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Detection of coronary artery disease by iodine-123-labeled iodophenyl-9-methyl pentadecanoic acid SPECT: Comparison with thallium-201 and iodine-123 BMIPP SPECT

Kazuki FUKUCHI, Shinji HASEGAWA, Yasushi ITO, Hitoshi YAMAGUCHI, Jun YOSHIOKA, Toshiisa UEHARA and Tsunehiko NISHIMURA

Division of Tracer Kinetics, Biomedical Research Center, Osaka University Medical School

To evaluate the ability to detect coronary artery disease (CAD) with a new iodine-123 labeled branched fatty acid analog, iodophenyl-9-methyl pentadecanoic acid (9MPA), we performed 9MPA, iodine-123 BMIPP and thallium-201 SPECT in patients with CAD. Twenty-four patients (11 with effort angina and 13 with myocardial infarction) were studied. In all patients, 9MPA SPECT was obtained at 15 min after injection. Twenty-three patients underwent stress-redistribution ^{201}Tl SPECT and 9 patients also underwent BMIPP myocardial fatty acid imaging. The regional uptakes of 9MPA, BMIPP and ^{201}Tl were scored semiquantitatively and the segmental agreements were compared among them. In the segment-to-segment comparison, 9MPA showed reduced activity in comparison to stress-redistribution ^{201}Tl imaging. The defect score of 9MPA was significantly greater than that of redistribution ^{201}Tl images ($p < 0.001$). In addition, segmental 9MPA uptake was lower than BMIPP and its defect score was significantly greater than that of BMIPP ($p < 0.05$). When coronary angiography was used as the criterion, 9MPA showed higher sensitivity and lower specificity than stress-redistribution ^{201}Tl ($p < 0.01$). In conclusion, fatty acid metabolic imaging with 9MPA is a sensitive but nonspecific detector of CAD.

Key words: iodine-123-iodophenyl-9-methyl pentadecanoic acid, coronary artery disease, thallium-201, iodine-123 BMIPP.

INTRODUCTION

RADIOLABELED FATTY ACID ANALOGS have attracted attention as cardiac imaging agents for the identification of myocardial metabolic changes in ischemic heart disease.[1,2] For single photon emission computed tomography (SPECT), iodine-123-15-(*p*-iodophenyl)-3-*R*,*S*-methylpentadecanoic acid (BMIPP) imaging is now widely used, because it is a structurally modified fatty acid that has prolonged retention time in the myocardium.[3,4] Myocardial accumulation of BMIPP is less than that of flow tracers in patients with coronary artery disease (CAD), so that BMIPP is more sensitive for detecting myocardial ischemia associated with coronary artery stenosis than perfusion imaging.[5–8]

Recently a modified free fatty acid analog, iodine-123-15-(*p*-iodophenyl)-9-*R*,*S*-methylpentadecanoic acid (9MPA), containing a phenyl ring on carbon-15 and a methyl branch of carbon-9, was developed (Fig. 1).[9] 9MPA undergoes direct β-oxidation three times before inhibition of further β-oxidation by the branched-methyl group, unlike BMIPP which is stored in the cytosolic triglyceride pool, because the methyl group in the β-position inhibits entry of the activated fatty acid into β-oxidation.[10] 9MPA may therefore reflect β-oxidation in mitochondria better than BMIPP but only a few studies have reported preliminary results.[11,12]

The purpose of this study was to assess the usefulness of 9MPA SPECT as a myocardial fatty acid metabolic imaging method for detection of ischemic or infarcted myocardium in comparison with BMIPP and ^{201}Tl in

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For reprint contact: Tsunehiko Nishimura, M.D., Ph.D., Division of Tracer Kinetics, Biomedical Research Center, Osaka University Medical School, 2–2 Yamada-oka, Suita, Osaka 565–0871, JAPAN.

E-mail: nisimura@tracer.med.osaka-u.ac.jp

patients with CAD.

