CLINICAL EVALUATION OF STRESS MYOCARDIAL SCINTIGRAPHY WITH THALLIUM-201 IN PATIENTS WITH ISCHEMIC HEART DISEASE

-Semiquantitative Analysis of Single Dose Myocardial Imaging-

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In order to evaluate the usefulness of a stress Tl-201 myocardial scintigraphy in semiquantifying the myocardial perfusion, 10 normal subjects and 71 patients with coronary artery diseases were studied with sequential imaging over 3 hours.

Myocardial to background ratio (M/B) in the exercise phase was significantly higher in the normal subject group than in the coronary artery disease groups. Three hours after exercise (redistribution phase), M/B decreased significantly in the normal subject group but remained unchanged in the coronary artery disease groups. Percent change of M/B with exercise was lower in the effort angina pectoris group (97 ± 11.2%) and the old myocardial infarction group (101 ± 14.5%) than in the normal subject group (127 ± 12%). Sensitivity and specificity of this method were 93% and 47%, respectively. Out of 11 patients with variant angina pectoris, 9 patients showed positive scintigram. Of the 9, however, 6 cases were without organic coronary stenosis in the coronary angiography. There was a significant correlation between M/B on redistribution images (RD·M/B) and ejection fraction determined by left ventriculograms (r = 0.61, p < 0.001), indicating a close relation between the amount of the residual viable myocardium and the left ventricular function.

M/B and its percent change with stress Tl-201 myocardial scintigraphy reflect the myocardial perfusion and myocardial perfusion reserve and their semiquantitative analysis provides a useful means for detection of ischemic heart disease.

Key Words:
Stress myocardial scintigraphy with Tl-201
Single dose myocardial imaging
Myocardial to background ratio (M/B)
Percent change of M/B

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served by myocardial scintigraphy with intravenous administration of Tl-201 in acute and old myocardial infarction with myocardial scar and variant angina with transient myocardial ischemia, and even unstable angina in a pain-free period.

There are many reports that the sensitivity and specificity of stress Tl-201 myocardial scintigraphy for the detection of ischemic heart disease are superior to those of conventional exercise electrocardiography.

However, identification of myocardial ischemia by visual inspection of myocardial scintigrams is sometimes difficult because it involves subjective evaluation of images.

The purpose of the present study is to semiquantify the myocardial perfusion by sequential myocardial imaging over 3 hours after a single dose of Tl-201 and to evaluate the usefulness of this method in detecting ischemic heart disease.

MATERIAL AND METHODS

Ten subjects without evidence of coronary artery disease and 71 patients with clinically diagnosed coronary artery diseases were studied. Subjects without evidence of coronary artery disease were 4 subjects with atypical chest pain with normal coronary arteriograms and left ventriculograms and 6 volunteers with normal exercise electrocardiograms. Nine were male and one was female with a mean age of 38 years (range, 25–53).

Patients with coronary artery disease were 67 males and 4 females with a mean age of 53 years (range, 23–72). Of the 71 patients, 42 had a history of prior myocardial infarction, 18 had effort angina with chest pain on effort and 11 showed ST-segment elevation in ECG with chest pain and were diagnosed as variant type of angina pectoris.

Stress Tl-201 myocardial scintigraphy was carried out in an imaging laboratory. The ECG was recorded in multiple conventional leads (III, V3, V5) at one min intervals and monitored continuously until 5 min after exercise. Blood pressure was measured with a sphygmomanometer. The exercise test was performed using an upright Monark bicycle ergometer and the workload was set at 25 watts initially and increased by a 25 watt increment every 3 min until further exercise was limited by chest pain or severe fatigue, or until the heart rate reached 150 per min.

Tl-201 was injected at the peak of exercise and the patient was encouraged to continue exercise at the same level for additional one min before stopping. Tl-201 was administered intravenously in a dose of 2 mCi followed by a flush injection of 10 ml saline solution.

Myocardial imaging began 10 min after tracer administration. Images were recorded in a supine position in the anterior, 45 degree left anterior oblique, and left lateral views. A Toshiba jumbo gamma camera (GCA 401 type) equipped with a converging collimator was used. Images were recorded with a 25% window centered on the mercury X-ray peaks (80 keV).

Exercise images were obtained with accumulation of 400,000 counts and all of the data of the Tl-201 studies were stored in a computer (MDI Series 8000) for standardized image formation with 9 point smoothing using a 16 shade color scale. Imaging was repeated 3 hours later for redistribution images in a similar fashion.

