Significance of Increased Lung Thallium Uptake During Adenosine Thallium-201 Scintigraphy

Shigeyuki Nishimura, John J. Mahmarian, and Mario S. Verani

Section of Cardiology, Department of Internal Medicine, Baylor College of Medicine and The Methodist Hospital, Houston, Texas

To determine the relationship of lung ^{201}Tl activity during adenosine scintigraphy to the presence and extent of coronary artery disease, we investigated 132 subjects comprising 4 groups: 36 normal volunteers, 19 patients with angiographically normal coronaries, 29 patients with single-vessel (>50% luminal stenosis) and 48 patients with multivessel coronary artery disease. Lung activity was quantified relative to maximal myocardial activity in both an early anterior planar image (pretomography) and the unprocessed tomographic image in the anterior projection. A good correlation was found for the lung-to-heart ratio assessed by planar and tomographic imaging ($r = 0.83$, $p < 0.0001$), but the ratio was higher with planar imaging. The lung-to-heart ratio in the planar images was significantly higher in patients with multivessel disease compared to those with single-vessel disease ($p < 0.05$) or volunteers and subjects with normal coronary arteries combined ($p < 0.001$). A lung-to-heart ratio of >0.45 in the planar images (upper 95% confidence limit for the normal subjects) was found in 6 (21%) single-vessel disease and 17 (35%) multivessel disease patients. Patients with elevated lung thallium activity during adenosine infusion had more hypoperfused myocardial segments ($p = 0.007$), more segments with redistribution ($p = 0.04$) and larger initial perfusion defect size ($p = 0.04$) than those with normal lung activity. Thus, evaluation of lung activity during adenosine thallium scintigraphy provides supplementary information regarding the severity of coronary artery disease and extent of myocardial hypoperfusion.

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Increased lung ^{201}Tl activity immediately after exercise reflects transient left ventricular dysfunction in patients with extensive coronary artery disease (CAD) (*1–6*), and is a strong predictor of future cardiac events (*7*). Dipyridamole, by increasing the endogenous adenosine level, indirectly induces pharmacologic coronary vasodilation and is an alternative method to exercise stress for detecting coronary stenoses with ^{201}Tl scintigraphy (*8–12*). As is true with exercise, increased lung ^{201}Tl activity after dipyridamole infusion correlates well with the presence of CAD (*13*) and is associated with thallium redistribution and left ventricular dilatation (*14,15*). Although lung ^{201}Tl activity has been traditionally assessed by planar images obtained in the anterior projection, a recent report has demonstrated that similar information may be obtained by quantitative analysis of lung activity from the anterior projection in images acquired during exercise single-photon emission computed tomography (SPECT) (*16*).

Strauss and Pitt (*17*) and Leppo et al. (*18*) have used ethyl adenosine and adenosine, respectively, in combination with ^{201}Tl to create or accentuate myocardial blood flow heterogeneity in dogs with coronary ligatures. Following these earlier experimental studies, we have recently proposed using an intravenous infusion of adenosine in conjunction with SPECT for the noninvasive diagnosis of patients with CAD (*19*). Thus, the purpose of this study was to determine the clinical significance of ^{201}Tl lung activity quantified from planar (immediately pre-SPECT) and SPECT images after administration of adenosine.

METHODS

Study Population

The study population consisted of 132 subjects who underwent adenosine ^{201}Tl SPECT. Subjects were excluded from study entry according to previously reported criteria (*19*). None of the subjects had previous coronary artery bypass surgery or percutaneous coronary angioplasty, and none had primary valvular disease or cardiomyopathy. Thirty-six subjects (30 men, 6 women, mean age (mean ± standard deviation) 30± 5 yr) were normal volunteers and all had a low probability (<2%) of CAD by Bayesian analysis and did not undergo coronary angiography.

Ninety-six of the subjects were patients (64 men and 32 women, mean age 64± 13 yr, range 37 to 87 yr) who had coronary arteriography in close temporal relation (<3 mo) to the adenosine SPECT. Adenosine scintigraphy was performed in these subjects for the following reasons: assessment of chest pain (56%) or screening for CAD (19%) in patients who were unable to perform an exercise test because of associated peripheral vascular or neurological disease; risk stratification late after myocardial infarction (14%); and evaluation of shortness of breath (11%).

