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Assessment of Fatty Acid Uptake in Ischemic Heart Disease without Myocardial Infarction

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To assess the clinical value of ^{123}I fatty acid analog, ^{123}I-β-methyl iodophenyl pentadecanoic acid (BMIPP) was imaged at rest in coronary patients without prior myocardial infarction. The BMIPP findings were compared with various clinical parameters. **Methods:** Thirty-one patients with ischemic heart disease (19 with unstable angina, 12 with stable angina), without myocardial infarction underwent BMIPP SPECT at rest, coronary arteriography, rest/stress thallium SPECT and left ventriculography exams. **Results:** Regional decrease of BMIPP was seen in 63% of the myocardial areas at risk, whereas regional perfusion decrease at rest was observed only in 35% ($p < 0.01$). The BMIPP decrease was more often seen in the unstable group (79%) than stable group (38%) ($p < 0.01$). Stress-induced ischemia was seen in 77% of segments with decreased BMIPP uptake in unstable group and in 57% in the stable group. Frequency and severity of BMIPP abnormality increased with the severity of stress-induced ischemia ($p < 0.005$) and the severity of coronary artery stenosis ($p < 0.005$). In addition, regional BMIPP abnormality was related to severity of wall motion abnormalities ($p < 0.005$). While 67% of segments with a wall motion abnormality showed BMIPP decrease, 36% with normal wall motion also showed BMIPP decrease ($p < 0.01$). **Conclusion:** Abnormal fatty acid metabolism was often observed at rest in patients with ischemic heart disease without history of myocardial infarction, and the abnormalities were related to severe myocardial ischemia and regional wall motion abnormalities.

Key Words: iodine-123-BMIPP; coronary artery disease; emission computed tomography; thallium-201

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In patients with frequent and severe ischemic episodes, myocardial metabolic abnormalities, such as metabolic switching from fatty acid utilization to glucose utilization, is often observed, even at rest (*1,2*). Patients with coronary artery disease often have regional asynergy in spite of no history of myocardial infarction (*3–7*). Moreover, metabolic alteration is often associated with regional asynergy (*8,9*).

Iodine-123-labeled β-methyl iodophenyl pentadecanoic acid (BMIPP) is a branched fatty acid analog that enters the myocardial cells but is not catabolized in the fatty acid oxidative chain. Therefore, BMIPP distribution may provide information about myocardial fatty acid uptake and metabolism (*10–13*).

The purpose of this study is to assess the ability of ^{123}I-BMIPP to detect ischemic myocardium as an area of metabolic abnormality in comparison to ^{201}Tl, which detects ischemic myocardium as an area of perfusion abnormality. In addition, the clinical significance of decreased ^{123}I-BMIPP uptake was evaluated in comparison to other clinical parameters such as coronary artery stenosis, stress thallium findings and wall motion abnormalities in patients without evidence of myocardial infarction.

MATERIALS AND METHODS

Patients

Thirty-one patients with ischemic heart disease were included in this study (19 men, 12 women; age 48–84 yr, mean age 66.4 ± 8.2 yr). All patients had at least one coronary artery stenosis over 75% on coronary arteriography (CAG). None of the patients had a history or electrocardiographic evidence of myocardial infarction. The patients were divided into unstable angina group ($n = 19$) and stable angina group ($n = 12$). The criteria for unstable angina were either new onset, worsening symptoms or chest pain at rest (*14*).

Radiopharmaceuticals

Iodine-123-BMIPP was obtained commercially. BMIPP contained 111 MBq ^{123}I-labeled 15-(para-iodophenyl)-3(R,S)-methyl pentadecanoic acid (0.6 mg) dissolved in 10.5 mg of ursodeoxycholic acid as a solvent.

Protocol

All patients underwent BMIPP SPECT imaging at rest. Images were obtained 20 min after administration of 111 MBq ^{123}I-BMIPP under a fasting state using a rotating single-head gamma camera equipped with low-energy, all-purpose collimation. The acquisition time was 30 sec per view, with 32 views collected over 180° from the RAO 45° to the LPO 45° projection. The energy window was set at 159 keV ± 10%.

Nine patients underwent a ^{201}Tl SPECT imaging at rest 10 min postadministration of 111 MBq ^{201}Tl under fasting state, with the same camera and acquisition mode used in the BMIPP study. The energy window was set at 70 keV ± 10%.

