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Enhanced regional washout of technetium-99m-sestamibi in patients with coronary spastic angina

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Background: Reverse redistribution and rapid washout of ^{99m}Tc-sestamibi are observed in patients with acute myocardial infarction and may indicate viable myocardium. However, the clinical significance of this phenomenon has not been rigorously examined in other cardiac diseases. Thus, we investigated whether reverse redistribution and washout of ^{99m}Tc-sestamibi could be used in the diagnosis and follow-up of patients with coronary spastic angina. ***Methods:*** Thirty patients diagnosed as coronary spastic angina were examined. During coronary arteriography, spasm was induced by provocation test with ergonovine, and only total or subtotal occlusion was considered positive. Myocardial perfusion tomography was obtained 45 min (early) and 3 hr (delayed) after ^{99m}Tc-sestamibi injection. Segmental defect score was visually graded from 0 (normal) to 4 (defect), and a total defect score was determined as the sum of defect scores for all segments. Washout rate of ^{99m}Tc-sestamibi from the myocardium was calculated for each segment. After medical treatment with calcium antagonists and nitrates for 3 months, ^{99m}Tc-sestamibi imaging was repeated. ***Results:*** Out of 30 patients, on the early images 17 (57%) patients demonstrated decreased ^{99m}Tc-sestamibi uptake in spastic segments; on the other hand, 24 (80%) patients did decreased ^{99m}Tc-sestamibi uptake in spastic segments on delayed images. Total defect scores in delayed images were higher than those in early images (6.9 ± 0.3 vs. 3.6 ± 0.4, $p < 0.01$). Reverse redistribution of ^{99m}Tc-sestamibi was observed in 17 out of 30 patients (57%) with coronary spastic angina. Washout rate of ^{99m}Tc-sestamibi from spastic segments was higher than that from non-spastic segments ($16 \pm 2\%$ vs. $11 \pm 5\%$, $p < 0.01$). After medical treatment, washout rate from spastic segments was decreased to 10 ± 4 ($p < 0.01$), and left ventricular ejection fraction was increased from $63 \pm 8\%$ to $73 \pm 4\%$ ($p < 0.01$). ***Conclusion:*** Rapid washout of ^{99m}Tc-sestamibi was observed in patients with coronary spastic angina and might indicate that the ability of myocyte to retain the tracer was impaired due to repetitive brief ischemia by coronary spasm. The early and delayed ^{99m}Tc-sestamibi imaging provides useful information for the diagnosis and responses to the treatment in patients with coronary spastic angina.

Key words: ^{99m}Tc-sestamibi, reverse redistribution, washout, spastic angina

INTRODUCTION

A PATTERN of reverse redistribution is defined as either the worsening of an initial perfusion defect or the appearance of a new perfusion defect on the redistribution images.[1,2] Reverse redistribution of thallium-201 (^{201}Tl) has been extensively reported in patients with coronary artery disease for the past two decades.[3–6] Recently, it has been demonstrated that this phenomenon is evident on the technetium-99m sestamibi (^{99m}Tc-sestamibi) images.[7–9] Reverse redistribution is associated with rapid washout of ^{99m}Tc-sestamibi and is frequently observed after direct percutaneous transluminal coronary angioplasty in acute

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myocardial infarction.[7] This phenomenon indicates the patency of the infarct-related artery, preserved contractile response to dobutamine, and functional recovery in the chronic state.[7–9] Thus reverse redistribution and enhanced washout of ^{99m}Tc-sestamibi may suggest that the ability of cardiomyocyte to retain the tracer is impaired in viable but damaged myocardium. However, the clinical significance of this phenomenon has not been rigorously examined in other cardiac diseases.

It has been well established that coronary artery spasm plays an important role in the pathogenesis of angina pectoris and acute coronary syndrome.[10] However, the precise mechanism responsible for coronary spasm still remains to be elucidated. Coronary artery spasm occurs most often in patients at rest, particularly from midnight to early morning.[10] Patients with coronary spastic angina often demonstrate abnormal left ventricular regional wall motion, probably due to myocardial stunning after repetitive coronary spasms.[11,12]

The purpose of the present study was to examine serial changes in myocardial ^{99m}Tc-sestamibi uptake in patients with coronary spastic angina. We also investigated whether reverse redistribution and washout of ^{99m}Tc-sestamibi could be used in the diagnosis and follow-up of patients with coronary spastic angina.

