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Clinical implication of reverse redistribution on ^{99m}Tc-sestamibi images for evaluating ischemic heart disease

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Objective: The purpose of this study was to clarify the usefulness of ^{99m}Tc-sestamibi (MIBI) delayed imaging in the assessment of the severity of myocardial ischemia in patients with coronary artery stenosis. ***Methods:*** Forty-three angina pectoris with coronary stenosis of greater than 75% were enrolled in this study. Myocardial perfusion SPECT images were obtained 1 and 6 hours after an intravenous injection of MIBI at rest. Stress myocardial perfusion SPECT images were also acquired after the injection of MIBI. And myocardial fatty acid metabolism images were obtained 30 minutes after the injection of BMIPP at rest. Myocardial perfusion SPECT images were divided into 20 segments which were semiquantitatively assessed according to a 4-level defect score scale: score 0 (normal) to score 3 (severely); then the extent score (ES) and severity score (SS) were calculated. ***Results:*** The sensitivity for myocardial ischemia showed the highest rate at 88.3% with MIBI delayed SPECT. According to the coronary angiography findings, MIBI stress SPECT and MIBI delayed SPECT detected the severity and extent of ischemia with more sensitivity than MIBI early SPECT in 12 patients (group A) with stenosis of more than 75% but less than 90% ($p < 0.01$). Even though MIBI stress SPECT detected the severity and extent of ischemia in 31 patients (group B) with stenosis of more than 90% but less than 100%, there was no significant difference between MIBI stress SPECT and MIBI delayed SPECT. BMIPP SPECT revealed significant differences between group A and group B regarding the severity of myocardial ischemia. MIBI reverse redistribution was observed in 33 patients and no significant difference existed between groups A and B. ***Conclusions:*** Myocardial washout of MIBI was frequently observed in patients with angina pectoris and the detection accuracy for ischemia was high. MIBI imaging is considered useful for assessment not only of myocardial perfusion but also mitochondrial function. The imagings with BMIPP and delayed MIBI could serve to determine the severity of myocardial ischemia more accurately.

Key words: reverse redistribution, ischemic heart disease, sestamibi, BMIPP

INTRODUCTION

MORE THAN 90% of myocardial ^{99m}Tc-sestamibi (MIBI) is localized within mitochondria.[1] It has been considered that MIBI bound to the inner myocardium tends to remain for a relatively long period of time without redistribution or reverse redistribution.[2] However, reverse redistribution is observed when myocardial MIBI washout is accelerated after the sub-acute phase or after revascularization, especially in patients with acute myocardial infarction, and several authors have reported that MIBI delayed images are similar to images obtained in the early phase of myocardial infarction.[3–7] It is considered that the

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mitochondrial membrane potential and MIBI retention ability are significantly involved in this phenomenon and that an increase of the membrane potential causes a decrease of MIBI retention in the myocardium.[8–11] Furthermore, it is reported that myocardial MIBI washout increases in the viable myocardial tissue of the infarcted area and tends to significantly decrease in areas with a severe defect.[5,12,13] However, there are few studies on reverse redistribution in patients with angina pectoris.

Iodine-123-β methyl-p-iodophenyl-pentadecanoic acid (BMIPP), which is considered to reflect fatty acid metabolism, is used to diagnose angina pectoris and effort angina, although its diagnostic sensitivity is not very high. Therefore it is more useful in determining the effort of myocardial salvage and predicting recovery of wall motion after acute myocardial infarction revascularization.

With regard to angina pectoris, stress myocardial perfusion imaging is considered to be the best method for visualizing ischemia. However, MIBI delayed imaging at rest may contribute to further assessment of the severity of myocardial ischemia diagnosis.

In this study we compared nuclear cardiology techniques (MIBI stress image, MIBI early image at rest, MIBI delayed image at rest and fatty acid metabolism image with BMIPP) for their usefulness in the diagnosis of stable angina in patients with significant coronary artery stenosis.

