RATIO OF LUNG TO HEART THALLIUM-201 UPTAKE ON EXERCISE AND DIPYRIDAMOLE STRESS IMAGING IN CORONARY ARTERY DISEASE

— Implication of SPECT —

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To examine whether measurements of lung thallium-201 (TI-201) uptake with single photon emission computed tomography (SPECT) following exercise or dipyridamole infusion provide complementary information as reported in planar imaging, we examined 140 patients undergoing exercise or dipyridamole TI-201 SPECT and coronary arteriography for the diagnosis of coronary artery disease (CAD). On the reconstructed coronal tomographic image, regions of interest were placed over the left upper lung field and the left ventricular myocardium. Lung to heart ratio (L/H ratio) was calculated as a fraction of average TI-201 counts per pixel in the lung divided by those in the myocardium. An L/H ratio of larger than a value of mean + 2 standard deviation, derived from patients without significant coronary stenosis, was considered as abnormal. The patients with abnormal L/H ratio on exercise TI-201 SPECT had larger extent and severity scores of TI-201 defects on the initial image, lower left ventricular ejection fraction, higher end-diastolic pressure and higher incidence of multi-vessel CAD than those with the normal ratio. However, in dipyridamole studies, abnormal L/H ratio did not relate to scintigraphic or hemodynamic severity. These data confirmed that increased lung TI-201 uptake after exercise suggested the presence of extensive CAD or left ventricular dysfunction. However, L/H ratio might be less useful in dipyridamole studies. Thus, quantitative measurements of L/H ratio with exercise but not dipyridamole SPECT could provide additional information related to the involved cardiac pump performance in CAD.

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Japanese Circulation Journal Vol.57, May 1993 379

Exercise thallium-201 (TI-201) myocardial perfusion imaging has widely been accepted as a useful tool for the noninvasive evaluation of coronary artery disease (CAD). The presence of increased lung TI-201 activity in the immediate postexercise imaging was noted in patients with extensive CAD. Although the mechanisms of increased lung TI-201 uptake remain unclear, increased pulmonary venous pressure associated with left ventricular dysfunction during exercise has been considered as the most relevant cause. A quantitative assessment of lung TI-201 activity expressed as the ratio of lung to myocardial counts (L/H ratio) in planar imaging has been utilized as a sign

Key words:
Thallium-201
Coronary artery disease
Exercise
Dipyridamole
TABLE 1 PATIENTS CHARACTERISTICS

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<td>59±7</td>
</tr>
<tr>
<td>range (year)</td>
<td>38–73</td>
<td>38–72</td>
</tr>
<tr>
<td>male (%)</td>
<td>49 (70%)</td>
<td>49 (70%)</td>
</tr>
<tr>
<td>myocardial</td>
<td>31 (44%)</td>
<td>30 (43%)</td>
</tr>
<tr>
<td>infarction (%)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (30%)</td>
<td>21 (30%)</td>
</tr>
<tr>
<td>1</td>
<td>18 (26%)</td>
<td>17 (24%)</td>
</tr>
<tr>
<td>2</td>
<td>16 (23%)</td>
<td>14 (20%)</td>
</tr>
<tr>
<td>3</td>
<td>15 (21%)</td>
<td>18 (26%)</td>
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</table>

*significant coronary stenosis was defined as 75% or greater stenosis

uptake in 140 patients undergoing exercise or dipyridamole TI-201 imaging.

METHODS

Subjects

Seventy consecutive patients who had dipyridamole TI-201 tests and coronary arteriography for suspected CAD at Yamagata University Hospital in the 2 year period from April 1988 to March 1990 were enrolled in the present study. From 165 patients who had exercise TI-201 tests and coronary arteriography during the same period, we selected 70 patients to match the age and gender for the dipyridamole group, without any information related to clinical, TI-201, and angiographic findings. None of matched patients had undergone coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. The patients' characteristics are summarized in Table I. Significant coronary stenosis was defined as 75% or more stenosis in main epicardial arteries or major branches. There were no differences in incidence of myocardial infarction or in prevalence of responsible coronary artery stenosis. The study protocol was approved by the Yamagata University Committee on Human Research.