METHODS

Subjects and Study Protocol

We studied 30 patients diagnosed as coronary spastic angina. There were 22 men and 8 women with a mean age of 63 years (range 38 to 81). Ten control subjects of 5 men and 5 women (a mean age of 65 years) were also studied. Myocardial single photon emission computed tomography (SPECT) with ^{99m}Tc-sestamibi was performed in all patients. Coronary arteriography with provocation test was performed within 1 week after ^{99m}Tc-sestamibi imaging for the diagnosis of coronary spasm. None of patients had a history of myocardial infarction. Patients with organic coronary stenosis of greater than 50% were excluded from the present study. No medication except short-acting sub-lingual nitrate was given in all patients throughout the study period. After ^{99m}Tc-sestamibi imaging and diagnostic coronary arteriography were performed, patients were given calcium antagonists and nitrates. Myocardial perfusion SPECT with ^{99m}Tc-sestamibi was repeated after medical treatment with calcium antagonists and nitrates for 3 months. Written informed consent was obtained from all patients, and the Institutional Review Board on human research approved the study protocol.

Cardiac Catheterization

All patients underwent coronary arteriography with provocation test using standard percutaneous technique. After a control arteriogram was obtained, ergonovine maleate was selectively infused into the coronary arteries at doses of 6, 20 and 40 μg.[13] When patients had chest pain associated with ST-segment changes, coronary arteriography was performed. If patients had no symptoms, contrast medium was injected 3 min after the ergonovine infusion. When coronary spasm was induced and did not resolve spontaneously, 3 mg of isosorbide dinitrate was infused into the coronary artery. Provocation test was considered to be positive only when the following criteria were satisfied: 1) total or subtotal coronary occlusion, 2) significant ST-segment changes on electrocardiogram, and 3) chest pain suggestive of myocardial ischemia.[13–15] Coronary spasm was induced in all 30 patients in the present study.

Biplane left ventriculography was performed before coronary arteriography. Left ventricular ejection fraction was measured by Simpson's method.[16]

Myocardial Perfusion Imaging with ^{99m}Tc-Sestamibi

A dose of 740 MBq of ^{99m}Tc-sestamibi was administered intravenously under resting conditions throughout an overnight fast. After the injection, patients had their breakfast to reduce subdiaphragmatic activity of the tracer, and SPECT images were obtained at 45 min and 3 hr after the injection.[7–9] All images were acquired in the resting state using a three-head rotating gamma camera equipped with a low-energy, high-resolution collimator (Multispect 3, Siemens Medical Systems, Chicago, IL) as previously reported. Seventy-two images were collected over a 360-degree arc with a 40-second acquisition time per projection. Energy discrimination was provided by a 15% window centered on the 140 keV photopeak. The data were stored on a 64 × 64 matrix. Data processing was performed on a nuclear medicine computer system (Icon, Siemens). A series of contiguous transaxial images of 6 mm thickness were reconstructed by means of a filtered back-projection algorithm without attenuation correction. These transaxial images were then reoriented in the short axis and vertical long axis of the left ventricle.

Two independent observers who were blinded to the patients' data analyzed myocardial distribution of ^{99m}Tc-sestamibi separately. Two consecutive slices from the short axis in the basal- and mid-ventricle, and one from the vertical long axis for the apex were selected for the analysis of the segmental uptake. The left ventricular myocardium was divided into 9 segments corresponding the anterior, septal, inferior and lateral walls of at basal- and mid-ventricular segments in the short axis view, and an apical segment in the vertical long axis view.[7,9] Regional ^{99m}Tc-sestamibi uptake was graded as follows: normal (0), mildly reduced (1), moderately reduced (2), severely reduced (3), and defect (4). The reverse redistribution was defined as an increase of more than 1 in the segmental grade at 3 hr delayed images.[7–9] Total defect score (TDS) was calculated as sum of regional grading scores for each image. The grading was settled by consensus between the two observers. When they disagreed on

