Iodinated Free Fatty Acid and ^{201}Tl Uptake in Chronically Hypoperfused Myocardium: Histologic Correlation Study

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^{123}I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) is a tracer for the evaluation of ischemic heart disease. The purpose of this study was to assess the relationship between ^{123}I-BMIPP uptake and myocardial fibrosis. **Methods:** Fifteen patients who underwent cardiac surgery were examined by imaging with ^{201}Tl and ^{123}I-BMIPP, and histologic specimens were taken during surgery. The relative uptake of ^{201}Tl (%Tl) and that of ^{123}I-BMIPP (%BMIPP) were calculated. The percentage of fibrosis (%fibrosis) was analyzed with the specimen. **Results:** %Tl correlated strongly with %fibrosis ($r = -0.94$; $P < 0.001$). %BMIPP also correlated significantly with %fibrosis ($r = -0.88$; $P < 0.001$), but the change in %BMIPP looked biphasic. In the category of only mild fibrosis, %BMIPP showed a steep decrease. ^{123}I-BMIPP–^{201}Tl mismatch was found only for fibrosis <20%. **Conclusion:** ^{123}I-BMIPP gave specific information about metabolic changes that occurred in ischemic myocardium without severe fibrotic changes.

Key Words: ^{123}I-BMIPP; ^{201}Tl; myocardial fibrosis; metabolism

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In fasting patients, free fatty acid metabolism nourishes normal myocardium but is suppressed in ischemic myocardium. Recently, many radioiodinated fatty acid tracers have been developed for the detection of metabolically altered myocardium using SPECT equipment.

^{123}I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) is an iodinated analog of pentadecanoic acid (*1*). Many clinical studies have shown decreased regional uptake of ^{123}I-BMIPP relative to flow tracer uptake in ischemic but viable myocardium (*2*). However, only a few reports concern the correlation between ^{123}I-BMIPP uptake and myocardial histology (*3*).

The purpose of this study was to compare ^{123}I-BMIPP imaging findings with the histologic changes of chronically hypoperfused myocardium.

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MATERIALS AND METHODS

Patients

Table 1 summarizes the characteristics of the study group, which comprised 15 patients with coronary artery disease (CAD) (2 women, 13 men; mean age, 64 ± 11 y) who were scheduled for cardiac surgery. In all patients, the proximal left anterior descending arteries had significant stenosis and CAD had been clinically diagnosed at least 1 y previously. Seven patients had clinically diagnosed transmural myocardial infarction and had no evidence of acute infarction within at least 1 mo before the surgery. The other 8 patients had clinically diagnosed angina pectoris. Four patients had diabetes mellitus. The study protocol was approved by the institutional ethical committee of Kyoto University, and all patients gave written informed consent to participate in the study.

Cardiac Catheterization

Selective preoperative coronary angiography was performed using the Judkins technique. The left and right coronary arteries were imaged in multiple views. Stenosis was considered significant if the luminal diameter was narrowed by ≤70%. The preoperative coronary angiography was always performed within 3 mo of surgery.

SPECT Imaging Protocols

^{201}Tl and ^{123}I-BMIPP SPECT were performed within 2 wk before surgery. All images were obtained with a dual-head SPECT scanner (Optima; General Electric Medical Systems, Milwaukee, WI) equipped with low-energy general-purpose collimators and a 180° circular orbit, starting at the 45° right anterior oblique position. For each patient, 32 projection images requiring 30 s each were obtained.

After fasting for at least 5 hr, and while at rest, each patient received an injection of approximately 111 MBq ^{123}I-BMIPP. SPECT was performed 15–20 min later. The ^{123}I-BMIPP was prepared and supplied by Nihon Mediphysics (Nishinomiya, Japan) and contained approximately 111 MBq carrier-free ^{123}I-BMIPP dissolved in 10.5 mg ursodeoxycholic acid.

On a different day, SPECT was performed approximately 5–10 min after injection of 72 MBq ^{201}Tl in resting patients. The total

TABLE 1
Patient Characteristics

Patient No.	Sex	Age (y)	Diagnosis	%Stenosis LAD	LCX	RCA	Left ventriculogram findings (segment)	Diabetes mellitus
1	M	77	MI	99			Aneurysmal motion (3)	Negative
2	M	47	MI	99	99	90*	Reduced motion (1, 4, 6)	Negative
							Akinesis (2)	Negative
							Diskinesis (3)	Negative
3	M	73	MI	90			Normal motion	Negative
4	M	70	MI	100		75*	Aneurysmal motion (2, 3)	Negative
							No motion (6)	Negative
5	M	58	AP	75	100	90	Normal motion	Negative
6	M	60	AP	90	90†	90	Normal motion	Positive
7	M	72	AP	100			Normal motion	Negative
8	M	80	AP	90‡			Normal motion	Negative
9	M	49	AP	100	99†	90*	Normal motion	Negative
10	F	64	AP	99	100	75	Reduced motion (4, 5)	Negative
11	M	61	MI	75		75	Akinesis (2, 3, 6)	Positive
12	M	45	AP	90	100	50	Normal motion	Negative
13	M	66	MI	100		99	Reduced motion (2, 3)	Negative
14	M	66	AP	75	99†	99	Normal motion	Positive
15§	F	70	MI	90		99	Akinesis (4, 5)	Positive

