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Clinical Usefulness of Metabolic Imaging in Patients with Unstable Angina : Assessment with Emission Tomography Using ^{123}I-β-methyl-iodo-phenyl Pentadecanoic Acid

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The clinical usefulness of single-photon tomography using both a beta-methyl-branched fatty acid analog, ^{123}I-15- (p-iodophenyl) -3-methyl pentadecanoic acid (BMIPP) and Tl-201 was assessed in 6 patients with unstable angina. Within 4 days after angina attack, BMIPP and Tl-201 single-photon emission tomography (SPECT) were performed during a pain-free period within 2 days of one another. BMIPP uptake was decreased compared to Tl-201 uptake (discordant) in all patients (100%) and in 11/54 (20%) of myocardial segments.The discordant BMIPP uptake was seen more often in segments exhibiting wall motion abnormalities (hypokinesis) in comparison to segments showing normal wall motion (77% vs 5%, $p < 0.005$). Thus, BMIPP imaging may provide a novel means of identifying patients with metabolically disturbed myocardium, particularly among patients with unstable angina.

key words

Unstable angina
^{123}I-β-methyl-indo-phenyl pentadecanoic acid (BMIPP)
Thallium-201

Introduction

Fatty acids are the major fuel used as the energy source of the normal myocardium.[1,2] Therefore, various iodinated fatty acid analogs have been proposed to investigate regional myocardial metabolism.[3-7] Radioiodinated straight-chain fatty acids are cleared for the myocardium reflecting oxidation of fatty acid, while methyl-branched fatty acid analogs are trapped in the myocardium.[8-10] The latter, such as β-methyl-iodo-phenyl pentadecanoic acid (BMIPP), may allow for single-photon emission computed tomography (SPECT) because of their prolonged residence time in the myocardium. In patients with myocardial infarction, several studies have been conducted of regional differences between the myocardial accumulation of Tl-201 and that of BMIPP after rest injection.[11,12] However, very little is known regarding the usefulness of BMIPP in patients with unstable angina. The present study in patients with unstable angina was thus conducted to clarify the clinical significance of BMIPP in the assessment of ischemic myocardium in

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patients with unstable angina in comparison with Tl-201 perfusion and regional wall motion assessed by two - Dimensional (2D) echocardiography.

Material and Methods

Patient selection.

This study included 6 patients admitted to Hyogo Medical Center for Adults with the diagnosis of unstable angina between November, 1993 and November, 1994. All of the patients presented with the following characteristics: class Ⅲ B according to the Braunwald classification of unstable angina (13) ; confirmation of diagnosis of coronary artery disease by coronary angiography, with documentation of at least a 50% luminal narrowing in one artery; the patient developed a new episode of chest pain typical of myocardial ischemia after admission to hospital; each of BMIPP, Tl-201, and 2D echocardiogrphy studies during a pain-free periods within 4 days after the episode of chest pain in the hospital; no evidence of either old myocardial infarction as documented by diagnostic Q waves on the electrocardiogram (ECG) or acute myocardial infarction as documented by the absence of diagnostic QRS changes on ECG and the absence of an elevation of total and MB creatine kinase in serum samples obtained serially at 8-hour intervals for at least 24 hours, and no recurrent angina or recurrent ST segment/T wave changes indicative of myocardial ischemia observed on the 12-lead ECG.

Protocol

All patients underwent BMIPP and Tl-201 SPECT imaging at rest using a rotating gamma camera (GC90A, Toshiba) equipped with a low-energy, general-purpose collimator. Three millicuries (111 MBq) of BMIPP were injected at rest in a fasting state. SPECT imaging was started 30 min later, at which time 32 views over 180 from the right anterior oblique (RAO) to the left posterior oblique (LPO) positions at 30 sec / view were collected. Tl-201 SPECT was performed within 2 days after the BMIPP study. Fifteen minutes after injection of 3 mCi (111MBq) Tl-201 at rest, SPECT imaging was performed and 32 views of 30 sec each were collected. In each SPECT study, a series of transaxial images were reconstructed using filtered back projection, after which cardiac short-axis, vertical long-axis, and horizontal long-aixs slices were reorganized. No attenuation correction was applied.

Image Analysis

BMIPP and Tl-201 SPECT images were interpreted by three independent observers who were unaware of the clinical history and angiographic findings of the patients. The left ventricular myocardium was divided into nine segments (Fig 1). Uptake was determined visually for each of the 9 segments using 4 point scoring system (3 = normal, 2 = mildly reduced, 1 = moderately reduced, 0 =markedly reduced). The final readings represent either total agreement or the consensus opinion of two of the three obser-

vers. When the scores in a segment were different for the two tracers, the segment was considered to show discordant uptake. When the scores were the same, the segment was considered to show concordant uptake.

