Lung Thallium-201 Uptake After Stress Testing in Patients with Coronary Artery Disease

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SUMMARY We observed increased lung thallium-201 (201TI) activity on initial stress myocardial images in patients with coronary artery disease (CAD). To assess the clinical significance of this finding, initial and 2-hour delayed 201TI images were stored in a computer immediately after supine stress testing in 49 patients (39 with CAD and 10 controls). Regions of interest over the heart and lung were selected on the computer-generated images and quantitative lung 201TI activity was expressed as a percentage of maximal myocardial 201TI activity per picture element (lung 201TI index) for each imaging time. The lung 201TI index was then compared with (1) the extent of CAD at catheterization, (2) resting left ventricular ejection fraction by multigated blood pool scintigraphy, (3) the results of the initial 201TI stress myocardial perfusion images, and (4) qualitative assessment of initial lung 201TI uptake after stress. In 10 control patients the mean initial lung 201TI index was 37.6 ± 2.5% (± SEM). In 29 patients with two- and three-vessel CAD, the mean initial lung 201TI index was elevated, at 53.5 ± 2.2% (p < 0.001 compared with controls). While in 10 patients with one-vessel CAD, the mean initial lung 201TI index was 45.6 ± 3.6% (p = NS compared with controls). Patients with CAD decreased their mean lung 201TI index from initial to delayed images (p < 0.05), but control patients did not. When a lung 201TI index of 54.5% (2 SD above the control mean) was chosen as abnormal, patients who had CAD and an abnormal initial lung 201TI index had significantly reduced resting ejection fractions (mean 58.2 ± 2.5%) compared with patients who had CAD and a normal lung 201TI index (mean 66.0 ± 2.1%) (p < 0.05). Patients with CAD and four or five of six abnormal segments on the initial myocardial perfusion images had higher initial lung 201TI indexes (mean 59.1 ± 13.0%) compared with patients with CAD and one or no abnormal segments on the initial myocardial perfusion images (mean 44.5 ± 10.3%) (p < 0.01). Initial lung 201TI indexes determined quantitatively correlated with the qualitative assessment of initial lung 201TI uptake after stress.

The finding of elevated lung 201TI activity on stress myocardial images correlates with increased severity of underlying coronary artery disease and left ventricular dysfunction. 201TI lung activity after stress can be easily quantitated.

THALLIUM-201 (201TI) myocardial imaging performed in conjunction with exercise has improved the diagnostic accuracy of the exercise ECG for the detection of significant coronary artery disease.1-3 We have observed marked pulmonary uptake of 201TI on initial images in some patients after stress testing. The clinical significance of this finding was assessed in relation to the extent of coronary artery disease, resting left ventricular hemodynamic function and the presence and extent of stress-induced 201TI myocardial perfusion defects.

Methods

Patient Selection

Forty-nine patients referred for cardiac catheterization and coronary arteriography for the evaluation of chest pain were prospectively studied. There were 36 males and 13 females, ages 31-68 years (mean 53.6 years). All patients underwent cardiac catheterization within 1 week of the 201TI study. Propranolol therapy was not altered before the 201TI study. Patients with recent myocardial infarction, unstable angina or physical disability limiting exercise were excluded.

Cardiac Catheterization and Angiography

All patients underwent left-heart catheterization, coronary arteriography and left ventriculography. Coronary arteriograms were read by two independent observers. Significant stenosis was defined as a 50% or greater reduction in the intraluminal diameter of a coronary artery in at least two projections.

