# Quantitation of Postexercise Lung Thallium-201 Uptake During Single Photon Emission Computed Tomography

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To test the hypothesis that analysis of lung thallium uptake measured during single photon emission computed tomography (SPECT) yields supplementary clinical information as reported for planar imaging, quantitative analysis of lung thallium uptake following maximal exercise was performed in 40 clinically normal subjects (Group 1) and 15 angiographically normal subjects (Group 2). Lung thallium uptake was measured from anterior projection images using a ratio of heart-to-lung activities. Seventy subjects with coronary artery disease (CAD) (Group 3) determined by angiography (≥70% luminal stenosis) underwent thallium perfusion SPECT. Thirty-nine percent of these subjects had multivessel and 61% had single vessel CAD. Lung thallium uptake was elevated in 47 of 70 (67%) Group 3 subjects. Group 3 subjects with elevated lung thallium uptake did not differ from Group 3 subjects with normal lung thallium uptake with respect to extent or distribution of coronary artery disease, left ventricular function, or severity of myocardial ischemia as determined by exercise and redistribution thallium SPECT. Thus, the measurement of thallium lung uptake from anterior projection images obtained during SPECT frequently identifies patients with CAD, but it may not provide supplementary information regarding the extent of myocardial ischemia or ventricular dysfunction.

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Exercise and redistribution myocardial perfusion imaging with thallium-201 ($^{201}Tl$) is a widely utilized technique for the noninvasive detection of coronary artery stenoses in patients with chest pain and suspected coronary artery disease (CAD). Utilizing planar imaging techniques, sensitivities, and specificities ranging from 80% to 90% have been reported for the correct identification of patients (*1–3*). Attempts at using planar imaging to identify the total number of individually stenosed coronary arteries have reported less favorable results, i.e., analysis of planar images alone frequently underestimates the extent of CAD present (*4*). As a result, alternative noninvasive markers that might indicate extensive coronary disease have been sought. The presence of increased pulmonary thallium activity immediately postexercise in patients with extensive CAD and/or left ventricular dysfunction was reported by Boucher et al. (*5*). Increased pulmonary thallium activity has been associated with more extensive coronary disease in further studies at their institution (*6–12*) and others (*13–16*). A quantitative assessment of lung thallium activity expressed as the ratio of pulmonary to myocardial counts has been proposed (*7*) and utilized as a marker to identify extensive coronary disease (*9,11,14,15*). Recently, however, the inability of this quantitative method of assessing lung thallium activity to identify patients with extensive CAD has been reported (*14*). Further investigation in this area appears warranted.

Advances in nuclear camera and computer technology have permitted tomographic imaging of the myocardium. As compared to planar imaging techniques, myocardial perfusion imaging with thallium and single photon emission computed tomography (SPECT) has been reported to improve the accurate identification of patients with coronary artery disease (*17–20*) and the correct determination of the number of stenosed coro-

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nary arteries (*21–23*). SPECT imaging involves the brief acquisition of a series of planar projection images. Whether the measurement of lung thallium uptake from the anterior planar projection image obtained during SPECT imaging is feasible is unknown. Furthermore, whether the quantitative measurement of lung thallium activity provides supplemental diagnostic information in patients undergoing SPECT imaging is unknown. To test the hypothesis that analysis of pulmonary thallium uptake measured from the anterior projection image obtained during SPECT would yield results similar to those reported for planar imaging techniques, we performed quantitative analyses of lung thallium uptake using the anterior projection images obtained during SPECT in normal subjects and derived the normal range of values for this measurement. We then examined the utility of the measurement of lung uptake of thallium in a population of patients with CAD documented angiographically undergoing perfusion imaging with thallium SPECT.