Echocardiographic studies

After the patient was placed in the left lateral decubitus position, 2D echocardiograms were obtained with a Toshiba ultrasound machine equipped with a 2.5 MHz transducer. 2D

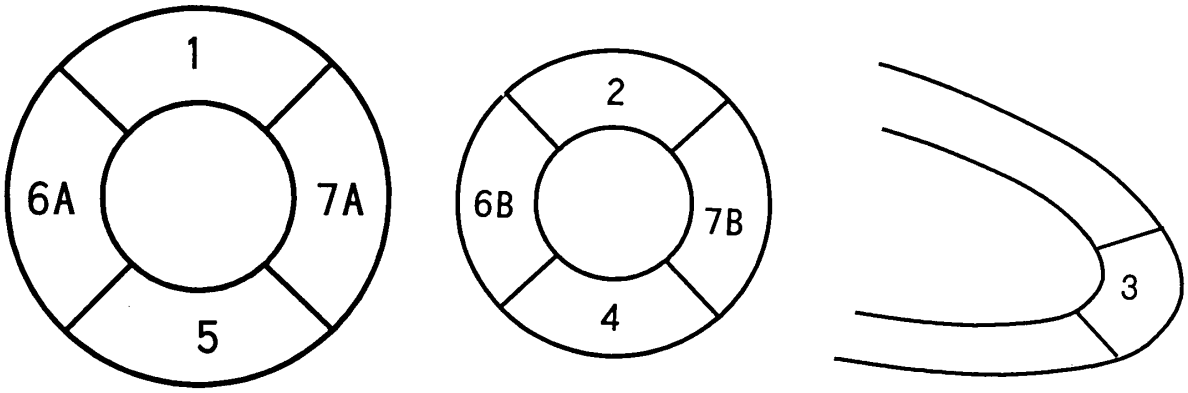

Figure 1. Nine regions of interest on 2 reconstructed short-axis slices and 1 vertical long-axis slice.

echocardiography studies were performed at serial times whenever logistically possible. An attempt was made to acquire three views of the heart (parasternal long-axis, parasternal short-axis, and apical four-chamber) at each time point. All studies were performed by an experienced sonographer. The parasternal short-axis and apical four-chamber views were used for analysis. To assess changes in regional wall motion, the left ventricular wall was divided into 9 segments which corresponded to the 9 segments examined in SPECT (Fig 1). Wall motion was evaluated semiquantitatively using the recorded real-time image. Scores were assigned to each segment, as follows: -1 = hyperkinesis, 0 = normal, 1 = hypokinesis, and 2 = akinesis.

Coronary Arteriography

Selective coronary arteriography was performed with the Judkins technique within 1 month following the other studies. Significant coronary artery disease was defined as › 50% narrowing of the luminal diameter of one or more major epicardial coronary arteries as assessed by two experienced independent observers.

Statistical Analysis

Frequencies were compared using the chi-square or Fisher's exact test when there were only a few samples. A probability (p) value of less than

0.05 was considered significant.

Results

Clinical and angiographic characteristics

The clinical and angiographic characteristics of the six patients are presented in Table 1. There were 5 men and 1 woman; their ages ranged from 45 to 76 years (mean age, 68 years). At angiography, 2 patients showed one-vessel, 3 two-vessel, and 1 three-vessel disease. The duration and character of the index chest pain ranged from a 15-minutes continuous episode to 35 minutes of intermittent pain. All patients showed transient T waves changes, ST segment changes, or both during the pain. In every patient the medical therapy was given at the discretion of the attending physician. All patients were treated with the aspirin and nitrates, five patients were treated with calcium channel blockers, and four with b-blockers.

BMIPP findings

All of the 6 patients showed abnormal BMIPP uptake, while only 3 patients showed abnormal Tl-201 uptake. In each patient, reduced BMIPP uptake compared to Tl-201 uptake (discordant uptake) was found in at least one myocardial segment. There were only 2 segments showing higher BMIPP uptake compared to the Tl-201 uptake. Of the total of 54 segments, 41 (78%) showed the same scores for BMIPP and Tl-201 uptake, indicating concordant distribution (Tl uptake = BMIPP uptake). However, 11 segments (20%) showed a lower

Table 1. Clinical and angiographic data in the patients with unstable angina.