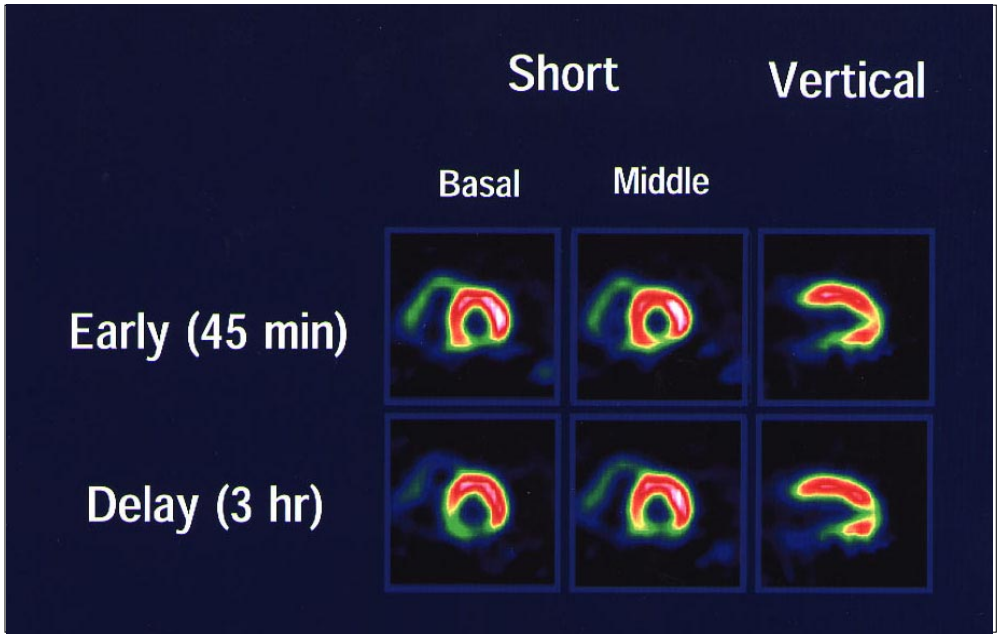

Fig. 1 Early and delayed perfusion images with ^{99m}Tc-sestamibi of a patient with coronary spastic angina. Spasm was induced in the right coronary artery by ergonovine maleate in this patient. Reverse redistribution of ^{99m}Tc-sestamibi is observed in the inferior myocardial segments.

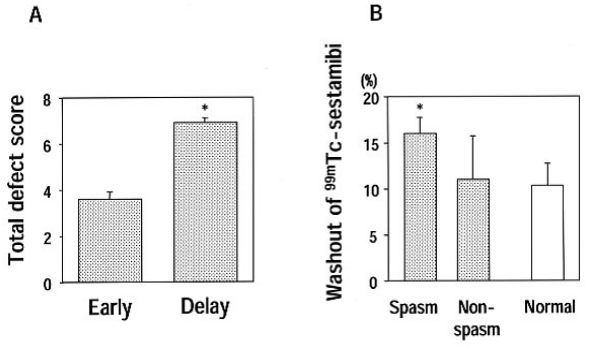

Fig. 2 A: Total defect scores on the early and delayed images. B: Comparisons of myocardial ^{99m}Tc-sestamibi washout rates among normal subjects, spastic and non-spastic segments of patients with coronary spastic angina. *p < 0.01

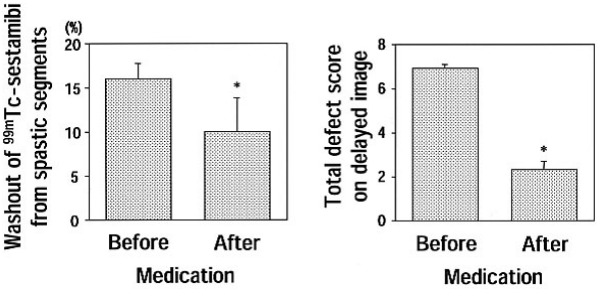

Fig. 3 Changes in ^{99m}Tc-sestamibi washout rate from spastic segments (*left*) and total defect score on delayed images (*right*) after medical treatment with calcium antagonists and nitrates. *p < 0.01

the results, the third observer reviewed the image and made the final judgment. The vascular territories of three major coronary arteries were assigned in principle as follows; the anterior, septal and apical segments were assigned to the territory of the left anterior descending artery, the inferior segments to the territory of the right coronary artery and the lateral segments to the territory of the left circumflex artery, respectively. However, because of variation of vascular supply, minimal extension of a perfusion defect into the adjacent territory was considered as a perfusion defect of the predominant territory.