## MATERIALS AND METHODS

### Study Population

One hundred and forty subjects form the basis of this report. Forty consecutive subjects (Group 1) with a low probability (<5%) of CAD by Bayesian analysis of age, sex, and treadmill results were prospectively studied (*24*). These subjects did not undergo cardiac catheterization. Their mean age was 40 ± 11 yr, and 50% of them were men. Fifteen consecutive subjects (Group 2) with chest pain syndromes but normal coronary arteriography and left ventriculography were prospectively recruited from the catheterization laboratory to undergo thallium imaging. Their mean age was 52 ± 11 yr, and 27% were men. Group 3 consisted of 70 consecutive subjects with chest pain syndromes and coronary arteriographic evidence of coronary stenosis ≥70% luminal narrowing scheduled to undergo perfusion imaging with thallium SPECT before or after coronary arteriography for evaluation of suspected ischemic syndromes. Data on these patients were accumulated prospectively. Their mean age was 54 ± 8 yr, and 90% were men. Fifteen consecutive unselected subjects (Group 4), scheduled to undergo maximal exercise thallium SPECT imaging for chest pain syndromes, also were prospectively studied as described below. These subjects did not undergo cardiac catheterization. All subjects provided informed consent for the clinically indicated study.

### Cardiac Catheterization Studies

Group 2 and 3 subjects underwent standard left heart catheterization procedures. Left ventricular end-diastolic pressure was measured at rest before contrast injection for 10 beats and averaged. Left ventriculography was performed before coronary arteriography in the 30° right anterior oblique (RAO) projection. Left ventricular ejection fraction was calculated by the standard area-length method. Selective coronary arteriography was performed using either the Sones or Judkins techniques using multiple projections with angulated views. The arteriographic studies were analyzed by two experienced angiographers without knowledge of the scintigraphic results. Significant CAD was defined as at least one vessel with a 70% or greater luminal narrowing.

### Exercise Testing

Symptom-limited maximal treadmill exercise testing was performed in all subjects according to the Bruce protocol. Electrocardiographic leads II, aVF, and V5 were monitored throughout exercise and 12-lead electrocardiograms were recorded at the completion of each stage of stress and recovery. Blood pressure was measured by cuff sphygmomanometry at similar intervals. The predicted maximal heart rate was calculated as 220 minus age in years. The pressure rate product was calculated as the product of the peak systolic blood pressure and the peak heart rate. ST segment depression indicative of myocardial ischemia was considered present if there was ≥1.0mm ST segment depression for at least 80 msec in a lead in which the ST segment was isoelectric at rest. Antianginal medications were not discontinued prior to exercise testing.

### Scintigraphic Imaging

Tomographic imaging was performed within 2 mo of cardiac catheterization in all Group 2 and 3 subjects. Groups 1–3 were imaged according to the following protocol. One minute before termination of exercise, 2.5–3.2 mCi of thallium-201 ($^{201}Tl$) were injected intravenously. Patients were monitored for 5 min post-exercise. Tomographic imaging was then initiated using a rotating wide field-of-view gamma camera (Technicare Omega 500 Sentinel or Gemini 700, Solon, OH) equipped with a low-energy, high resolution parallel hole collimator interfaced to a dedicated nuclear medicine computer system (Technicare 560, Solon, OH). Image sets were obtained at 60 equally spaced positions, approximately an anterior 180° orbit from 45° RAO to 45° LPO. Each projection image was acquired for 20 sec. Energy discrimination was provided by dual 20-percent windows centered over the 80 and 167 keV photopeaks of thallium. Images were acquired as 64 × 64 byte matrices. Projection images were corrected on-line for energy, linearity, and uniformity using a 400-million count flood correction matrix. In all patients, redistribution images were obtained 4 hr post-exercise.

Group 4 patients were imaged using a modified protocol so that an early anterior planar image (pre-SPECT) could be obtained and compared to the corresponding SPECT projection image. Patients were monitored for only 2 min following the completion of exercise. A 300,000 count planar image in the anterior position was then obtained. Standard SPECT imaging as described above was then begun.

### Analysis of Pulmonary Thallium Uptake

In all subjects, the unprocessed projection image acquired as part of the postexercise SPECT projection set that corresponded to the anterior position (number 16 of 60) was identified. This projection image was selected because the ability to spatially distinguish myocardial and pulmonary regions of interest (ROIs) was greatest with this view and for comparison with previous published studies using anterior planar images. In Group 4 subjects, the 300,000 count anterior planar image (pre-SPECT) also was analyzed. The pulmonary thallium activity was measured using a ROI interest method as previously described (*9*). Separate ROIs were defined for those areas of the left lung and myocardium that demonstrated the greatest activities. The lung ROI was constructed so that it was separated from the anterolateral myocardial wall by at least 3 pixels and included 55 to 80 pixels. The myocardial ROI was placed over the myocardial wall with the greatest count density and included 6 to 10 pixels. The lung/heart ratio was the mean counts/pixel in the lung ROI divided by that in the myocardial ROI (*9*).

