Detection of Coronary Artery Stenosis in Children With Kawasaki Disease

Usefulness of Pharmacologic Stress $^{201}$Tl Myocardial Tomography

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This study determined the feasibility and accuracy of quantitative $^{201}$Tl myocardial single-photon emission computed tomography (SPECT) after dipyridamole infusion to detect coronary obstructive lesions in children with Kawasaki disease. $^{201}$Tl distribution after dipyridamole infusion was measured in 23 normal children, and with these normal values, quantitative analysis of SPECT was performed in 49 patients. Thirty-four patients had coronary stenosis 90% or greater on angiograms. Side effects resulting from systemic vasodilation were observed in about 70%. Angina pectoris and ischemic ST changes were observed only in patients with coronary stenosis. These symptoms disappeared after aminophylline infusion. Results of visual and quantitative analysis of SPECT were compared. SPECT data were shown on two-dimensional polar maps, and the extent and severity scores were calculated. The sensitivity of SPECT for detection of overall coronary stenosis was 91% (visual analysis) and 88% (quantitative analysis). The specificity of SPECT was 60% visually and 93% quantitatively. The sensitivity of quantitative analysis to detect individual coronary stenosis was similar to that of visual analysis. However, the specificity of visual analysis to detect individual coronary artery stenosis was significantly less than that of quantitative analysis. From these data, we conclude that quantitative analysis of myocardial SPECT after dipyridamole infusion is a safe and accurate diagnostic method for identifying coronary stenosis in children with Kawasaki disease.

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Coronary artery aneurysm occurs in about 10–20% of patients with Kawasaki disease and often leads to coronary obstruction. Myocardial infarction and angina pectoris may also occur in such patients. Therefore, it is desirable to detect the progressive aggravation of coronary aneurysm to stenotic lesions. Two-dimensional echocardiography can detect coronary aneurysm, but this method has a limitation in detecting coronary stenosis. Although electrocardiography is also used to recognize myocardial ischemia in Kawasaki disease, its sensitivity to detect coronary stenosis is relatively low. Coronary angiography is an accurate method to assess coronary artery involvement in Kawasaki disease. However, because angiography cannot be repeated very often, it is sometimes difficult to monitor progressive changes from aneurysms to stenotic lesions.

In adults, exercise $^{201}$Tl myocardial scintigraphy is well documented to be a sensitive method in detecting myocardial ischemia. In young children, however, the exercise test is sometimes difficult to perform.

As an alternative method to the exercise test, myocardial scintigraphy after intravenous dipyridamole infusion has been reported to be useful in adults, but its usefulness in children has not been evaluated. The purpose of the present study is to determine the feasibility and accuracy of myocardial scintigraphy after dipyridamole infusion in detecting coronary obstructive lesions in children with Kawasaki disease.

Methods

This study consisted of two parts. In part 1, normal spatial distribution of $^{201}$Tl after dipyridamole infusion was determined in 23 subjects with normal coronary arteries. In part 2, myocardial scintigraphy with dipyridamole infusion was per-
formed and analyzed visually and quantitatively, with the data obtained in part 1, in 49 patients with Kawasaki disease with and without coronary stenosis. In part 2, we also compared the scintigraphic findings after dipyridamole infusion with those obtained with exercise testing in six patients. Radiation exposure and potential risk of 201Tl scintigraphic study were explained to the families, and alternative examinations with less risk were also discussed. Informed consent to perform stress test and scintigraphic examination was obtained from all families.

Patients

In part 1, 23 subjects (group 1) were considered not to have coronary lesions. These subjects were divided into two groups according to their age: 11 subjects 9 years or less (range 3–9 years; mean, 6 years) and 12 subjects 9 years or older (range 11–19 years; mean, 14 years). Eleven subjects under 9 years old had a history of Kawasaki disease, but coronary angiography revealed normal coronary arteries. The group over 9 years of age consisted of two patients with Kawasaki disease with normal coronary arteries and 10 subjects who visited our hospital for the evaluation of chest pain (no history of Kawasaki disease). Although coronary angiography was not performed in these 10 subjects, physical examination, electrocardiograms, and echocardiograms showed no abnormalities.

