COMPARISON OF ADENOSINE AND TREADMILL EXERCISE THALLIUM-201 STRESS TESTS FOR THE DETECTION OF CORONARY ARTERY DISEASE

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KOZUE IKEDA, M.D. AND HITONOBU TOMOIKE, M.D.

To determine the clinical usefulness of adenosine Tl-201 imaging for the evaluation of coronary artery disease, 22 patients with suspected coronary artery disease who underwent adenosine and exercise Tl-201 single photon emission computed tomography (SPECT) were studied. The peak levels of heart rate (83 vs 123 bpm, p<0.001), systolic blood pressure (124 vs 164 mmHg, p<0.001), diastolic blood pressure (70 vs 86 mmHg, p<0.01) and rate pressure products (10220 vs 20410 bpm×mmHg, p<0.001) were markedly smaller during adenosine infusion than during exercise. Segmental agreements between adenosine and exercise tests were 90% (218 of 242 segments) regarding the presence of perfusion defects and 89% (215 of 242 segments) regarding the presence of redistribution. Regional Tl-201 uptake (r=0.85, p<0.001) and the extent (r=0.75, p<0.001) and intensity (r=0.83, p<0.001) of Tl-201 defects during adenosine testing were closely correlated with those of exercise testing. Adenosine and exercise tests showed similar sensitivities for the identification of individual coronary stenosis (85% vs 78%). However, in patients who were unable to perform adequate exercise (maximal heart rate<120 bpm), the sensitivity of adenosine imaging tended to be higher than that of exercise imaging (92% vs 69%, p=0.07). Adenosine Tl-201 imaging is an alternative to the exercise test for assessing the severity and loci of coronary artery disease, especially in patients who are unable to perform adequate physical exercise.

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MYOCARDIAL Tl-201 imaging has been widely accepted as a noninvasive test for the diagnosis of coronary artery disease.1–3 Dipyridamole prevents the cellular uptake of adenosine and elevates the level of adenosine in blood and tissue, thereby potentiating its vasodilatory effect.4,5 The vasodilatory effects of dipyridamole on coronary blood flow are thus indirect, and maximal coronary vasodilation can not be achieved in a substantial number of patients with a standard intravenous dose of dipyridamole.6,7 Furthermore, it is often necessary to use aminophylline as an antagonist to reverse the side effects of dipyridamole, because the hemodynamic effects of intravenous dipyridamole last for more than 10 min.8 Adenosine is a potent vasodilator with a short half-life (less than 2 sec).9 Near-maximal coronary vasodilation can be achieved safely with intravenous infusion of adenosine at a rate of 0.14 mg/kg/min.10 Recently, thallium-201 (Tl-201) myocardial perfusion imaging during intravenous adenosine infusion has been reported to be safe and useful for diagnosis of coronary artery disease.11–14 Several investigators15–17 have recently re-

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ported that TI-201 imaging during adenosine infusion has a diagnostic value similar to that of exercise. However, a detailed site-to-site comparison between adenosine and exercise with regard to TI-201 uptake in the myocardium has not been performed.

The purpose of the present study was to determine the usefulness and limitations of adenosine TI-201 testing. We particularly focused on regional TI-201 uptake in the myocardium. The size and intensity of TI-201 defects were assessed quantitatively with adenosine and exercise testing and compared on a segment-by-segment basis.

**METHODS**

**Subjects**

Fifty-five consecutive patients underwent adenosine TI-201 imaging from July to December 1991 for the diagnosis of coronary artery disease at Yamagata University Hospital. From among these 55 patients, 22 patients who also underwent exercise TI-201 imaging within 1 week after the adenosine test were enrolled in this study. The study group consisted of 12 males and 10 females with a mean age of 63±8 years (range 47–76). Nine patients had old myocardial infarction. Based on the coronary arteriographic findings, 6 patients had single-vessel disease, 9 had double-vessel disease, 1 had triple-vessel disease, and 6 had no significant coronary artery stenosis. Significant coronary stenosis was defined as a percent luminal diameter narrowing of 75% or more in either main epicardial arteries or major branches. All scintigrams were performed for clinical purposes after informed consent was obtained. The study protocol was approved by the Yamagata University Committee on Human Research on June 20, 1991.