Fifty-two of the 96 patients who had angiography (54%) lacked historical and electrocardiographic (pathologic Q-waves in appropriate leads) evidence of prior myocardial infarction, whereas 29 patients (30%) had infarction by both criteria. The latter patients underwent the test in stable condition at least one month after

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For reprints contact: Mario S. Verani, MD, FACC, FACP, Professor of Medicine, Baylor College of Medicine, Director, Nuclear Cardiology, The Methodist Hospital, Section of Cardiology, 6535 Fannin, F-905, Houston, TX 77030.

myocardial infarction. In 15 patients (18%), infarction was questionable because they met either historical (n = 10) or electrocardiographic (n = 5) criteria, but not both.

Antianginal medications were being used by 73 of the 96 patients (76%). Thirty patients (31%) were taking a calcium channel blocker, a beta-adrenergic blocker or an oral nitrate preparation, and 43 (45%) were on two or more of these antianginal agents. No medications were taken on the morning of the test.

Study Protocol

The study protocol was approved by our Institutional Review Boards for Human Research and all patients gave informed consent.

All studies were performed after approximately 12 hr of fasting. Patients who were taking dipyridamole had this drug discontinued at least 12 hr preceding the test. Adenosine (Adenoscan®) was supplied by Medco Research Inc. (Los Angeles, CA) as a sterile, isotonic aqueous solution at a concentration of 6 mg/ml (2 ml vials) and was infused using a previously reported method (*19*). In short, adenosine was infused into a proximal antecubital vein at a rate of 140 μg/kg/min for a total of 6 min using a volumetric pump infusion system. Thallium-201 (mean ± s.d. = 3.10± 0.14 mCi) was injected into a contralateral vein and flushed 3 min prior to discontinuing the adenosine infusion.

The electrocardiogram was constantly monitored throughout the study using three standard leads. Vital signs and a 12-lead electrocardiogram were recorded prior to, at every minute during and for the first 5 min after the adenosine infusion.

Analysis of Electrocardiograms

The electrocardiograms were interpreted as abnormal if there was >1 mm flat or downsloping ST-segment depression or a 1.5-mm upsloping ST segment depression 80 msec after the J point. In patients with baseline ST-segment or other abnormalities (pacemaker rhythm in two and left bundle branch block in three patients), the electrocardiograms were considered nondiagnostic.

Thallium-201 Myocardial Imaging

In all subjects, a planar anterior image was acquired immediately after completing the adenosine infusion on a 128 × 128 matrix, for 5 min, and followed by SPECT acquisition. The unprocessed anterior projection SPECT image was selected for analysis of heart-to-lung thallium activity because myocardial and lung regions of interest (ROIs) can be best standardized in this view (*16*). The average time interval between the anterior planar image and the corresponding SPECT anterior projection image was 16 min.

Computer Quantification of SPECT

Tomographic imaging was performed with a large field of view, single crystal, rotating gamma camera (ADAC ARC 3000–3300) equipped with a high-resolution, parallel-hole collimator with a septal length and thickness of 33 and 0.15 mm, respectively. Imaging commenced 5 min after completion of the adenosine infusion and was repeated 4 hr later. Image acquisition and processing were done using previously reported methods (*12,19–21*).

Visual assessment of the tomographic slices was performed as previously reported from our laboratory (*12,19–21*). The left ventricle was divided into myocardial segments as follows: septal, anterior, inferior, posterior and lateral segments. An image was considered abnormal if there was a decrease of ^{201}Tl uptake in any segment. Perfusion defects were graded on a four-point scale: 0 (severely diminished uptake), 1 (moderately diminished uptake), 2 (mildly diminished uptake) and 3 (normal uptake). The presence or absence of redistribution was noted. Tomographic images were interpreted by consensus of two investigators who had no knowledge of the coronary arteriographic findings.

Thallium-201 tomography was quantified using a computerized two-dimensional polar map of the three-dimensional myocardial radionuclide activity. This method has been previously described in detail (*12,19–21*). The map of each subject was statistically compared with an adenosine normal data bank previously generated in our laboratory. The patient's polar map was assessed using previously reported criteria (*19*).

We have recently analyzed the intra- and interobserver reproducibility of SPECT for quantifying perfusion defects and visually detecting the presence and site of scintigraphic reversibility (*20*). The intra- and interobserver agreements for visually identifying patients with reversible perfusion defects by scintigraphy were 88% and 80%, respectively. The intra- and interobserver agreements for assessing the coronary artery corresponding to each perfusion defect were 94% and 90%, respectively. Linear regression analysis of intra- and interobserver comparisons of quantified defect sizes yielded correlation coefficients of 0.95 ($p < 0.0001$) in both cases.

