Detecting Viable Hibernating Myocardium in Chronic Coronary Artery Disease
— A Comparison of Resting $^{201}$TI Single Photon Emission Computed Tomography (SPECT), $^{99m}$Tc-Methoxy-Isobutyl Isonitrile SPECT After Nitrate Administration, and $^{201}$TI SPECT After $^{201}$TI-Glucose-Insulin Infusion —

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To identify and quantify the amount of viable hibernating myocardium in patients with chronic coronary artery disease, resting $^{201}$TI single photon emission computed tomography (SPECT) was compared with $^{99m}$Tc-methoxy-isobutyl isonitrile (MIBI) SPECT after nitrate infusion (nitrate-$^{99m}$Tc-MIBI) and $^{201}$TI SPECT after $^{201}$TI with glucose-insulin-potassium infusion ($^{201}$TI-GIK) in 25 patients. Twenty-one patients also underwent completely left ventriculography beforehand and 5±4 months afterwards. SPECT images were divided into 9 segments and scored visually from 0 (normal uptake) to 3 (absent). The defect score was calculated as the summation of the total scores (TDS) in each patient. The TDS of nitrate-$^{99m}$Tc-MIBI images (6.3±4.3) and $^{201}$TI-GIK images (5.8±4.2) were significantly lower than the 7.4±4.3 of resting $^{201}$TI images (p<0.01). Based on the improvement of the TDS, the sensitivity of $^{201}$TI-GIK imaging (85%) was significantly higher (p<0.05), and that of nitrate-$^{99m}$Tc-MIBI imaging (79%) also tended to be higher (p<0.08), than that of $^{201}$TI imaging (62%) in detecting viable myocardium. The specificity of the 3 methods was almost the same. The nitrate-$^{99m}$Tc-MIBI and $^{201}$TI-GIK methods were more useful than the resting $^{201}$TI method for evaluating viable hibernating myocardium. Furthermore, the $^{201}$TI-GIK method may provide a more accurate estimate of the amount of viable myocardium than the nitrate-$^{99m}$Tc-MIBI method. (Jpn Circ J 2000; 64: 937–942)

Key Words: Hibernation; Nitrate-$^{99m}$Tc-MIBI; $^{201}$TI-GIK; $^{201}$TI-rest

In patients with chronic coronary artery disease (CAD), it is clinically important to distinguish viable myocardium from nonviable myocardium to determine whether revascularization will be beneficial.1,2 Although positron emission tomography (PET) is considered the gold standard for assessing myocardial viability, alternative procedures based on radionuclide imaging have been proposed. Thallium-$^{201}$TI myocardial scintigraphy has been widely used to detect myocardial viability using either late redistribution4 or a reinjection imaging technique5. The technetium-$^{99m}$Tc-methoxy-isobutyl isonitrile (MIBI) and $^{99m}$Tc-tetrofosmin are new myocardial perfusion imaging agents that are used as alternatives to conventional $^{201}$TI imaging6-10 However, several studies have suggested that $^{99m}$Tc-MIBI cardiac imaging may underestimate the presence of myocardial viability11-16 although one study showed that rest $^{99m}$Tc-MIBI and $^{201}$TI myocardial imaging detect myocardial viability equally well.17 Furthermore, other studies suggest that $^{99m}$Tc-MIBI cardiac imaging with nitrate administration enhances detection of viable myocardium.18-21 A recent study by Tartagni et al describes a new method for cardiac imaging after infusion of $^{201}$TI, insulin and potassium in a glucose solution, which improved the detection of viable myocardium.22 Insulin is well known to augment the myocardial uptake of potassium through translocation of Na–K ATPase from the cytosol to the sarcolemma23,24 Likewise, $^{201}$TI is taken up by myocardium through Na–K ATPase25,26 and its uptake may be enhanced by insulin administration. We compared resting $^{201}$TI imaging with resting $^{99m}$Tc-MIBI imaging after nitrate administration, and resting $^{201}$TI imaging after $^{201}$TI with glucose-insulin-potassium infusion, for detecting severely hypoperfused, but viable myocardium in patients with CAD.