In part 2, 49 patients (37 males and 12 females; mean age, 9 years) underwent cardiac catheterization within 3 months of 201Tl imaging. These patients were divided into two groups according to the presence or absence of coronary stenotic lesions. Group 2A consisted of 15 patients who had coronary aneurysms without stenotic lesions on the coronary angiogram. This group included 11 male and four female patients ranging in age from 4 to 14 years (mean, 9 years). The years since the initial onset of Kawasaki disease ranged from 1 to 12 years (mean, 7 years). Group 2B included 34 patients who had coronary aneurysms and stenosis greater than 90% on the coronary angiogram. There were 26 male and eight female patients ranging in age from 4 to 19 years (mean, 9 years). The years since the initial onset of Kawasaki disease ranged from 3 to 16 years (mean, 7 years). In group 2B, 21 patients had single-vessel, 12 patients had two-vessel, and one patient had three-vessel stenosis or obstruction. In 21 patients with single-vessel disease, 11 patients had right coronary, eight had left anterior descending, and two had left circumflex coronary artery disease. In 12 patients with two-vessel disease, eight patients had stenosis at the right coronary and left anterior descending artery, and four patients had left main coronary disease. In group 2B, old myocardial infarction was suspected in 13 patients from their history or electrocardiograms.

Coronary Angiography and Interpretation

Selective coronary angiography was performed in all patients in part 2, and the findings were used as a standard for the presence or absence of coronary stenosis. The location of coronary aneurysms and stenosis was determined according to the American Heart Association reporting system. In the present study, we considered coronary narrowing greater than 75% to be significant, and the data were used as a standard for calculating sensitivity and specificity of 201Tl scintigraphy. The percentage of coronary stenosis was calculated with the nearest normal-appearing portion of the coronary artery (either distal or proximal to the stenosis) as a standard. The development of intercoronary collateral circulation was classified into two categories: 1) poor and 2) good collaterals. Poor collateral circulation was defined as no or almost no visualization of the coronary artery distal to the stenosis through collateral flow. Good collateral circulation was defined as sufficient visualization of the distal coronary artery by collateral flow.

Protocol of Dipyridamole Infusion and Exercise

Patients were instructed to fast the morning of the test and to discontinue medications of nitrates or calcium channel blockers for 12 hours before the test. No sedation was used before or during the test. Dipyridamole (0.56 mg/kg) was infused intravenously during 4 minutes. In patients who had no chest pain or no significant changes in blood pressure and on the electrocardiogram (ECG), additional dipyridamole (0.14 mg/kg) was infused during 1 minute (cumulative dose, 0.70 mg/kg). A dose of 2.0–3.0 mCi 201Tl was injected 9 minutes after beginning the dipyridamole infusion. Two minutes after injection of 201Tl, aminophylline (3–5 mg/kg) was infused slowly to antagonize the effects of dipyridamole in all patients. 201Tl-absorbed dose estimates were 2–4 rad (kidney) and 0.8–1.2 rad (whole body). During the procedures, heart rate, blood pressure, and ECG were monitored, and changes or side effects were recorded. If chest pain or significant ECG change appeared during dipyridamole infusion, the infusion was stopped, and 201Tl was administrated immediately. Aminophylline was also infused 1–2 minutes after the injection of 201Tl.