MATERIALS AND METHODS

Twenty-four patients (11 with effort angina and 13 with myocardial infarction, 56.8 ± 10.1 years old) were studied. The patients were considered eligible for this study on the basis of clinical symptoms suggestive of CAD in association with either an abnormal exercise test, prior abnormal perfusion study, a prior history of myocardial infarction (based on the standard clinical definition of at least two of the following: prolonged chest pain, increase in creatine kinase MB, and transient Electrocardiographic changes) or coronary arteriography demonstrating significant stenosis of at least one major vessel.

Coronary angiograms were obtained in 22 patients. Cineangiograms were assesses by an experienced angiographer unaware of the clinical and scintigraphic data. The extent of coronary artery disease was defined as the number of the vessels with ≥ 75% stenosis, or for patients with a coronary artery bypass graft, ≥ 75% stenosis in both the native vessels as well as the graft vascular supply. Three patients had significant stenosis in three vessels, 11 patients in two vessels and 8 patients in one vessel (mean 1.8 vessels per patient).

This study was performed under the standard ethical guideline of the Osaka University Hospital and written informed consent was obtained from each subject prior to the study.

Radiopharmaceuticals

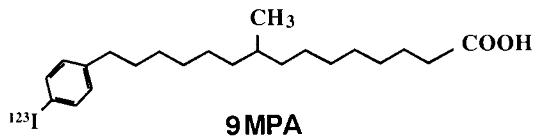
9MPA was prepared and supplied by Daiichi Radioisotope Laboratory Co., Ltd. (Tokyo, Japan). Its radiochemical purity was more than 98%, and its specific activity was 400 MBq/mg. 9MPA (167 MBq, 0.3 mg) was dissolved in 30 mg of hydroxypropil-β-cyclodexystolin as a solvent.

9MPA-SPECT

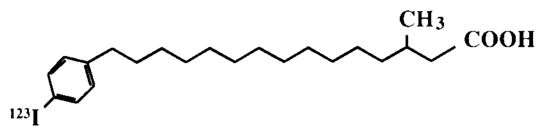
The patients fasted overnight, then 167 MBq of 9MPA was injected intravenously. Myocardial SPECT acquisition was performed 15 min after 9MPA administration and SPECT data were acquired as follows. A rotating triple headed gamma camera (GCA9300HG/A, Toshiba Co., Ltd., Tokyo, Japan) equipped with a low-energy, general purpose collimator was used for acquisition of the data from 20 projections over 360° for 30 sec per projection. Energy was discriminated by means of a 20% window centered over a 160-keV photopeak. The images were acquired on a 64 × 64 matrix and stored on a hard disk for further processing.

Stress-redistribution ^{201}Tl-SPECT

Twenty-three patients received exercise to stress-redistribution ^{201}Tl SPECT on a bicycle ergometer within 2 weeks of 9MPA studies. During both studies, no changes in clinical features were found in any of the patients.



9MPA



BMIPP

Fig. 1 Structural formulae of iodine-123-15-(*p*-iodophenyl)-9-*R*,*S*-methylpentadecanoic acid (9MPA) and iodine-123-15-(*p*-iodophenyl)-3-*R*,*S*-methylpentadecanoic acid (BMIPP).

Exercise began with a workload of 25 W and was increased at 25 W intervals for every 2 min stress period. Exercise was terminated when severe chest pain, serious arrhythmia, ST depression of more than 0.2 mV and/or fatigue occurred. One minute before the cessation of exercise, 111 MBq of ^{201}TlCl was injected intravenously, and the patient continued exercising for 1 min. At 10 min after the injection, stress SPECT images were obtained. After an interval of 180 min, redistribution SPECT was performed. In 19 patients, the same SPECT system used for 9MPA imaging was used for data acquisition and reconstruction except that the energy was discrimination centered at the 70 keV with a 20% window. In the remaining four patients, a dual-headed SPECT (RC-2500IV, Hitachi Medical Co., Ltd., Tokyo, Japan) with low-energy, high-resolution parallel-hole collimators was used for ^{201}Tl imaging.