Quantitative Analysis of Heart and Lung ^{201}Tl Activity

The myocardial and lung ^{201}Tl activities on both planar and tomographic anterior images were determined using ROIs measuring 5.0 × 5.0 (planar) and 2.5 × 2.5 pixels (SPECT) in size. The ROIs were placed on three myocardial segments (anterolateral, apical, and inferior) and in the medial aspect of the left upper lung field, approximately 5 (planar) and 2.5 (SPECT) pixels superior to the anterolateral myocardial segment and 5 (planar) and 2.5 (SPECT) pixels lateral to the mediastinal photon deficient area. The lung-to-heart ^{201}Tl activity ratio was calculated as the mean counts per pixel in the lung region divided by the highest mean counts in the myocardial regions.

Images were analyzed by an observer blinded to the clinical data. To determine the intraobserver reproducibility of the heart and lung thallium activities, one observer analyzed all studies on two separate occasions at least 1 mo apart. Interobserver variability was determined by having the data processed by a second observer, blinded to the clinical data, in 30 randomly chosen subjects (8 subjects without CAD and 22 with single- or multivessel disease).

Coronary Angiography

Selective coronary cineangiography was performed in multiple views using standard techniques. Coronary stenoses in the three major coronary arteries were measured with calipers by an experienced angiographer and expressed as percent luminal diameter stenosis. Stenosis of the left main trunk was considered as two-vessel disease involving the left anterior descending and left circumflex arteries. Stenosis severity was graded in the following manner: normal (<25%), insignificant (26%–50%), moderate (51%–69%) and severe (>70%). Contrast left ventriculography was performed in the 30° right anterior oblique projection. Left ventricular ejection fraction (LVEF) was calculated by the area-length method.

We have previously reported our interobserver agreement for estimating angiographic stenosis severity (*18*). Linear regression analysis between the percent stenosis measured by two observers

yielded correlation coefficients of 0.95 ($p < 0.0001$) for all vessels and 0.77 ($p < 0.0001$) for those with >50% stenosis. In vessels defined as normal or having insignificant stenoses and in those with significant (>50%) stenoses, the interobserver agreement was 96% and 99%, respectively. Moreover, interobserver agreement was 84% when vessels were classified as having either moderate (51%–69%) or severe (>70%) stenosis.

Statistical Analysis

Comparisons of heart and lung uptake and the lung-to-heart ratios among different groups of patients were performed with the unpaired test or the Wilcoxon-rank-sum test (when the data failed the normality test). Frequency data were compared using the Fisher's exact test. Comparisons of sensitivity and specificity in different patient groups, as well as the frequency of thallium redistribution among patients with and without infarction, were obtained with chi-square analysis. The data are expressed as mean ± standard deviation. A p value of <0.05 was considered significant.

Intra- and interobserver comparisons of lung-to-heart ratios were performed using paired t-tests and linear regression analysis.

RESULTS

Angiographic Findings

Seventy-seven patients had significant coronary stenoses, of whom 29 (38%) had single-vessel and 48 (62%) had multivessel disease. The remaining 19 patients who underwent coronary angiography had either normal coronary arteries (n = 9) or insignificant disease (n = 10).

Adenosine Infusion Results

Adenosine infusion significantly decreased systolic and diastolic blood pressures and increased the heart rate and rate-pressure product (Table 1).

Chest, throat or jaw pains occurred in 66 subjects (50%). These symptoms resolved within 1–2 min after terminating the infusion.

Electrocardiographic ST-segment depression occurred in 21 subjects (16%), 16 of whom had chest pain during adenosine infusion. Eighteen of these subjects also had complete or partial ^{201}Tl redistribution. All subjects with significant ST-segment depression had significant CAD by angiography.