**Adenosine TI-201 Protocol**

All cardiovascular medications were discontinued for at least 12 h before the adenosine test, except for short-acting sublingual nitrates. Adenosine was infused intravenously at a rate of 0.14 mg/kg/min for 6 min\textsuperscript{11,12} using an infusion pump (Nakagawa-Seikousha, Co., Ltd.). Three minutes after the start of adenosine infusion, a 111 MBq dose of TI-201 was bolus administered into a separate vein. Blood pressure was measured every min at the left arm by a standard cuff method, and 12-lead ECG was continuously monitored during the testing.

**Exercise TI-201 Protocol**

Exercise was performed on a treadmill using a modified Bruce protocol\textsuperscript{18} Blood pressure was measured every minute at the left arm by a standard cuff method, and CMR-lead ECG was continuously monitored during the testing. Exercise was discontinued when angina, dyspnea, ischemic ST depres-
TABLE I  HEMODYNAMIC RESULTS: COMPARISON OF ADENOSINE AND EXERCISE

<table>
<thead>
<tr>
<th></th>
<th>adenosine</th>
<th></th>
<th>exercise</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>basal</td>
<td>peak</td>
<td>basal</td>
<td>peak</td>
</tr>
<tr>
<td>heart rate</td>
<td>66±12</td>
<td>83±14**</td>
<td>73±14</td>
<td>123±19*</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic blood pressure</td>
<td>140±21</td>
<td>124±24**</td>
<td>142±23</td>
<td>164±25*</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diastolic blood pressure</td>
<td>80±10</td>
<td>70±12**</td>
<td>81±10</td>
<td>86±11*</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rate pressure products</td>
<td>9217±2354</td>
<td>10220±2110**</td>
<td>9882±2810</td>
<td>20410±4527*</td>
</tr>
<tr>
<td>(beats/min x mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression</td>
<td>6 (27%)</td>
<td></td>
<td>11 (50%)</td>
<td></td>
</tr>
<tr>
<td>(n (%))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chest pain</td>
<td>5 (23%)</td>
<td></td>
<td>6 (27%)</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.001 vs basal value
+ p<0.001 vs exercise

TABLE II  SIDE EFFECTS

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>headache</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>flushing</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>nausea</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>abdominal discomfort</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>II AV block (Wenckebach type)</td>
<td>3 (14%)</td>
</tr>
</tbody>
</table>

Image Interpretation

To evaluate the presence of perfusion defects, 2 short axis images at the basal and apical levels and a vertical long axis image at the mid left ventricle were used (Fig. 1-A). The regions of decreased TI-201 uptake were assessed by 2 independent observers who were not given any information regarding the clinical history or angiographic findings of the patients. A 5-point system was used to evaluate the level of myocardial TI-201 uptake: 4=normal, 3=slightly reduced, 2= reduced, 1=severely reduced, 0=no activity. In interpreting early and delayed images, an uptake score of less than 2 in at least 1 segment in the early image was considered to represent a perfusion defect. An increase of 1 or more in the uptake score in at least 1 segment in the delayed image was considered to represent redistribution. The grading of myocardial TI-201 uptake was settled by consensus between the 2 observers. When there was any disagreement on the results, a third observer reviewed the images, and his judgment was chosen. The coronary territories were defined as shown in Fig. 1-

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Fig. 2. Adenosine and exercise TI-201 images from a 56-year-old female patient with angina pectoris. In both adenosine and exercise images, perfusion defects were observed in the infero-posterior region of the left ventricle on the early images, but had completely redistributed on the delayed images.

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**Data Analysis**

For quantitative evaluation of regional TI-201 uptake, regions of interest (ROI), 4×4 pixels in size (6×6 mm), were placed over the myocardium on 2 short axis images as shown in Fig. 1-B. TI-201 uptake in each ROI was normalized to the maximal value in the myocardium.

Circumferential profile analysis was applied to each of the short axis slices from the apex to the base. The minimal value of TI-201 uptake in each patient was defined from these circumferential profiles and used as an index of the intensity of perfusion defects. These circumferential profiles were plotted in polar coordinates and arranged into a bull’s-eye map. Gender-matched normal profiles after exercise were derived from 18 male and 13 female normal subjects. The same normal profiles were used for both exercise and adenosine TI-201 imaging. In the present study, each pixel was compared with the corresponding pixel in the gender-matched normal profile. When TI-201 uptake in each pixel was less than 2.5 SDs below the mean normal, these pixels were displayed on a color-coded map. The ratio of the number of pixels below normal limits to the total number of pixels was defined as the extent score which represented the size of perfusion defects.