BMIPP-SPECT

An intravenous bolus injection of 111 MBq iodine-123-15-(*p*-iodophenyl)-3-*R*,*S*-methylpentadecanoic acid (BMIPP) was given at rest in nine patients (6 with effort angina and 3 with myocardial infarction) within 2 weeks of 9MPA studies. Each patient was instructed to fast overnight before BMIPP. Data acquisition was started 15 min after radionuclide injection by means of the same SPECT system and the same acquisition protocol as used for the 9MPA study.

Image Reconstruction and Analysis

9MPA, stress ^{201}Tl, redistribution ^{201}Tl and BMIPP images were processed on a computer (GMS-5500A, Toshiba Co., Ltd., Tokyo, Japan). The projections were reconstructed with a Shepp and Logan convolution filter, and high frequency noise was decreased with post-reconstruction Butterworth filtering (cutoff = 0.28 cycle/pixel, power factor = 8). Attenuation correction was not performed.

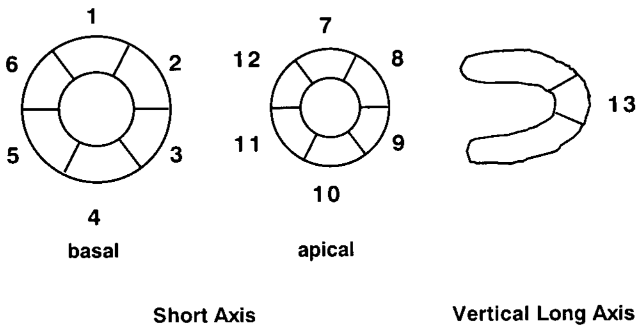


Fig. 2 Segmentation schema used for regional quantitative analysis of myocardial SPECT.

Table 1 Relationship of 9MPA and stress ^{201}Tl uptake scores in the total myocardial segments

Stress Tl	9MPA 0	1	2	3	Total
0	138	21	7	6	202
1	22	18	7	2	53
2	7	6	12	15	24
3	0	1	5	32	20
Total	167	46	31	55	299

0 = normal uptake; 1 = mild decreased; 2 = decreased; and 3 = absent uptake

Table 2 Relationship of 9MPA and redistribution ^{201}Tl uptake scores in the total myocardial segments

RD Tl	9MPA 0	1	2	3	Total
0	153	29	11	10	203
1	14	14	13	11	52
2	0	3	6	16	25
3	0	0	1	18	19
Total	167	46	31	55	299

0 = normal uptake; 1 = mild decreased; 2 = decreased; and 3 = absent uptake

All SPECT images were read separately and blindly to analyze the differences in tracer distribution in the left ventricular myocardium. The left ventricular myocardium was divided into 13 segments (Fig. 2) to score 9MPA, ^{201}Tl and BMIPP uptake in each segment with the consensus of three experienced observer with a four-grade system (0 = normal uptake, 1 = mild decreased, 2 = decreased and 3 = absent uptake). When the score in each segment was different for both tracers, the segment was considered to show discordant uptake. When the score was the same, the segment was considered to show concordant uptake.

To compare with coronary angiographic findings, scintigraphic region was by ascribing the septum and anterior walls to the left anterior descending coronary artery, the lateral wall to the circumflex artery and the inferior wall to the right coronary artery.

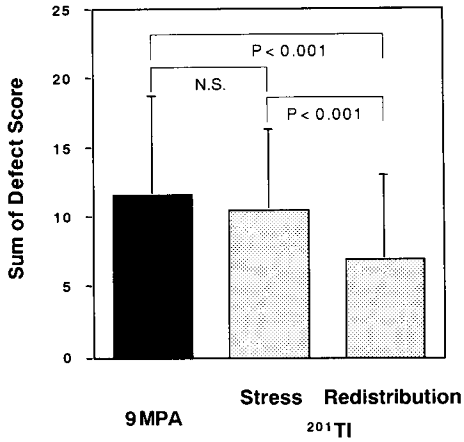


Fig. 3 Comparison of the sum of defect scores between 9MPA, stress ^{201}Tl and redistribution ^{201}Tl images.