Six patients in group 2B performed an exercise test with a supine bicycle ergometer within 2 weeks after the dipyridamole infusion test. The ECG, heart rate, and blood pressure were recorded before and then every minute during and after exercise for 5 minutes. Exercise was performed to a symptom-limited end point, and the increment of work load at every minute was 10 W (body height<130 cm) or 15 W (≥130 cm). At peak exercise, a dose of 2–3 mCi 201Tl was injected, and exercise was terminated approximately 1 minute later.
**Figure 1.** Bullseye maps with dipyridamole infusion test in a patient with obstruction at the left anterior descending and right coronary artery. $^{201}$TI activity is displayed in a color scale from red to blue. There are anteroseptal and inferoposterior perfusion defects in the stress bullseye map (upper left). The redistribution bullseye map is normal (upper right). In the washout bullseye map, decreased washout is shown in the anteroseptal and inferoposterior area (lower left).

**Single-Photon Emission Computed Tomography**

Myocardial single-photon emission computed tomography (SPECT) was performed twice: within 10 minutes of the injection of $^{201}$TI and after 4 hours of the initial examination. The studies were performed with a rotating gamma camera equipped with a low-energy high-resolution parallel hole collimator interfaced to a digital minicomputer (LFOV-ZLC, Shimadzu Scintipac 2400, Kyoto, Japan). The camera was rotated from a 60° left posterior oblique to a 30° right anterior oblique position of the patient. Thirty images were obtained for 25 seconds each at 6° intervals. In patients under 130 cm in height, the images were obtained with $\times 1.25$ magnification and for 35 seconds each. Contiguous transaxial tomograms were reconstructed into 6 mm thick multiple sections. Thereafter, the tomographic images along the short and long axes of the heart were reorganized from the set of transaxial tomograms according to the method described by Borrello et al.$^{13}$

**Visual Analysis of Single-Photon Emission Computed Tomography**

The SPECT images were analyzed visually by the consensus interpretation of two experienced observers who were unaware of the clinical diagnosis or the angiographic findings. The vertical long-axis slices were divided into anterior, apical, and inferior regions. The short-axis slices were divided into anterior, septal, inferior, and lateral regions. The horizontal long-axis slices were divided into septal, apical, and lateral regions. A four-point scoring system was used for each wall: 0=normal, 1=mildly reduced tracer concentration, 2=moderately reduced tracer concentration, and 3=markedly reduced tracer concentration.

**Two-Dimensional Polar Representations and Quantitative Analysis**

The usefulness of the new analytic methods of $^{201}$TI scintigraphy, which has been described in adults,$^{14,15}$ was evaluated in this study. The circum-
ferential count profiles for each short-axis cut were generated from the most apical to the most basal cut and were represented as polar maps (bullseye maps) according to the method described by Garcia et al.14 (Figure 1). On the short-axis cut, each point in the circumferential profiles represents the maximum count per pixel, along a radius extending from the center of the left ventricle to the limit of the radius of the left ventricle. The circumferential profiles for each slice were constructed by the computer from the value of 60 radii spaced at 6° intervals. Each point in the profiles was normalized by the maximum pixel value found in all slices of the left ventricle. In this mapping, the apex corresponds to the center of the map, and the most basal cut corresponds to the outermost circle (Figure 2). In addition to the thallium distribution, percent washout of 201TI from the myocardium was determined as follows:

\[
\% \text{ washout} = \frac{201\text{TI uptake at stress} - 201\text{TI uptake 4 hours later}}{201\text{TI uptake at stress}} \times 100
\]

In part 1, normal values of circumferential profiles were developed. With these values, the extent and severity maps and scores were determined by the method of Nakajima et al.15 The extent map displayed the area of 201TI uptake or washout that deviated more than 2 standard deviations from the normal value. The severity map expressed the degree of deviation of the abnormal area shown in the extent map from the normal value. The degree of deviation was displayed as a color scale level from red to blue (Figure 3). The extent and severity scores were then automatically calculated with the values of circumferential profiles as follows:

\[
\text{extent score} = \frac{\text{number of points with a value under 2 SD}}{\text{total number of points in the extent map}}
\]

\[
\text{severity score} = \frac{\sum (1 - \frac{\text{patient value less than 2 SD}}{\text{mean - 2 SD}}) \times 1,000}{\text{total number of points in the extent map}}
\]

For calculation of the severity score, if the patient value was within 2 standard deviations, it was considered to be equal to the mean value minus 2 standard deviations.

