SIMULTANEOUS DUAL MYOCARDIAL IMAGING WITH IODINE-123-β-METHYL IODOPHENYL-PENTADECANOIC ACID (BMIPP) AND THALLIUM-201 IN PATIENTS WITH CORONARY HEART DISEASE

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To assess the clinical value of simultaneous dual myocardial imaging with iodine-123-β-methyl-iodophenyl-pentadecanoic acid (^{123}I-BMIPP) and thallium-201 (^{201}Tl), myocardial imaging was performed at rest and during exercise in seven patients with coronary heart disease.

When ^{123}I-BMIPP and ^{201}Tl images were compared, the initial exercise and resting images agreed 87% and 64%, respectively. In the initial resting images, the regional uptake of ^{123}I-BMIPP was frequently less than that of ^{201}Tl. The incidence of exercise-induced reversible defects by ^{201}Tl in the Tl>BMIPP regions was significantly higher than that in the Tl=BMIPP regions (57% vs 4%, $p<0.01$) and the incidence of coronary narrowing of more than 90% in the Tl>BMIPP regions was also significantly higher than that in the Tl=BMIPP regions (91% vs 38%, $p<0.01$). In addition, this disparity (Tl>BMIPP) was found more frequently in regions with abnormal wall motion than in regions with normal wall motion (hypokinetic regions; 68%, severe hypokinetic or akinetic regions; 50%, vs normokinetic regions; 4%, $p<0.01$). In contrast, the uptake of ^{123}I-BMIPP correlated closely with that of ^{201}Tl in normal myocardium and the uptake of both ^{123}I-BMIPP and ^{201}Tl was severely reduced in myocardium with severe ischemia during exercise and prior infarction. These results indicate that dual myocardial imaging with ^{123}I-BMIPP and ^{201}Tl may provide a unique means of identifying patients with metabolically disturbed myocardium, such as hibernating and stunned myocardium.

(*Jpn Circ J* 1994; **58:** 107–115)

UNDER normal physiological conditions, oxidative metabolism of free fatty acids provides 40 to 60 percent of the energy used by the heart[1,2] Myocardial ischemia induces characteristic changes in myocardial metabolism. Thus, there has been considerable interest in cardiac imaging using radiolabeled fatty acids[3–8] Extensive research using positron emission tomography has shown that fatty acid metabolism is altered in ischemic and necrotic myocardium[5,7–10] However, positron cameras and radiopharmaceuticals are currently not widely available. If similar data could be obtained with a single photon emitting radiopharmaceutical, the

Key words:
Thallium-201
^{123}I-BMIPP
Dual imaging
Myocardial ischemia
Fatty acid

(Received May 10, 1993; accepted September 16, 1993)

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TABLE I CLINICAL FEATURES

Patients	*Age/Sex*	*Prior MI*	*Coronary Angiography %Diameter Stenosis*			*Collateral Circulation*
			LAD	*LCX*	*RCA*	
1	*50/M*	*Q (11y)*	*100*	*50*	*99*	*LAD-LAD, RCA-LAD, LCX-RCA*
2	*55/F*	–	*?*	*?*	*?*	*?*
3	*64/M*	*Q (5y)*	*100*	*99*	*90*	*LAD-LAD, RCA-LAD, LCX-RCA*
4	*59/M*	*non-Q (3y)*	*90*	*90*	*90*	–
5	*71/F*	*non-Q (2m)*	*0*	*90*	*90*	*LAD-RCA, LCX-RCA*
6	*72/F*	*non-Q (3y)*	*50*	*75*	*99*	*LAD-RCA*
7	*65/M*	*non-Q (3y)*	*90*	*25*	*0*	–

LAD=Left anterior descending artery, LCX=Left circumflex artery, (m)=month before myocardial imaging, MI=myocardial infarction, non-Q=non Q wave infarction, Q=Q wave infarction, RCA=Right coronary artery, (y)=year before myocardial imaging