MATERIALS AND METHODS

Subjects

The study population consisted of 43 patients (12 women and 31 men, mean age: 69 ± 10 years, coronary lesion: 1-vessel disease 23 patients, 2-vessel disease 16 patients, 3-vessel disease 4 patients) with angina pectoris (unstable angina: 5 patients, old myocardial infarction: 5 patients, stable angina: 33 patients) who were diagnosed with stenosis by coronary angiography. Cases within six months after onset of acute myocardial infarction and regions that underwent revascularization were excluded. According to the IRB (Institutional Review Board), informed consent was obtained from all patients before the tests, based on sufficient understanding of the tests to be employed, including the predicted exposure dose. During the course of the study, patients were also informed and given an explanation of the test results as appropriate (Table 1).

Examination protocol

Percutaneous coronary angiography (CAG) was performed to determine the percentage of stenosis based on the AHA classification and the location and level of the lesion. On MIBI SPECT images were obtained using a two-day protocol (rest SPECT or stress SPECT). The myocardial perfusion images at rest were obtained 1 hour after injecting 740 MBq of MIBI (myocardial perfusion early imaging at rest: MIBI early SPECT) and 6 hours after injection

Table 1 Study group (n = 43) angina pectoris

• Male/female	31/42
• Age in years (range)	68.8 ± 9.89 (35–86)
• History of hypertension	20 (46%)
• History of diabetes mellitus	13 (30%)
• History of hyperlipidemia	10 (23%)
• History of smoking	15 (34%)
• ECG abnormality	25 (58%)
• 1DV/2VD/3VD	23/16/4

Data are presented as number (%) of patients.
ECG = electrocardiogram: 1VD/2VD/3VD = single-vessel/two-vessel/three-vessel disease.

(myocardial perfusion delayed imaging at rest: hereinafter MIBI delayed SPECT). The myocardial perfusion stress (treadmill loading or ATP loading: 0.15 mg/kg/min) images were obtained 1 hour after injecting 740 MBq of MIBI (MIBI stress SPECT). Furthermore, myocardial fatty acid metabolism images at rest were acquired 30 minutes after injecting 148 MBq of BMIPP (BMIPP SPECT). These tests were performed during the four days after admission.

Data collection and analysis

A Toshiba double-headed gamma camera was used to collect and analyze imaging data. MIBI SPECT imaging conditions were: a low-energy high-resolution collimator (LEHR), with a 141 keV ± 10% energy window and 64 × 64 matrix. SPECT projection data were collected at 6° increments over 360°, 25 seconds per image. The BMIPP SPECT imaging conditions were as follows: a low-energy all-purpose collimator (LEGP), with a 160 keV ± 10% energy window and 64 × 64 matrix. SPECT projection data were collected at 6° increments over 360°, 20 seconds per image. Transverse images were reconstructed by the filtered backprojection method, with a Butterworth filter for processing and a Ramp filter for backprojection. No scatter or absorption correction was performed. As it is well known that MIBI accumulates selectively in the liver and biliary tract system, patients were given 200 m*l* of water to prevent scatter, especially from the hepatobiliary system.[14,15]

Measurement parameters and evaluation method

Left ventricular short-axis SPECT images were divided into 18 segments in 3 sections lengthwise from apex to base, and the apex of the long axis images was divided horizontally into two segments for a total of 20 segments.

The divided segment regions were semiquantitatively assessed according to a 4-level defect score scale (DS): score 0 (normal uptake), score 1 (slightly reduced uptake), score 2 (moderately reduced uptake) and score 3 (severely reduced uptake). Extent score (ES) was defined as the total number of the segments exhibiting deteriorating uptake. Severity score (SS) was defined as the total number of the defect score.

The Δ SS value was defined as the difference between the delayed image SS and early image SS.

All data are presented as the average ± standard deviation. Differences were assessed for statistical significance using a t-test. The level of significance was set at $p < 0.05$.

RESULTS

Detection of uptake abnormality with MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT and BMIPP SPECT

Figure 1 shows the sensitivity for uptake abnormality with MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT and BMIPP SPECT. Uptake abnormalities corresponding to the area of coronary abnormal were detected in 33 patients (76.7%) by MIBI stress SPECT, 26 patients (60.4%) by MIBI early SPECT, 38 patients (88.3%) by MIBI delayed SPECT and in 28 patients (65.1%) by BMIPP SPECT.