201TI Stress Imaging

Patients underwent graded, supine exercise testing in the fasting state using a table especially equipped with a bicycle ergometer (Cardiac Stress Systems, Engineering Dynamics Corp.). The ECG and blood pressure response at rest and during exercise were monitored. The work load was adjusted to 150 kpm/min initially, and increased by 150 kpm/min every 2 minutes until chest pain, dyspnea, leg fatigue, or ST-segment depression equal to or greater than 2 mm by electrocardiography developed. One and one-half millicuries of 201thallous chloride (New England Nuclear) were then injected through an indwelling venous catheter and exercise was continued for an additional 30 seconds. Myocardial imaging com-
menced immediately with a mobile gamma camera (Ohio Nuclear Series 120) interfaced to a portable computer (MUGA Cart, Medical Data Systems) equipped with a medium-sensitivity, parallel-hole collimator. Images were obtained in the anterior and 50° left anterior oblique projections. Images were collected in a 128 X 128 matrix format for 6 minutes. Delayed images were obtained 2–3 hours after exercise. Images were stored on computer discs or magnetic tape for later processing. Field uniformity of the camera was checked and corrected each day using a cobalt-57 disc source for flood images. The energy window was centered on the 60–80-keV mercury X-ray peak of 201TI with a 30% window. Approximately 200,000 counts were collected per image.

Multigated Blood Pool Imaging for Ejection Fraction Analysis

After the delayed 201TI images were obtained, gated blood pool imaging was performed at rest to determine left ventricular ejection fraction. The patients were given 3 mg of i.v. stannous pyrophosphate (New England Nuclear), followed 20–30 minutes later by 20 mCi of technetium-99m pertechnetate to complete the labeling of in vivo red blood cells. Patients were then imaged supine in the 50° left anterior oblique projection with the gamma camera equipped with a high-resolution, parallel-hole collimator. The camera was set at the 140-keV photo peak of technetium-99m with a 30% energy window. The imaging effects of the previously administered dose of 201TI were considered minimal because the technetium-99m photon flux was calculated to be 500 times greater than the 201TI photon flux in this energy window. Images were collected with the mobile computer coupled to an electrocardiographic gating device (Brattle Physiologic Synchronizer). The cardiac cycle was divided into 28 equal segments. A total of 200,000 counts was collected in each of 28 frames. Imaging time ranged from 5–10 minutes, depending on heart rate.

Lung 201TI Analysis

The analog anterior 201TI studies were interpolated from a 128 X 128 word-mode matrix to a 64 X 64 word-mode matrix and displayed on a cathode ray tube for quantitative analysis. Two independent observers used a computerized light pen to identify a region of interest over one of the three segments of myocardium in the anterior view (anterolateral, apical or inferior) with the highest count density, and a region of interest over the left upper lung field (fig. 1). A printout of the counts per picture element for each region of interest was then derived for each of the 201TI images (immediate and 2-hour delay). Lung 201TI activity was expressed as a percentage of the maximal myocardial counts for each image (lung 201TI index). The results obtained by the two observers were averaged for each determination. One observer determined the lung 201TI index a second time at least 2 months after the initial determination to assess intraobserver variance.

A qualitative assessment of lung 201TI uptake was made by each of two independent observers for each image. A grade of 0 was chosen for qualitatively normal pulmonary uptake, 1+ for moderately increased pulmonary uptake that was greater than normal but less than myocardial activity, and 2+ for greatly increased pulmonary activity that approached myocardial activity. Half grades were allowed. The grades of the two observers were averaged for each observation.

Myocardial 201TI Analysis

Two independent observers graded each segment of the anterior (anterolateral, apical and inferior) and the left anterior oblique (septal, apical-inferior and posterior) 201TI scans at each imaging time. The grades ranged from 0 (minimum myocardial activity) to +2 (normal myocardial activity), with grades increasing by increments of 0.5. The grades obtained by the two observers for each segment at each imaging time were averaged. Any segment with an average grade less than 1.5 immediately after exercise was considered abnormal.

Ejection Fraction Analysis

The multigated blood pool scan ejection fraction at rest was determined from the left anterior oblique projection using a semiautomatic edge-detection program. A box was positioned to encompass the entire left ventricle at end-diastole. Beginning at the center of the ventricle, the program searched outward in a radial fashion until a matrix point was reached that satisfied one of two criteria: (1) the two-dimensional second derivative was equal to zero, or (2)

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**Figure 1.** Representative thallium-201 images of a patient with coronary artery disease and increased lung uptake in the anterior projection immediately after maximal supine stress testing. Image on the right shows the regions of interest used for the calculation of lung-to-heart ratios. The patient had significant three-vessel coronary artery disease. The lung thallium-201 index for this patient was 62%.
the number of counts at a matrix point was less than a given threshold value selected by the observer. In this manner, the left ventricular edge was defined for each frame. A background region of interest was selected by the program for a region outside the end-systolic frame. Ejection fraction was calculated as the background-subtracted end-diastolic counts minus end-systolic counts divided by end-diastolic counts.