Stress ^{201}Tl SPECT was performed in 28 patients. In the unstable angina group, 16 patients could undergo stress ^{201}Tl SPECT after their condition stabilized. Reinjection images were used to assess myocardial perfusion at rest in 20 patients. The interval between BMIPP and the resting or reinjection thallium study was within 1 wk in 26, 2 wk in 3 and 4 wk in 2 patients. None of them underwent any revascularization procedures or had changes in medication between the BMIPP and thallium studies. Contrast ventriculography (LVG) in the RAO and LAO projections was performed in 29 patients to assess regional wall motion at rest.

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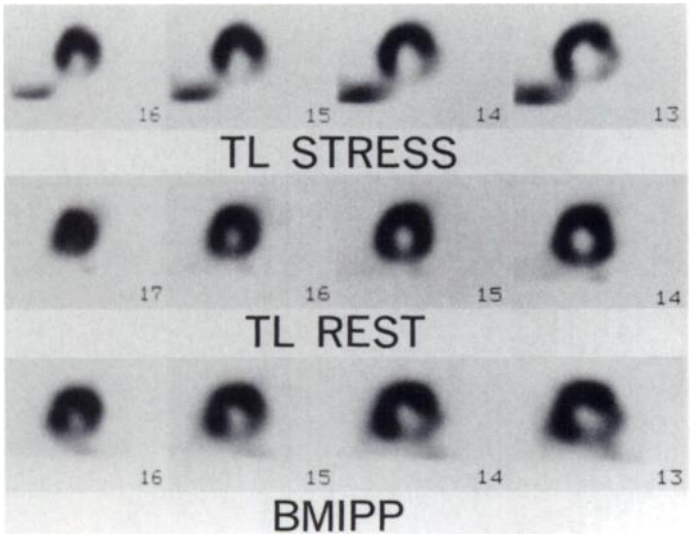

FIGURE 1. Series of short-axis slices of stress-thallium (top row), rest thallium (middle row) and BMIPP images (bottom row) of a 55-yr-old man with unstable angina. Stress-induced ischemia is seen in the infero-lateral wall, with almost normal perfusion at rest. Decreased uptake of infero-lateral wall is also observed in BMIPP at rest.

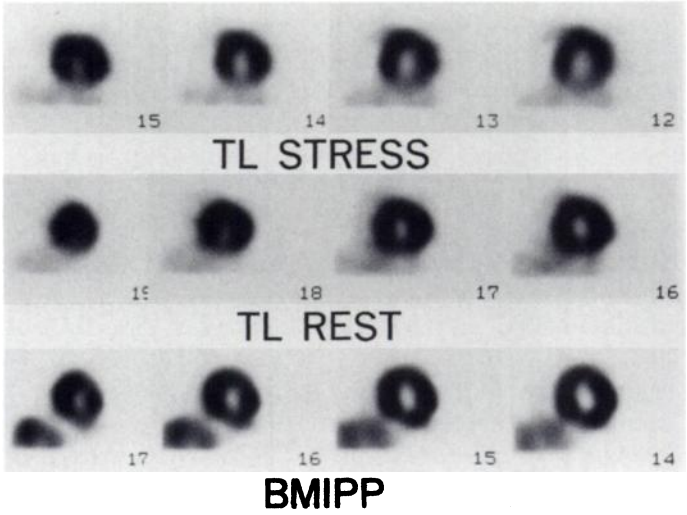

FIGURE 2. Series of short-axis slices of stress-thallium (top row), rest thallium (middle row) and BMIPP images (bottom row) of a 63-yr-old woman with stable effort angina. Stress-induced ischemia is seen in the inferior wall, with normal perfusion at rest. BMIPP at rest also reveals no focal decrease.

Image Analysis

The myocardial wall was divided into seven segments (antero-basal, anterior, apical, inferior, posterobasal, septal and lateral walls) according to AHA criteria on SPECT and LVG images. To compare CAG results with SPECT and LVG results, we assumed one anterobasal, two anterior and six septal segments as LAD territories, seven lateral segments as the LCx territory and four inferior and five posterobasal segments as the RCA territories.