Lung ^{201}Tl Activity

Reproducibility of Lung ^{201}Tl Activity. The paired measurements of lung-to-heart ratios were 0.39±0.08 versus 0.39±0.08 (p = ns) when assessed twice by the same observer and 0.39±0.08 versus 0.39±0.09 (p = ns) when assessed once by two different observers. The mean intra- and interobserver percent differences for the lung-to-heart

TABLE 1
Clinical, Angiographic and Hemodynamic Variables at Rest and During Adenosine Infusion

	Healthy volunteers (n = 36)	Normal coronary arteries (n = 19)	Single-vessel disease (n = 29)	Multivessel disease (n = 48)
Age (yr)	30±5	65±14	64±12	64±14
Men	30 (83%)	9 (47%)	15 (52%)	40 (83%)
Catheterization (no. of pts)				
LVEF (%)	—	66±12	63±12	53±15‡‡
LVEDP (mmHg)	—	14±7	15±9	17±9
Adenosine Test				
Baseline				
Systolic BP (mmHg)	119±8	144±26**	144±30**	135±27**
Diastolic BP (mmHg)	77±10	83±11§	79±13	81±13§
Heart rate (bpm)	66±13	75±15§	75±13**	74±15§
RPP (bpm·mmHg·10^2)	79±11	108±31**	109±34**	100±32**
At peak effect				
Systolic BP (mmHg)	112±13‡	136±31**	129±31‡***	121±27‡§
Diastolic BP (mmHg)	71±10†	77±13*§††	66±13†	71±12‡
Heart rate (bpm)	93±18‡	90±17‡	93±19†	83±16†§
RPP (bpm·mmHg·10^2)	104±20‡	125±45*	120±42*	100±30
Chest, throat or jaw pain	18 (50%)	10 (53%)	13 (45%)	25 (52%)
ST-Segment depression	1 (3%)	0	7 (24%)	13 (27%)

* $p < 0.05$ vs. baseline.
† $p < 0.01$ vs. baseline.
‡ $p < 0.001$ vs. baseline.
§ $p < 0.05$ vs. healthy volunteers.
** $p < 0.01$ vs. healthy volunteers.
†† $p < 0.05$ vs. healthy volunteers.
‡‡ $p < 0.05$ vs. normal coronary arteries and single-vessel disease.
*** $p < 0.05$ vs. single-vessel disease.
BP = blood pressure, LVEDP = left ventricular end-diastolic pressure and RPP = rate pressure product.

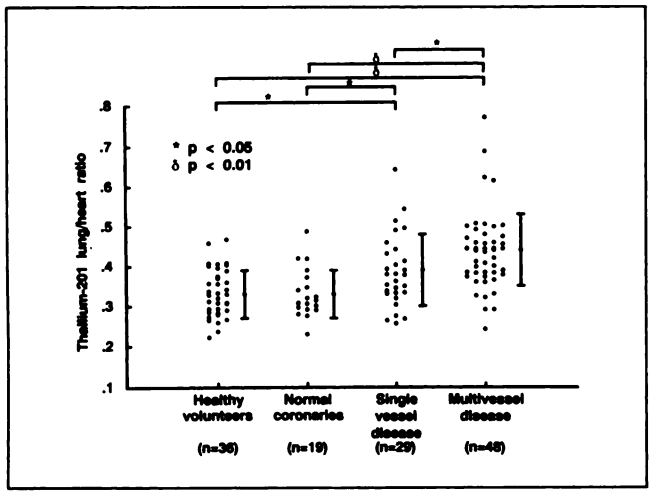

FIGURE 1. Thallium-201 lung-to-heart ratios in all patient groups.

ratio were small (3.3%±4.1% and 3.4%±7.1%, respectively). Linear regression analysis yielded correlation coefficients of 0.98 (lung-to-heart ratio 1 = 0.011 + 0.98 × lung-to-heart ratio 2, $p < 0.00001$) and 0.95 (lung-to-heart ratio 1 = 0.038 + 0.90 × lung-to-heart ratio 2, $p < 0.00001$), respectively, for the intra- and interobserver comparisons.

Excellent intraobserver reproducibility for the absolute lung and myocardial ^{201}Tl counts was found, with correlation coefficients of 0.99 and 0.97, respectively. Likewise, the interobserver reproducibility for assessing these same variables was excellent, with correlation coefficients of 0.99 and 0.99, respectively.

Lung ^{201}Tl Activity By Planar and SPECT Imaging. Figure 1 and Table 2 summarize the ^{201}Tl lung-to-heart ratio on planar imaging in all subject groups. The lung-to-heart ratio was significantly higher in patients with CAD than in normal volunteers or in subjects with normal coronary arteries. The maximal absolute myocardial and lung counts in the planar and SPECT images were greater in healthy volunteers than in the other subject groups.