Statistical Analysis

Statistical analysis was performed using either the paired or unpaired two-tailed t test. Data for groups of patients were expressed as a mean ± SEM. Comparison between quantitative lung 201TI indexes and the number of abnormal myocardial segments on the myocardial images immediately after stress was made by a one-way analysis of variance and the Newman-Keuls multiple comparison test. Interobserver and intraobserver variance for determinations of the lung 201TI index were derived from two-way analyses of variance. The variances were expressed as ±1 standard deviation. The correlation between lung 201TI index and rest radionuclide ejection fraction was assessed using a linear regression analysis.

Results

Clinical and Angiographic Findings

Thirty-nine of the 49 patients had significant coronary artery disease and 10 did not. Ten patients had significant one-vessel coronary artery disease and 29 had significant multivessel coronary artery disease. The mean percentage of predicted maximal heart rate achieved for all patients with coronary artery disease during supine bicycle exercise was 67.5 ± 2.1%, whereas that of the control groups was 75.5 ± 4.3% (p = NS).

The mean left ventricular end-diastolic pressure at rest for control patients was 8.9 ± 1.9 mm Hg. The left ventricular end-diastolic pressure for patients with coronary artery disease tended to be somewhat higher than that of the control group, at 12.0 ± 1.1 mm Hg (p = NS). The resting ejection fraction by gated blood pool imaging was 66.6 ± 2.7% for the control patients and 62.2 ± 1.6% for patients with coronary artery disease (p = NS).

The sensitivity of the stress myocardial 201TI perfusion scan (analysis of wall 201TI content alone) for coronary artery disease was 89% and the specificity was 70%.

Quantitative Lung 201TI Index and the Extent of Coronary Artery Disease

Figure 1 is an example of a 201TI imaging study that shows increased lung 201TI activity after stress. Figure 2 shows the initial lung 201TI index for control patients, patients with one-vessel coronary artery disease and for patients with two- or three-vessel coronary artery disease. The mean initial lung 201TI index for control patients was 37.6 ± 2.5%. Patients with one-vessel coronary artery disease tended to have a higher mean initial lung 201TI index (45.5 ± 3.6%, p < 0.10), whereas patients with two- or three-vessel coronary artery disease had a significantly elevated mean initial lung 201TI index of 53.5 ± 2.2% (p < 0.001 vs control). Patients with coronary artery disease on propranolol therapy showed no significant difference in mean initial lung 201TI index (52.0 ± 2.5%) compared with patients who had coronary artery disease but were not on propranolol therapy (48.8 ± 2.8%).

An initial lung 201TI index of 54.5% or greater was defined as abnormal (mean for normals plus 2 standard deviations). Three of 10 patients (30%) with one-vessel coronary artery disease and 12 of 29 patients (41%) with two- and three-vessel coronary artery disease had abnormal lung 201TI indexes. Table 2 lists the prevalence of drug usage in the patient groups. There was no significant difference in the prevalence of nitrate, diuretic, digitalis, cigarette, or propranolol usage in patients with coronary artery disease with or without an abnormal lung 201TI index. The mean lung 201TI index was 35.6 ± 2.9% for the five normal smokers and 41.2 ± 3.6% for the five normal non-smokers (p = NS).
The interobserver variance for determining the lung \(^{201}\text{TI}\) index was 2.3% (1 standard deviation) and the intraobserver variance was 1.3% (1 standard deviation).

**Quantitative Lung \(^{201}\text{TI}\) Index Over Time**

As a group, patients with coronary artery disease had a significant decrease in mean lung \(^{201}\text{TI}\) index from the initial to the 2-hour image (\(p < 0.001\)), but the controls did not (fig. 3). Patients with two- or three-vessel coronary artery disease had a 15.9 ± 8.4% mean fall in lung \(^{201}\text{TI}\) index. This was a greater decline in lung activity than the 11.9 ± 7.0% mean fall in patients with one-vessel coronary artery disease (\(p < 0.05\)). The mean lung \(^{201}\text{TI}\) index on the delayed images were not significantly different between the control group (33.8 ± 1.5%), the group with one-vessel coronary artery disease (33.6 ± 1.5%), and the group with two- or three-vessel coronary artery disease (37.1 ± 1.2%).