Exercise test

All patients underwent graded treadmill exercise testing according to a modified Bruce protocol. Cardiovascular medications were all discontinued for at least 24 h before the exercise stress testing, except for short-acting sublingual nitrates. Blood pressure was measured every minute in the left arm by a standard cuff method, and CM5-lead ECG was continuously monitored during the testing. The criteria for the termination of the exercise test were severe angina, dyspnea, ischemic ST depression, serious arrhythmia, or fatigue. A dose of 74 MBq of TI-201 was injected intravenously 1 min before the termination of exercise.

Dipyridamole test

Cardiovascular medications were discontinued in the same manner as the exercise testing. Dipyridamole was infused intravenously at a rate of 0.14 mg/kg/min for 4 min according to the protocol reported by

Japanese Circulation Journal Vol.57, May 1993
Albro et al.16 Six minutes after the termination of dipyridamole infusion, 74 MBq of Ti-201 was intravenously administered. If symptoms, hemodynamic responses, or ECG changes were severe or prolonged, 125 mg of aminophylline was given intravenously 2 min after the Ti-201 injection.17

**TI-201 imaging**

Cardiac imaging was begun 10 min after the Ti-201 injection in both exercise and dipyridamole tests. All studies were obtained on a large field-of-view rotating gamma camera (Siemens, ZLC-7500 Digi-trac) equipped with a parallel hole, high-resolution collimator.17,18 Thirty two planar acquisitions were performed during a 180 degree rotation from the 30 degree right anterior oblique to the 60 degree left posterior oblique projections. Each 64×64 matrix was collected for 40 sec during each of the 32 steps and contained 150,000 to 200,000 counts. A delayed image was obtained 3 h later. Patients were carefully repositioned for the delayed image acquisition with a laser-positioning device.

**Quantitative measurements of lung Ti-201 uptake**

Data processing was performed on a nuclear medicine computer system (Shimadzu, Scintipac 700). A series of contiguous transaxial images, which included the lung field as well as the myocardium, were reconstructed by means of a filtered back projection algorithm without attenuation correction. Transaxial images were further processed according to anatomical axis, then coronary tomographic slices, each 6 mm thick, were obtained. Separate square regions of interest (ROI) were defined for areas of the left upper lung field (6×6 pixels in size) and the left ventricular myocardium (4×4 pixels in size) on the coronary image as shown in Fig. 1. The lung ROI was placed over the most intense activity in the lung and was usually at least 5 pixels above the anterior myocardial wall. The myocardial ROI was placed over the myocardium with the peak count density. The L/H ratio was calculated as a fraction of the mean counts per pixel in the lung divided by those in the myocardium.

Images were analyzed twice by the same observer at least 2 weeks apart to determine intraobserver variability in 18 subjects. L/H ratio was also independently calculated by the second observer to obtain interobserver variability.
Fig. 2. Correlations of the L/H ratio measured for the same observer on separate occasions (2-A) and between two independent observers (2-B).

Fig. 3. Relation between L/H ratio and the presence and extent of coronary artery disease. In both exercise and dipyridamole studies, patients with 2 and 3 vessel disease (VD) have greater L/H ratio than those with 0 VD. Horizontal lines indicate normal upper limits defined as mean + 2 standard deviations value in patients with 0 VD.

*p<0.01, **p<0.001 vs 0 VD

Analysis of myocardial tomography

Transaxial images were further processed to obtain oblique tomographic slices. Oblique, orthogonal tomograms, each 6 mm thick, were reconstructed parallel to the short axis of the left ventricle. Circumferential profile analysis was applied to each of the short axis slices from base to apex. These circumferential profiles were plotted in polar coordinates and arranged into a bull's eye map. Files for normal male and female had been constructed separately from 18 men and 13 women with normal coronary arteries. For the patients study, each pixel was compared with the corresponding pixel in the gender-matched normal profile. Pixels that were more than 2.5 standard deviations below the mean were defined as abnormal, and displayed on a color-coded standard deviation map. The ratio of the number of abnormal pixels to the total was defined as an extent score. A severity score was calculated as the sum of the standard deviations below the mean normal profile for all abnormal pixels. The extent score and the severity score were used as quantitative indices which show the extent and severity of perfusion abnormality.
Fig. 4. Comparison of the proportion of abnormal L/H ratio between in patients with single-vessel disease (SVD) and multi-vessel disease (MVD). In exercise TI-201 SPECT, an abnormal L/H ratio was observed more frequently in patients with MVD than in those with SVD. However, only 5 of 32 patients with MVD showed an abnormal L/H ratio in dipyridamole TI-201 SPECT.