Figure 2 illustrates the significant differences in the lung-to-heart ratio between the planar and SPECT images in all four subject groups ($p < 0.001$). The lung-to-heart ratio was significantly higher on planar than on SPECT imaging in healthy volunteers, in those with normal coronary arteries and in patients with single or multivessel CAD. Linear regression analysis between the planar and SPECT lung-to-heart ratios in all subjects yielded a correlation coefficient of 0.83 (lung-to-heart ratio by SPECT = 0.063 + 0.77 × lung-to-heart ratio by planar, $p < 0.0001$) (Fig. 3).

Combined Quantitative Tomography and Lung ^{201}Tl Activity for Identifying CAD. An abnormal lung-to-heart ratio, defined as >0.45 in the planar image (the upper boundary of the 95% confidence limit in the healthy volunteer and normal coronary groups), occurred in 6 of 29 (21%) patients with single-vessel and 17 of 48 (35%) with multivessel disease. However, abnormal lung-to-heart ratio (>0.42) on SPECT was found in only 3 patients (10%) with single-vessel and 10 (21%) with multivessel CAD. All patients with an abnormal lung-to-heart ratio in the SPECT images had an abnormal ratio in the planar images. The overall sensitivity of the lung-to-heart ratio for identifying patients with CAD was only 30% by planar imaging and 17% by SPECT (p = ns).

Quantitative SPECT analysis of myocardial activity failed to detect 11 (14%) of the 77 patients with CAD, 6 of whom had multivessel disease. Lung activity in the

TABLE 2
Perfusion Defect Size and Lung/Myocardial ^{201}Tl Activity

	Healthy volunteers	Normal coronary arteries	Single-vessel disease	Multivessel disease
Perfusion defect size (%)	0	1±2	11±17*	19±17**
Completely reversible defects	0	0	12	21
Planar				
Myocardial counts/pixel‡‡	163±33†	123±36	107±33	114±32
Lung counts/pixel‡‡	54±12‡	41±16	42±16	47±14
Lung/heart ratio††	0.33±0.06	0.33±0.06	0.39±0.09§	0.44±0.09**
SPECT				
Myocardial counts/pixel	151±30†	102±34	94±30	102±30
Lung counts/pixel	43±8†	31±10	29±12	37±10
Lung-to-heart ratio	0.29±0.06	0.30±0.07	0.31±0.07	0.36±0.09§

* $p < 0.01$ vs. healthy volunteers and normal coronary arteries.
† $p < 0.01$ vs. normal coronary arteries, single-vessel disease and multivessel disease.
‡ $p < 0.01$ vs. normal coronary arteries and single-vessel disease, and $p < 0.05$ vs. multivessel disease.
§ $p < 0.05$ vs. healthy volunteers and normal coronary arteries.
** $p < 0.05$ vs. single-vessel disease.
†† $p < 0.001$ planar vs. SPECT in each subject group.
‡‡ $p < 0.01$ planar vs. SPECT in each subject group.

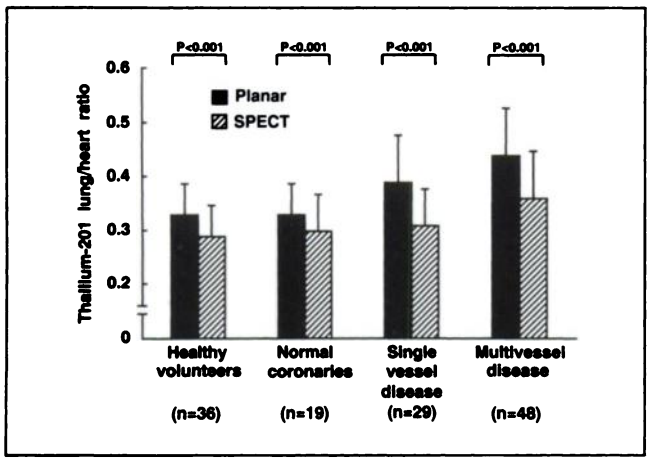

FIGURE 2. Thallium-201 lung-to-heart ratios during planar and SPECT imaging.

patients with false-negative SPECT images was abnormally high in one of five patients with single-vessel disease and in three of six patients with multivessel disease. The sensitivity for detecting CAD increased to 91% (70/77) from 86% (66/77) by using combined quantitative tomography and lung activity (difference not significant).