Methods

Patients

The study population consisted of 25 patients (23 males, 2 females; aged 56–76 years, mean age, 68±10 years) with angiographically documented CAD and with left ventricular dysfunction. Nine patients had significant stenosis of all 3 major vessels, 13 patients had significant stenosis of 2 major coronary vessels and 3 patients had significant stenosis of only 1 major coronary vessel (defined as a 75% luminal reduction). The mean left ventricular ejection fraction (LVEF) by left ventriculography (LVG) was 44±11%. All patients had a chronic myocardial infarction (12 anterior, 4 lateral and 18 inferior) that was documented clinically and

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by electrocardiography and they had not undergone previous revascularization. Nine patients had 2 infarcted major coronary vessels. The patient numbers of 75%, 90%, 99% and 100% stenosis of infarcted vessels were 1, 2, 9 and 22, respectively (Table I). No patients, however, had an acute myocardial infarction within 3 months of the study. Patients with diabetes or glucose intolerance were excluded from the study. The scintigraphic studies used were resting 201Tl single photon emission computed tomography (SPECT) imaging, 99mTc-sestamibi SPECT imaging after nitrate infusion and 201Tl SPECT imaging after 201Tl-glucose-insulin-potassium infusion, all of which were performed after a 12-h overnight fast and in the absence of antianginal medication. After scintigraphic examinations and LVG, all patients underwent coronary revascularization; coronary artery bypass graft was performed in 15 patients and percutaneous transluminal coronary angioplasty in 10 patients. None had clinical evidence of perioperative or postangioplasty myocardial infarction. One patient had occlusion in the graft after coronary artery bypass grafting and 3 had restenosis after angioplasty. All patients gave informed consent in accordance with the guidelines of the hospital’s Human Clinical Study Committee prior to participation in the study.

Resting Thallium-201 SPECT
All patients underwent 201Tl imaging after a 30-min rest period. 201Tl (111 MBq) was injected intravenously and the images were acquired 15 min after the injection (Fig. 1).

Technetium-99m-Sestamibi SPECT
Within 1 week of the resting 201Tl study, 99mTc-MIBI imaging was performed after an overnight fast to minimize gallbladder activity. Patients were instructed to consume milk just before imaging. After 5 mg of isosorbide dinitrate, in 20 ml isotonic saline solution, was infused over 5 min, 99mTc-MIBI (500 MBq) was injected 5 min later and then imaging began 30 min later (nitrated-99mTc-MIBI) (Fig. 1).

Glucose-Insulin Thallium-201 SPECT
SPECT imaging was also performed within 1 week of the resting 201Tl study. After a 30-min infusion of 201Tl (111 MBq) in 250 ml of 10% glucose plus insulin (5U) and 10 mmol potassium chloride (201Tl-GIK), imaging was begun 15 min later (Fig. 1). Two catheters were inserted in the antecubital veins, one for infusion of the radiolabeled solution and one for blood sampling. The infusion rate was adjusted automatically and blood samples were taken at the beginning and end of the infusion and 30 min later. Plasma glucose, potassium activity and plasma-free insulin were measured.

Myocardial SPECT Imaging
Myocardial SPECT imaging was performed using a 3-headed SPECT system with low-energy, high-resolution, parallel-hole collimators. The detector system was interfaced to a dedicated nuclear medicine computer. A total of 72 projection images were obtained over 360° in 5° increments, with 40s per view for resting 201Tl, 99mTc-MIBI and 201Tl-GIK SPECT. The energy discriminator was centered on 72 keV for 201Tl with a 30% window, and 140 keV for 99mTc-MIBI with a 15% window. The data were recorded in 64x64 matrices on a magnetic disk. To reconstruct transaxial tomographic images from each acquisition, Butterworth and ramp filters were used. The parameter of the Butterworth filter was order 8, and the cutoff frequency was 0.24–0.28 cycle/ pixel. Short- and long-axis slices, 5-mm thick, were also generated.