Statistics

The values of the data were presented as mean ± one standard deviation. Chi-square test was used to compare the differences in proportion. The L/H ratio was compared using one-way analysis of variance. An unpaired t-test was used for the comparison of extent score, severity score, heart rate, blood pressure, rate pressure products, left ventricular ejection fraction, end-diastolic pressure and cardiac index between patients with normal and abnormal L/H ratio. The L/H ratios for the same observer on separate occasions and between two independent observers were examined using linear regression analysis. A p value <0.05 was considered significant.

RESULTS

Lung heart ratio and extent of coronary artery disease

The L/H ratio was highly reproducible in repeated measurements by the same observer (r=0.95, p<0.001) and between two independent observers (r=0.94, p<0.001) as shown in Fig. 2. The mean absolute differences between ratios obtained by the same observer and the 2 observers were 1.3±1.0% and 1.5±1.1%, respectively.

Fig. 3 shows the relation between L/H ratio and the presence and extent of coronary artery disease. In exercise TI-201 studies, patients with 2 and 3 vessel disease groups had larger L/H ratios than those without significant coronary stenosis (16±7% and 17±4% vs 10±2%, p<0.001, respectively). In dipyridamole studies, L/H ratios in patients with 2 and 3 vessel disease were a little larger than those in patients without significant coronary stenosis (15±3% and 15±4% vs 11±3%, p<0.01, respectively).

When an L/H ratio larger than mean±2 standard deviations in patients without significant coronary stenosis was considered as abnormal, normal upper limits were 15% and 18% in exercise and dipyridamole TI-201 SPECT, respectively. In exercise studies, 6 of 18 (33%) patients with single-vessel disease and 20 of 31 (65%) patients with multi-vessel disease showed an abnormal L/H ratio (Fig. 4). Frequency of abnormal L/H ratio was higher in patients with multi-vessel disease than in those with single-vessel disease (p<0.001). In contrast, in the dipyridamole studies, only 5 of 32 (16%) patients with multi-vessel disease showed an abnormal L/H ratio (p<0.001 vs exercise), and the proportion of abnormalities was not different between patients with single-vessel and with multi-vessel disease (12% vs 16%).

L/H ratio was compared between the patients with and without left anterior descending artery (LAD) stenosis. There were no differences (exercise: 16±5% vs 12±5%, dipyridamole: 14±3% vs 14±2%).

We compared the L/H ratio between patients with and without myocardial infarction. L/H ratio was greater in patients with myocardial infarction than those without (exercise: 16±4% vs 13±4%, p<0.05, dipyridamole: 15±4% vs 13±2%, p<0.05).

Among 49 patients with CAD, both exercise and dipyridamole TI-201 SPECT was performed in 13 patients. The 2 TI-201 studies were performed 3 to 14 days apart (mean 5±4 days). L/H ratio after exercise was larger than that after dipyridamole (16±4% vs 13±3%, p<0.01). The proportion of abnor-
TABLE II COMPARISON OF SCINTIGRAPHIC FINDINGS AND HEMODYNAMIC RESULTS BETWEEN NORMAL AND ABNORMAL L/H RATIO