Elevated lung activity was found in 1 of 19 subjects with normal coronary arteries (specificity 95%). Abnormal myocardial thallium uptake by quantitative SPECT analysis was present in 2 of 19 angiographically normal subjects (specificity 89%).

Correlates of the Lung ^{201}Tl Activity. There was a weak, negative ($r = -0.36$, $p = 0.0003$) correlation between lung-to-heart ratio and peak heart rate during adenosine infusion in the total patient cohort.

Patients with multivessel disease had a lower LVEF (53%±15%) than those with single-vessel disease (63%± 12%, $p < 0.05$) or normal coronary arteries (66%±12%, $p < 0.05$). However, the lung-to-heart ratio was not linearly related to resting LVEF ($r = -0.20$, $p = 0.21$). Moreover, there was no significant correlation between the lung-to-heart ratio and resting left ventricular end-diastolic pressure.

Myocardial perfusion defects were detected in 66 of 77 patients (86%) with CAD. As shown in Table 2, the SPECT perfusion defect size was greater in patients with multivessel disease than in those with single-vessel disease (19%± 17% versus 11%±17%) ($p < 0.05$), but linear regression analysis showed no linear correlation between the lung-to-heart ratio and the perfusion defect size on the early tomograms ($r = 0.18$, $p = 0.24$).

There was also no significant difference in the lung-to-heart ratio between the 20 patients with and the 76 patients without ST-segment depression during adenosine infusion (0.41±0.10 versus 0.38±0.10, respectively, p = ns). However, among 35 patients with completely reversible defects during adenosine SPECT, 13 patients showed ischemic ST-segment depression. These 13 patients had a significantly higher lung-to-heart ratio than the 21 without ST-segment depression (0.46±0.07 versus 0.37±0.06, respectively, $p < 0.05$).

Twenty-three patients with significant CAD and an elevated (>0.45) lung-to-heart ratio were compared to 54 patients with significant disease and a normal ratio with respect to clinical, angiographic, hemodynamic and scintigraphic variables (Table 3). Patients with an elevated lung-to-heart ratio had a greater frequency of prior myocardial infarction, were more likely to have angiographic collateral circulation and had a lower LVEF (Table 3). They also had a larger initial defect size, more abnormal segments on the initial SPECT images and more segments with redistribution. There was, however, no significant correlation between the lung-to-heart ratio and age, gender, history of heart failure, angina pectoris or hypertension, use of antianginal medications and the frequency of angina or ischemic ST depression during adenosine infusion.

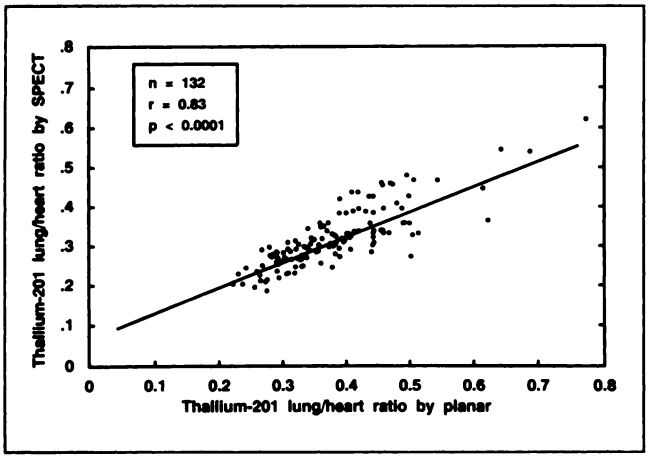

FIGURE 3. Correlation between ^{201}Tl lung-to-heart ratios by planar and by SPECT imaging.

DISCUSSION

Lung ^{201}Tl Activity During Planar and SPECT Imaging

Our findings indicate that lung ^{201}Tl activity was significantly higher on planar than on SPECT imaging. Although the correlation of lung-to-heart ratios between these two imaging methods was good ($r = 0.83$), 8 of 17 patients with an elevated ratio in the planar image acquired immediately after adenosine infusion had a normal ratio in the anterior SPECT image, which was acquired an average of 16 min later. These data suggest that assessment of the lung activity in the anterior planar projection, prior to acquiring the SPECT images, provides more sensitive and useful diagnostic information with respect to both the presence and extent of CAD than evaluating lung thallium uptake in the anterior frame of the SPECT study.