Statistical Analysis

Data are expressed as means ± SD. Comparisons among groups were performed with the paired nonparametric Wilcoxon t-test. Paired proportions were compared with the McNemar's symmetry chi-square test. The weighted sensitivities and specificities were calculated for 9MPA and stress-redistribution ^{201}Tl SPECT. The 95% and 99% confidence intervals of the weighted sensitivities and specificities were also calculated and the individual intervals were compared.[13] Probability values less than 0.05 were considered significant.

RESULTS

Comparison between 9MPA and ^{201}Tl Imaging

The 9MPA abnormalities at rest were seen in all patients except in one subject with angina. In the segment-to-segment comparison, the concordance rate between 9MPA and stress ^{201}Tl images was 66.9% (200/299 seg.) but 19.4% (58/299 seg.) of the total segments showed that the degree of 9MPA abnormality was increased as compared with stress ^{201}Tl (Table 1). In all segments, the degree of 9MPA abnormality was larger than that of stress ^{201}Tl ($p < 0.05$). In the comparison between 9MPA and redistribution ^{201}Tl images, the concordance rate was 63.9% (191/299 seg.), and 30% (90/299 seg.) of all segments showed a higher abnormal 9MPA uptake than redistribution ^{201}Tl (Table 2). The degree of 9MPA abnormality was also larger than that of redistribution ^{201}Tl in the total segment analysis ($p < 0.001$).

The overall defect score for 9MPA images (11.5 ± 7.2) in each patient was significantly increased relative to that of redistribution ^{201}Tl images (6.9 ± 6.1, $p < 0.001$) whereas there was no significant difference between 9MPA and stress ^{201}Tl (Fig. 3).

Table 3 Sensitivity and specificity of 9MPA and stress-redistribution ^{201}Tl in 23 patients in relation to coronary angiography

	9MPA	Stress-redistribution ^{201}Tl
Sensitivity (%)	84.6*	81.1
Specificity (%)	33.3*	51.7
Positive predictive value (%)	62.3	68.2
Negative predictive value (%)	62.5	68.2

*; $p < 0.01$

Table 4 Relationship of 9MPA and BMIPP uptake scores in the total myocardial segments

BMIPP	9MPA				Total
	0	1	2	3	
0	71	9	1	1	82
1	2	3	2	0	7
2	0	0	8	8	16
3	0	0	1	11	12
Total	73	12	12	20	117

0 = normal uptake; 1 = mild decreased; 2 = decreased; and 3 = absent uptake

When coronary angiography was used as the criterion, 9MPA abnormality was demonstrated in 33/39 of the segments with significant coronary artery stenosis, whereas ^{201}Tl abnormality was only seen in 30/37 of the segments. Sensitivity was higher for 9MPA than for stress-redistribution ^{201}Tl ($p < 0.01$) but 9MPA had significantly less specificity than stress-redistribution ^{201}Tl ($p < 0.01$) (Table 3).

Comparison between 9MPA and BMIPP

In the segment-to-segment comparison, the concordance rate between 9MPA and BMIPP was 79.5% (93/117 seg.) but 17.9% (21/117 seg.) of the total segments showed a higher 9MPA uptake score than that of BMIPP (Table 4). In all segments, the degree of 9PMA abnormality was larger than that of BMIPP ($p < 0.01$).

In addition, the sum of defect score of 9MPA (10.7 ± 7.7) in each patient was more greater than that of the BMIPP uptake score (8.3 ± 8.1, $p < 0.05$) (Fig. 4).

Case Presentation

A 51-year-old woman suffered from myocardial infarction. Coronary obstruction was evident in the left anterior descending artery. Stress-redistribution ^{201}Tl SPECT showed residual myocardial ischemia in the infarcted antero-apical myocardium. The 9MPA abnormality in the antero-apical area was more extensive than that indicated by stress ^{201}Tl imaging, whereas the degree of BMIPP abnormality was intermediate between stress and redistribution ^{201}Tl imaging (Fig. 5).