The segmental uptake and washout of ^{99m}Tc-sestamibi were calculated by placing two regions of interest (ROIs) on each myocardial segment of the slice as previously described.[7–9] The segmental uptake was analyzed by grouping and averaging the ROIs, and expressed as a percent of the maximal counts in the left ventricle. These ROIs were identically placed on the early and delayed images, and the clearance of ^{99m}Tc-sestamibi was calculated from the segmental counts in the early (Ce) and delayed (Cd) images as follows;

$$\text{Washout (\%)} = (Ce - Cd \times Cf) \times 100/Ce$$
$$Cf = 1/(1/2)^x,\ x = (Td - Te)/6$$

(Td, time for delayed image; Te, time for early image)

The analyses of segmental washout of ^{99m}Tc-sestamibi were repeated in 10 patients by the same observer and by the second observer on a separate day, and intra- and inter-observer variability of the analyses were determined. The data of segmental washout of ^{99m}Tc-sestamibi were reliable because excellent correlations were obtained from the repeated analyses.[8,9]

Statistical Analysis

Data were presented as mean ± one standard deviation. Continuous variables were compared by a paired or unpaired t test. A value of $p < 0.05$ was considered significant.

RESULTS

Regional uptake and washout of ^{99m}Tc-sestamibi in coronary spastic angina

A total of 270 myocardial segments were analyzed for 30 patients. Out of 30 patients, 17 (57%) and 24 (80%) patients demonstrated decreased ^{99m}Tc-sestamibi uptake on early and delayed images, respectively. In these 24 patients, 22 out of 26 segments (85%) with decreased ^{99m}Tc-sestamibi uptake were regions with coronary spasm induced by intra-coronary ergonovine injection. Figure 1 demonstrates early and delayed ^{99m}Tc-sestamibi images of a patient with coronary spastic angina. Coronary spasm was induced by ergonovine infusion in the right coronary artery. Decreased uptake of ^{99m}Tc-sestamibi in the inferior wall was more evident on delayed images than on early images, indicating enhanced washout of ^{99m}Tc-sestamibi.

As shown in Figure 2-A, total defect scores were increased from early images to delayed images (3.6 ± 0.4 vs. 6.9 ± 0.3, $p < 0.01$). Reverse redistribution of ^{99m}Tc-sestamibi was observed in 17 of 30 patients (57%) with coronary spastic angina. Regional washout rate of ^{99m}Tc-sestamibi was calculated and compared among normal control subjects, normal and spastic segments of patients with coronary spastic angina. As shown in Figure 2-B, washout rate of ^{99m}Tc-sestamibi from spastic segments was higher than those from non-spastic segments and normal subjects (16 ± 2% vs. 11 ± 5% and 10 ± 3%, $p < 0.01$).

Patients with coronary spastic angina were divided into 3 groups according to the duration of disease history. There were 12 patients with the duration of less than 30 days, 12 patients from 30 to 120 days, and 6 patients of more than 120 days. There were no significant differences in ^{99m}Tc-sestamibi defect score on delayed images (4.8 ± 3.0, 4.8 ± 3.0, and 4.5 ± 1.3) and washout rate (13.7 ± 5.1%, 17.5 ± 4.6%, and 15.5 ± 3.8%) among the 3 groups. The severity of chest pain was subjectively graded as mild, moderate, and severe. There were no differences in ^{99m}Tc-sestamibi defect score on delayed images (6.2 ± 1.7, 4.3 ± 2.7, and 4.8 ± 3.5) and washout rate (15.0 ± 5.1%, 15.9 ± 5.0%, and 14.7 ± 4.2%) among the 3 groups.

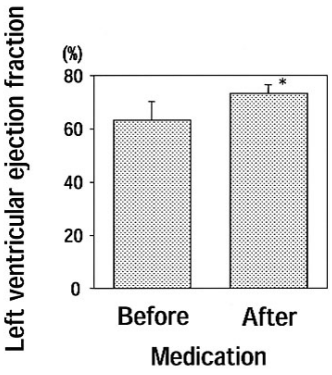

Fig. 4 Changes in left ventricular ejection fraction after medication. *$p < 0.01$

Changes in ^{99m}Tc-sestamibi washout and left ventricular function after medical treatment

After medical treatment with calcium antagonists and nitrates for 3 months, chest pain was suppressed in all patients. Enhanced washout rate from spastic segments was reduced from 16 ± 2% to 10 ± 4% ($p < 0.01$) after medical treatment (Fig. 3). Total defect scores on delayed images were also decreased from 6.9 ± 0.3 to 2.3 ± 0.5 ($p < 0.01$) after medication. Left ventricular ejection fraction (LVEF) was increased from 63 ± 8% to 73 ± 4% ($p < 0.01$) after medication in patients with coronary spastic angina (Fig. 4). Regional LVEF in normal and spastic segments of patients with coronary spastic angina were 69 ± 8% and 58 ± 9% ($p < 0.01$), respectively, before medical treatment. After the treatment, regional LVEF was increased to 75 ± 2% ($p < 0.05$) in normal segments and to 69 ± 5% ($p < 0.01$) in spastic segments.