Images were analyzed by an observer blinded to the clinical data. One observer analyzed all studies on two separate occasions at least 2 wk apart to determine intraobserver variability. Interobserver variability was determined by a second observer blinded to the clinical data. This observer determined lung/heart ratios on 20 Group 1 and 40 Group 3 patients.

#### Thallium Tomography Analysis

Transaxial sections including the entire cardiac volume were reconstructed using filtered back projection. Vertical long-axis and short-axis sections were extracted from the transaxial reconstructed volume. The vertical long-axis section and short-axis sections corresponding to the apical, mid, and basal portion of the left ventricle were analyzed using circumferential profile activity curves. Activity curves were generated from radial searches for maximal myocardial thallium activity from the ventricular center at six-degree intervals. Each of the three short-axis sections were divided into eight equal regions and, including the apical portion of the vertical long-axis section, 25 regions were analyzed. Data from subjects in Group 3 were compared to a gender-matched data set derived from Group 1 subjects. Myocardial regions on the immediate postexercise images from Group 3 subjects that demonstrated activities <2.5 s.d. below the mean value of group 1 subjects were considered abnormal, and the number of abnormal regions was determined. Abnormal myocardial regions on the immediate images were considered ischemic when redistribution images demonstrated slow thallium clearance (>2.5 s.d. from Group 1 data). The number of ischemic segments was determined.

#### Statistical Analysis

Reported are values expressed as a mean ± 1 s.d. Comparisons of means were made with either the Student's test or one-way analysis of variance using Newman-Keul's multiple comparison test. Frequency data were compared using the Fisher's test. Interobserver and intraobserver variability, the relationships between clinical variables and lung/heart ratios, and the relationship between the lung/heart ratio measurements (pre-SPECT and SPECT) in Group 4 subjects were examined using linear regression analysis.

## RESULTS

### Angiographic Findings

The 15 subjects in Group 2 had normal left ventricular regional wall motion and systolic function (mean ejection fraction 73 ± 5%, range 53%–90%). All subjects had either normal arteriographic results or insignificant CAD (≤25% luminal stenosis). Of the 70 subjects in Group 3, 43 subjects (61%) had single vessel disease, and 27 (39%) had multivessel CAD. Significant stenosis of the left anterior descending was present in 39 subjects (56%). The mean left ventricular ejection fraction (LVEF) for Group 3 was 63.2% ± 11.3% (range 36%–84%). Nine (13%) subjects in Group 3 had a resting LVEF < 50%.

### Exercise Test Results

The results of the maximal exercise tests are reported in Table 1. Compared to Groups 1 or 2 patients, Group 3 patients exercised for a shorter duration, to a lower peak heart rate, percent of predicted maximal heart rate, and pressure-rate product. Group 3 subjects had a greater frequency of chest pain and electrocardiographic changes as compared to Group 1, but not Group 2, subjects.

### Lung/Heart Ratio Analysis

The lung/heart ratio was a highly reproducible measurement both between observers ($R = 0.94$, $p < 0.001$) and for the same observer on separate occasions ($R = 0.95$, $p < 0.001$). There was no significant difference in the mean lung/heart ratios of Group 1 and 2 subjects (Fig. 1). Furthermore, there was no significant difference in the mean lung/heart ratios of Group 2 subjects with and without ischemic electrocardiographic responses. Therefore, the data from Group 1 and 2 subjects were combined. For these 55 subjects, the mean lung/heart ratio was 0.24 ± 0.04, and the 95% upper confidence limit for normals was 0.33 (Fig. 1). There was no significant relationship between the peak heart rate and the lung/heart ratios in these subjects ($R = 0.17$, p = NS).