**Coronary Arteriography**

Coronary arteriography was performed using a standard Judkins’ technique. All angiograms were evaluated by 2 experienced cardiologists who had no information relating to the clinical history or scintigraphic findings of the patients. When there was a disagreement on the severity of coronary stenosis, a third observer reviewed the study, and his judgment was chosen. Significant coronary stenosis was defined as a lumen diameter narrowing of 75% or more in either main epicardial arteries or major branches.

**Statistics**

The results are reported as the mean±1 standard deviation. The differences in hemodynamic variables in the adenosine and exercise tests were compared by a paired t-test. The regional TI-201 uptake, minimal TI-201 uptake and extent scores of TI-201 defects with adenosine were compared with those of exercise using linear regression analysis. The chi-square test was used to examine the significance of differences in sensitivity, specificity and accuracy between adenosine and exercise tests. A p value < 0.05 was considered significant.

**RESULTS**

Adenosine infusion reduced systolic blood pressure by 16 mmHg and increased heart rate by 17 bpm (Table I). The rate pressure products increased from 9217±2354 to 10220±2110 bpm x mmHg (p<0.0001). Changes in hemodynamic variables during stress were much smaller during the adenosine test than during the treadmill exercise test (p<0.001). During adenosine infusion, 6 patients had an ischemic ECG response, and 5 had chest pain. Other side effects are
shown in Table II. All of the side effects disappeared within 2 min after discontinuing the adenosine infusion.

Representative adenosine and exercise TI-201 images from a 56-year-old female patient with angina pectoris are shown in Fig. 2. The patient had 90% coronary stenosis at the proximal right coronary artery. Adenosine TI-201 images were of good quality. Complete redistribution of TI-201 was observed in the infero-posterior region of the left ventricle on both adenosine and exercise images.

The agreement between the initial perfusion defects and delayed redistribution of TI-201 as assessed by adenosine and exercise imaging is summarized in Fig. 3. Exact agreement was noted in 20 of 22 (91%) patients regarding the presence of perfusion defects and in 19 of 22 (86%) patients regarding the presence of redistribution. Topological agreement was noted in 218 of 242 (90%) segments regarding the presence of perfusion defects and in 215 of 242 (89%) segments regarding the presence of redistribution based on a segment-by-segment comparison (Fig. 3-B).

Regional TI-201 uptake in the myocardium was assessed quantitatively with adenosine and exercise imaging and compared (Fig. 4-A). Regional TI-201 uptake with adenosine was closely correlated to that with exercise imaging.
(r=0.85, p<0.001). As shown in Fig. 4-B and 4-C, the extent of TI-201 defect (r=0.75, p<0.001) and level of minimal TI-201 uptake (r=0.83, p<0.001) in the adenosine and exercise images were closely correlated.

Fig. 5-A shows the sensitivity, specificity and accuracy of TI-201 scintigraphy during adenosine and exercise tests with regard to the detection of patients with coronary artery disease and to the identification of individual coronary stenosis. There were no demonstrable differences between the 2 tests.

The patients were then divided into 2 groups according to the maximal heart rate achieved during exercise; 14 patients in group 1 (heart rate ≤ 120 bpm), and 8 patients in group 2 (heart rate < 120 bpm). In group 1, the sensitivities of the 2 tests for the identification of individual coronary stenosis were similar (79% vs 86%) However, in group 2, the sensitivity of adenosine testing tended to be higher than that of the exercise test (92% vs 69%, p=0.07, Fig. 5B).

Two patients showed an ischemic response in the adenosine test but not in the exercise test (Table III-A). In both cases, the max-
TABLE III  CHARACTERISTICS OF PATIENTS SHOWING DISCORDANT FINDINGS

--- A. True positive adenosine test and false negative exercise test

<table>
<thead>
<tr>
<th>No.</th>
<th>angiographic findings</th>
<th>scintigraphic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>LAD</td>
<td>LCX</td>
</tr>
<tr>
<td>1.</td>
<td>#6 75%</td>
<td>#12 99% Adenosine</td>
</tr>
<tr>
<td></td>
<td>#9 75%</td>
<td>Exercise</td>
</tr>
<tr>
<td>2.</td>
<td>#12 99% Adenosine</td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

--- B. True positive exercise test and false negative adenosine test

<table>
<thead>
<tr>
<th>No.</th>
<th>angiographic findings</th>
<th>scintigraphic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>LAD</td>
<td>LCX</td>
</tr>
<tr>
<td>1.</td>
<td>#2 75%</td>
<td>#9 90% Adenosine</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>+</td>
</tr>
</tbody>
</table>

RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; inf, inferior; ant, anterior; sep, septal; lat, lateral; HR, heart rate; SBP, systolic blood pressure; bpm, beats per minute; STdep, ST depression; +: positive; -: negative.

imal heart rate achieved during exercise was less than 120 bpm, and the stenotic region was noted at the obtuse marginal artery. The profile of a patient who showed an ischemic response in the exercise test but not in the adenosine test is shown in Table III-B.