DISCUSSION

In the present study, we performed myocardial perfusion SPECT with ^{99m}Tc-sestamibi in patients with coronary spastic angina. The faster washout of ^{99m}Tc-sestamibi from spastic segments indicated that myocardial retention of ^{99m}Tc-sestamibi was impaired in these segments. After medical treatment with calcium antagonists and nitrates, enhanced washout of ^{99m}Tc-sestamibi was reduced and reverse redistribution was disappeared. Left ventricular ejection fraction improved after medication, suggesting that myocardial segments with reverse redistribution may indicate stunned myocardium with reversible dysfunction probably due to repetitive myocardial ischemia by coronary spasm.

Reverse redistribution and rapid washout of ^{99m}Tc-sestamibi

Unlike ^{201}Tl, mechanisms for cellular uptake and retention of ^{99m}Tc-sestamibi involve passive diffusion across the plasma and mitochondrial membranes in response to the large negative transmembranous potentials.[17] It has

been recognized that ^{99m}Tc-sestamibi appears to show relatively fixed retention and minimal redistribution in the myocardium.[18–21] Thus, ^{99m}Tc-sestamibi permits the delayed imaging after the injection in the clinical setting. However, ^{99m}Tc-sestamibi image does not freeze myocardial perfusion in a certain situation. We have reported that reverse redistribution of ^{99m}Tc-sestamibi is evident in patients with acute myocardial infarction after successful coronary revascularization.[7–9] This phenomenon is associated with a patent infarct-related artery, mismatch with fatty acid tracer, and functional recovery in the chronic state.[7,8] We also demonstrated that a pattern of reverse redistribution of ^{99m}Tc-sestamibi indicates dysfunctional but viable myocardium with preserved contractile response to dobutamine stimulation and may represent reversible mitochondrial dysfunction due to myocardial ischemia.[9]

However, reverse redistribution of ^{99m}Tc-sestamibi has not been previously examined in other cardiac diseases. In the present study, we reported for the first time, to our knowledge, that ^{99m}Tc-sestamibi redistributed in myocardial segments with coronary spasm. Abnormal left ventricular wall motion has been reported in patients with coronary spastic angina.[11] A close relation between repetitive brief ischemia and myocardial stunning has been suggested in patients with coronary spastic angina.[12] In patients with coronary spastic angina whose anginal attacks were controlled completely by medical treatment, improvement in ^{123}I-β-methyl-iodophenyl-pentadecanoic acid (BMIPP) uptake was reported.[14] In the present study, enhanced washout of ^{99m}Tc-sestamibi reduced and left ventricular ejection fraction improved after medication. These data suggest that reverse redistribution of ^{99m}Tc-sestamibi may represent stunned viable myocardium by repetitive brief ischemia due to coronary spasm.

Clinical implication of delayed ^{99m}Tc-sestamibi imaging in patients with coronary spastic angina

The diagnosis of coronary spastic angina essentially depends on the demonstration of coronary spasm by intracoronary injection of ergonovine maleate or acetylcholine.[22] Since ischemia is not usually induced by exercise stress, routine perfusion imaging is not sensitive enough to detect patients with coronary spastic angina. The usefulness of myocardial imaging with ^{123}I-BMIPP[14] and ^{123}I-metaiodobenzylguanidine[15] to detect patients with coronary spastic angina has been previously reported. However, we demonstrated here that additional delayed imaging after single injection of ^{99m}Tc-sestamibi was useful to detect myocardial functional abnormalities associated with coronary spastic angina.

The clinical significance to acquire the redistribution images of ^{99m}Tc-sestamibi has not been completely established. From the present study, early and delayed imaging of ^{99m}Tc-sestamibi can be used to select the patients who need coronary arteriography with provocation test. ^{99m}Tc-sestamibi imaging can also determine the past history of myocardial ischemic damage by coronary spasm and evaluate the efficiency of medical treatment.

CONCLUSION

Enhanced washout of ^{99m}Tc-sestamibi was observed in coronary spastic angina and might suggest that the ability of cardiomyocyte to retain the tracer was impaired in viable but damaged myocardium. Serial early and delayed imaging of ^{99m}Tc-sestamibi provides valuable information about functional characteristics of the ischemic myocardium in patients with coronary spastic angina.

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