Utilizing the normal range of lung/heart ratios derived from the 55 normal subjects, 47 (67%) subjects in Group 3 demonstrated elevated ratios. When the 47 Group 3 subjects with elevated ratios were compared to the 23 Group 3 subjects with normal ratios, there were no significant differences with regards to clinical, exercise test, angiographic or scintigraphic variables (Table 2). Group 3 subjects with single vessel disease had the same mean lung/heart ratio as subjects with

**TABLE 1**
**Exercise Test Results in Groups 1–3**

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Peak HR (bpm) | 175 ± 12* | 144 ± 19* | 131 ± 20 |
| % MPHR | 96 ± 5* | 86 ± 9* | 79 ± 12 |
| PRP (× 10-2) | 320 ± 51* | 273 ± 62* | 222 ± 44 |
| Exercise time (sec) | 649 ± 125* | 497 ± 125* | 419 ± 98 |
| Chest pain | 0* | 4 (27%) | 25 (36%) |
| Ischemic response | 0* | 5 (33%) | 28 (40%) |

* $p < 0.01$ compared to Group 3 subjects
Data are mean ± s.d.
BPM = beat/minute; HR = heart rate; %MPHR = % maximal predicted heart rate; PRP = pressure-rate product; SEC = seconds.

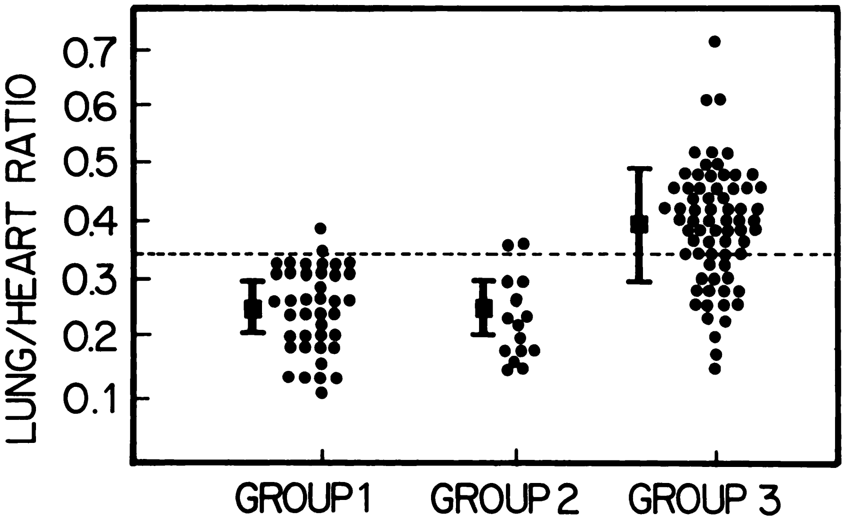



**FIGURE 1**
Individual lung/heart activity ratios for 40 clinically normal subjects (Group 1), 15 angiographically normal subjects (Group 2), and 70 subjects with CAD disease determined by angiography (Group 3). The dashed horizontal line represents a lung/heart activity ratio of 0.33 (mean + 2 s.d. of Groups 1 and 2). The vertical bars represent the mean ± s.d. for each group. The mean values of Group 1 and 2 subjects were significantly lower than Group 3 subjects ($p < 0.001$).

multivessel disease (0.37 ± 0.09 single vessel disease versus 0.37 ± 0.09 in multivessel disease, p = NS). While there was a weak correlation between peak heart rate and the lung/heart ratio in Group 3 subjects (R = 0.26, p = 0.02), there was no significant relationship between the measured lung/heart ratios and the extent of CAD, resting LVEF, resting left ventricular end-diastolic pressure, exercise duration, or the time of initiating SPECT imaging following exercise.