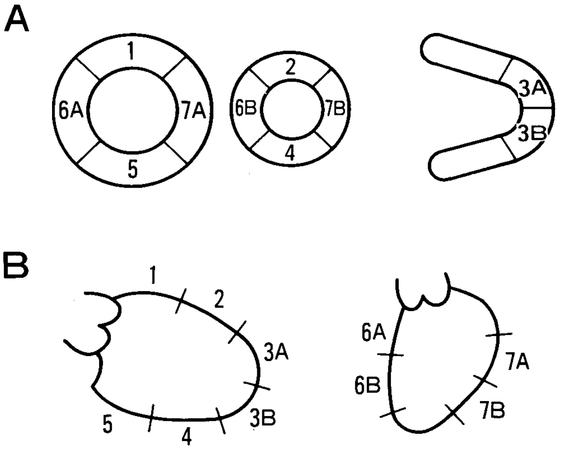


Fig.1. A: Ten regions of interest on 2 reconstructed short-axis slices and 1 vertical long-axis slice. B: Ten left ventricular segments analyzed by left ventriculography. The ten segments nearly corresponded to the segments in the SPECT image.

technique could be applied at many institutions with available equipment. A β-methyl-branched fatty acid analogue, iodine-123-β- methyl- iodophenyl- pentadecanoic acid (BMIPP) has been proposed as a probe for myocardial fatty acid utilization as assessed by single-photon emission computed tomography (SPECT), because of its long retention in the myocardium.[11-13] Recently, we demonstrated that ^{123}I-BMIPP imaging and autoradiogreaphy revealed impaired regional fatty acid utilization, which was independent of regional perfusion, in patients and hamsters (Bio 14.6) with hypertrophic cardiomyopathy.[14,15] The present study was undertaken 1) to investigate whether myocardial imaging with ^{123}I-BMIPP shows a myocardial distribution different from that with ^{201}Tl in patients with coronary heart disease, and 2) to characterize ischemic myocardium using dual myocardial imaging.

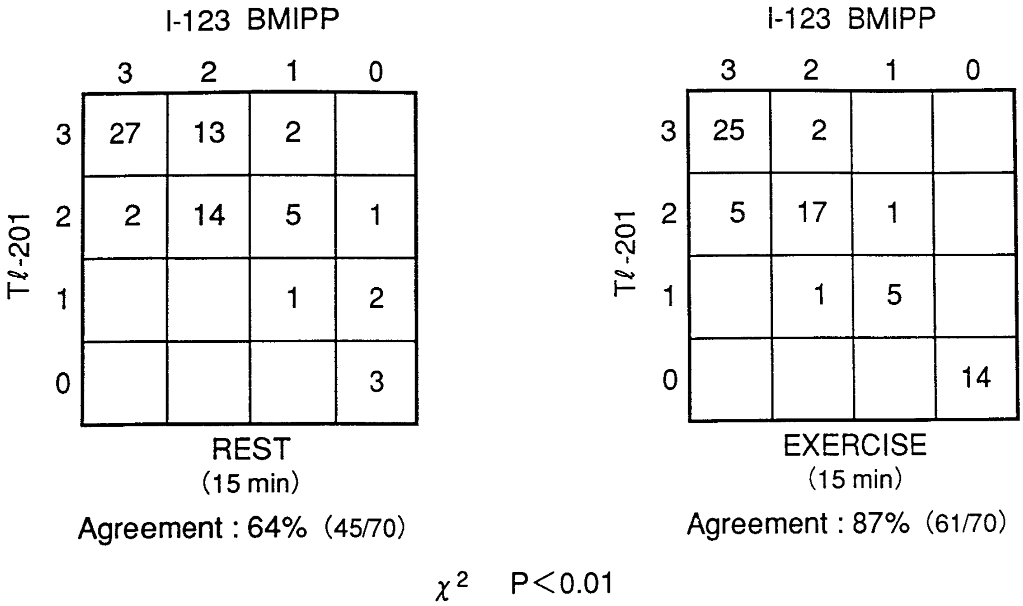
MATERIALS AND METHODS

Patient Population (Table I)

The patient population consisted of 7 patients (3 female, 4 male) with stable exertional angina and exercise-induced ischemic electrocardiographic changes (more than 1.0 mm horizontal or down-sloping ST depression). Six patients had prior infarction (2 had Q wave infarction and 4 had non-Q wave infarction), but none of the patients except one who had had an infarction 2 months previously, had had a myocardial infarction within the past year. Their ages ranged from 50 to 72 years with a mean of 62 years. Informed written consent was obtained prior to enrollment in the study. The study protocol and consent form were approved by the Hamamatsu University School of Medicine Human Subject Protection Committee.