An abnormally elevated (>0.45) lung-to-heart ^{201}Tl ratio was found in 30% of patients with CAD on planar imaging

TABLE 3
Clinical, Hemodynamic, Angiographic and Scintigraphic Variables in Patients with Elevated and Normal Lung-to-Heart (L/H) Ratios

	Elevated L/H ratio (n = 23)	Normal L/H ratio (n = 54)	p Value
Clinical Findings			
Age	60±15	65±13	ns
Men	20 (87%)	37 (69%)	ns
History of chest pain	17 (74%)	36 (67%)	ns
Prior infarction	15 (65%)	14 (26%)	0.003
History of CHF	5 (22%)	5 (9%)	ns
Hypertension	7 (30%)	13 (24%)	ns
Beta-blocker use	4 (17%)	7 (13%)	ns
Calcium antagonist use	12 (52%)	38 (70%)	ns
Nitrate use	11 (48%)	27 (50%)	ns
Adenosine Test Results			
Lowest SBP (mmHg)	119±25	125±25	ns
Lowest DBP (mmHg)	71±13	67±12	ns
Peak HR (bpm)	84±17	85±17	ns
Peak RPP (bpm·mmHg·10^2)	100±31	108±37	ns
Chest pain	13 (57%)	25 (46%)	ns
ST-segment depression	9 (39%)	11 (20%)	ns
Angiography			
LAD stenosis	19 (83%)	35 (65%)	ns
Multivessel disease	17 (74%)	30 (56%)	ns
Collaterals	13 (57%)	15 (28%)	0.04
LVEF (%)	49±22	61±12	0.02
LVEDP (mmHg)	18±10	15±10	ns
Scintigraphic Results			
No. of abnormal segments/patient			
Initial perfusion defect	1.9±1.4	1.1±0.8	0.007
Redistribution	1.4±1.3	0.8±0.8	0.04
No redistribution	0.5±0.7	0.3±0.5	ns
Initial defect size (%)	21±18	13±16	0.04
Redistributing size (%)	16±16	9±12	ns

CHF = congestive heart failure; DBP = diastolic blood pressure; HR = heart rate; LAD = left anterior descending artery; LVEDP = left ventricular end-diastolic pressure; RPP = rate pressure product; and SBP = systolic blood pressure.

performed immediately after adenosine infusion. Although this prevalence is lower than that found during exercise thallium scintigraphy, which ranges from 38% to 67% (*2–5*), it is similar to that reported during dipyridamole thallium imaging in patients with CAD (*13,15*). When either an abnormal lung-to-heart ratio or a perfusion defect was used as evidence of CAD, the sensitivity of adenosine thallium scintigraphy increased slightly (from 86% to 91%).

A high lung ^{201}Tl activity during exercise has been reported to be an important marker of poor prognosis (*1–4,7*). Whether an increased thallium lung activity during adenosine scintigraphy is also an independent prognostic indicator of future events in patients with CAD remains to be proven.

Correlates of Elevated Lung ^{201}Tl Activity

A significant increase in ^{201}Tl lung activity has been previously reported in patients with CAD undergoing dipyridamole ^{201}Tl scintigraphy (*13,15*). The present study demonstrates that lung ^{201}Tl activity during adenosine infusion is also often increased and is related to the presence of angiographically documented CAD. Patients with multivessel disease had a significantly higher lung activity in comparison to subjects with normal coronary arteries and those with single-vessel disease.

In this study, patients with an elevated lung-to-heart ratio had a lower LVEF, larger perfusion defect size and more segments with redistribution than those with a normal lung-to-heart ratio. The latter observation is in keeping with previous reports on exercise (*1–4,6,22*) as well as dipyridamole (*15*) thallium scintigraphy. The lack of a linear correlation between the lung-to-heart ratio and perfusion defect size or ejection fraction may be due to beta error because of the relatively small number of patients.

Myocardial perfusion defects during pharmacologic coronary vasodilation are produced by coronary flow heterogeneity, which in turn is dependent on coronary stenosis severity and consequent abnormalities in flow reserve (*23*). Therefore, although perfusion defects during adenosine thallium SPECT do not necessarily denote ischemia, we

found that patients with elevated lung activity had a larger number of segments with redistribution.

Lung thallium activity during adenosine infusion was inversely correlated with peak heart rate, probably because pulmonary transit time decreases at higher heart rates. This finding is also consistent with previous observations during exercise thallium scintigraphy (*2,5*).