**TABLE 2**
Determinants of Elevated Lung/Heart (L/H) Thallium Ratios in Subjects with Coronary Artery Disease

| | Elevated L/H (n = 47) | Normal L/H (n = 23) | p |
|---|---|---|---|
| Age (yr) | 54.4 ± 8.3 | 53.4 ± 8.9 | NS |
| Men | 45 (96%) | 18 (78%) | NS |
| Prior infarction | 30 (64%) | 12 (52%) | NS |
| Hypertension | 22 (47%) | 10 (43%) | NS |
| Beta-blocker | 19 (40%) | 11 (48%) | NS |
| Treadmill angina | 14 (30%) | 11 (48%) | NS |
| ST depression | 19 (40%) | 9 (39%) | NS |
| Peak heart rate | 130 ± 21 | 134 ± 18 | NS |
| %MPHR | 78 ± 12 | 81 ± 11 | NS |
| PRP (×10-2) | 216 ± 44 | 236 ± 42 | NS |
| Exercise time (sec) | 418 ± 122 | 418 ± 133 | NS |
| $^{201}$Tl segments abnormal | 7.6 ± 4.8 | 6.6 ± 4.5 | NS |
| $^{201}$Tl segments ischemic | 3.3 ± 3.4 | 2.3 ± 3.3 | NS |
| Single vessel CAD | 29 (62%) | 14 (61%) | NS |
| Multivessel CAD | 18 (38%) | 9 (39%) | NS |
| LAD disease | 27 (59%) | 12 (52%) | NS |
| Most severe stenosis | 89 ± 12% | 93 ± 10% | NS |
| LVEF (%) | 61 ± 12 | 64 ± 11 | NS |
| LVEDP (mmHg) | 15 ± 6 | 13 ± 5 | NS |

Data are mean ± s.d.
CAD=coronary artery disease; LAD=left anterior descending artery; LVEDP=left ventricular end-diastolic pressure; LVEF=left ventricular ejection fraction; %MPHR=% maximal predicted heart rate; NS=nonsignificant; PRP=pressure-rate product; T1=thallium.

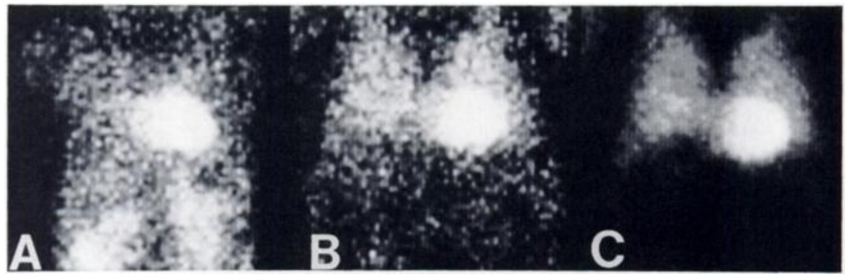
### Pre-SPECT Versus SPECT Derived Measurements

The mean time from thallium injection to the commencement of SPECT imaging was 718 + 280 sec in Group 1 subjects, 693 ± 144 sec in Group 2 subjects, and 688 ± 104 sec in Group 3 subjects (p = NS). Therefore, the anterior projection image used for analysis (number 16 of 60 projection images) was obtained ~17 min following the injection of thallium. In order to investigate the effect of the time of acquisition of the anterior image on the lung/heart ratio, Group 4 patients were imaged twice in the anterior position, once using planar imaging for 300,000 counts at a mean time of 5.5 min postinjection (pre-SPECT), and again as part of the SPECT acquisition protocol at a mean time of 17 min following the injection of thallium (Fig. 2). The measured lung/heart ratios from the anterior SPECT projection image correlated well with the values measured on the pre-SPECT planar images (R = 0.96, $p < 0.0001$). For the 15 Group 4 subjects, the mean lung/heart ratio assessed from the anterior SPECT projections was ~10% lower than that for the pre-SPECT planar images (0.28 ± 0.07 SPECT versus 0.31 ± 0.09 for pre-SPECT, p = NS). The subjects with the highest lung/heart ratios on the pre-SPECT images tended to show the greatest percent decrease in the lung/heart ratio on the later SPECT derived measurements (Fig. 3).