*Posterior descending branch.
†Obtuse marginal branch.
‡Left main trunk.
§Biopsy was unsuccessful in this patient.
LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; MI = myocardial infarction; AP = angina pectoris.
Segment 1 is the anterobasal wall; segment 2, the anteroapical wall; segment 3, the apex; segment 4, the inferoapical wall; segment 5, the inferobasal wall; segment 6, the septum; and segment 7, the lateral wall.

duration of each ^{201}Tl and ^{123}I-BMIPP SPECT acquisition was approximately 10 min.

Image Analysis

Transaxial images were used for determining the regions of interest. In each instance, 2 circular regions of interest (8 mm in diameter) were placed on the anterior wall corresponding to the site of biopsy and were averaged. One same-sized circular region of interest was placed on the maximum-count pixel in each image and used for normalization of each image. The normalized ^{123}I-BMIPP uptake (%BMIPP) and the normalized thallium uptake (%Tl) were calculated. ^{123}I-BMIPP–^{201}Tl mismatch was also calculated and was confirmed if %Tl exceeded %BMIPP by 10%.

Microscopic Examination

During the surgery of each patient, a single transmural biopsy specimen (1 × 10 mm) was taken from the anterior wall of the left ventricle, between the distal left anterior descending artery and the last diagonal branch, using a Monopty 211810 biopsy needle (Bard Urological Division, Covington, GA). Each specimen was fixed with a 6:3:1 mixture of 100% ethanol:100% chloroform:100% acetate. The sections were treated with Masson stain to quantify fibrosis.

To assess the amount of fibrosis in the myocardium, a grid with vertical and horizontal lines providing 11 × 11 intersections (121 points) was used (*4*). The number of points overlying a certain structure was counted with light microscopy at a magnification of ×200. The procedure was repeated 20 times on different areas of the specimen. The points counted in the connective tissue were expressed as the percentage of the points counted in tissue as a whole (%fibrosis). Blood vessels and perivascular interstitial cells were excluded from the analysis.

Statistical Analysis

The data were reported as mean ± SD and were analyzed statistically using a least-squares linear regression method. $P < 0.05$ was considered significant.

RESULTS

Good biopsy specimens were obtained from 14 patients, who were then included in the analysis. The specimen from the other patient was small and not suitable for histologic analysis, probably because of technical error. All 15 patients showed no complications after biopsy.

Correlation Between SPECT Findings and Myocardial Fibrosis

The biopsy specimens showed %fibrosis values ranging from 1.1% to 79.4%. The 2 patients who underwent aneurysmectomy showed the highest %fibrosis (57.3% and 79.4%).

Myocardial fibrosis correlated inversely and significantly with the SPECT findings. Table 2 and Figure 1 show all SPECT data and the correlation coefficients and probability values. An excellent inverse correlation was found between %Tl and %fibrosis ($y = -0.96x + 78.7$, where y = %Tl and

TABLE 2
SPECT and Histologic Data of Each Patient

Patient no.	%Fibrosis	%BMIPP	%Tl
1	57.3	14.3	18.0
2	36.8	28.6	37.1
3	10.3	70.2	74.5
4	79.4	13.9	13.5
5	11.9	70.7	78.3
6	1.1	71.5	83.3
7	2.4	77.0	77.6
8	6.3	80.6	72.1
9	9.2	71.0	75.2
10	12.0	53.5	61.2
11	13.2	46.2	58.2
12	13.9	42.4	67.6
13	18.1	22.9	39.1
14	5.0	88.7	81.3

x = %fibrosis) ($r = -0.94$; $P < 0.001$). A good inverse correlation between %BMIPP and %fibrosis was also found ($y = -0.92x + 71.9$, where y = %BMIPP and x = %fibrosis) ($r = -0.88$; $P < 0.001$). However, %BMIPP tended to decrease sharply within the narrow range of mild fibrosis (%fibrosis < 15%) and to decrease only gradually within the range of moderate to severe fibrosis (%fibrosis ≤ 15%) in comparison with %Tl. Within the narrow range of mild fibrosis, a significant inverse correlation was also found between %BMIPP and %fibrosis, and the slope of the regression line was very steep ($y = -2.4x + 87.8$, where y = %BMIPP and x = %fibrosis) ($r = -0.73$; $P < 0.05$). Within the range of moderate to severe fibrosis, %BMIPP was very low and did not change significantly in relation to %fibrosis ($y = -0.2x + 29.7$, where y = %BMIPP and x = %fibrosis) ($r = -0.76$; P = not significant). The change in %BMIPP in relation to %fibrosis seemed biphasic (Fig. 2).