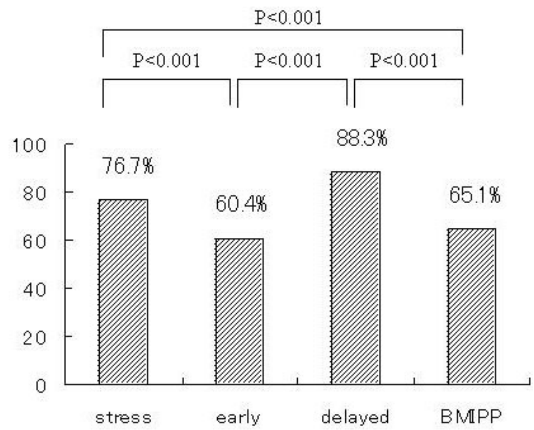

Fig. 1 Comparison of sensitivity between MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT and BMIPP SPECT. The sensitivity of each image with SS ≥ 1 defined as positive was compared in cases of more than 75% stenosis. stress: MIBI stress SPECT, early: MIBI early SPECT, delayed: MIBI delayed SPECT, BMIPP: BMIPP SPECT.

There were significant differences between MIBI stress SPECT and MIBI early SPECT, and between MIBI stress SPECT and BMIPP SPECT ($p < 0.001$). On the other hand, no significant difference was observed between MIBI stress SPECT and MIBI delayed SPECT. There was a significant difference between MIBI early SPECT and MIBI delayed SPECT ($p < 0.001$), but no significant difference was observed between MIBI early SPECT and BMIPP SPECT. Furthermore, a significant difference was observed between MIBI delayed SPECT and BMIPP SPECT ($p < 0.001$)

Severity score and extent score in patients distributed based on their angiographic findings

According to the CAG findings, patients were divided into group A (stenosis of greater than 75% but less than 90%) and group B (stenosis of greater than 90% but less than 100%). MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT and BMIPP SPECT were performed and the respective severity and extent scores were determined.

i. Group A: 12 patients. Their SS and ES were 4 ± 5.65 and 2.91 ± 3.89 in MIBI stress SPECT, 1.58 ± 3.17 and 1.16 ± 2.44 in MIBI early SPECT, 4.83 ± 5.23 and 3.08 ± 3.23 in MIBI delayed SPECT and 1.83 ± 2.85 and 1.41 ± 2.06 in BMIPP SPECT, respectively. Significant differences were observed between MIBI stress SPECT and MIBI early SPECT ($p < 0.05$), MIBI early SPECT and MIBI delayed SPECT ($p < 0.01$) and between MIBI delayed SPECT and BMIPP SPECT ($p < 0.01$), with regard to severity scores and extent scores. However, no significant differences were observed between MIBI stress SPECT and MIBI delayed SPECT, MIBI stress SPECT and BMIPP SPECT and MIBI early SPECT and BMIPP SPECT (Fig. 2).

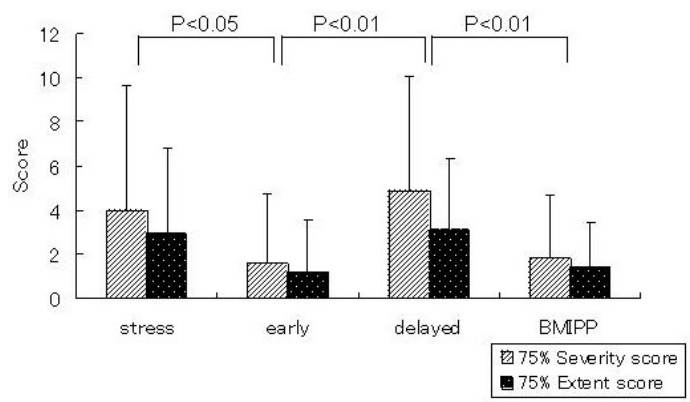

Fig. 2 Severity and extent scores by MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT and BMIPP SPECT for Group A. Comparison of scores for stress, early, delayed resting images and BMIPP image between 75% severity score and 75% extent score. Data are expressed as mean ± SD.