Study Protocol

Patients were asked to fast for at least 4 hr prior to stress testing and rest testing. All of the patients underwent stress testing 1 week after rest testing. In rest imaging, 111 MBq of ^{201}Tl and 111 MBq of ^{123}I-BMIPP were injected intravenously. In stress testing, subjects underwent a symptom-limited multistage ergometer exercise test. Modified 12-



I-123 BMIPP, Tℓ-201

	3	2	1	0
3	27	13	2	
2	2	14	5	1
1			1	2
0				3

REST
(15 min)
Agreement : 64% (45/70)

I-123 BMIPP, Tℓ-201

	3	2	1	0
3	25	2		
2	5	17	1	
1		1	5	
0				14

EXERCISE
(15 min)
Agreement : 87% (61/70)

χ^2 P<0.01

Fig.2. Agreement in the visual segmental score between the initial ^{123}I-BMIPP and ^{201}Tl images at rest and during exercise.

lead electrocardiograms were recorded at rest, during each minute of exercise, and during recovery. At peak exercise, 111 MBq of ^{201}Tl and 111 MBq of ^{123}I-BMIPP were injected (i.v.) sequentially and the patient continued to exercise for 1 min.

Imaging Protocol and Analysis of Images

Simultaneous dual-energy images were obtained with a rotating gamma camera (ZLC 7500, Siemens) that was equipped with a low-energy, all-purpose, collimator and interfaced to a computer system (Scintipac 2400, Shimadzu). Two separate 20% windows were centered with one on the ^{201}Tl photopeak (80 KeV) and the other on the ^{123}I photopeak (159 KeV). Initial imaging was begun at 15 min after injection. Delayed images were obtained 3 hours after injection. Thirty-two projections over 180 degrees from the 45-degree right anterior oblique position to the 45-degree left posterior oblique position were acquired in a 64×64 matrix of a 38 cm field of view for 30 seconds per image. Orthogonal images were generated by oblique angle reconstruction which produced vertical long-axis, short-axis, and horizontal long-axis slices, each 6 mm thick. No attenuation, scatter or spillover correction was applied. Uptake was determined visually for each of the 10 segments (Fig. 1A) using a 4 point scoring system (3=normal, 2=mildly reduced, 1=moderately reduced, 0=markedly reduced). The final readings reported represent either total agreement or a consensus opinion of two of three observers.

Coronary Angiography and Analysis of Left Ventriculograms

Coronary angiography and left ventriculography were preformed within 3 months of myocardial imaging, except in one patient. Coronary angiograms were assessed by visual interpretation. Biplane contrast ventriculography was performed in the 30 degree RAO and 60 degree LAO projections and assessed for 10 segments (Fig. 1B) which nearly corresponded to the 10 segments in SPECT (Fig. 1A). For analysis of left ventriculograms the cine films were projected and the end-diastolic and end-systolic endocardial contours were traced from the frames with maximum and minimum volume, respectively, from a normal nonpostpremature sinus beat. Wall motion was measured by the centerline method along 100 chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours, normalized by the end-diastolic perimeter, and expressed in units of standard deviations (SDs) from the mean motion in 137 normal subjects![16] Regional wall motion abnormalities were defined as follows: normokinesis; more than −SD, hypokinesis; between −1SD and −2SD; se-

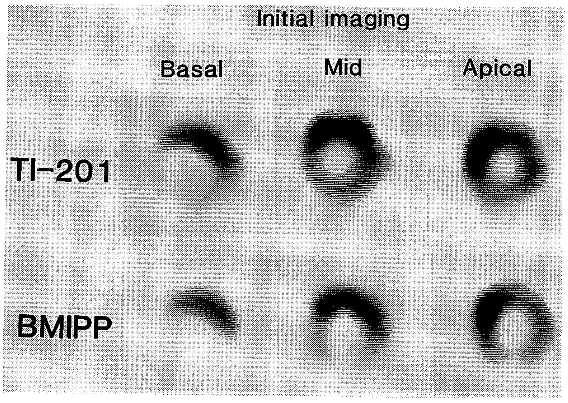


Fig.3. Initial resting dual SPECT imaging with ^{201}Tl (upper panel) and ^{123}I-BMIPP (lower panel) in patient 5. SPECT images show short-axis slices in basal, mid, and apical portions. The uptake of ^{123}I-BMIPP is less than that of ^{201}Tl in the inferior region.

vere hypokinesis or akinesis; less than −2SD.

Statistical Analysis

Data were expressed as the mean±1SD. Proportions were compared using the chi-square test or Fisher's exact test when there were only a few samples. Values of $p<0.05$ were considered statistically significant.