The segments were visually scored by a four-point grading system as follows: 0 = normal uptake or wall motion, 1 = mildly decreased uptake or wall motion, 2 = decreased uptake or wall motion and 3 = absent uptake or akinesis. Similarly, coronary artery stenosis was graded as stenosis <75%, 75–90%, 90–99%, and ≥99% in diameter.

Statistical Analysis

Chi square analysis was used to determine the differences between the proportions of abnormal and normal of the BMIPP and thallium uptake scores. BMIPP scores are expressed as mean ± s.d. Differences in the BMIPP score in relation to coronary stenosis, stress thallium scores and LVG findings were compared using analysis of variance. Probability values of less than 0.05 on Scheffe's F-test were considered to be significant.

RESULTS

BMIPP abnormalities at rest were seen in all patients with unstable angina (19/19) (Fig. 1) and in only 8/13 patients with stable angina (Fig. 2) ($p < 0.01$) (Table 1). Similarly, thallium abnormalities at rest were seen in 15/19 patients with unstable angina and in only 4/12 patients with stable angina ($p < 0.01$). BMIPP findings and CAG findings were compared in the segments supplied by coronary arteries with stenosis >75%. A BMIPP abnormality was demonstrated in 34/54 (63%) of the segments supplied with the coronary artery with 75% stenosis, whereas a thallium abnormality was seen only in 19/54 (35%) ($p < 0.01$). In addition, BMIPP was abnormal in 26/33 (78%) myocardial segments in patients with unstable angina and only in 14/44 (32%) in stable angina ($p < 0.01$). Furthermore, BMIPP abnormalities were more frequently seen than resting thallium abnormalities in the unstable and stable angina groups ($p < 0.01$).

The degree of the BMIPP abnormality significantly increased with the severity of coronary artery stenosis ($p < 0.005$) (Fig. 3). The BMIPP score was 0.462 ± 0.790 in the segments with stenosis <75%, 0.769 ± 0.832 with 75%-90% stenosis, 1.045 ± 1.174 with 90%-99% stenosis, 1.526 ± 1.172 with stenosis ≥99%. A significant difference in the BMIPP score was observed between the segments with angina <75% and ≥99% stenosis. In the unstable angina group, the BMIPP score was 0.625 ± 0.924 in segments with <75% stenosis, 1.333 ± 0.816 with stenosis 75%-90%, 1.235 ± 1.200 with 90%–99% stenosis, 2.400 ± 0.843 with ≥99% stenosis ($p < 0.005$). A significant difference in the BMIPP score was observed between the segments with angina <75% and ≥99% stenosis ($p < 0.05$). In the stable angina group, however, the BMIPP score did not differ among the groups (Fig. 3).

There was good correlation between the segments with abnormal BMIPP uptake and those with stress-induced ischemia. In the unstable angina group, 44/57 (77%) segments with decreased BMIPP had decreased perfusion, whereas 43/55 (78%) segments with normal BMIPP had normal perfusion on stress thallium scan. In the stable angina group, only 15/26 (58%) segments with decreased BMIPP had decreased perfusion, whereas 54/58 (93%) segments with normal BMIPP had normal perfusion on the stress thallium scan. The degree of BMIPP abnormality significantly increased with the severity of stress-induced ischemia in both groups ($p < 0.005$ each) (Fig. 4). (Unstable angina group thallium Ex score 0: 0.327 ± 0.695, thallium Ex score 1: 1.000 ± 0.943, thallium Ex score 2: 1.444 ± 1.042, thallium Ex score 3: 2.050 ± 1.050, Stable

TABLE 1
Frequency of Abnormal Findings in Patients and Myocardial Regions Supplied by Coronary Arteries with Stenosis >75%

		Overall	Unstable AP	Stable AP
Patients	BMIPP	27/31 (0.87) *	19/19 (1.00) *	8/12 (0.67)
	Thallium	19/31 (0.61)	15/19 (0.79) *	4/12 (0.33)
Segments	BMIPP	34/54 (0.63) *	26/33 (0.79) *	8/21 (0.38) *
	Thallium	19/54 (0.35)	15/33 (0.45) *	4/21 (0.19)