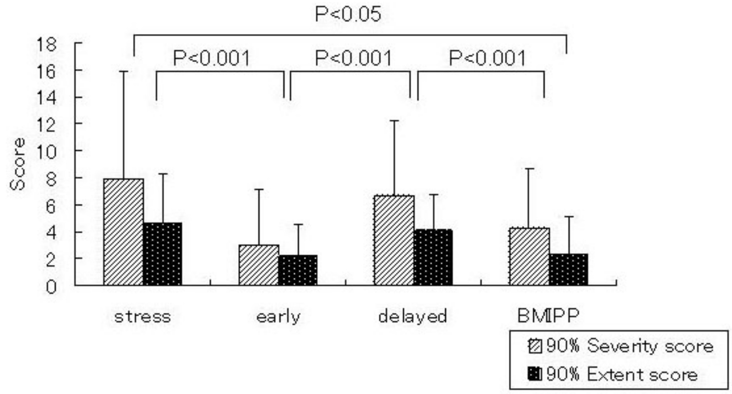

Fig. 3 Severity and extent scores by MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT and BMIPP SPECT for Group B. Comparison of scores for stress, early, delayed resting images and BMIPP image between 90% severity score and 90% extent score. Data are expressed as mean ± SD.

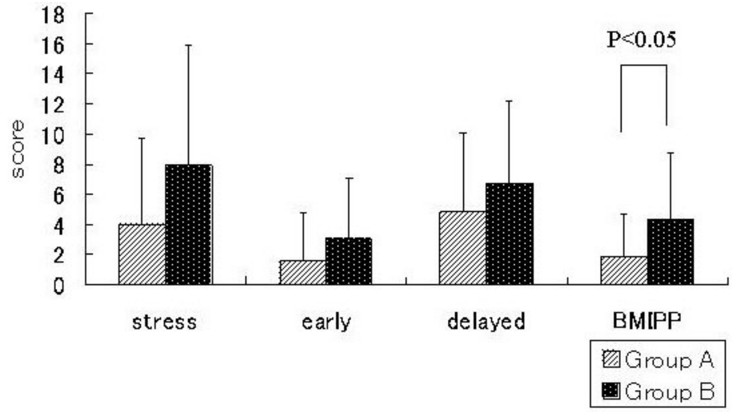

Fig. 4 MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT and MBIPP comparison of Group A with Group B by SPECT. The SS values for each image according to the level of stenosis (moderate, severe) were compared. No significant difference was observed in delayed resting image, while significant difference was observed in BMIPP image. Data are expressed as mean ± SD.

ii. Group B: 31 patients. Their SS and ES were 7.93 ± 7.99 and 4.64 ± 3.66 in MIBI stress SPECT, 3.03 ± 4.03 and 2.25 ± 2.29 in MIBI early SPECT, 6.67 ± 5.49 and 4.06 ± 2.79 in MIBI delayed SPECT and 4.35 ± 4.37 and 2.77 ± 2.80 in BMIPP SPECT, respectively. There were significant differences between MIBI stress SPECT and MIBI early SPECT ($p < 0.001$), MIBI stress SPECT and BMIPP SPECT ($p < 0.05$), MIBI early SPECT and MIBI delayed SPECT ($p < 0.001$), and between MIBI delayed SPECT and BMIPP SPECT ($p < 0.001$) regarding severity scores and extent scores. However, no significant differences were observed between MIBI stress SPECT and MIBI delayed SPECT and MIBI early SPECT and BMIPP SPECT. Thus, for patients with severe coronary stenosis, MIBI stress SPECT is the most useful to assess ischemia, followed by MIBI delayed SPECT (Fig. 3).

Evaluation of the severity of myocardial ischemia

We compared the severity of myocardial ischemia in group A and group B. Group A showed lower severity scores compared to group B either by MIBI stress SPECT, MIBI early SPECT, MIBI delayed SPECT or BMIPP SPECT. As for BMIPP SPECT, a significant difference was observed between group A and group B ($p < 0.05$); while there were no significant differences between them in MIBI stress SPECT, MIBI early SPECT and MIBI delayed SPECT (Fig. 4).