In each image of the exercise and redistribution stages in the 45 degree left anterior oblique view, a region of interest (ROI) was selected in the myocardial segments (anteroseptal, posterolateral, inferior) and the left upper and middle lung fields and the concentration of Tl-201 was counted for a preset counting time of 240 seconds. The mean of the counts of the left upper and middle lung fields was defined as the background count. The ratio of the myocardial count to the background count (M/B) was calculated for each segment (Fig. 1). Percent change of M/B was expressed as the percent of

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M/B in the exercise image to that in the redistribution image. Selective coronary arteriography was performed in 43 patients in multiple projections with the Judkins or Sones technique. The patient was considered to have significant coronary artery disease if one or more major coronary arteries had 75 percent or greater narrowing of the luminal diameter.

Left ventriculography was also performed in the 30 degree right anterior oblique projection and the left ventricular volume was calculated using Greens method?

In 10 normal subjects, M/B on exercise (EX-M/B) was 3.64 ± 0.64, M/B on redistribution (RD-M/B) was 2.87 ± 0.35, and percent change of M/B was 127 ± 12%. These values were regarded to represent normal scintigrams (Table I). Scintigrams which showed lower values than the mean minus one SD were diagnosed as representing positive ischemic segments. For the analysis of M/B, a myocardial segment corresponding to the site of ischemic change on ECG (either in exercise test or in spontaneous attack) was selected.

The correlation between ischemic segments of the myocardium as shown by stress scintigrams and significant stenosis of the main coronary arteries as documented by arteriograms was studied in each of the 3 segments and each of the 3 main arteries. Using the result of coronary arteriography, the sensitivity and specificity of stress scintigraphy were calculated for the corresponding segment.

Sensitivity was defined as the number of patients with true positive ischemic scintigrams (based upon analysis of M/B and its percent change) divided by the total number of patients with positive arteriograms; specificity as the number of patients with true negative scintigrams divided by the total number of patients with negative arteriograms; false negative incidence as the number of patients with false negative scintigrams divided by the total number of patients with negative scintigrams; false positive incidence as the number of patients with false positive scintigrams divided by the total number of patients with positive scintigrams.

Statistical analysis of the data was performed using unpaired t test and analysis of variance to assess differences between groups, and the significance of correlation between parameters was determined by using linear regression analysis. Results are expressed as the mean ± 1 SD.

RESULTS
Normal Subjects Groups (Table I)
EX-M/B in 10 normal subjects was 3.63 ±
Fig. 2. Serial changes in M/B from exercise to redistribution images in control subjects and patients with IHD.

Fig. 3. The grade of changes in M/B from redistribution to exercise images in control subjects and patients with IHD.

0.66 (mean ± SD) in the anteroseptal, 3.69 ± 0.80 in the posterolateral, and 3.61 ± 0.51 in the inferior segment. It decreased to 2.81 ± 0.3, 2.93 ± 0.47, 2.86 ± 0.3, respectively, at the redistribution phase after 3 hours of exercise.

M/B values of the three myocardial segments were almost the same and there was no significant difference among them. Percent change of M/B was 129 ± 13.5% in the anteroseptal, 126 ± 14.1% in the posterolateral, and 126 ± 8.13% in the inferior segment and there was no significant difference among the three.

The mean value of 30 myocardial segments in normal subjects was 3.64 ± 0.64 for EX·M/B, 2.87 ± 0.35 for RD·M/B, and 127 ± 12% for percent change of M/B and these values were considered to be the indices of normal regional myocardial perfusion.

Coronary Artery Disease Groups (Table II)
EX·M/B of the ischemic segments was 2.32 ± 0.68 in the old myocardial infarction group, 2.91 ± 0.67 in the effort angina group and 3.2 ± 0.51 in the variant angina group. EX·M/B was significantly lower in the coronary artery disease groups than in the normal subjects group and it was significantly lower in the old myocardial infarction group than in the effort angina group and the variant angina group.
RD·M/B was 2.97 ± 0.48 in the effort angina

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<th>Stress Scintigram</th>
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<td><strong>Total</strong></td>
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<td><strong>Sensitivity</strong></td>
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<td><strong>Specificity</strong></td>
<td>7/15 (47%)</td>
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group and $3.07 \pm 0.52$ in the variant angina group and similar to the value in the normal subjects group. RD-M/B in the old myocardial infarction group remained low at $2.29 \pm 0.55$ and it was significantly lower than in other groups (Fig. 2).