SPECT data analysis was based on 1 vertical long-axis slice and 2 short-axis slices. In each patient, the corresponding vertical long- and short-axis tomograms from resting 201Tl, 99mTc-MIBI and 201Tl-GIK SPECT sets were aligned. One vertical long-axis slice and 2 short-axis views from the apical and basal ventricular levels were chosen for comparison. The vertical long-axis slice was used to evaluate the apical region, whereas each short-axis slice was divided into 4 segments (Fig. 2). All SPECT images were displayed and analyzed by 3 experienced observers who were unaware of the patient’s clinical history. Semiqualitative visual analysis was performed by assigning regional tracer activities on a 4-point scoring system (defect score): 0 = normal uptake, 1 = mildly reduced uptake, 2 = definitely reduced uptake and 3 = absent. Disagreements in interpretation were resolved by consensus. The defect score was calculated as the summation of the total scores (TDS) in each patient. We hypothesized that myocardial viability was maintained as a defect score of 2 or less (TDS ≤ 2).
Table 1: Vessel Distribution, Infarcted Region and % Stenosis of Infarcted Vessel

<table>
<thead>
<tr>
<th>Vessel distribution</th>
<th>Resting TI</th>
<th>Nitrate-MIBI</th>
<th>TI-GIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVD</td>
<td>3</td>
<td>150</td>
<td>152</td>
</tr>
<tr>
<td>2VD</td>
<td>13</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>3VD</td>
<td>9</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Infarcted region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>12</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Lateral</td>
<td>4</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Inferior</td>
<td>18</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>% Stenosis of infarcted vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td>1</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>90%</td>
<td>2</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>99%</td>
<td>9</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>100%</td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Differences in Defect Score in the 225 Myocardial Segments

<table>
<thead>
<tr>
<th>Score</th>
<th>Resting TI</th>
<th>Nitrate-MIBI</th>
<th>TI-GIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>140</td>
<td>150</td>
<td>152</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>27</td>
<td>24</td>
</tr>
</tbody>
</table>

Left Ventriculography

Contrast LVG was acquired in the 30° right anterior oblique projection (RAO) and the 45° left anterior oblique projection (LAO), with the patient supine. For regional wall motion analysis, the left ventricular wall was divided into 7 segments using American Heart Association classification, including 5 RAO and 2 LAO segments, and the wall motion of each segment was evaluated using the following 6-point grading system: -1 = dyskinesis, 0 = akinesis, 1 = severe hypokinesis, 2 = moderate hypokinesis, 3 = mild hypokinesis, and 4 = normokinesis (Fig 3). Improvement in wall motion was defined as an improvement in the wall motion score by 1 point or greater. All patients underwent LVG before and 4–6 months (5±4 months) after coronary revascularization.

Correspondence of Segments Between LSVG and SPECT Images

Segment number 1–5 of LSVG corresponded to the same segment number of the SPECT image. Segment number 6 of LSVG corresponded to segment numbers 6 and 7 of the SPECT images. Segment number 7 of LSVG also corresponded to segment numbers 8 and 9 of the SPECT images. The regional tracer activities of the septal and lateral walls in the SPECT images were estimated as the mean of the basal and apical segments, when we compared these tracer activities with the wall motion of the septal or lateral wall (Figs 2, 3).

Statistical Analysis

All data are presented as the mean±SD. A paired Student’s t-test was used to test the difference between paired data. Chi-square analysis was used to compare the percentages of sensitivity and specificity. A p value of less than 0.05 was considered statistically significant.