The diagnostic accuracy of the quantitative interpretations was compared with that of the visual interpretations of the SPECT images. For assigning a defect to a specific coronary lesion on the bullseye extent map, the territories of individual coronary arteries were determined according to the method of Garcia et al.14 In this system, 3 o'clock on the bullseye map was defined as 0°. By clockwise rotation, the territory of the left circumflex artery was from −45° to 60°, the territory of the right coronary artery was from 60° to 120°, and the remaining area was defined as the territory of the left anterior descending artery. On visual analysis of tomographic images, the territory of the left anterior descending artery included the anterior wall and septum, that of the right coronary artery included the inferior wall, and that of the left circumflex artery included the lateral wall. Isolated apical defects were not assigned to a specific artery.

**Statistical Analysis**

The \( \chi^2 \) test with Yates’ correction was used to determine the significance of difference in the observed occurrence of symptoms and ECG changes. Differences in hemodynamic change between patients with stenotic and nonstenotic coronary arteries were evaluated with Student’s \( t \) test. McNemar’s test16 was used to assess significance of the difference in the sensitivity and specificity between quantitative and visual interpretations. One-way analysis of variance was used to determine the difference in the relative uptake of 201TI of the left ventricular wall. A \( p \) value less than 0.05 was considered significant.

**Results**

**Dipyridamole Infusion Test**

A full dose (0.70 mg/kg) of dipyridamole could be infused in all patients in groups 1 and 2A and in 29 of 34 patients in group 2B. In four patients in group 2B, dipyridamole infusion was stopped at 0.56 mg/kg, and in one patient at 0.35 mg/kg, because of the appearance of chest pain and ECG changes during dipyridamole infusion. Maximum changes in heart rate and blood pressure that occurred during dipyridamole infusion are summarized in Table 1.
FIGURE 3. Bullseye extent and severity maps after dipyridamole infusion from the same patient in Figure 1. The pixel CT bullseye map (upper left) is identical to the upper-left figure of Figure 1. In the extent bullseye map (upper right), pixels less than 2 SD below normal are displayed in black. The anteroseptal and inferior perfusion defects are apparent. In the severity bullseye map (lower left), the severity of perfusion defect is shown in color scale from red to blue. Severe perfusion defects are present in the septal area. The extent and severity scores are also shown. CT, computed tomography.

Systolic blood pressure decreased by more than 20 mm Hg in 9% of the patients in group 1, in 7% in group 2A, and in 6% in group 2B. Maximum decrease of the systolic blood pressure was 25 mm Hg in groups 1 and 2A and 21 mm Hg in group 2B. ECG changes and symptoms during and after dipyridamole infusion are shown in Table 2. Nineteen of 34 patients in group 2B (56%) experienced chest pain or ST segment depression. In all these patients, chest pain and ECG changes disappeared within several minutes after administration of aminophylline. These 19 patients consisted of eight with single-vessel, 10 with two-vessel, and one with three-vessel disease. Chest pain and ST depression occurred more frequently in patients with two- or three-vessel disease than in patients with single-vessel disease (11 of 13 patients with two- or three-vessel disease [85%] vs. eight of 21 patients with single-vessel disease [38%]). In the single-vessel disease patients, neither the location nor

<table>
<thead>
<tr>
<th>Group</th>
<th>Before infusion</th>
<th>During or after infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Normal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>112±13</td>
<td>103±12</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>59±10</td>
<td>56±9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75±12</td>
<td>116±17*</td>
</tr>
<tr>
<td>Group 2A (Aneurysm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>110±9</td>
<td>104±13</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>58±13</td>
<td>56±7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76±12</td>
<td>110±14*</td>
</tr>
<tr>
<td>Group 2B (Stenosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>107±13</td>
<td>100±12*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>61±10</td>
<td>57±7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>80±14</td>
<td>113±12*</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