Percent change of M/B was $101 \pm 14.5\%$ in the old myocardial infarction group, and $97 \pm 11.2\%$ in the effort angina group. There was no increase in M/B with exercise in these two groups. The variant angina group showed slight increase in percent change of M/B ($106 \pm 21.6\%)$ but the value was highly variable among patients. Percent change of M/B was significantly smaller in the coronary artery disease groups than in the normal subject group (Fig. 3).

Comparison between Stress TI-201 Myocardial Scintigraphic and Coronary Arteriographic Findings. (Table III)

Of 28 patients who had significant organic stenosis of the coronary arteries, 26 patients showed positive myocardial scintigrams with exercise (sensitivity 93%), but 2 had normal myocardial scintigrams. Seven of 15 patients who had normal coronary arteriograms showed normal myocardial scintigrams with exercise (specificity 47%), but 8 patients showed positive myocardial scintigrams.

Of 34 patients who were diagnosed to have coronary artery disease with positive myocardial scintigrams, 8 had normal coronary arteriograms (false positive 24%) and 2 of 9 patients with normal myocardial scintigrams had significant organic stenosis of the coronary arteries (false negative 22%).

Six of 8 patients with false positive myocardial scintigrams had variant angina pectoris and 2 had old myocardial infarction. One of 2 cases with old myocardial infarction had normal coronary arteries and the other one had insignificant organic stenosis of the coronary arteries. One of 2 patients with false negative myocardial scintigrams had old transmural myocardial infarction, and the other had subendocardial infarction.

Correlation between M/B on Redistribution Images (RD-M/B) and Ejection Fraction Determined with Left Ventriculograms (Fig. 4)

There was a significant correlation between RD-M/B and ejection fraction calculated from left ventriculograms in 29 patients ($r = 0.61$, $p < 0.001$). Patients with low RD-M/B had significantly lower ejection fraction than those with normal RD-M/B.

DISCUSSION

Strauss et al. reported that the initial myocardial uptake of TI-201 was related to myocardial perfusion as measured by microspheres. Diminished myocardial TI-201 uptake was observed during chest pain induced by exercise of spontaneous attack and serious ischemic heart diseases such as acute or old myocardial infarction and unstable angina pectoris. TI-201 scintigraphy has been advocated for evaluation of regional myocardial perfusion and myocardial perfusion reserve in patients with suspected myocardial ischemia.

Myocardial areas supplied by the critically narrowed coronary arteries may demonstrate normal tracer uptake at rest but when the tracer is injected during exercise they may show relatively decreased concentration in comparison to normally perfused areas. However, it is difficult in many instances to evaluate small changes in regional myocardial tracer concentration by visual inspection. This is because transient perfusion defects are usually observed only in cases with severe coronary artery disease, whereas hypoperfusion images are observed in mild and moderate cases with coronary artery disease. Furthermore, it is reported that defects on scintigrams did not occur because of the uniform reduction of tracer uptake even in severe proximal triple-vessel disease. In addition, interpretation of scintigrams is difficult and often other clinical data should be taken into consideration in visual evaluation of the scintigram. The present study was conducted in an attempt to quantify the regional TI-201 concentration in the myocardium.

A ratio of the concentration of TI-201 in the myocardium relative to that in the lungs (M/B) and changes in this index 3 hours after exercise were examined in 71 patients with coronary artery diseases such as old myocardial infarction, effort angina pectoris, and variant angina pectoris and in 10 normal subjects.

EX-M/B in the coronary artery disease groups was significantly lower than in the normal subject group and especially patients with old myocardial infarction showed the lowest value of M/B.

Percent change of M/B remained unchanged at 97% in the effort angina pectoris group and at 101% in the old myocardial infarction group.

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compared to 127% in the normal subjects group. As the initial myocardial Tl-201 uptake represents the distribution of myocardial blood flow, these indices may indicate the degree of myocardial perfusion. Using these indices, it is relatively easy to separate the patients with coronary artery disease from normal subjects objectively.

M/B 3 hours after exercise (RD*M/B) was of the same value among patients with effort angina, variant angina pectoris and normal subjects but was significantly lower in patients with old myocardial infarction than in other groups. The low value of M/B in the old myocardial infarction group suggests a decrease of viable myocardial cells.