^{123}I-BMIPP–^{201}Tl Mismatch

Four patients showed a ^{123}I-BMIPP–^{201}Tl mismatch (Fig. 1). Three of 4 patients showed only mild %fibrosis, and the value in the fourth patient was only 18.1%. Patients with a %fibrosis value > 20% did not show a ^{123}I-BMIPP–^{201}Tl mismatch.

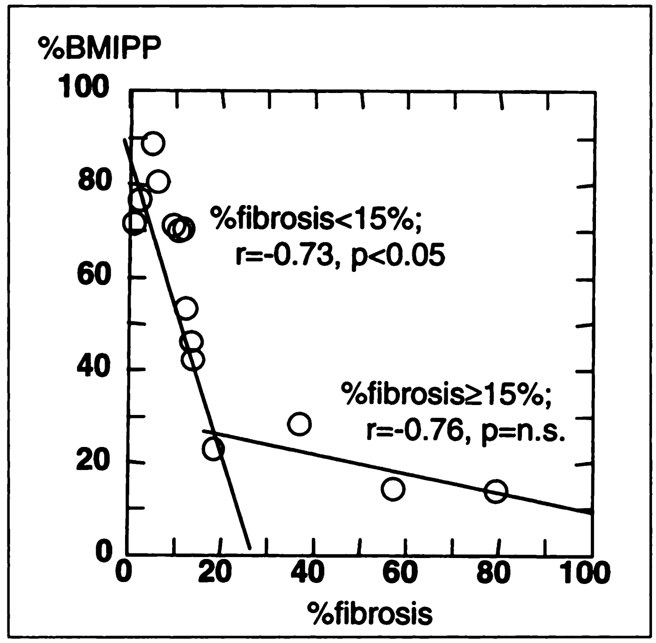

FIGURE 2. Biphasic change of %BMIPP in relation to %fibrosis.

DISCUSSION

This study showed that ^{123}I-BMIPP reveals SPECT findings different from those of ^{201}Tl. %Tl uptake in resting patients showed a good linear, inverse correlation with myocardial fibrosis. However, %BMIPP sharply decreased within the narrow range of mild fibrosis, indicating a biphasic decrease in ^{123}I-BMIPP uptake in relation to myocardial fibrosis.

Zimmermann et al. (*5*) showed that residual ^{201}Tl uptake in myocardium correlates with myocardial fibrosis. They used planar ^{201}Tl images for analysis, but their results were consistent with the linear correlation we found between %Tl

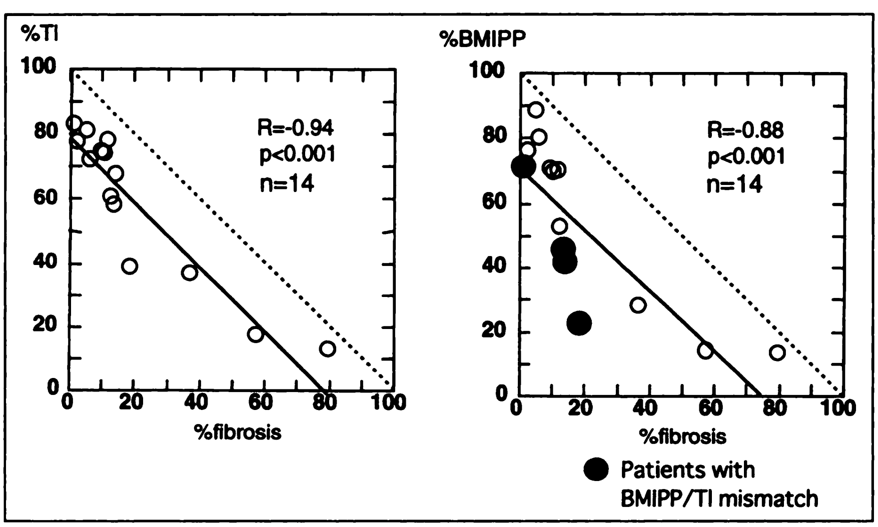

FIGURE 1. Correlation between %fibrosis and SPECT parameters.

and %fibrosis. This consistency suggests that ^{201}Tl uptake in resting patients is a good index for myocardial fibrosis.

On the other hand, the steep regression in ^{123}I-BMIPP uptake and the ^{123}I-BMIPP–^{201}Tl mismatch that we found in the absence of severe fibrosis suggest that ^{123}I-BMIPP revealed metabolic changes in ischemic myocardium that showed no severe fibrotic changes. For further understanding of the ^{123}I-BMIPP findings, investigation of structural changes, especially mitochondrial, is needed.

CONCLUSION

In an evaluation of the relationship between histologic changes and ^{123}I-BMIPP–thallium findings in patients with CAD, ^{201}Tl uptake showed a good inverse correlation with fibrosis, but ^{123}I-BMIPP uptake showed a biphasic decrease in relation to fibrosis. A ^{123}I-BMIPP–^{201}Tl mismatch was observed only in patients with mild fibrosis. ^{123}I-BMIPP may provide specific information about metabolic changes in ischemic myocardium that shows minimal fibrotic changes.

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