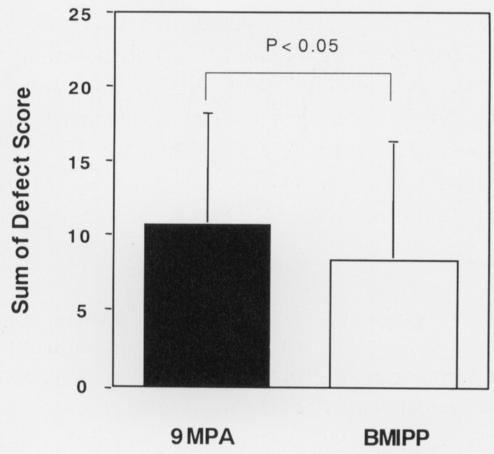


Fig. 4 Comparison of the sum of defect scores between 9MPA and BMIPP images.

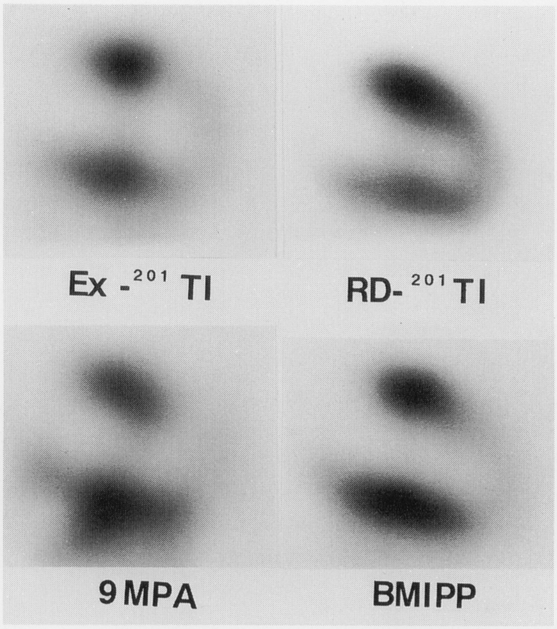


Fig. 5 Representative images of myocardial infarction. Stress-redistribution ^{201}Tl (upper panel), 9MPA images (left lower panel), and BMIPP images (right lower panel).

DISCUSSION

In cardiac nuclear medicine, various fatty acid analogs have been developed to assess myocardial fatty acid metabolism noninvasively. For example, BMIPP is widely used as a reliable indicator in SPECT studies because an abnormal myocardial BMIPP uptake is often associated with severe myocardial ischemia and abnormal left ventricular wall motion.[14,15] On the other hand, 9MPA may express myocardial β-oxidation in mitochondria better than BMIPP because 9MPA undergoes direct β-oxidation three times before inhibition of further β-oxidation by the branched-methyl group unlike BMIPP.[9–11] We therefore expected 9MPA to reflect some degree of myocardial β-oxidation and to be a more sensitive indicator of myocardial metabolic alteration than BMIPP or myocardial perfusion SPECT. The present study indicated that decreased 9MPA uptake in patients with CAD is more frequently observed than ^{201}Tl or BMIPP defects at rest. 9MPA is a suitable agent for myocardial fatty acid imaging for detecting CAD.

Discrepancy between 9MPA and ^{201}Tl SPECT

In this study, segment-to-segment comparison showed that a decreased 9MPA uptake was more marked than stress or redistribution ^{201}Tl. In addition, the sum of the defect score for 9MPA was also significantly higher than that for redistribution ^{201}Tl, whereas there was no significant difference between 9MPA and stress ^{201}Tl. These results indicated that 9MPA provides comparable information with stress ^{201}Tl in terms of the reduction of aerobic metabolism in abnormal perfused lesions in patients with CAD.