## DISCUSSION

The results of this investigation demonstrate that the quantitative assessment of postexercise pulmonary thallium activity from anterior projection images acquired as part of SPECT imaging is feasible and reproducible. These data indicate that among clinically or angiographically normal subjects, SPECT derived measurements of pulmonary thallium activity are typically one-

**FIGURE 2**
(A) Anterior projection image from a healthy volunteer demonstrating lung and myocardial ROIs. (B) Anterior projection image acquired as part of the tomographic projection image set from a patient with CAD, demonstrating elevated postexercise lung thallium uptake. (C) Anterior planar image acquired for 300,000 counts before tomographic imaging from the same patient as in B.




third or less than that of the myocardium. Furthermore, more than two-thirds of subjects with angiographically proven CAD demonstrate elevated pulmonary thallium activity, suggesting the presence of exercise-related left ventricular dysfunction and pulmonary venous hypertension. Although pulmonary thallium activity was frequently elevated in subjects with CAD, no relationship between the presence of elevated pulmonary thallium activity and extensive CAD or resting left ventricular dysfunction could be demonstrated.

Tomographic imaging is emerging as the preferred imaging technique, particularly with increasing demands for accurate, noninvasive localization of individual coronary stenoses before and after catheter or surgical revascularization procedures. In order to examine the feasibility and utility of incorporating this measurement with standard SPECT imaging protocols, we analyzed lung thallium uptake using the anterior SPECT projection image. Several important differences between conventional anterior planar images and SPECT anterior projection images exist. These differences could affect the measurement of lung thallium uptake. The SPECT projection images were acquired for only 20 sec, during which typically only 40,000–50,000 counts were obtained. The initiation of tomographic acquisitions requires more computer interaction and attention to patient and detector positioning. Therefore, tomographic acquisitions frequently cannot be started as soon as planar studies. Furthermore, if one begins with the 45° RAO projection, the projection image corresponding to the anterior position is obtained ~5 min following the start of SPECT imaging. Another difference in the imaging techniques is that during conventional planar imaging the detector is placed as close as possible to the subject's chest. During SPECT imaging using a circular orbit, the detector is frequently several centimeters from the chest wall while in the anterior position. This varies to some extent with the subject's body habitus. A final difference between the two imaging techniques is that during planar imaging the patients keep their arms at their sides. During SPECT imaging, either the injection arm or both arms are kept beside the head. Greater tissue cross-talk from arm and pectoral muscle activity would be anticipated during standard planar imaging due to their closer proximity to the field of view and the heart in the arms down position.

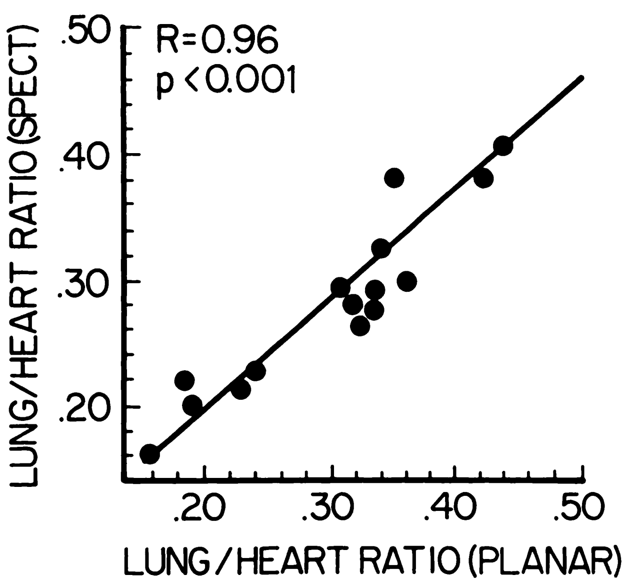



**FIGURE 3**
Correlation between the lung/heart activity ratio determined from an early anterior planar image (PLANAR) and the anterior projection image acquired during SPECT in 15 consecutive subjects with chest pain syndromes referred for thallium perfusion imaging. The equation was SPECT lung/heart activity = 0.047 + 0.749 (PLANAR lung/heart activity).