<table>
<thead>
<tr>
<th></th>
<th>exercise</th>
<th></th>
<th></th>
<th>dipryidamole</th>
<th></th>
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<tr>
<td></td>
<td>normal</td>
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<td>abnormal</td>
<td>p value</td>
<td>normal</td>
<td>abnormal</td>
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<tr>
<td></td>
<td>n=23</td>
<td>n=26</td>
<td></td>
<td>n=42</td>
<td>n=7</td>
<td></td>
<td></td>
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<tr>
<td>extent score (initial)</td>
<td>27±20</td>
<td>43±24</td>
<td>0.02*</td>
<td>34±21</td>
<td>46±20</td>
<td>0.16</td>
<td></td>
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<td>severity score (initial)</td>
<td>38±41</td>
<td>72±62</td>
<td>0.03*</td>
<td>58±60</td>
<td>88±68</td>
<td>0.24</td>
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<tr>
<td>extent score (delayed)</td>
<td>19±17</td>
<td>31±23</td>
<td>0.06</td>
<td>20±19</td>
<td>36±19</td>
<td>0.05*</td>
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<tr>
<td>severity score (delayed)</td>
<td>22±31</td>
<td>41±50</td>
<td>0.14</td>
<td>24±39</td>
<td>52±47</td>
<td>0.10</td>
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<tr>
<td>peak heart rate (beats/min)</td>
<td>124±24</td>
<td>116±22</td>
<td>0.22</td>
<td>76±14</td>
<td>73±11</td>
<td>0.57</td>
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<td>peak systolic blood pressure (mmHg)</td>
<td>168±29</td>
<td>166±26</td>
<td>0.79</td>
<td>135±29</td>
<td>129±22</td>
<td>0.43</td>
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<tr>
<td>peak RPP (mmHg×beats/min)</td>
<td>21138±5583</td>
<td>19723±6461</td>
<td>0.42</td>
<td>10293±2961</td>
<td>9336±2157</td>
<td>0.43</td>
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<td>angina (%)</td>
<td>6 (26%)</td>
<td>12 (46%)</td>
<td>0.15</td>
<td>8 (19%)</td>
<td>0 (0%)</td>
<td>0.21</td>
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<tr>
<td>ST depression (%)</td>
<td>8 (35%)</td>
<td>14 (54%)</td>
<td>0.18</td>
<td>11 (24%)</td>
<td>2 (29%)</td>
<td>0.76</td>
<td></td>
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<tr>
<td>LVEF rest (%)</td>
<td>66±12</td>
<td>57±14</td>
<td>0.03*</td>
<td>63±15</td>
<td>54±8</td>
<td>0.15</td>
<td></td>
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<tr>
<td>LVEF stress (%)</td>
<td>62±14</td>
<td>55±12</td>
<td>0.12</td>
<td>63±13</td>
<td>53±12</td>
<td>0.06</td>
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<tr>
<td>EDP (mmHg)</td>
<td>12±3</td>
<td>15±3</td>
<td>0.01*</td>
<td>12±4</td>
<td>13±5</td>
<td>0.91</td>
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<td>C.I. (l/min²)</td>
<td>3.6±0.7</td>
<td>3.2±0.8</td>
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<td>3.2±0.8</td>
<td>3.1±0.6</td>
<td>0.90</td>
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RPP: rate pressure products, LVEF: left ventricular ejection fraction, EDP: end-diastolic pressure, C.I.: cardiac index
*: statistically significant

mal L/H ratio was higher in exercise than in dipryidamole TI-201 SPECT (69% vs 15%, p<0.01).

Comparison of scintigraphic findings and hemodynamic results between patients with normal and abnormal L/H ratio

Out of 49 patients with significant coronary stenosis, 26 (53%) and 7 (14%) showed an abnormal L/H ratio in exercise and dipryidamole TI-201 imaging, respectively. Comparison of scintigraphic findings and hemodynamic results in patients with CAD between normal and abnormal L/H ratio are summarized in Table II. In exercise studies, patients with an abnormal L/H ratio had larger extent and severity scores of TI-201 defects on the initial image (extent: 43±24 vs 27±20, p<0.02, severity: 72±62 vs 38±41, p<0.03), lower left ventricular ejection fraction (57±14% vs 66±12%, p<0.03), and higher end-diastolic pressure (15±3 vs 12±3 mmHg, p<0.01) than those with normal ratio. However, in dipryidamole studies, a significant difference between patients with normal and abnormal L/H ratio was observed in only the extent score on the delayed image (20±19 vs 36±19, p<0.05).

DISCUSSION

The increased lung TI-201 uptake after exercise was more preferentially observed in patients with multi-vessel disease than those with single-vessel disease. The abnormal L/H ratio in exercise TI-201 SPECT was associated with the presence of severe CAD, extensive TI-201 defects, and left ventricular dysfunction as reported in planar imaging. However, the L/H ratio in dipryidamole TI-201 SPECT was less useful for the identification of patients with severe CAD or left ventricular dysfunction.