**DISCUSSION**

Adenosine TI-201 single photon emission computed tomography (SPECT) showed a sensitivity and specificity for the detection of coronary artery disease comparable to those of exercise TI-201 SPECT. Several investigators have recently reported that adenosine TI-201 imaging has a diagnostic value similar to that of exercise imaging for the diagnosis of coronary artery disease. However, a detailed site-to-site comparison of regional TI-201 uptake in the myocardium with adenosine and exercise TI-201 imaging has not been performed. In the present study, we assessed regional TI-201 uptake in the myocardium quantitatively, and compared the results obtained by adenosine and exercise imaging on a segment-by-segment basis. Since there are individual variations in coronary anatomy, we divided each slice of the short axis into 4 segments for evaluation by visualization. We used minimal uptake to assess the severity of a defect instead of the severity score, because we did not have a normal profile of adenosine stress. Our data demonstrated an excellent agreement between adenosine and exercise TI-201 imaging regarding either the presence or absence of the perfusion defect (218/242: 90%) and of redistribution (215/242: 89%). Furthermore, the size (r=0.83) and intensity (r=0.75) of TI-201 defects with adenosine correlated well with those using exercise.

In exercise stress testing, it is known that the level of exercise affects the ability to detect myocardial ischemia. Inadequate exercise results in "false negative" images and underestimation of the extent of coronary artery disease. Recently, pharmacologic stress imaging has been proposed as an alternative to exercise stress test not only for detection of coronary artery disease but also for predicting risk stratification. Currently, dobutamine and dipyridamole have been practically applied in pharmacologic stress tests. Dobutamine exerts positive inotropic and chronotropic effects on the heart and results in an increase of myocardial oxygen demand. Thus, in the presence of fixed coronary artery stenosis, a supply-demand mismatch occurs, and myocardial ischemia ensues. In contrast, dipyridamole increases

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coronary blood flow, but not myocardial oxygen demand. The predominant mechanism of TI-201 perfusion defects during dipyrدامole infusion is flow heterogeneity between territories supplied by normal coronary artery and those supplied by stenotic arteries.\textsuperscript{1–3}

Pharmacologic stress tests may be particularly useful in patients who can not perform adequate exercise testing, since a more uniform level of stress can be achieved in a pharmacologic stress test.\textsuperscript{26} In the present study, the sensitivities of adenosine and exercise imaging for the identification of individual coronary stenosis were comparable in patients who achieved adequate exercise (79\% vs 86\%). However, in patients who could not perform adequate exercise, the sensitivity with adenosine tended to be higher than that with exercise (92\% vs 69\%, p=0.07). In the 2 patients who showed an ischemic response with adenosine but not with exercise, the maximal heart rate achieved during exercise was less than 120 bpm, and the stenotic region was noted in the obtuse marginal artery. Since adenosine is a more potent vasodilator than exercise,\textsuperscript{10} the larger accumulated counts of TI-201 in the myocardium may facilitate better image quality with adenosine than with exercise. Thus, perfusion abnormalities may be more readily detected in adenosine SPECT than in exercise SPECT.

One patient (Table III-B) showed a true positive exercise test but a false negative adenosine test in the inferior segment. Since adenosine infusion increases liver uptake more than exercise stress, our interpretations regarding inferior segments may have been affected.

**CONCLUSION**

Regional TI-201 uptake in the myocardium and the size and intensity of TI-201 defects after adenosine infusion were closely correlated with those after exercise. In patients who failed to achieve maximal exercise, TI-201 imaging with adenosine had greater diagnostic accuracy than that after exercise. These data indicate that adenosine is a promising pharmacologic stressor which is useful, practical and safe. TI-201 imaging during adenosine infusion is an alternative to exercise tests for the noninvasive diagnosis of coronary artery disease.

**Acknowledgments**

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