RESULTS

Results of Exercise Testing

Patients exercised on a bicycle ergometer to a peak heart rate of 107±18 beats/min and a heart rate-blood pressure (double) product of 19,157±2,930. All of the patients stopped because of angina and showed significant ST depression on electrocardiogram.

Results of Coronary Angiography

Six patients underwent coronary angiography and all had a luminal narrowing of more than 90% in one or more of the main coronary arteries (Table I). Two patients showed total obstruction of the left anterior descending artery, but its territories were well perfused by collaterals from other coronary arteries.

Dual-Isotope SPECT with ^{201}Tl and ^{123}I-BMIPP

There were no adverse clinical reactions to the administration of ^{123}I-BMIPP in any of the studies, and both ^{201}Tl and ^{123}I-BMIPP provided high contrast tomograms of the left ventricular myocardium. Agreement between the visual segmental scores in the initial images with the two radionuclides is shown in Fig. 2. In the initial exercise images, 61 of 70 segments were scored identically, resulting in 87% agreement. In contrast, only 45 of 70 segments in the initial resting images were scored identically, resulting in 64% agreement. Thus, the agreement of the initial resting images was lower than that of the initial exercise images ($p<0.01$). Furthermore, the regional uptake of ^{12} ^{3}I-BMIPP was frequently less than that of ^{201}Tl in the resting images. An example is shown in Figs. 3 and 4.

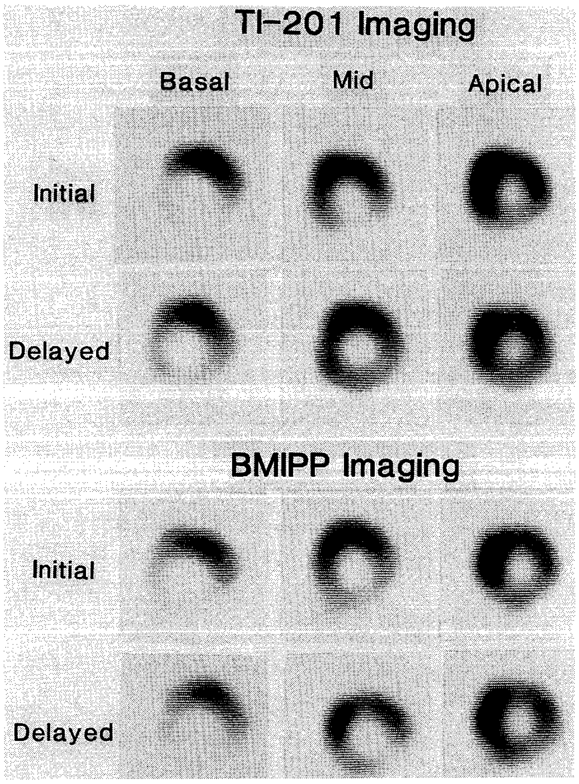


Fig.4 Exercise dual SPECT initial and delayed imaging with ^{201}Tl (upper panel) and ^{123}I-BMIPP (lower panel) in patient 5. ^{201}Tl SPECT images show a transient defect in the inferior region. In ^{123}I-BMIPP SPECT images, the uptake of ^{123}I-BMIPP decreases similarly to the uptake of ^{201}Tl in the same region, but does not show redistribution.

In rest imaging, the two agents showed different patterns of reversibility from initial imaging to delayed imaging in 9 of 70 segments. Of these, 6 segments that were normal by ^{201}Tl showed nonreversible defects in ^{123}I-BMIPP imaging. In exercise imaging, the two agents showed different patterns in 11 of 70 segments. These 11 segments were