Sestamibi reverse redistribution

MIBI reverse redistribution was calculated by comparing MIBI early SPECT and MIBI delayed SPECT and assuming reverse redistribution in areas with a defect score increased by more than 1. Reverse redistribution was observed in 33 patients; 9 patients (75.0%) in group A and 24 patients (77.7%) in group B; the average Δ washout value was 3.25 and 3.77 respectively, with no significant difference between the two groups (Fig. 5).

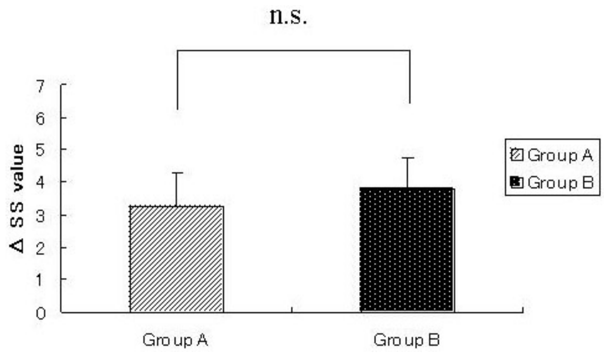

Fig. 5 The Δ SS values according to the level of stenosis (moderate, severe) were compared. No significant difference was observed between the groups. Δ SS = (delayed SS) − (early SS). delayed SS: Severity score on MIBI delayed SPECT, early SS: Severity score on MIBI early SPECT. Data are expressed as mean ± SD.

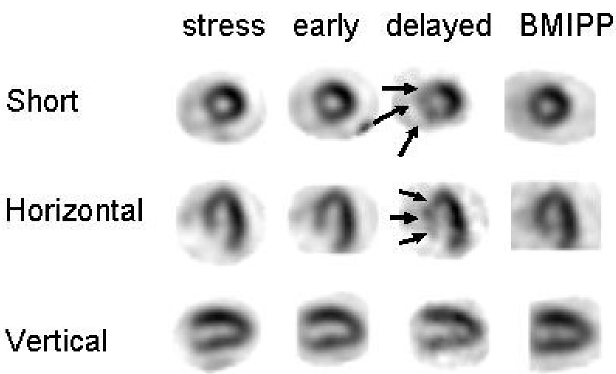

Fig. 6 Myocardial images of a 78-year-old woman for stress, early, delayed and BMIPP. No significant abnormal perfusion is observed on the stress images, early images or BMIPP images. However, the delayed images show severely reduced uptake in the septal and inferior regions. stress: MIBI stress SPECT, early: MIBI early SPECT, delayed: MIBI delayed SPECT, BMIPP: BMIPP SPECT.

CASE REPORT

This is the case of a 78-year-old woman with angina pectoris. Her chief complaint was loss of consciousness. She had been under treatment for high blood pressure for 30 years. Additionally, she had been under treatment for facial spasm for the past 7–8 years. She was admitted to our hospital for a detailed physical check up and treatment due to sudden loss of consciousness.

The patient was subjected to ATP (adenosine triphosphate disodium) stress scintigraphy on the second day of hospitalization (Fig. 6). During stress endurance, no symptoms such as chest pain suggesting myocardial ischemia were observed. Although MIBI stress SPECT showed wall rarefaction in the septum, it detected no decrease of MIBI uptake and myocardial ischemia was negative. The MIBI early SPECT performed on the following day showed normal myocardial uptake of the tracer. However, MIBI delayed SPECT showed a decrease of myocardial uptake extending from the septum to the inferior wall, together with an increased washout. Furthermore, additional tests with BMIPP SPECT showed no obvious abnormalities and myocardial fatty acid metabolism appeared to be normal.

CAG was performed for a thorough examination and a 75% stenotic lesion was detected in LAD. Left ventriculography (LVG) showed a favorable wall stroke, and LVEF was 57%. Based on the clinical course and CAG, the patient was treated with anti-coagulants and was subjected to percutaneous transluminal coronary angioplasty (PTCA).