*$p < 0.01$

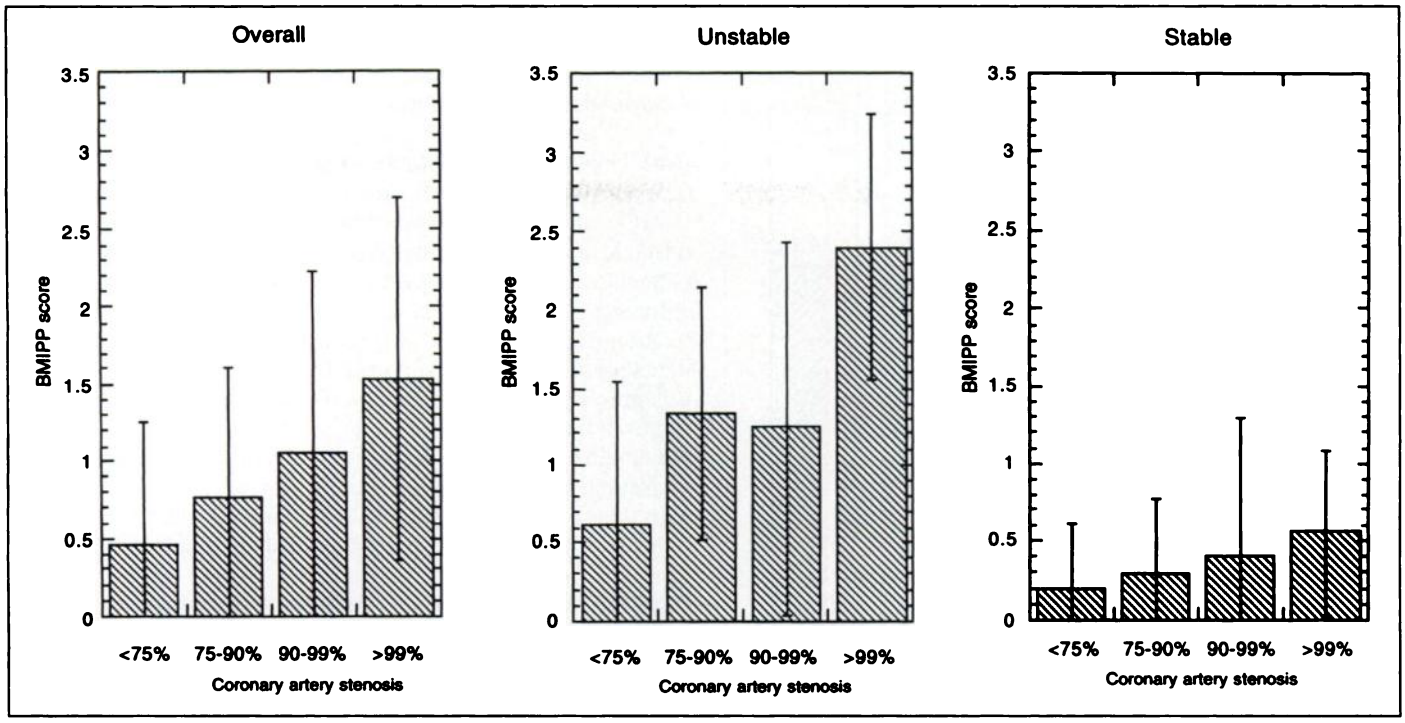

FIGURE 3. Relationship between the severity of coronary artery stenosis and BMIPP defect score in angina pectoris. Figures of overall patients, unstable angina group and stable angina group are demonstrated. Each bar represents means and one s.d. of the BMIPP score.

angina group thallium Ex score 0: 0.069 ± 0.532, thallium Ex score 1: 0.600 ± 0.548, thallium Ex score 2: 0.632 ± 0.684, thallium Ex score 3: 2.000 ± 1.414).

In the unstable angina group, significant differences in the BMIPP score were observed between the segments with thallium Ex scores 0 and ($p < 0.05$). In the stable angina group, significant differences in the BMIPP score were observed between the segments with thallium Ex scores 2 and 3 ($p < 0.05$).