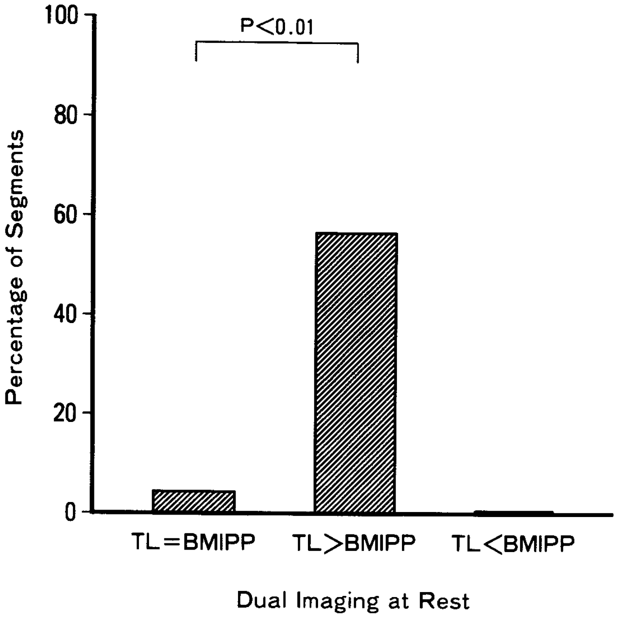


Fig.5. Relationship wetween initial resing dual imaging and the incidence of exercise-induced reversible defects by ^{201}Tl in exercise imaging.

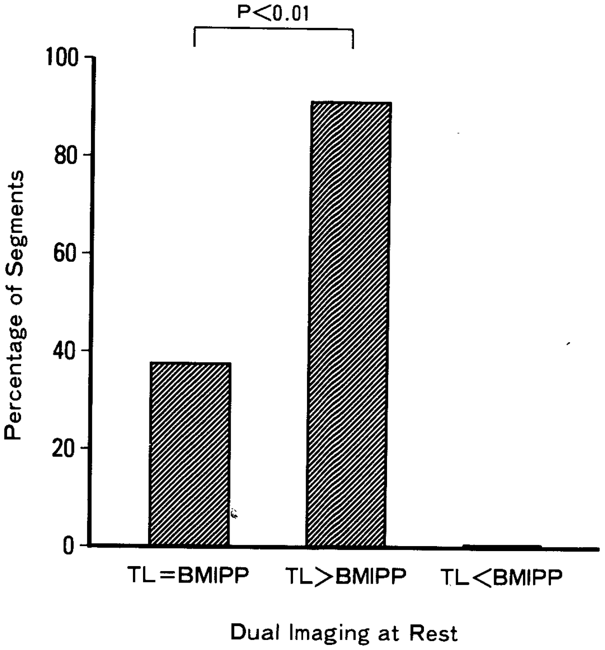


Fig.6. Relationship between initial resting dual imaging and incidence of coronary narrowing of more than 90%.

considered to have reversible defects by ^{201}Tl and nonreversible defects by ^{123}I-BMIPP. These findings showed that there was no clinically significant myocardial redistribution of ^{123}I-BMIPP.

Relationship Between the Initial Images in Dual-Isotope Rest Imaging and the Incidence of Exercise-induced Reversible Defects in ^{201}Tl Imaging.

The incidence of exercise-induced reversible defects by ^{201}Tl in regions in which the uptake scores in the initial resting images showed Tl=BMIPP, Tl>BMIPP, and Tl<BMIPP was 4% (2/45), 57% (13/23), and 0% (0/2), respectively. The incidence of exercise-induced reversible defects by ^{201}Tl in the Tl>BMIPP regions in the resting images was significantly higher than that in the Tl=BMIPP regions ($p<0.01$) (Fig. 5). Regions in which the uptake of both ^{201}Tl and ^{123}I-BMIPP was severely reduced and no redistribution of ^{201}Tl was found in resting or exercise images, were regarded as infarcted areas.

Relationship Between the Initial Dual-Isotope Rest Imaging and the Severity of Coronary Narrowing

The incidence of coronary narrowing of more than 90% in regions in which the uptake scores in the initial resting images showed Tl=BMIPP, Tl>BMIPP, and Tl<BMIPP was 37% (13/35), 91% (21/23), and 0% (0/2), respectively. The incidence of coronary narrowing of more than 90% in the Tl>BMIPP regions was significantly higher than that in other regions ($p<0.01$) (Fig. 6). However, the Tl=BMIPP regions contained normal and infarcted myocardium. In infarcted areas, Tl=BMIPP and the uptake of both agents was severely reduced.

Relationship Between Regional Wall Motion and Disparity (Tl>BMIPP) in the Initial Dual-Isotope Resting Images.