Results

A total of 225 myocardial segments were analyzed. Normal and abnormal resting 201TI uptakes were found in 140 (62%) and 85 (38%) myocardial segments, respectively. Of the 85 segments with abnormal tracer uptake, 18 (21%) showed a mildly reduced uptake, 37 (43%) showed a severely reduced uptake and 30 (35%) segments had no uptake.

Normal and abnormal nitrate-99mTc-MIBI uptakes were found in 150 (67%) and 75 (33%) myocardial segments, respectively. Of the 75 segments with abnormal tracer uptake, 18 (24%) showed a mildly reduced uptake, 30 (40%) showed a severely reduced uptake and 27 (36%) segments had no uptake. In 29 (34%) of the 85 segments with abnormal resting 201TI uptake, nitrate-99mTc-MIBI uptake was better than the resting 201TI uptake. On the other hand, only 6 (7%) segments on the nitrate-99mTc-MIBI images showed a lower uptake than that seen on the resting 201TI images.

Normal and abnormal 201TI-GIK uptakes were found in 152 (68%) and 73 (32%) myocardial segments, respectively. Of the 73 segments with abnormal tracer uptake, 24 (33%) showed a mildly reduced uptake, 25 (34%) showed a severely reduced uptake and 24 (33%) segments had no uptake. In 33 (39%) of the 85 segments with abnormal resting 201TI uptake, 201TI-GIK uptake was better than the resting 201TI uptake. On the other hand, there was no segment in which the resting 201TI uptake was better than the 201TI-GIK uptake. In 17 (23%) of the 75 segments with abnormal nitrate-99mTc-MIBI uptake, 201TI-GIK uptake was better than the nitrate-99mTc-MIBI uptake. However, only 6 (8%) segments with 201TI-GIK uptake showed a lower uptake than with nitrate-99mTc-MIBI (Table 2).

The TDS of nitrate-99mTc-MIBI imaging (6.7±4.3) and 201TI-GIK imaging (5.8±4.2) were both significantly lower than that of resting 201TI imaging (7.4±4.3) (p<0.01) (Fig 4).

Of the total 147 myocardial segments in the 21 patients...
with a complete LVG study, excluding the 1 patient with bypass occlusion and the 3 patients with restenosis, 92 (63%) segments showed normal or mild hypokinesia on LVG, 55 (37%) showed a definite wall motion abnormality, which included 11 segments with moderate hypokinesia, 24 with severe hypokinesia and 20 with akinesis or dyskinesis. Of the 55 segments with a definite wall motion abnormality, 39 (71%) had improved on the follow-up LVG, but 16 (29%) had not. The sensitivity and specificity of the different imaging modalities for detecting myocardial viability on the basis of improvement in wall motion are shown in Fig 5. The sensitivity of nitrate-99mTc-MIBI imaging (79%) tended to be higher than that of resting 201TI imaging (62%) (p<0.08). The sensitivity of 201TI-GIK imaging (85%) was significantly higher than that of resting 201TI imaging (p<0.05). The specificity of rest 201TI imaging and 201TI-GIK imaging was 88% and that of nitrate-99mTc-MIBI imaging was 82%.

Plasma serum glucose, insulin and potassium levels were measured at the beginning and end of GIK infusion. Insulin levels were affected significantly by the exogenous administration of insulin (7.1±6.0 μIU/ml at baseline vs 120±88 mM/l after GIK infusion; p<0.0005). Serum glucose levels increased during GIK infusion, from 102±16 mg/dl to 219±40 mg/dl, and then rapidly decreased over the following 30 min to 126±44 mg/dl. Potassium levels were not affected by this infusion (4.3±0.4 mmol/L at baseline vs 4.3±0.4 mmol/L after GIK infusion).

Fig 6 is a representative case, a 70-year-old man with a 90% stenosis of the right coronary artery and an old inferior myocardial infarction. Perfusion defects was found on 201TI imaging, which improved on nitrate-99mTc-MIBI imaging, and improved further on 201TI-GIK imaging. The wall motion of this area also improved after percutaneous transluminal coronary angioplasty, with improvement of the LVEF from 48% to 54%.