Patient No.	Age(yr) / Gender	Duration of chest pain	Medications				Associated illness		Angiographic data
			BB	CB	NT	ASA	DM	HTN	No.of diseased vessels (culprit lesion)
1	76/M	25~30min	−	+	+	+	−	+	1 (LAD)
2	75/M	30~35min	+	+	+	+	+	+	3 (LCX)
3	45/F	10min	+	+	+	+	+	+	1 (RCA)
4	75/M	15~20min	+	+	+	+	−	+	2 (LCX)
5	70/M	10min	−	+	+	+	+	−	2 (LCX)
6	66/M	10~15min	+	−	+	+	+	−	2 (LAD)

M; male, F: female, BB; ß-blocker, CB; calcium channel blokers, NT; nitrates, ASA; asprin, DM; diabetes mellitus, HTN; hypertension, LAD; left anterior descending coronary artery, LCX; left circumflex coronary artery, RCA; right coronary artery, +; present, −; absent.

	3	2	1	0
3	39	3	6	1
2	1	1	1	0
1	0	1	1	0
0	0	0	0	0

3 = normal ; 2 = mildly reduced ; 1 = moderatoly reduced ; and 0 = defect

Figure 2. Relationship of I-123 BMIPP and Tl-201 uptake scores in the total of myocardial segments.

BMIPP uptake score than Tl-201 score (Tl › BMIPP) (Fig 2). Among these 11 segments, 10 segments showed normal Tl-201 uptake. Representative BMIPP and Tl-201 images observed in this study are shown in Figure 3.

Relationship to echocardiographic findings

Wall motion abnormalities

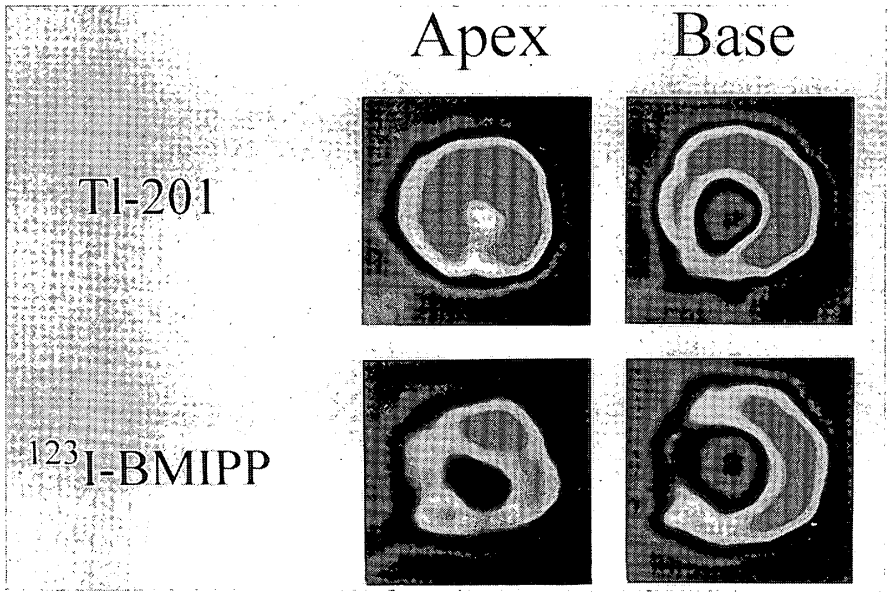

Figure 3. Mid and apical portions of short-axis slices of Tl-201 images and BMIPP images in patient 1. BMIPP uptake is severely reduced in the septal region (6A), where Tl-201 uptake is not reduced (discordant).

(hypokinesis) were observed on the echocardiogram in all 6 patients and in 11/54 myocardial segments. Of 11 segments with wall motion abnormalities, 8 showed discordant BMIPP uptake (Tl uptake › BMIPP uptake). The relationship between regional wall motion (hypokinesis) and this discrepancy is shown in Figure 4. The incidence of discordant uptake (Tl › BMIPP) in normokinetic and hypokinetic regions was 5% (2/43) and 73% (8/11), respectively. This discrepancy was more frequently found in segments with abnormal wall motion than in those with normal wall motion ($p < 0.005$).