There was a good correlation between RD*M/B and ejection fraction determined with left ventriculograms (Fig. 4). This result suggests that RD*M/B reflects the amount of the residual myocardium which is responsible for left ventricular function. In brief, evaluating the M/B and its percent change with exercise with stress Tl-201 myocardial scintigraphy helps diagnosis of coronary artery disease and it may be utilized for the evaluation of myocardial perfusion reserve.

The M/B is determined by two factors: (1) Tl-201 myocardial uptake and (2) Tl-201 lung uptake. Although the myocardial uptake is the primary factor to prescribe the M/B value, we observed that Tl-201 lung activity increased on the exercise image and decreased on the redistribution image in patients with coronary artery disease. From this fact, Tl-201 lung activity has an important effect upon the M/B. There are some papers concerning the clinical significance of evaluation of Tl-201 lung activity. It was reported that the elevated Tl-201 lung activity on the exercise images correlated well with the severity of the underlying coronary artery disease and the left ventricular dysfunction. Thus, increased pulmonary concentration of Tl-201 suggests exercise-induced left ventricular dysfunction. Our results suggest that M/B is useful for not only detecting coronary artery disease but also assessing its severity. But in chronic left ventricular failure caused by valvular heart disease or primary cardiomyopathy, the M/B may show abnormal values resulting in increased Tl-201 lung uptake. This fact should be taken into consideration in the interpretation of M/B and its percent change in cases with heart failure.

In our study, the sensitivity and specificity of this method was 93% and 47%, respectively. The sensitivity of this method for coronary artery disease was similar to other reports but specificity was lower. The reason for the lower specificity was related to 8 cases with false positive scintigrams. Six of 8 false positive scintigrams were obtained in variant angina patients. These 6 cases who complained of chest pain at midnight with ST segment elevation in ECG had no significant organic stenosis of the coronary arteries and these attacks may have been related to coronary spasm. When the patients with variant angina were excluded, specificity increased by 28% (sensitivity 92%, specificity 75%, false positive 8%, false negative 25%).

We sometimes observed slight spastic changes of the coronary arteries on coronary arteriograms by interventions such as hand grip test and cold pressor test without ECG changes and symptoms. In some of our patients with false positive scintigrams, partial coronary spasm may have actually been induced by dynamic exercise.

In the present study, 9 of 11 cases with variant angina pectoris were diagnosed as positive with stress Tl-201 myocardial scintigraphy. Since the concentration of Tl-201 in the myocardium is affected by conditions such as metabolic acidosis as well as the reduction of myocardial blood flow, the high sensitivity for variant angina pectoris in our study may reflect altered Tl-201 kinetics caused by metabolic acidosis induced by partial coronary artery spasm on exercise.

Two false negative cases had transmural and subendocardial myocardial infarction. None of them showed perfusion defects on images and M/B increased significantly with exercise. It may have been caused by a small infarcted area surrounded by a large amount of residual viable myocardium. While no collateral pathway was observed on coronary arteriograms in our cases, it has been postulated that the effects of collateral pathway may possibly be a cause for false negative scintigrams.

Although myocardial segments in patients with three-vessel disease are perfused by severely stenotic coronary arteries, they demonstrate uniform uptake of Tl-201 with no perfusion defects because there is no distributional gradient among segments. Such cases are often diagnosed as false negative. In the present study, however, 3 cases with three-vessel disease were diagnosed as positive using stress Tl-201 myocardial scintigraphy, i.e., patients with three-vessel disease did not show false negative scintigrams in our study.

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This suggests clinical usefulness of our method for detection of multivessels coronary artery disease.

Sensitivity and specificity for diagnosing coronary artery disease by sequential imaging technique after a single intravenous dose of TI-201 are compatible with those by comparing exercise and resting images performed with one week interval. It is easier to diagnose coronary artery disease with our semiquantitative analysis than with visual inspection. Also, with our method, it is possible to assess the severity of underlying coronary artery disease.

The sequential imaging technique after a single dose of TI-201 offers additional advantage such as reduced cost, convenience to the patient and lower radiation exposure.

This method is utilized not only for diagnosis of ischemic heart disease but also for the assessment of the results of aorto-coronary bypass graft surgery and the effects of drug therapy. Thus, it is expected that clinical application of this method will continue to increase.

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REFERENCES