The degree of BMIPP abnormality significantly increased with the severity of the LVG abnormality ($p < 0.005$) (Fig. 5). The BMIPP score was 0.577 ± 0.906 in segments with normal wall motion, 1.190 ± 1.250 in segments with mild hypokinesis and 2.429 ± 0.787 with hypokinesis. Significant differences in BMIPP scores were observed between segments with normal wall motion and mild hypokinesis ($p < 0.05$) and those with mild hypokinesis and hypokinesis ($p < 0.05$). Sixty-eight percent (19/28) of the segments with abnormal wall motion had decreased BMIPP uptake, whereas only 36% (62/175) segments with normal regional wall motion ($p < 0.01$) had decreased BMIPP uptake.

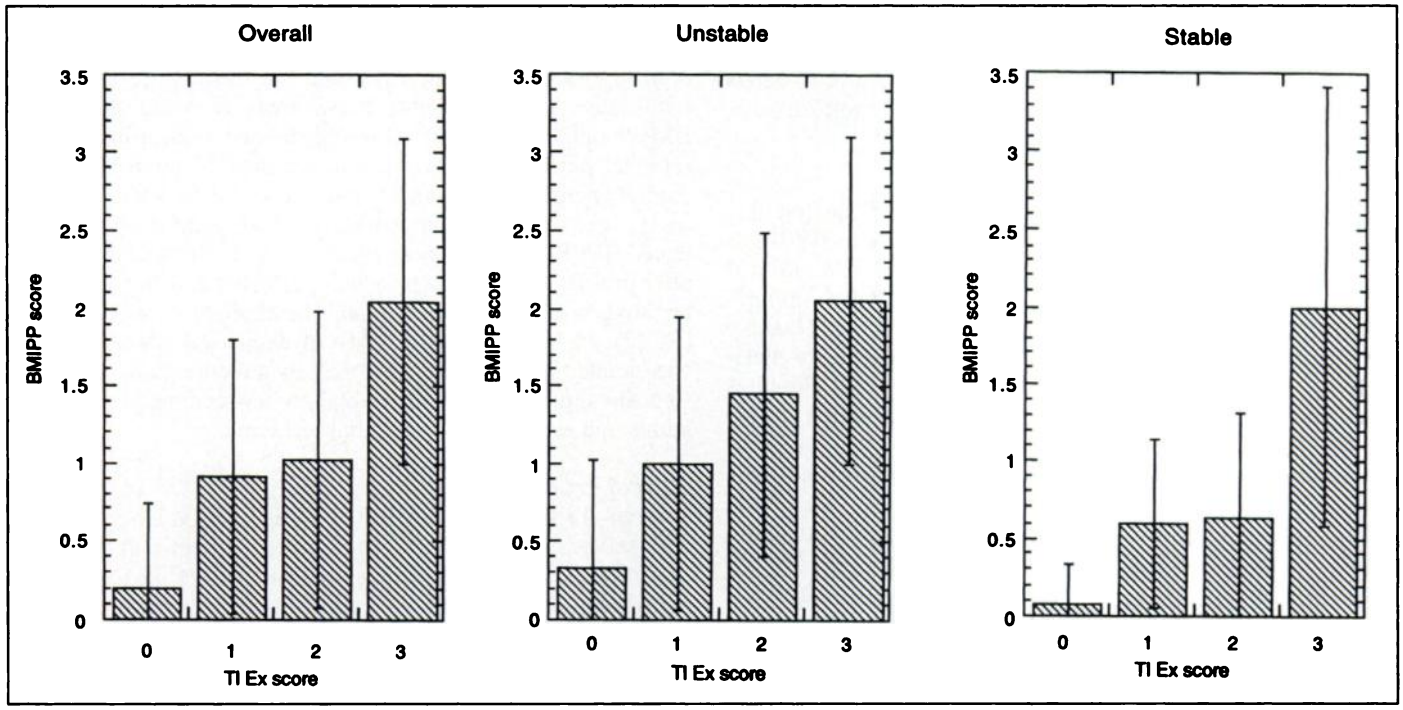

FIGURE 4. Comparison of defect scores of stress thallium and BMIPP at rest. Figures of overall patients, unstable angina group and stable angina group are demonstrated. Each bar represents means and one s.d. of the BMIPP score.