**Lung \(^{201}\text{TI}\) Index and Resting**

**Left Ventricular Hemodynamic Function**

Though slightly higher, there was no significant difference between the mean resting left ventricular end-diastolic pressure for patients with coronary artery disease and an abnormal initial lung \(^{201}\text{TI}\) index (\(n = 17\), mean 13.0 ± 1.8 mm Hg) and that for patients with coronary artery disease and a normal initial lung \(^{201}\text{TI}\) index (\(n = 22\), mean 10.0 ± 1.1 mm Hg). Patients with coronary artery disease and an abnormal initial lung \(^{201}\text{TI}\) index had a significantly lower resting ejection fraction (mean 58.2 ± 2.5%) compared with patients with coronary artery disease and a normal initial lung \(^{201}\text{TI}\) index (mean 66.1 ± 2.1%) (\(p < 0.02\)) (fig. 4). Linear repression analysis for lung \(^{201}\text{TI}\) index vs rest ejection fraction yielded \(r = 0.40\).

**Quantitative Lung \(^{201}\text{TI}\) Index and \(^{201}\text{TI}\) Myocardial Distribution**

Figure 5 shows the relationship of lung \(^{201}\text{TI}\) index to the number of abnormal myocardial segments on the initial \(^{201}\text{TI}\) myocardial images. Patients with four or five of six abnormal segments had a higher mean lung \(^{201}\text{TI}\) index (mean 59.1 ± 4.9%) than patients with only one or no abnormal segment (mean 44.5 ± 2.0%) (\(p < 0.01\)). Patients with two or three abnormal myocardial segments tended to have lung \(^{201}\text{TI}\) indexes of an intermediate value (mean 50.8 ± 3.3%) (\(p = \text{NS}\) vs other groups).

**Effects of Propranolol Therapy**

Twenty-seven of the 39 patients (69%) with significant coronary artery disease and four of the 10 patients (40%) in the control group were taking propranolol at the time of the study. Table 1 shows that there was no significant difference in the percentage of predicted maximal heart rate achieved with exercise, left ventricular end-diastolic pressure, ejection fraction, lung \(^{201}\text{TI}\) index, or number of abnormal myocardial segments for patients with coronary artery disease taking or not taking propranolol. Table 2
shows no significant difference in the prevalence of propranolol usage in patients with coronary artery disease and a normal lung 201TI index (16 of 24, 67%) compared with patients with coronary artery disease and an abnormal lung 201TI index (11 of 15, 73%). The mean lung 201TI index was 40.5 ± 5.7% for the four normal patients taking propranolol and 37.0 ± 1.6% for the six normal patients not taking propranolol (p = NS).

The sensitivity of the stress myocardial perfusion scan (analysis of wall 201TI content alone) for coronary artery disease was 89% (24 of 27) for the 31 patients taking propranolol and 92% (11 of 12) for the 18 patients not taking propranolol (p = NS). The specificity of the test was 50% (two of four) for the 31 patients taking propranolol and 83% (five of six) for the 18 patients not taking propranolol (p = NS).

Quantitative and Qualitative Lung 201TI

There was a reasonable and significant linear correlation between qualitative and quantitative approaches to assessing lung 201TI uptake (r = 0.72, p < 0.0001). Patients with a lung 201TI index of 54.5% or greater (2 standard deviations above the control mean) had a mean qualitative pulmonary 201TI score of 1.2 ± 0.1% compared with a mean of 0.5 ± 0.4% for patients with a lung 201TI index less than 54.5% (p < 0.0001).