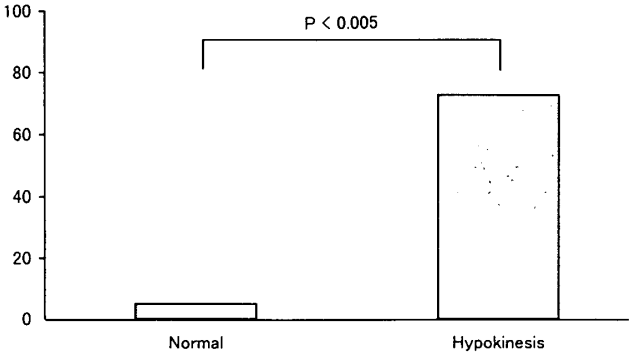

Figure 4. Relationship between left ventricular regional wall motion abnormality and the rate of the discordance (Tl>BMIPP).

Discussion

In the present study abnormal BMIPP uptake was found in all six of the patients examined, and discrepancies between the findings for Tl-201 and BMIPP as a metabolic tracer were also noted. Most of these discrepancies were noted in areas showing regional wall motion abnormality with relatively well preserved perfusion. Thus, decreased BMIPP uptake may indicate a metabolic abnormality associated with the functional failure in patients with unstable angina.

BMIPP as a metabolic tracer

The initial uptake of BMIPP by the myocardial cell is dependent on regional myocardial blood flow, and BMIPP is not metabolized via beta-oxidation, but mainly trapped in the triglyceride fraction.[9,10] Therefore, myocardial BMIPP accumulation appears to be associated with triglyceride synthesis.[14] These properties, together with the stability of it's iodine label, make it a useful tracer providing comprehensive information regarding certain metabolic functions. Since Yonekura et al. first reported a difference between the distributions of a methyl-branched fatty acid and of Tl-201 in hypertensive rats[15], the divergent behaviour of BMIPP compared to Tl-201 has been reported in several myocardial diseases. Recently Tamaki et al. and Geeter et al. have shown that areas in which BMIPP is relatively decreased compared to Tl-201 are more frequently observed after recent myocardial infarction, as well as in areas supplied by revascularized arteries.[11,12] However, no previous study has serially assessed the BMIPP uptake in patients with unstable angina.

Interpretation results

This study revealed a decrease in BMIPP uptake as compared to Tl-201 uptake in patients with unstable angina. Interestingly, such discordant BMIPP uptake was often observed in the areas showing a regional wall motion abnormality but relatively well preserved perfusion. In patients with acute myocardial infarction many studies have documented discordant BMIPP uptake compared to Tl-201, and the affected areas are highly likely to include areas with post-ischemic ventricular dysfunction, so-called "stunned myocardium".[11,12] PET studies have indicated sustained metabolic abnormalities under experimental and clinical conditions, including suppressed fatty acid utilization and enhanced glucose utilization.[16-17] Our clinical results are consistent with these PET findings. Evidence of stunned myocardium has also been observed in instances of unstable

angina. Nixon et al.[18] documented persistent regional wall motion abnormalities with echocardiography in patients with unstable angina, even during the pain-free period. Several days were required for the contractile function of this stunned tissue to return to normal. Furthermore, recently Jeroudi et al. also have reported that myocardial stunning occurred in unstable angina and a prolonged depression of contractile function might persist 24 hours or even longer.[19] In contrast, the discordant BMIPP uptake compared to Tl-201 uptake was not often seen in patients with stable angina.[20] Thus, in view of the above considerations, the most plausible explanation for the decreased BMIPP uptake compared to Tl-201 uptake is thought to be myocardial stunning. However, we cannot rule out the possibility that the decreased BMIPP uptake could be the result of myocardial hibernation. While this possibility cannot be completely excluded, it is unlikely because in the areas showing regional wall motion abnormality, Tl-201 uptake was most preserved. Recurrent bouts of ischemia cannot be completely excluded, but are unlikely because no patient experienced recurrent angina during the interval in which BMIPP and Tl-201 were performed.

Limitations

One limitation of the present study is that the BMIPP and Tl-201 studies were not performed on the same day. However, simultaneous dual myocardial imaging with BMIPP and Tl-201 would have adversely affected the image quality, and for this reason the BMIPP and Tl-201 studies were not performed simultaneously but were completed within as short an interval as possible. Other limiting factors include the relatively small size of the patient group studied. Further comparative studies involving a much larger sample size will be required to confirm the true significance of the decreased uptake of BMIPP in unstable angina.

Conclusions and implications

In patients with unstable angina, the uptake of BMIPP shows relatively greater decrease than the uptake of Tl-201. In addition, this discrepancy is often observed in areas showing left ventricular dysfunction with relatively well preserved perfusion. Thus, the measurement of BMIPP uptake may be potentially useful in identifying metabolic alterations in patients with unstable angina.

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