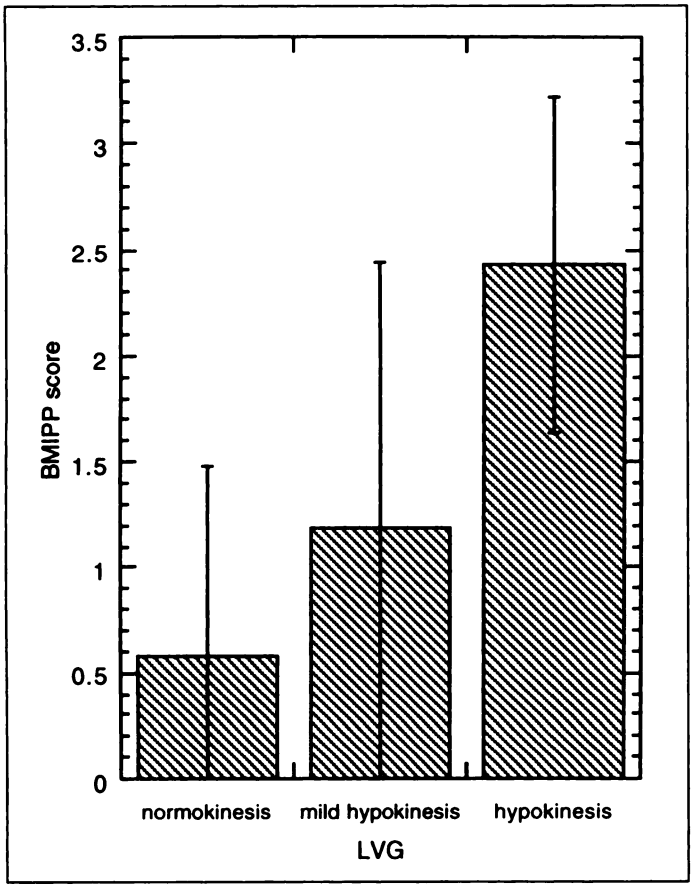

FIGURE 5. Relationship between the severity of LVG abnormality and BMIPP defect score. Each bar represents means and one s.d. of the BMIPP score.

DISCUSSION

The present study indicated that decreased BMIPP uptake was often observed at rest in patients with coronary artery disease without prior myocardial infarction. These findings were more prominent in patients with unstable angina than those with stable angina. In addition, decreased BMIPP uptake was related to stress-induced ischemia, severe coronary stenosis and abnormal wall motion. These results are suggestive of the clinical significance of BMIPP, which may be useful to detect risk areas at rest in patients with ischemic heart disease, especially patients with unstable angina.

Uptake Mechanism of BMIPP

BMIPP is a three-methyl-branched fatty acid analog that enters the myocardial lipid pool. The initial uptake of BMIPP is largely determined by regional myocardial blood flow and it is incorporated into the endogenous lipid pool. Unlike straight-chain fatty acids such as palmitate or iodophenyl-pentadecanoic acid (IPPA), BMIPP is not directly catabolized by beta-oxidation and therefore stays in the lipid pool (*10–13*). Previous clinical and basic studies have indicated discordance between regional BMIPP uptake and flow tracer distribution (*15–23*). The results of clinical studies comparing BMIPP and PET findings indicate that BMIPP uptake represents fatty acid uptake, while decreased BMIPP uptake relative to thallium perfusion reflects the presence of glucose metabolism (*24–26*).

BMIPP and CAG Findings

In the study of coronary artery disease without myocardial infarction, the severity of BMIPP decrease was related to those of coronary stenosis. Ischemic episode is more frequent in myocardial segments with severe coronary artery stenosis than in those with mild stenosis, as the flow reserve is more limited (*27,28*). Metabolic alteration is often seen in myocardial segments with frequent ischemia (*9,29*). Therefore, decreased BMIPP uptake was often observed in segments with severe stenosis than those with mild stenosis.

BMIPP Findings in Unstable Angina

When the patients were divided into subgroups, decreased BMIPP uptake was more frequently seen in patients with unstable angina than those with stable angina. Additionally, patients with unstable angina had a significant relation between coronary stenosis and decreased BMIPP, while no significant relation was observed in patients with stable angina. Patients in the stable group are successfully treated and rarely have ischemic episodes even in myocardial segments with severe stenosis, whereas ischemia is frequently observed in the unstable angina group, as the criteria of unstable angina were: worsening chest pain, chest pain at rest or new onset of chest pain. These results indicate that the metabolic alteration appears in areas with severe and prolonged ischemic episodes.