The relationship between regional wall motion and disparity (Tl>BMIPP) in the initial resting images is shown in Fig. 7. The incidence of disparity (Tl>BMIPP) in normokinetic, hypokinetic, and severe hypokinetic or akinetic regions was 4% (1/24), 68% (15/22), and 50% (7/14), respectively. These results demonstrate that disparity was more frequently found in regions with abnormal wall motion than in regions with normal wall motion ($p<0.01$). The incidence of disparity (Tl>BMIPP) in severe hypokinetic or akinetic regions was less than that in hypokinetic regions because regions with severe

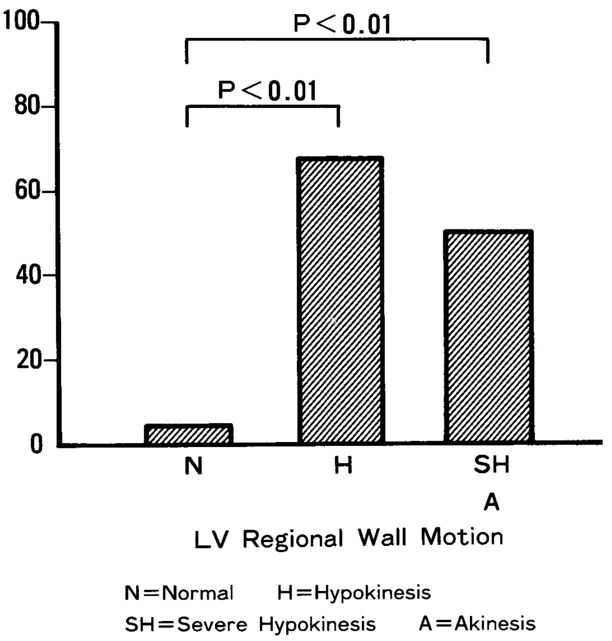


Fig.7. Relationship between left ventricular regional wall motion and the disparity (Tl>BMIPP) in initial resting images. A=akinesis, H=hypokinesis, N=normal, SH=severe hypokinesis

hypokinesia or akinesia contained infarcted tissue.

DISCUSSION

Myocardial Perfusion Imaging and Metabolic Imaging

Myocardial perfusion imaging has been used to assess myocardial blood flow and viability in patients with chronic stable or unstable angina pectoris and in patients with acute myocardial infarction. The initial myocardial uptake of ^{201}Tl after intravenous injection is directly proportional to nutrient coronary blood flow and the myocardial extraction fraction for ^{201}Tl.[17–20] In the presence of irreversible myocardial injury, the intracellular transport and concentration of ^{201}Tl are markedly reduced,[21,22] and regional wall motion abnormality is also observed. Prolonged postischemic cardiac dysfunction after acute ischemia (myocardial stunning)[23] and persistent cardiac dysfunction secondary to chronic ischemia with viable but poorly contractile myocardium (hibernating myocardium)[24,25] have recently been demonstrated. In both of these conditions myocardial asynergy may not be accompanied by diminished uptake of ^{201}Tl (well perfused asynergy).[26–28] Myocardial asynergy without reduced uptake of ^{201}Tl may be associated with mild ischemia at rest or post-ischemic metabolic disturbances. Mild ischemia inhibits fatty acid metabolism but stimulates glycolysis.[2] Moreover, repeated episodes of transient ischemia lead to regional depletion of glycogen or high-energy phosphate stores, and reversible injury to other critical myocardial cellular processes prolongs mechanical recovery.[23] This condition may also be detected by metabolic imaging, but not by perfusion imaging.

In the present study, we obtained simultaneous dual myocardial images with ^{123}I-BMIPP and ^{201}Tl at rest and during exercise in patients with coronary heart diseae. The results of our study suggest that (1) the uptakes of ^{201}Tl and ^{123}I-BMIPP are normal and identical in normal myocardium in resting and exercise images, (2) the uptake of ^{123}I-BMIPP is frequently less than that of ^{201}Tl in initial resting images in regions with severe coronary narrowing, exercise-induced ^{201}Tl reversible defect during exercise, and/or asynergy, although the uptake of ^{123}I-BMIPP is decreased similarly to the uptake of ^{201}Tl in exercise images in regions with severe exercise-induced ischemia during exercise, and (3) the uptake of both ^{201}Tl and ^{123}I-BMIPP in resting and exercise images is severely reduced in myocardium with prior infarction.