Assessment of lung TI-201 uptake during SPECT: Technical considerations

As compared to planar imaging, myocardial imaging with SPECT has a better diagnostic accuracy for detecting patients with CAD, because the SPECT system permits a 3-dimensional representation of myocardial TI-201 distribution. However, the clinical implications of increased lung TI-201 uptake during SPECT have not been adequately explored. Kahn et al have reported that measurements of lung TI-201 uptake during SPECT do not provide sup-
Lung TI-201 uptake during SPECT

Supplementary information regarding the extent of myocardial ischemia or ventricular dysfunction. Delay in commencing imaging after exercise decreases the chance to detect the phase of increased lung TI-201 uptake, because TI-201 washout from the lung is fast. However, the lung TI-201 uptake in planar images includes TI-201 activity in skeletal muscle, connective tissue and lung. The assessment of lung TI-201 uptake during SPECT may be as useful as the planar imaging, because the precise determination of lung TI-201 uptake per se is possible due to its 3-dimensional processing. The method of measuring lung TI-201 uptake during SPECT reported by Kahn et al used an anterior projection image which was acquired as part of SPECT imaging. Therefore, TI-201 uptake in muscle and costal was included in the lung ROI as planar images. In the present study, to eliminate contamination by extra-lung tissue, we used reconstructed coronal tomographic images to measure lung TI-201 uptake. To minimize the statistical error in assessing lung TI-201 counts, we used the large size of lung ROI (6x6 pixels) to accumulate enough counts (more than 1000 counts). As shown in Fig. 2, quantitative assessment of lung TI-201 uptake from coronal tomographic images in the present study was feasible and reproducible despite the lower count densities in the images analyzed.

We monitored CMR-lead ECG during the testing, because body surface ECG mapping indicated that exercise or dipyridamole-induced ST depression usually included CMR-lead. However, 12-lead ECG monitoring may be desirable since, in some cases, ECG changes are detected on only leads.

Possible mechanisms of increased lung TI-201 uptake: Comparison of exercise and dipyridamole stress imaging

Increased lung TI-201 activity has been correlated with exercise-induced increases in pulmonary capillary wedge pressure. Increased extravascular lung water, in a model of acute pulmonary edema, has been shown to have a linear correlation to lung TI-201 uptake. Increased pulmonary TI-201 uptake after exercise suggests the development of left ventricular dysfunction due to exercise-induced myocardial ischemia, as well as cardiac pump failure at rest due to myocardial infarction. In the present study, patients with increased L/H ratio during SPECT showed larger extent and severity scores of TI-201 defects, lower left ventricular ejection fraction, higher end-diastolic pressure, and higher incidence of multi-vessel CAD as reported in studies using planar imaging. Okada et al reported that abnormally increased lung TI-201 activity after dipyridamole did not relate to the severity of CAD in planar images. Villanueva et al showed that increased lung TI-201 uptake after dipyridamole in the planar images might be a marker of severe CAD as with exercise TI-201 imaging. However, they did not assess the coronary angiographic and hemodynamic correlates of increased L/H ratio after dipyridamole. Furthermore, no previous studies have reported the prevalence and significance of increased L/H ratio in dipyridamole TI-201 SPECT, although the SPECT system has increasingly been used because of its high diagnostic accuracy for CAD.

Dipyridamole-induced vasodilation causes unfavorable endocardial/epicardial blood flow distribution in the area distal to a critical stenosis due to a "coronary steal" phenomenon. Regional lactate production in areas supplied by stenosed coronary arteries was documented in patients who received intravenous dipyridamole infusion. Therefore, dipyridamole-induced changes in myocardial blood flow ensued in the production of ischemic left ventricular dysfunction sufficient to raise the left ventricular filling pressure and, thus, pulmonary capillary pressure. However, the occurrence of left ventricular dysfunction due to myocardial ischemia is infrequent in the dipyridamole test. In the present study, ischemic ST depression in ECG was more frequently observed after exercise than after dipyridamole (45% vs 27%, p<0.01). TI-201 defects induced by dipyridamole are caused by a flow maldistribution between normally perfused and abnormally perfused myocardium, and reversible TI-201 defects are shown without the occurrence of myocardial ischemia. This might explain the present results that the presence of abnormally in-
increased L/H ratio in dipyridamole TI-201 imaging failed to identify the patients with extensive myocardial ischemia.

**Conclusion**

Quantitative analysis of lung TI-201 activity after the treadmill exercise could identify the patients with functionally severe CAD or left ventricular dysfunction. However, L/H ratio in dipyridamole TI-201 SPECT did not correlate with the clinical severity of CAD. Thus, L/H ratio in exercise but not dipyrideramole TI-201 SPECT provides additional information related to the involved cardiac pump performance in CAD.

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