BMIPP Findings and Stress-Induced Ischemia

The location of BMIPP decrease was associated with those of stress-induced myocardial hypoperfusion on the stress thallium scan. Furthermore, there was significant correlation between the severity of stress-induced hypoperfusion and the BMIPP score. In the unstable angina group, a BMIPP score of the segments with thallium Ex score 0 significantly differed from those with thallium Ex score 1. In the stable angina group, s significant difference was present between thallium Ex scored 2 and 3. Decreased BMIPP uptake means the presence of severe ischemia. In unstable state, severe ischemia seem to occur even in the myocardial segments with mild stress-induced ischemia. In the stable state, severe ischemia is only occurring in the myocardial segments with severe stress-induced ischemia.

BMIPP Findings and Regional Wall Motion

The present study showed reduced BMIPP uptake in the areas with severe regional asynergy in patients without prior myocardial infarction. A previous report indicated a discordant decrease in BMIPP uptake with relatively preserved perfusion in areas showing regional wall motion abnormality in patients with myocardial infarction (*21,23*). Our results are consistent with these findings. Thus, these areas showing discordant BMIPP uptake may likely represent stunned myocardium where regional perfusion is present, but regional function and myocardial energy metabolism are reduced (*3,5,8,9*). More interestingly, areas with normal contraction sometimes showed reduced BMIPP uptake. These areas may be in the recovery phase after prolonged ischemia in which perfusion and function were restored, but recovery of regional metabolism is taking longer (*21,22*). In addition, the severity of decreased BMIPP uptake was related to those of regional dysfunction and coronary stenosis, indicating a close correlation between metabolic alterations and severity of myocardial ischemia.

Clinical Implications

From our findings, a BMIPP abnormality is often associated with severe coronary stenosis and severe ischemia. It would be useful to survey metabolic function on BMIPP at rest before performing any stress tests or coronary arteriography, particularly patients in whom force stress is contraindicated, such as the elderly, disabled and patients with probable unstable angina. Further follow-up studies are necessary to determine the prognostic value of BMIPP SPECT at rest in patients with ischemic heart disease.

CONCLUSION

Decreased BMIPP uptake relative to thallium perfusion was often seen at rest in patients with coronary artery disease without myocardial infarction. This decreased BMIPP uptake is probably a result of prolonged and severe myocardial ischemia which is often associated with regional wall motion abnormality.

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Regional Abnormality of Iodine-123-MIBG in Diabetic Hearts

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Autonomic neuropathy along with cardiac denervation is one of the prognostic factors of diabetic patients. The aim of this study was to establish qualitative and quantitative assessment of diabetic cardiac denervation using [^{123}I]metaiodobenzylguanidine (MIBG). **Methods:** The study population consisted of 31 diabetic patients and 12 control subjects (C). Diabetic patients were classified into the following three groups according to their presentation of neuropathy: N0, without neuropathy; N1, mild neuropathy; N2, severe neuropathy. All subjects underwent triple-phase MIBG scanning, including dynamic planar imaging as well as early and delayed planar and SPECT imaging. Myocardial uptake ratios of MIBG and heart-to-mediastinum count ratios (H/M) were calculated as global uptake indices. Inferior-to-anterior count ratios and coefficients of variation were calculated as regional distribution indices. The washout rate of the inferior wall and whole myocardium were also studied. **Results:** MIBG abnormalities were obvious in the inferior wall, which gradually spread to the adjacent segments. All indices of regional uptake showed a significant difference ($p < 0.01$) among the groups, while only the H/M of the late image showed significant differences in the two global uptake indices ($p = 0.02$). The washout rate of the inferior wall was enhanced with neuropathy. **Conclusion:** Diabetic neuropathy involves an MIBG abnormality in its early stages. Since this abnormality occurs in the inferior segment, an inferior-to-anterior count ratio, an index of regional MIBG uptake could be suitable for the evaluation of this condition because of its superior sensitivity.

Key Words: diabetes; autonomic neuropathy; iodine-123-MIBG

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Autonomic neuropathy is one of the significant prognostic factors for diabetic patients (*1*). Among these factors, cardiac denervation appears to be a major risk factor of sudden death (*2,3*). Autonomic neuropathy is usually assessed by physical examination (*3–5*) or spectral analysis of heart rate variability (*6,7*).

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