Discussion

Increased lung 201TI activity has been subjectively observed on initial myocardial images after treadmill exercise stress in some patients with coronary artery disease.4,5 We evaluated the significance of a quantitatively and qualitatively assessed increase in lung 201TI activity. The quantitatively derived lung 201TI index correlated well with qualitative evaluation. Calculation of the lung 201TI index was easily performed, requiring very little additional processing time. Identification of the left lung region and the area of the myocardium with the highest count density was not difficult. The possibility of inadvertent inclusion of a vessel in the left lung region of interest was not considered to be important, as Bradley-Moore and associates6 have shown that arterial 201TI concentration decreases rapidly after i.v. injection. Further, the left ventricular cavity showed minimal activity even on the initial images.

Table 1.

<table>
<thead>
<tr>
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<th>Normals (n = 10)</th>
<th>Coronary artery disease</th>
<th>p</th>
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<tbody>
<tr>
<td>Percent predicted maximal heart rate (%)</td>
<td>75.5 ± 4.3</td>
<td>65.3 ± 3.5</td>
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<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>8.9 ± 1.9</td>
<td>12.4 ± 2.4</td>
<td>8.6 ± 2.5</td>
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<td>Ejection fraction (%)</td>
<td>66.6 ± 2.7</td>
<td>61.9 ± 2.0</td>
<td>64.4 ± 3.5</td>
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<td>Lung 201TI index</td>
<td>37.6 ± 2.5</td>
<td>52.1 ± 2.5</td>
<td>48.8 ± 2.8</td>
</tr>
<tr>
<td>Number abnormal myocardial segments (6 possible)</td>
<td>0.50 ± 0.22</td>
<td>1.81 ± 0.30</td>
<td>1.83 ± 0.32</td>
</tr>
</tbody>
</table>

Abbreviation: 201TI = thallium-201.

Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Normals (n = 10)</th>
<th>Coronary artery disease</th>
<th>Abnormal lung 201TI* (n = 15)</th>
<th>p</th>
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<tr>
<td>Nitrites</td>
<td>0</td>
<td>7 (29%)</td>
<td>7 (47%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (50%)</td>
<td>12 (50%)</td>
<td>7 (47%)</td>
<td>NS</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4 (40%)</td>
<td>16 (67%)</td>
<td>11 (73%)</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 80 mg/day</td>
<td>1 (10%)</td>
<td>9 (38%)</td>
<td>6 (40%)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 80 mg/day</td>
<td>3 (30%)</td>
<td>7 (29%)</td>
<td>5 (33%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*An abnormal lung thallium-201 (201TI) index was defined as ≥ 54.5% (mean for normals plus 2 standard deviations). A normal lung thallium-201 index was defined as < 54.5%.

Figure 5. Lung thallium-201 index (lung thallium-201 activity/maximal myocardial thallium-201 activity × 100%) on ordinate plotted against the number of abnormal myocardial segments on the initial myocardial thallium-201 perfusion scan after stress. Lung thallium-201 index values expressed as mean ± SEM.
Supine exercise was chosen for the present study for two reasons. First, supine exercise has been shown to induce elevations of left ventricular end-diastolic pressure more reliably than upright exercise. Second, patients are routinely scanned in the supine position regardless of their exercise position. Thus, by imaging and exercising the patients supine, the possible effect on lung $^{201}$TI activity of changing from the upright exercising position to the supine imaging position was eliminated.

The patients in this study achieved only a mean of 69 ± 20% of their predicted maximal exercise level for age based on heart rate response. However, it has been shown that although peak heart rates achieved during supine exercise are less than those during upright exercise, the cardiac work loads are comparable. The sensitivity of the stress $^{201}$TI images of 89% for the detection of coronary artery disease obtained in this study is consistent with the sensitivities reported in other studies using upright $^{201}$TI stress testing. Propranolol therapy did not appear to be associated with increased lung $^{201}$TI. There was no significant difference in the initial lung $^{201}$TI indexes for patients with coronary artery disease taking propranolol and for those not taking propranolol.

Relationship of Lung $^{201}$TI Index to Extent of Coronary Artery Disease

Increased lung $^{201}$TI activity appears to be related to the angiographically determined extent of coronary artery disease. A control group of patients who had no coronary artery disease had the lowest lung $^{201}$TI indexes immediately after stress, while groups of patients with coronary artery disease had elevations of their mean initial lung $^{201}$TI index in proportion to the number of vessels diseased. Patients with two- or three-vessel coronary artery disease tended to have a higher initial lung $^{201}$TI index than patients with one-vessel coronary artery disease, although this difference was not statistically significant.