*Significantly different from the value before infusion.
Table 2. Symptoms and Electrocardiographic Changes During Dipyridamole Infusion Test

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Group 1</th>
<th>Group 2A</th>
<th>Group 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>9 (27%)*</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (26%)</td>
<td>4 (27%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (22%)</td>
<td>0 (0%)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Flushed</td>
<td>4 (17%)</td>
<td>4 (27%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Nausea or epigastric discomfort</td>
<td>5 (22%)</td>
<td>2 (13%)</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Total patients with one or more symptoms</td>
<td>16 (70%)</td>
<td>10 (67%)</td>
<td>22 (65%)</td>
</tr>
</tbody>
</table>

ECG changes

| Ischemic ST depression          | 0 (0%)  | 0 (0%)   | 18 (53%)* |
| (≥1 mm horizontal/≥2 mm J type)|         |          |          |
| ST elevation (≥1 mm)            | 0 (0%)  | 0 (0%)   | 1 (3%)   |
| T wave (inversion or flattening)| 6 (26%) | 6 (30%)  | 5 (15%)  |
| PQ prolongation                 | 0 (0%)  | 0 (0%)   | 5 (15%)* |
| Total patients with one or more ECG changes | 6 (26%) | 6 (30%)  | 24 (71%) |

ECG, electrocardiographic.
*Significantly different from groups 1 and 2A.

Normal Data in Group 1

Relative values of 201Tl distribution immediately after dipyridamole infusion are displayed in Figure 2. Of note, these values are the mean of 60 points. They were calculated to examine the regional difference in the 201Tl distribution and were not used to calculate the severity map and scores. In both age groups, the septal wall showed the highest 201Tl activity. In subjects 9 years old or less, the relative uptake in the anterior and lateral walls is significantly less than in subjects older than 9 years. In subjects older than 9 years, the relative uptake in the inferior wall was significantly less than that in subjects 9 years old or less.

Quantitative Criteria for Identifying Coronary Stenosis

To decide which quantitative criteria best separated the patients with coronary stenosis from those without stenosis, the effects of the varying criteria of extent score and severity score were examined in groups 2A and 2B (Table 3). A cutoff criterion of the extent score greater than or equal to 0.10 was selected to provide the best results for both sensitivity and specificity. In the severity score, a cutoff criterion greater than or equal to 5.0 was optimal.

Visual Compared With Quantitative Analysis

The sensitivity of SPECT for detecting coronary stenosis was 91% (visual analysis) and 88% (quantitative analysis). The specificity of SPECT was 60% visually and 93% quantitatively. The sensitivity and specificity of quantitative analysis were not significantly different from those of visual analysis. The capability of 201Tl tomography to identify stenosis in individual coronary arteries is shown in Table 4. The sensitivity and specificity of visual analysis and quantitative analysis were similar except that specificity of visual analysis for the left anterior descending artery region was significantly low.

Redistribution Phenomenon and Washout Abnormalities

In 30 patients who had perfusion defect on bullseye quantitative analysis, there were three types of redistribution phenomena. Complete redistribution (completely negative findings on delayed image) was found in 10 patients. Incomplete redistribution (partially improved perfusion defect after 4 hours) was found in 17 patients. No redistribution was detected in three patients.

