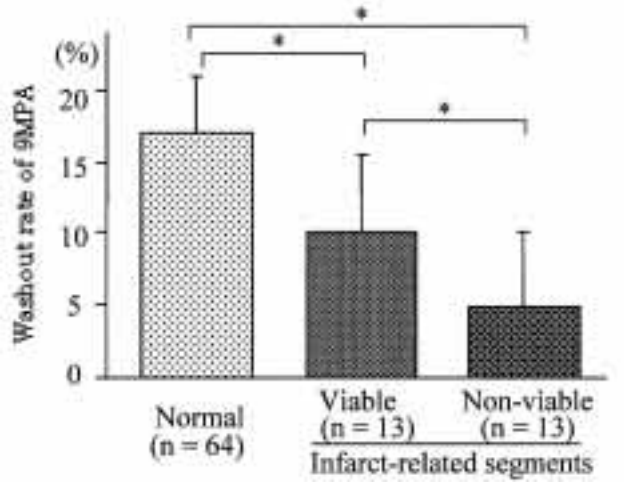

Fig. 3 Comparisons of myocardial clearance of 9MPA. *p < 0.05

Table 1 Characteristics of the patients

Patient	Age	Sex	IRA (% stenosis)	LVEF (%)
1	73	M	RCA (78)	55
2	67	M	LAD (88)	36
3	65	F	LCx (90)	57
4	63	F	LAD (38)	61
5	54	F	LCx (24)	62
6	64	M	LAD (80)	49
7	65	M	RCA (63)	47

IRA; infarct-related artery, LVEF; left ventricular ejection fraction, RCA; right coronary artery, LAD; left anterior descending artery, LCx; left circumflex artery

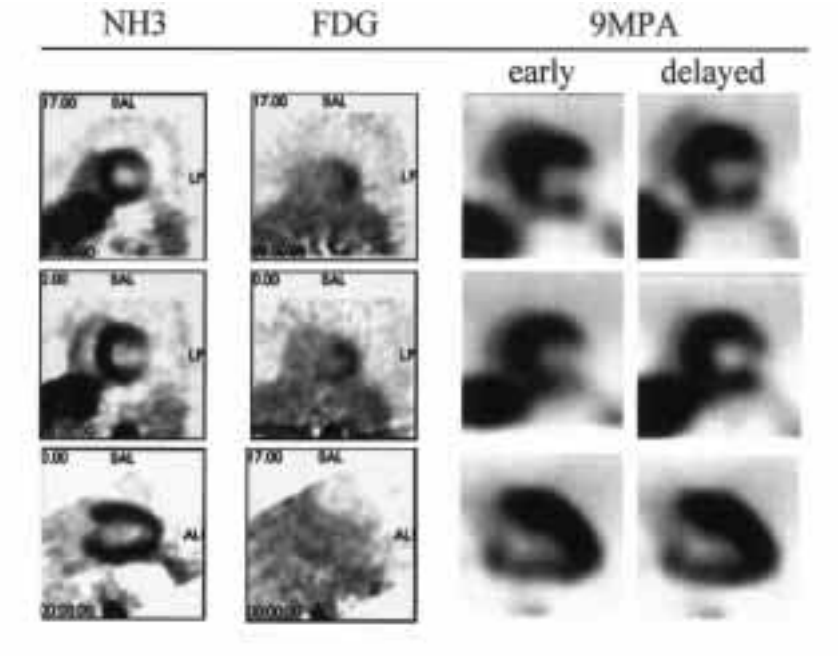

Fig. 4 A 65-yr-old female with prior myocardial infarction (patient no. 3). Her left circumflex artery was 90% of luminal narrowing. NH_3-PET images showed hypoperfusion in the lateral left ventricular segments. Increased FDG uptake was observed within the hypoperfused segments, suggesting the presence of residual viability within infarct-related area. Early 9MPA-SPECT showed reduced accumulation in the lateral left ventricular segments. Reversible defect of 9MPA was observed within the infarct-related segments on delayed images.

Table 2 Finding of 9MPA-SPECT and FDG-PET (n = 26)