Discussion
Myocardial contractile dysfunction in patients with chronic CAD can be caused either by cellular necrosis or hibernation. In contrast to necrotic tissue, hibernating myocardium may recover function after revascularization and so it is clinically important to differentiate viable from necrotic myocardium.

Myocardial viability is determined by PET on the basis of preserved metabolic activity, irrespective of hypoperfusion or the presence of abnormal wall motion at rest. A mismatch pattern between perfusion and 18F-fluorodeoxyglucose (FDG) images indicates ischemic or hibernating myocardium with a high probability of recovery of left ventricular contractile function after revascularization.

Although 201TI uptake may be considered an accurate marker of myocardial viability, the functional recovery after coronary revascularization is the most important variable. We evaluated the clinical significance of myocardial viability based on the sensitivity and specificity of wall
motion improvement following revascularization in a subgroup of 21 patients. The results of that study showed that the 201TI-GI method was the most sensitive, the nitrate-99mTc-MIBI method was next and the resting 201TI method was the least sensitive for detecting viability. The specificity of the 3 methods was almost equivalent. Maurea et al defined a reversible defect as an improvement in the activity on nitroglycerin 99mTc-MIBI images compared with reduced activity on resting 99mTc-MIBI images. Their sensitivity and specificity of such images, on the basis of improvement in wall motion, were 88% and 89%, respectively. Bisi et al similarly reported that the sensitivity and specificity of these tests were 95% and 88%. The reason for the lower sensitivity in our results may be related to the fact that we evaluated the wall motion using a 6-point grading system and the improvement in wall motion was defined as an improvement in the wall motion score by 1 point or greater. However, no reports have estimated the amount of viable myocardium using the correlation between 201TI-GI infusion imaging and improved wall motion following revascularization, so we may have used a more rigorous index than previous investigators. Tartagni et al reported 44% (74%) and 25% (74%) severely hypoperfused segments in resting 201TI and 201TI-GI infusion studies, respectively, in patients with chronic CAD (p<0.001). Their results suggest that the 201TI-GI infusion method is better at detecting viable myocardium than the resting 201TI method, which concords with our results. Instead of insulin administration, Chiba et al used glucose loading to stimulate secretion of endogenous insulin and showed that this maneuver produced filling in some regions labeled as defects by conventional 201TI imaging.

**Study Limitations**

Some limitations in this study should be considered. First, there is a difference in energy level between 99mTc-MIBI and 201TI. In addition, the uptake of 201TI is lower than that of 99mTc-MIBI especially at the inferior to septal wall. However, we did not take this difference into account when analyzing the SPECT images.

Second, we obtained follow-up data after coronary revascularization from only a limited number of patients. Nonetheless, even though that data need to be confirmed in a larger series, our findings strongly suggest that nitrate-99mTc-MIBI and 201TI-GI imaging enhance the detection of viable myocardium.

Third, we estimated the amount of viable myocardium using resting 201TI imaging, which has been reported to underestimate viable myocardium when compared with rest-redistribution 201TI imaging. Maurea et al showed that 99mTc-MIBI uptake after nitroglycerin is significantly higher than that seen on rest-initial 201TI uptake scan, but is not different from rest-redistribution 201TI uptake. In the future, we plan to compare the abilities of nitrate-99mTc-MIBI and 201TI-GI imaging with rest-redistribution 201TI imaging to identify viable myocardium.

**Conclusion**

99mTc-MIBI imaging after nitrate administration and 201TI imaging after 201TI-GI infusion are significant improvements over resting 201TI imaging in identifying viable myocardium of patients with chronic CAD and impaired left ventricular function. 201TI imaging after 201TI-GI infusion may better estimate the amount of viable myocardium than 99mTc-MIBI imaging with nitrate administration.

**References**