Since stress ^{201}Tl imaging has been showed to be a reliable prognostic indicator in determining the severity of myocardial ischemia, stress ^{201}Tl scintigraphy is now widely used for detection of myocardial ischemia and viability in serial studies. In contrast, combined imaging with 9MPA and ^{201}Tl clearly showed perfusion-fatty acid metabolism mismatch in ischemic and jeopardized myocardium. In these areas, fatty acid utilization may be severely suppressed relative to perfusion, indicating a metabolic shift from fatty acid to glucose utilization under fasting conditions. Such metabolically impaired areas may be likely to show reversibility on stress ^{201}Tl imaging. These findings indicated that combined 9MPA and ^{201}Tl scintigraphy at rest may be useful as an alternative to conventional stress-redistribution ^{201}Tl scintigraphy. To clarify this issue, a greater number of clinical validations will be needed.

Discrepancy between 9MPA and BMIPP Uptake

In our preliminary comparison between 9MPA and BMIPP in a small number of patients, the sum of defect scores of 9MPA was significantly higher than that of BMIPP, and segment-to-segment comparison showed that myocardial 9MPA uptake was decreased more markedly than that of BMIPP. The discrepancy between 9MPA and BMIPP uptake in the same patients with CAD was considered to indicate different metabolic handling and thus reflecting different aspects of myocardial fatty acid metabolism.

The major difference between these molecules is that 9MPA undergoes direct β-oxidation three times, but BMIPP does not. 9MPA can be used as indicator of both myocardial β-oxidation and the cytosolic triglyceride pool, whereas BMIPP is mainly employed as an indicator of the status of the cytosolic triglyceride pool.[10]

BMIPP provides myocardial metabolic information independently of myocardial perfusion and has been reported to be advantageous for assessment of ischemic heart disease.[6,10,14] Compared with ^{11}C-palmitate, BMIPP uptake correlated well in terms of early uptake but not early clearance rates, indicating that BMIPP uptake reflects fatty acid retention rather than β-oxidation.[16] Considering the discrepancy between BMIPP uptake and myocardial β-oxidation, 9MPA may be better suited to noninvasive metabolic studies with SPECT systems than BMIPP.

Study Limitations

Previous studies suggested that the clearance rate of 9MPA which was observed in serial studies in reduced uptake areas is slower than in normal areas, because β-oxidation is decreased in ischemic but viable myocardium.[11,12] In our study, however, 9MPA SPECT was performed at only 15 min post-injection and sequential changes in myocardial 9MPA uptake were not evaluated. We focused on the ability of 9MPA imaging for the detection of CAD which is conventionally detected by BMIPP imaging.[7] The myocardial uptake of 9MPA is though to be stable and is not influenced by myocardial perfusion at 15 min post-injection. We found abnormal fatty acid metabolism in CAD by using 9MPA despite the single acquisition protocol.

9MPA imaging was not performed in healthy subjects since our study was performed as part of Phase II and III clinical trial in Japan. According to an earlier clinical trial in the USA, however, myocardial uptake was shown to be almost identical to that of ^{201}Tl in normal volunteers.[9] In addition, the number of CAD patients was limited and various types of CAD, such as single- and multi vessel diseases, or previous myocardial infarction, were studied in our patient group. This heterogeneity of patient characteristics may explain the high sensitivity of 9MPA, because approximately half of the patients had experienced previous myocardial infarction. To clarify the detectability of CAD more accurately, further studies involving more specific patient groups are necessary.

In this study, we did not perform a comparison between 9MPA uptake and ventricular function. It is well known that a lower BMIPP uptake as compared to that of ^{201}Tl or sestamibi uptake occurs in areas subtended by recanalized coronary arteries following thrombolysis.[5,15] A similar correlation between 9MPA uptake and the functional outcome can be expected, but further prospective studies involving patients undergoing revascularization are required to determine the clinical significance of 9MPA imaging.

In conclusion, a decreased 9MPA uptake art rest in patients with CAD is more frequently observed than redistribution ^{201}Tl or BMIPP defects. 9MPA is a suitable agent for myocardial fatty acid imaging and is sensitive but nonspecific for detecting myocardial ischemia or infarction.

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