Table 3. Effects of Criteria of Perfusion Abnormality on Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Extent score</th>
<th>Sensitivity (n=34)</th>
<th>Specificity (n=15)</th>
<th>Accuracy (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.15</td>
<td>29 (85%)</td>
<td>14 (93%)</td>
<td>43 (88%)</td>
</tr>
<tr>
<td>≥0.10</td>
<td>30 (88%)</td>
<td>13 (87%)</td>
<td>43 (88%)</td>
</tr>
<tr>
<td>≥0.05</td>
<td>30 (88%)</td>
<td>12 (80%)</td>
<td>42 (86%)</td>
</tr>
<tr>
<td>≥0.01</td>
<td>30 (88%)</td>
<td>10 (67%)</td>
<td>40 (82%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity score</th>
<th>Sensitivity (n=34)</th>
<th>Specificity (n=15)</th>
<th>Accuracy (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10.0</td>
<td>26 (76%)</td>
<td>14 (93%)</td>
<td>40 (82%)</td>
</tr>
<tr>
<td>≥5.0</td>
<td>30 (88%)</td>
<td>14 (93%)</td>
<td>44 (90%)</td>
</tr>
<tr>
<td>≥1.0</td>
<td>30 (88%)</td>
<td>12 (80%)</td>
<td>42 (86%)</td>
</tr>
</tbody>
</table>
Washout abnormality, in which percent washout was less than 2 standard deviations below normal, was observed in 30 patients in group 2B. There were two types of washout abnormality: diffuse washout abnormality, in which the entire bullseye map of washout rate was abnormal, and localized washout abnormality, in which the washout abnormality was confined to one or two coronary territories. The effect of adding washout analysis to the quantitative interpretation of the bullseye map on the sensitivity and specificity is shown in Table 4. Localized washout abnormality added one true-positive site in the left anterior descending territory and one false-positive site in the left circumflex territory. Diffuse washout abnormality occurred in nine patients, and seven of these patients had only one-vessel stenosis. Therefore, in the analysis of individual coronary territory, diffuse washout abnormality added two true-positive sites and 15 false-positive sites (Table 4).

**201TI Scintigraphy With Exercise**

In six patients who performed exercise testing, heart rate increased from 91±18 at rest to 167±24 beats/min at peak exercise. Blood pressure also increased from 116±28 to 146±28 mm Hg. In five of these six patients, scintigraphy showed positive findings for ischemia on exercise testing, whereas all of the six patients showed positive findings on dipyridamole testing. The grade and extent of perfusion defects after exercise testing, examined by visual inspection, were milder and smaller than those after dipyridamole infusion in all patients (Figure 4).

**Relations Between Angiographic and Scintigraphic Findings**

In group 2B, old myocardial infarction was suspected in 13 patients from the clinical history or ECG. The extent and severity scores in patients with infarction were compared with those in patients without infarction in group 2B (Table 5). In the infarction group, severity scores after dipyridamole infusion and extent and severity scores after redistribution were significantly greater than those in the noninfarction group. The ability of scintigraphy to differentiate coronary stenosis from total obstruction was analyzed in patients with single-vessel disease. Twelve patients had stenosis (90–99%), and nine had occlusion. There were no significant differences in the extent and severity scores between the stenosis and occlusion groups. Because there were no patients with milder stenosis in the present study, scintigraphic findings in patients with coronary stenosis less than 75% remained undetermined.

To evaluate the effect of collateral circulation on scintigraphic findings, the scintigraphic results were compared with the angiographic findings in patients with single-vessel disease. Six patients had poor and 15 had good collateral circulation. There were no significant differences in extent and severity scores between the groups with poor and good collateral circulation.

Two of 15 patients in group 2A showed perfusion abnormality. One of the two patients had a small aneurysm of the left anterior descending artery, and the perfusion defect was present in the anterior wall of the left ventricle. The other patient had a mildly dilated left anterior descending artery, and wall motion abnormality on left ventriculogram was also present in the anterior wall. In this patient, the

**Table 4. Sensitivity and Specificity to Detect Stenosis in Individual Coronary Arteries**

<table>
<thead>
<tr>
<th>Methods</th>
<th>LAD (n=21)</th>
<th>RCA (n=28)</th>
<th>LCx (n=29)</th>
<th>Sens</th>
<th>Spec</th>
<th>Sens</th>
<th>Spec</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullseye extent map</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>50</td>
<td>80</td>
<td>97</td>
<td>71</td>
<td>93</td>
</tr>
<tr>
<td>Bullseye extent map or washout map</td>
<td>100</td>
<td>64</td>
<td>90</td>
<td>86</td>
<td></td>
<td>86</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as %.