Ischemia-induced decreases in initial fatty acid uptake have been previously reported in studies with ^{11}C-palmitate, hexadecenoic acid, 16-hexadecanoic acid and heptadecanoic acid.[7,8,29–32] Ter-Pogossian et al. demonstrated a high correlation between enzymatic (serial plasma MB-CK method) and tomographic estimates of infarct size, and thus PET with ^{11}C-palmitate permitted quantification and localization of myocardial infarcts in patients with transmural myocardial infarction.[7] Schwaiger demonstrated in an experimental study using PET that during occlusion the regional decrease in perfusion was matched by a decrease in ^{11}C-palmitate uptake, and reperfused viable myocardium exhibited residual glucose metabolism with fluoro-18-deoxyglucose (FDG), whereas fatty acid oxidation remained impaired for an extended period of time.[33] In a study with ^{123}I-phenylphentadecanoic acid (IPPA), there was good agreement between the location of significant coronary artery stenosis and abnormalities in the initial distribution and clearance of IPPA.[34] These findings suggest that the initial distributions of ^{201}Tl and fatty acid tracers are related to regional myocardial blood flow in regions with severe ischemia and prior infarction, indicating that both the activity of Na^+-K^+ ATPase and fatty acid metabolism are diminished in these regions. The present findings that both myocardial perfusion and fatty acid metabolism in myocardium with severe exercise-induced ichemia and prior infarction are consistent with these previous findings. In contrast, in the resting condition, fatty acid metabolism decreases independent of regional myocardial perfusion in regions with well perfused asynergy and/or severe coronary narrowing. These findings are probably associated with mild ischemia and/or postischemic metabolic disturbances due to severe coronary stenosis.

Mechanism of Disparity Between Perfusion Imaging and Fatty Acid Imaging

Although some studies have shown a disparity between myocardial uptake of ^{123}I-BMIPP and regional myocardial perfusion in animal disease models, the mechanism of decreased myocardial fatty acid uptake has not yet been elucidated.[14,35,36] ^{123}I-BMIPP is not metabolized via beta-oxidation, but is mainly trapped in the triglyceride fraction, and myocardial BMIPP accumulation appears to be associated with triglyceride synthesis.[37,38] Fujibayashi et al. demonstrated that, following treatment with 2,4-dinitrophenol (an electron transport uncoupler), decreases in myocardial BMIPP accumulation correlated well with decreases in adenosine triphosphate, which is required in the first step of enzymatic conversion of fatty acids to acyl-CoA (a common pathway in fatty acid metabolism, such as triglyceride synthesis and beta-oxidation), while ^{201}Tl showed slightly increased accumulation in the myocardium.[39] Thus, the uptake of ^{123}I-BMIPP may reflect some aspect of mitochondrial function and/or myocardial fatty acid metabolism, such as incorporation into triglyceride storage poucts or an oxidative process responsible for the conversion of ^{123}I-BMIPP to polar catabolites.[40] Therefore, regions which showed disparity (Tl>BMIPP) in resting images may have been associated with disturbed fatty acid metabolism or mitochondrial dysfunction accompanied by mild ischemia at rest and/or repeated episodes of transient ischemia.

Limitations of the Study

^{123}I-BMIPP imaging was not performed in healthy subjects since our study was performed as a phase 3 clinical trial. Therefore, we could not compare ^{123}I-BMIPP images in patients with coronary artery disease to those in normal controls. However, the purpose of the present study was to compare myocardium with ischemia or infarction to normal myocardium in patients with coronary artery disease. In addition, earlier experimental studies using ^{123}I-BMIPP have shown that its myocardial distribution is almost consistent with that of regional perfusion in normal animals. Furthermore, although the disparity between the % uptake of ^{201}Tl and ^{123}I-BMIPP in normal myocardium was less than 15%, this disparity was frequently more than 15% in some regions. However, this disparity might be due to regional differences in the isotopes.

We did not apply a spillover correction, although in a phantom study, ^{123}I crosstalk in the ^{201}Tl window and ^{201}T1 crosstalk in the ^{123}I window were 34% and 20%, respectively. Even if we had applied a spillover correction such a correction is incomplete.[41]

CONCLUSION

Our present clinical study suggests that metabolic and perfusion characterization by dual myocardial imaging with ^{123}I-BMIPP and ^{201}Tl may provide a unique means of identifying patients with metabolically disturbed myocardium, such as hibernating myocardium and stunned myocardium. However, since we could not perform dual SPECT imaging or left ventriculography after revascularization, further study is required to clarify the value of this approach.

Acknowledgements

^{123}I-BMIPP was kindly supplied by Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan. We are grateful to Mr. Shinji Sakamoto, Mr. Michifumi Sawada, Ms.

Tomiko Tanahashi, and Ms. Yachiyo Itoh of the Radioisotope Division for their assistance.

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