DISCUSSION

Recent reports discuss that MIBI reverse redistribution frequently occurs in salvaged regions in patients subjected to successful revascularization for AMI at an early stage.[3–6] We clinically examined and determined a way to improve cardiac function in parallel with the correlation of mitochondrial disorder due to ischemia/reperfusion injury and fatty acid metabolic abnormality, based on comparative studies of MIBI delayed SPECT and BMIPP SPECT subsequent to AMI reperfusion. We showed that there was a correlation between the restitution of cardiac function and MIBI delayed SPECT as well as an improvement of the abnormal area on BMIPP SPECT, and suggested the possibility of obtaining images of stunned myocardium post-AMI reperfusion.[16] It was suggested that MIBI reverse redistribution varied depending on various elements such as time, ischemic area and extent of troubled regions, from AMI onset to reperfusion. This study intended to demonstrate the significance of the MIBI washout phenomenon in angina pectoris.

Detection of ischemia

MIBI reverse redistribution was observed in a high percentage of patients with coronary artery stenosis, and MIBI delayed SPECT detected ischemia with more sensitivity than myocardial perfusion SPECT images under stress. The significant difference between MIBI delayed SPECT and BMIPP SPECT, suggested that MIBI delayed SPECT was more sensitive to evaluate myocardial damage than fatty acid metabolism in patients with greater than 75% but less than 90% stenosis (group A). Furthermore, the significantly higher detection sensitivity of MIBI stress SPECT and MIBI delayed SPECT for myocardial ischemia indicated they are more useful than MIBI early SPECT and BMIPP SPECT in patients with greater than 90% but less than 100% stenosis (group B).

Coronary perfusion rate at rest remained steady in slightly injured and normal areas. However, while MIBI stress SPECT showed an increase in coronary perfusion in normal regions, areas affected by coronary stenosis showed only a slight increase. Thus, the myocardial uptake of the RI tracer was uneven in both areas, disclosing the different distribution of the tracer in myocardial perfusion images. In fact, MIBI stress SPECT disclosed coronary stenosis, while MIBI delayed SPECT was believed to reveal a disorder of mitochondrial function. Accumulation of Ca^{2+} in the mitochondria of the myocardial cells damaged by severe ischemia leads to significant dilatation of the mitochondria, decreasing mitochondrial activity and ATP-synthesis ability. Crane et al.[17] have suggested that the increase in calcium concentration was related to MIBI washout acceleration as MIBI myocardial retention depends on the calcium concentration in the myocardium, whereas MIBI retention improved when the calcium channel on the mitochondrial membrane was blocked. Therefore, differing results for detection of ischemia regardless of the fact that the same tracer is used can still be validated. However, myocardial mitochondrial membrane disorder does not necessarily correlate with coronary stenosis, and MIBI washout could be accelerated by coronary artery spasm in reversible ischemia.[18] This suggests that the level of coronary stenosis and the time-course strongly contribute to the occurrence of mitochondrial disorder.

Severity of myocardial ischemia and evaluation of prognosis

The purpose of stress myocardial perfusion imaging in patients suspected of having ischemic heart disease is to evaluate their prognosis rather than to confirm the diagnosis. Therefore, it is thought that stress myocardial perfusion imaging does not always have to correspond to the CAG findings. Non-invasive risk stratification of ischemic coronary artery disease enables proactive invasive operations by identifying the group of patients who are at a high risk of cardiac death or non-lethal infarction. It show that scintigraphic evaluation can contribute to avoid unnecessary invasive examinations in patients at a low risk of suffering a cardiovascular event.

The most useful benefit of myocardial stress scintigraphy is that, if the images show normality, the probability of death and myocardial infarction is low. The annual incidence of death and non-lethal myocardial infarction is less than 1% in patients with normal perfusion at the peak of stress, so there is little necessity for an invasive examination.[19] In this study, the detection rate of ischemia by MIBI stress SPECT was high and it was possible to assess the patients' condition with high sensitivity, especially in those with stenosis of more than 90%. In addition, MIBI stress SPECT was useful to detect abnormal myocardial perfusion in patients with ischemia of less than 90% by comparison with MIBI early SPECT. Furthermore, it was thought that MIBI stress SPECT was useful to determine the prognosis because the defect score varied in accordance with the level of stenosis.