LAD, left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery; Sens, sensitivity; Spec, specificity.

*Significantly different among three methods.

**Table 5. Relations Between Thallium Scores and Myocardial Infarction**

<table>
<thead>
<tr>
<th></th>
<th>Stress Extent</th>
<th>Stress Severity</th>
<th>Redistribution Extent</th>
<th>Redistribution Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarction (n=13)</td>
<td>0.48±0.18</td>
<td>69.2±50.2</td>
<td>0.32±0.22</td>
<td>38.0±47.4</td>
</tr>
<tr>
<td>Noninfarction (n=21)</td>
<td>0.37±0.23</td>
<td>38.0±34.7*</td>
<td>0.12±0.14*</td>
<td>6.4±10.6*</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

*Significantly different from patients with myocardial infarction.
location of perfusion defect corresponded to the site of wall motion abnormality.

**Discussion**

Kamiya et al. showed that the sensitivity of $^{201}$Tl planar scintigraphy at rest was markedly lower than that of exercise or dipyridamole stress test for the detection of coronary stenosis in Kawasaki disease. Their data suggest that resting myocardial scintigraphy is not suitable for screening of stenosis because resting coronary blood flow is not affected until coronary narrowing becomes very severe. Regional myocardial perfusion becomes markedly abnormal at elevated flow levels after potent vasodilatory stimuli such as exercise or dipyridamole infusion.

$^{201}$Tl scintigraphy after dipyridamole infusion has been used in adults who are unable to perform adequate exercise testing. The sensitivity and specificity of dipyridamole stress myocardial scintigraphy are not significantly different from those of the exercise test in adults. In the present study, the grade and extent of perfusion defect after the dipyridamole test was greater than that of the exercise stress test (Figure 4). From the data in Figure 4, the perfusion defect observed in the dipyridamole stress test may be missed in the exercise test. For the early detection of progression to stenosis, a more sensitive method is desirable. Therefore, in children, the dipyridamole stress test is thought to be more suitable for this purpose than the exercise stress test.

Although the intravenous dipyridamole stress test is known to be safe in adults, its safety in children has not been evaluated. In the present study, chest pain or ischemic ST depression disappeared within several minutes after administration of aminophylline. Even without symptoms, aminophylline was given to prevent possible adverse effects of dipyridamole. As a result, we did not experience serious side effects. The optimal loading dose of dipyridamole has not been established in children. Gould et al. used 0.56 mg/kg dipyridamole in adults. Picano et al. used a larger dose of dipyridamole (0.84 mg/kg in 10 minutes) for the dipyridamole-echocardiography test. Though we administered 0.56 mg/kg dipyridamole during 4 minutes in a preliminary study, there were some cases with false-negative findings on $^{201}$Tl myocardial SPECT. Therefore, we increased the cumulative dose to 0.7 mg/kg in this study. Although contraindication to the dipyridamole test is not clear, we did not perform this test in patients in an unstable ischemic state, severely ill patients, or those with bronchial asthma.