	9MPA	
	reversible defect	fixed defect
FDG viable	6	7
FDG non-viable	0	13

RESULTS

Among the findings of coronary angiography, none showed significant stenosis except in infarct-related arteries. The infarct-related arteries (3 left anterior descending arteries, 2 left circumflex arteries and 2 right coronary arteries) were patent in all 7 patients with residual luminal narrowing of 66 ± 26% (range 24% to 90%). Mean left ventricular EF was 52 ± 9% (range 36% to 62%) (Table 1). Of the 91 segments in 7 subjects screened, 27 segments (30%) showed reduced accumulation of 9MPA on early images. In these 27 segments, 26 (96%) were classified as IRS according to the findings of NH_3-PET. The mean WR of 9MPA in IRS were significantly lower than in 64 segments exhibiting normal NH_3 accumulation (8.8 ± 5.7% vs. 17.1 ± 3.9%; $p < 0.05$, Fig. 3). In IRS, reversible defect of 9MPA was observed in 6 (23%, Fig. 4) segments and fixed defect in 20 (77%) segments. FDG-PET showed residual tissue viability in 13 of 26 IRS. Of these 13 segments, reversible 9MPA defect was observed in 6 segments (46%) and fixed defect in 7 segments. In the remaining 13 segments without myocardial viability, all showed fixed 9MPA defect (Table 2). Reversible 9MPA defect was more frequently observed in ischemic but viable segments than in non-viable segments ($p < 0.05$). The sensitivity, specificity and accuracy of reversible 9MPA defect for the detection of myocardial viability were 46%, 100% and 73%, respectively. Myocardial WR of 9MPA was significantly slower in non-viable segments than in ischemic but viable segments (4.9 ± 5.1% vs. 10.1 ± 5.3%; $p < 0.05$, Fig. 3).

DISCUSSION

Accurate and noninvasive assessment of myocardial metabolism has played an important role in understanding the physiological condition of ischemic myocardium. PET with FDG or ^{11}C-acetate is now reported to allow excellent assessment of myocardial metabolism and viability. In patients with prior myocardial infarction, precise assessment of residual viability within an infarct-related area by means of PET is useful for determining whether or not coronary revascularization is indicated,[10] but PET is not yet widely available. Therefore, BMIPP-SPECT has been widely used for assessing myocardial fatty acid utilization,[1,2] but, to the best of our knowledge, single isotope imaging with BMIPP is not sufficient for assessing myocardial viability in patients with prior myocardial infarction, because reduced accumulation of BMIPP is observed not only in ischemic but viable myocardium, but also in non-viable tissue. Therefore, dual isotope imaging with BMIPP and perfusion tracer (i.e. ^{201}Tl) is needed to assess myocardial viability. Many reports have stated that reduced uptake of BMIPP relative to perfusion has predictive value for residual viability within an infarct-related area.[1,2]

9MPA, a new methyl-branched fatty acid analogue, is different from BMIPP in introducing methyl-branch into the ninth carbon location of the fatty acid chain to undergo beta-oxidation three times.[4–7] Therefore, clearance of 9MPA is expected to reflect beta-oxidation and myocardial viability. A few reports described how the clearance of 9MPA from ischemic myocardium was significantly slower than those from normal myocardium, and that the decreased 9MPA clearance reflects impairment of fatty acids metabolism.[4–6] In our present study, 26 of 27 (96%) segments showing reduced 9MPA uptake on early images corresponded with IRS according to the findings of NH_3-PET. Clearance of 9MPA from these segments was significantly slower than from 64 segments with normal NH_3 accumulation (8.8 ± 5.7% vs. 17.1 ± 3.9%; $p < 0.05$). In these 26 IRS, FDG-PET showed 13 segments as ischemic but viable and 13 segments as non-viable. Clearance of 9MPA from non-viable segments was significantly slower than that from ischemic but viable segments (4.9 ± 5.1% vs. 10.1 ± 5.3%, $p < 0.05$), so that clearance of 9MPA might reflect myocardial fatty acid metabolism and viability. Similarly, Fujiwara et al. reported that the clearance of 9MPA from non-viable segments was slower than that from viable segments in patients with acute coronary syndrome.[6] Our present results might be consistent with their report, but it is not fully investigated whether the presence of a reversible defect in 9MPA, resulting from different myocardial clearance from ischemic but viable and normal regions, indicates the residual viability within an infarct-related area. Chouraqui et al. reported that 9MPA correlates closely with ^{201}Tl for initial postexercise myocardial uptake and defect reversibility in patients with exercise-induced myocardial ischemia.[7] They suggested that defect reversibility of 9MPA appears to result from differential myocardial clearance from normal and ischemic regions. In our present study, the reversible defect of 9MPA is frequently observed in patients with prior myocardial infarction and closely related to the presence of residual viability within an infarct-related area. We speculated that the reversible defect of 9MPA is a predictor of preserved fatty acid metabolism within an infarct-related area. Nevertheless, it is likely that slower clearance of 9MPA from non-viable segments than from ischemic but viable segments is a disadvantage for detecting residual viability by using the phenomenon of reversible defect, but normalized % uptake of 9MPA on early images was significantly lower in

non-viable segments than in ischemic but viable segments ($52.3 \pm 2.6\%$ vs. $74.1 \pm 6.2\%$, $p < 0.05$). We speculated that this lower uptake of 9MPA on early images in non-viable segments caused fixed defect on delayed images. As a result, the sensitivity, specificity and accuracy of reversible 9MPA defect for the detection of residual viability were 46%, 100%, and 73%, respectively.

In conclusion, 9MPA has unique characteristics different from conventional fatty acid analogues and has important implications for clinical decision making in prior myocardial infarction.

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