Patients with two- or three-vessel coronary artery disease had the greatest decline in lung $^{201}$TI index from initial to 2-hour images compared with patients with one-vessel coronary artery disease and control patients. In fact, the control patients had lung $^{201}$TI indexes that remained unchanged over the 2-hour interval after stress. There was no significant difference in the lung $^{201}$TI indexes between the control group and the groups of patients with coronary artery disease 2 hours after exercise stress. Thus, it appears that both the quantity of lung $^{201}$TI activity on initial images after exercise and the clearance of activity over time correlate with the extent of coronary artery disease.

Relationship of Lung $^{201}$TI Index to Resting Left Ventricular Function

Patients with a lung $^{201}$TI index of 54.5% or greater (control mean plus 2 standard deviations) had significantly lower resting ejection fractions than patients with coronary artery disease and a lung $^{201}$TI index less than 54.5%. Patients with coronary artery disease and an abnormal initial lung $^{201}$TI index tended to have higher resting end-diastolic pressures than those with normal initial lung $^{201}$TI index, but this relationship was not statistically significant. Thus, there is evidence that an increased lung $^{201}$TI index is also related to abnormal left ventricular performance at rest.

Relationship of Lung $^{201}$TI Index to Myocardial Distribution of $^{201}$TI

The magnitude of the elevation in lung $^{201}$TI index on initial images was related to the number of abnormal myocardial segments. Patients with one or no abnormal segments had significantly lower lung $^{201}$TI indexes than patients with four or five abnormal myocardial segments. This observation suggests that the extent of myocardium jeopardized by diseased coronary arteries is an important determinant of stress-induced increases in lung $^{201}$TI activity. Myocardial distribution and lung $^{201}$TI activity are not precisely related for the following reasons. A defect in myocardial distribution of $^{201}$TI does not necessarily imply functional ischemia. Gewirtz and associates showed that transient defects in $^{201}$TI distribution occur after rest injection in the presence of normal segmental wall motion; this observation suggests that relative underperfusion can exist in the absence of functional ischemia. Accordingly, in addition to the extent of disease and decreased blood supply to the myocardium, increased demand is usually necessary to induce functional ischemia. The level of left ventricular stress should be another factor that affects the appearance of lung $^{201}$TI activity. On the other hand, diffuse subendocardial ischemia may occur in the presence of three-vessel coronary artery disease and may not show a segmental defect on a stress $^{201}$TI image, but may induce elevated lung $^{201}$TI activity.

Postulated Mechanism of Increased Lung $^{201}$TI Activity

In patients with significant coronary artery disease, exercise stress or atrial pacing frequently increases left ventricular end-diastolic pressure, increases left ventricular diastolic stiffness, impairs left ventricular relaxation and limits cardiac output. Accordingly, elevations of left ventricular end-diastolic pressure secondary to stress-induced ischemia may result in elevations of pulmonary venous pressure. Bingham et al., using an open-chest dog model, showed that increased extraction of $^{201}$TI in the lung can result from increases in left atrial pressure. Boucher and associates showed the relationship between exercise-induced increase in left ventricular end-diastolic pressure and increased lung $^{201}$TI index in patients undergoing cardiac catheterization. The elevation in pulmonary $^{201}$TI content is probably not due to blood pool activity; the extraction has been shown to be efficient, with approximately 85% of the administered $^{201}$TI extracted on each pass through the circulation, and no activity was evident in the left ventricular cavity.
In conclusion, lung 201TI activity can be easily evaluated quantitatively (normalized to peak myocardial activity) or qualitatively. Increased lung activity on images obtained immediately after stress correlates with increasing extent of coronary artery disease, increased number of perfusion defects on myocardial 201TI scan, and decreased left ventricular ejection fraction at rest. An abnormal lung 201TI index is very specific for coronary artery disease and when present, increases the certainty of an abnormal 201TI stress test.

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