SPECT yields a higher sensitivity than planar imaging in the detection of infarction in adults. The sensitivity and specificity of SPECT to detect coronary stenosis have been reported to be about 90% in adults. For detection of myocardial ischemia in Kawasaki disease, SPECT has also a higher accuracy compared with the planar imaging; therefore, only SPECT was used in the present study. The sensitivity of the visual interpretation of SPECT in the present study (about 90%) was similar to the adult value, but the specificity (60%) was lower than the adult value. A quantitative interpretation of myocardial scintigraphy is expected to avoid the problems of visual interpretation that include inter-observer variability and inability to quantify the extent of perfusion defect. A comprehensive method for quantification of myocardial SPECT has been recently developed in adults. This method shows the extent of the perfusion defect and washout abnormality on bullseye maps. In the present study, this method was used in children, and the data yielded a similar sensitivity and higher specificity compared with the visual analysis. In particular, the specificity for the left anterior descending arterial disease was significantly lower in the visual analysis. This may be, in part, due to the difference in the normal distribution pattern of $^{201}$Tl in children and adults. In children, the septal wall showed the highest uptake (Figure 2). This finding is strikingly different from that in adults, in which the lateral wall shows the highest activity. The relatively decreased activity of the anterolateral wall in children resulted in the false-positive finding in the visual analysis. Therefore, it may be important to recognize the age-related difference in the normal distribution pattern in children not only for the quantitative analysis but also for visual interpretations.

DePasquale et al. selected the criteria of mean±2.5 SD as the normal range in the bullseye $^{201}$Tl distribution map. In the present study, we tentatively selected mean±2 SD as a normal range of $^{201}$Tl distribution, and we used it to calculate extent and severity scores. The various criteria of extent and severity scores were then compared to identify the patients with coronary stenosis (Table 3). This procedure is essentially similar to that used to select the best criteria of the initial $^{201}$Tl distribution abnormality.

The sensitivity and specificity of the extent score and of the severity score were similar (Table 3). Although both scores were useful, the severity score included information on the abnormal area and on the mass of abnormally perfused myocardium. Therefore, it could be more useful for grading the ischemic myocardium.

Analysis of $^{201}$Tl washout has been reported to improve the detection of multiple vessel stenosis in adults. In the present study, however, washout analysis did not improve the diagnostic accuracy in detecting coronary stenosis. This was mainly due to the appearance of diffuse slow washout in patients with one-vessel disease. The reason for this remains unclear and needs further investigation.

Perfusion studies using SPECT have several advantages over other methods. First, patients with Kawasaki disease can be evaluated serially, and the aggravation from aneurysms to stenosis may be
detected in a long-term follow-up of patients. Second, the present method can detect the severity of myocardial damage (Table 5). Furthermore, myocardial perfusion state can be evaluated in patients with Kawasaki disease with no coronary stenosis on angiography. In the present study, one patient in group 2A, who had a mildly dilated left anterior descending artery, showed a constant perfusion defect in the anterior wall. The perfusion defect corresponded to the site of wall motion abnormality on the left ventriculogram. These findings may indicate that myocardial injury can occur in patients who have normal coronary arteries.

There are some limitations in the present test. Because of the poor spatial resolution of SPECT, assessing the myocardium in infants without cardiomegaly is difficult. In our experience, the minimal age that SPECT can be performed is 3 years in subjects without cardiomegaly. Furthermore, a relatively long time (20–30 minutes) is required to obtain SPECT data. Although we did not use any sedation, it would be difficult for young children under 3 years of age to undergo this test without sedation.

The degree of collateral circulation did not show any effect on thallium findings. This suggests that even good collateral flow was not sufficient to increase the myocardial perfusion to the ischemic area. However, dipyridamole stress thallium scintigraphy shows the relative difference of coronary flow reserve. The effect of collateral flow on coronary perfusion during exercise or at rest could not be determined from this study. In addition, in this study, one patient who had a small aneurysm without stenosis showed perfusion defect. Although coronary aneurysm can potentially cause perfusion abnormality, we could not determine definitely whether or not this perfusion defect indicates true perfusion abnormality. The effect of aneurysms on coronary perfusion needs further study.

In summary, the dipyridamole stress myocardial SPECT is a good diagnostic tool for identifying coronary stenosis in patients with Kawasaki disease and yields sensitivity and specificity of about 90% each. The dipyridamole test can be performed safely and used as an alternative method to exercise testing in children.

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References


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