We studied a larger population of clinically and angiographically normal subjects than all but one prior study (*9*) in order to assess the range of normal lung/heart ratios during SPECT acquisitions. Despite the greater age and the presence of chest pain syndromes in Group 2 as compared to Group 1 subjects, measurements of lung thallium uptake did not differ between angiographically and clinically normal subjects (Fig. 2). This observation has previously been reported by Brown et al. (*9*). We, therefore, combined the data from Groups 1 and 2, as others have done (*9*), to derive the 95% upper confidence limit for normal lung thallium uptake. The upper limit of normal lung/heart ratios determined during SPECT acquisitions (0.33) differs substantially from previous reports (*7,9,11,15*). These studies have found lung/heart ratios of ~0.50 as the 95% upper confidence limit. However, our value of 0.33 is very close to the upper limit of 0.30 reported by Levy et al. (*14*). The variability of normal values in these studies is likely due to characteristics of the normal study groups and the particular imaging and analysis protocols used. The time of acquisition of the anterior image relative to the injection of $^{201}$Tl would appear to be one of the most important variables in determining these differences. Rothendler et al. reported that the mean lung/heart ratio for 18 normal subjects decreased from 0.41 at 2 min postexercise to 0.36 at 18 min postexercise (*25*). We prospectively performed both early planar imaging (pre-SPECT) and standard SPECT imaging on a sub-group of subjects. In these subjects, over the 11–12 min between the acquisition of the pre-SPECT image and the anterior SPECT projection image, there was a small decrease in the mean lung/heart ratio. Extrapolated to the normal subjects (Groups 1 and 2), the imaging time alone does not explain the differences between the normal range in lung/heart ratios reported here and in other studies. This is supported by fact that studies reporting the lowest (*14*) and highest (*15*) normal ranges for lung/heart ratios both began acquisition of the anterior planar images within 6 to 7 min following injection of thallium. The great variability between reports highlights the need for each laboratory to establish independently normal limits for thallium lung uptake.

We found that analysis of lung thallium activity identified 67% of patients with CAD as abnormal. This compares in previous studies in which 38%–56% of patients with CAD had abnormal ratios (*7,9,14,15*). However, we were unable to discern any important clinical differences when subjects with CAD and elevated lung/heart ratios were compared to those with normal KAHN lung/heart ratios (Table 2). Specifically, the presence of an elevated lung/heart ratio in this study failed to identify patients with multivessel disease, depressed resting left ventricular function, or a greater extent of ischemia as assessed by quantitative thallium tomography. Although our observations differ from those reported by Boucher et al. (*5,7,9*), they are similar to those reported by Levy et al. (*14*). Among 92 patients with CAD, Levy et al. found elevated lung/heart ratios in 26% of subjects with single vessel disease and 36% of those with multivessel disease, not a significant difference (*14*). A possible limitation of the study population reported here is the relatively high percentage of patients (61%) with single vessel CAD. The relatively low lung/heart ratio and the lack of correlation between the ratio and the degree of CAD may be partially attributable to this fact. A further limitation of the study is that patients were exercised on anti-anginal medications often contributing to the lower peak heart rate achieved during stress testing in CAD patients. Another limitation of the current study is that only resting left ventricular function was assessed. We are unable to determine whether exercise induced left ventricular dysfunction and elevated lung thallium activity are related.

Pulmonary clearance of thallium is faster in patients with CAD and elevated levels (*14*). The later acquisition times during SPECT imaging may lead to an underestimation of pulmonary thallium activity in subjects with the highest levels. Therefore, some subjects with early abnormalities of lung thallium uptake may be classified as normal during SPECT imaging. An alternative imaging protocol such as was used in Group 4 subjects, where an early anterior image (pre-SPECT) is obtained before SPECT imaging is begun, requires further attention and may yield greater supplementary information regarding extensive myocardial ischemia. However, such an imaging protocol is more demanding and time consuming, and any supplemental information derived from an early planar image preceding SPECT imaging should not interfere with the prompt initiation of SPECT imaging.

## CONCLUSION

In many laboratories analysis of pulmonary thallium uptake during planar imaging has provided supplementary information regarding the presence of extensive CAD or impaired ventricular dysfunction. Quantitative analysis of pulmonary thallium activity from anterior projection images acquired during SPECT imaging is feasible and produces reproducible results despite lower count densities in the images analyzed. Normal limits may vary substantially between laboratories and must be considered in the interpretation of individual studies. In our experience, the observation of an elevated lung/heart ratio is common among subjects with CAD. However, the use of this index to identify highrisk patients undergoing SPECT thallium imaging will require further investigation before wider application can be recommended.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