BMIPP SPECT has been reported to be more sensitive than TI imaging in the diagnosis of ischemic heart disease. Besides, decreased uptake in BMIPP SPECT suggests advanced ischemia, as indicated by an abnormal Q-wave or inverted T-wave in the electrocardiograph or abnormal wall motion.[20] Furthermore, in patients with angina pectoris, it is reported that the higher the percentage of stenosis in the culprit lesion, the higher the frequency of abnormal BMIPP SPECT findings will be.[21] Itoh et al.[22] reported that BMIPP SPECT served to detect the decrease of BMIPP uptake with higher sensitivity and was useful for the detection of the ischemic region in patients with unstable angina. Myocardial necrosis and areas of the myocardium where fatty acid metabolism was suppressed due to ischemia were detected by BMIPP SPECT as decreased BMIPP uptake. Moreover, it was reported that BMIPP SPECT was useful to evaluate the culprit lesion and degree of myocardial ischemia, and that if coronary stenosis increased in a patient with effort angina, the patient would suffer repeated ischemia with daily exertion and develop fatty acid metabolic disorder. Therefore, BMIPP SPECT is useful to evaluate serious coronary stenosis and severe myocardial ischemia. A significant difference was observed between patients with stenosis of more than 90% and those with stenosis less than 90%, which suggests that BMIPP SPECT findings may reflect the degree of stenosis and severity of myocardial ischemia.

MIBI delayed SPECT revealed abnormal uptake with more sensitivity than BMIPP SPECT in patients with myocardial damage due to slight ischemia. MIBI retention depends on the mitochondrial membrane potential and it is considered to be more sensitive to myocardial ischemia than to an abnormality of the fatty acid metabolism.

Sestamibi washout in myocardial ischemia

The present study showed that MIBI washout increased in both group A and group B, and that abnormal uptake was due to reverse redistribution. Thus, MIBI delayed SPECT is considered useful to determine the extent of coronary ischemia.

ATP generation in the myocardium is mainly controlled by fatty acid and all reactions require oxygen. Accordingly, as blood flow decreases as a result of coronary stenosis, the amount of ATP decreases significantly. Itoh et al.[23] have demonstrated that the decrease of ATP in myocardial tissue was determined by the decrease of regional myocardial perfusion and its duration. In other words, at a regional myocardial perfusion of less than 20 m*l*/min/100 gm of tissue, the amount of ATP decreased 10 minutes after ischemia, while at a regional perfusion of 20 to 40 m*l*/min/100 gm of tissue, the decrease in ATP was observed only after 60 minutes. These results revealed that ATP production depended on the volume of blood supplied to the myocardium, and also that the decrease of mitochondrial membrane potential was coupled with the decrease of ATP synthesis.

MIBI is passively uptaken by the myocardium from blood depending on the concentration gradient and is retained in the mitochondria. Therefore, in myocardial cells where perfusion is slightly decreased, there seem to be small changes in mitochondrial membrane potential, and thus the MIBI retention capability of the myocardium may possibly be maintained at a fairly normal level for a limited period of time. However, when the supply of oxygen or fatty acid decreases below normal due to a decreased myocardial perfusion, MIBI retention capability is reduced because of an abnormal mitochondrial membrane potential and MIBI washout increases.

Myocardial MIBI washout can be detected by comparing early SPECT images with those of delayed SPECT, or the radioactivity counts. Δ washout values were similar in groups A and B. This result suggests that MIBI myocardial retention allowed sensitive detection of slight stenosis.

Furthermore, it has been reported that many patients with coronary spasm angina pectoris show BMIPP imaging abnormalities, indicating an abnormal fatty acid metabolism.[24,25] Additionally, MIBI washout was frequently observed in patients with coronary spasm angina pectoris.[18] This finding may indicate that the areas of stenosis correspond to the defect areas observed in MIBI delayed SPECT images. The role of MIBI washout should be investigated in future studies that evaluate the influence of coronary spasm.

MIBI washout is frequently observed in ischemic cardiac diseases. Taking images twice at rest is believed to be useful for understanding the condition in greater detail.

CONCLUSION

Washout phenomenon on the images of ^{99m}Tc-sestamibi was observed in patients with stable angina pectoris. It was also confirmed that ischemia detection accuracy was improved by the use of ^{99m}Tc-sestamibi delayed imaging. ^{99m}Tc-sestamibi delayed imaging was more sensitive than fatty acid metabolism imaging. Moreover, it functioned as a tracer for determining severity.

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