A previous study reported a linear correlation between lung ^{201}Tl activity and the extent of perfusion abnormalities during adenosine SPECT (*14*). Our results, in contrast, did not show such a linear correlation, probably because not all perfusion defects were associated with ischemia.

Postulated Mechanism of Increased Lung ^{201}Tl Activity

Increased lung thallium activity (lung-to-heart ratio) during adenosine infusion was due to an increase in lung activity relative to myocardial activity. Previous reports have also shown higher absolute lung thallium activity during exercise in patients with multivessel CAD (*4*).

Two hemodynamic markers have emerged as correlates of increased thallium extraction by the lungs during exercise thallium scintigraphy (*1–6,22*): (1) increased pulmonary transit time and (2) elevated left atrial pressure. Whether there is any direct effect of adenosine on thallium extraction by the lung is not known.

Increased lung activity in our study was related to the presence of angiographic collaterals. In experimental studies, coronary steal has been well demonstrated during pharmacologic vasodilation, especially in patients with collateral circulation (*25,26*). Therefore, in patients with both elevated lung activity and collaterals, elevated left atrial pressure resulting from transient left ventricular dysfunction due to myocardial ischemia, caused by coronary steal and facilitated by collateral vessels, may have occurred during adenosine infusion. Alternatively, the decreased myocardial compliance due to the greater than four-fold increase in myocardial blood flow, leading to increased wall stiffness ("myocardial erection"), may be another mechanism of increased pulmonary capillary wedge pressure. This mechanism is in keeping with a recent report suggesting that elevated pulmonary capillary wedge pressure during adenosine administration in patients with CAD is due to diastolic left ventricular dysfunction (*24*).

Study Limitations

ROI placement may impose substantial variability in the calculation of lung ^{201}Tl activity. However, the intra- and interobserver reproducibilities for assessing the lung-to-heart ratio were very high. Another factor which affects lung activity is the time of image acquisition. The lung-to-heart ratio in this study was lower than that on SPECT in a previous study (*14*), which employed adenosine to induce maximal coronary vasodilation. Therefore, normal limits for lung thallium activity should be established in each laboratory.

A possible limitation of this study is that only resting left ventricular function was compared to lung thallium activity. Thus, similar to previous reports using adenosine or dipyridamole, we are unable to determine whether the elevated lung thallium activity was due to transient left ventricular dysfunction during adenosine infusion.

A physiological factor, the peak heart rate during adenosine infusion, had a weak, negative correlation to lung activity in this study. This has also been noted during exercise thallium scintigraphy (*5*). Lung activity in patients taking beta-blockers theoretically might be higher because these drugs decrease the maximal heart rate reached during adenosine infusion in patients with CAD (*27*). However, in the present study, the lung-to-heart ratio was not significantly influenced by the use of beta-blockers.

Previous reports demonstrated conflicting results with respect to an association between elevated lung activity and left ventricular dilatation (*14,15,28*). Although in the present study we did not assess the presence of left ventricular dilatation, we have previously reported a significant association between lung thallium activity and left ventricular dilatation during exercise and adenosine thallium SPECT in patients undergoing both tests on different days (*29*).

CONCLUSIONS

In this study, lung thallium activity during adenosine infusion correlated with the presence and angiographic extent of CAD and with the presence of collateral circulation. Elevated lung ^{201}Tl activity on both planar and SPECT imaging during adenosine infusion was found in 30% and 17% of patients with CAD, respectively, and occurred predominantly in patients with lower LVEFs and larger perfusion defects which underwent thallium redistribution.

The lung activity during early planar imaging was significantly higher than that on SPECT, probably because of rapid lung ^{201}Tl clearance. Determination of thallium lung uptake during SPECT may therefore be a less sensitive marker of the extent of CAD. Lung ^{201}Tl activity, which may be readily calculated from the planar anterior projection images, with low inter- and intraobserver variability, is an indirect marker of the presence and extent of CAD. Its prognostic value for predicting future cardiac events remains to be determined.

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REFERENCES

1. Boucher CA, Zir LM, Beller GA, et al. Increased lung uptake of thallium-201 during exercise myocardial imaging: clinical, hemodynamic and angiographic implications in patients with coronary artery disease. *Am J Cardiol* 1980;46:189–196.

2. Bingham JB, McKusick KA, Strauss HW, Boucher CA, Pohost GM. Influence of coronary artery disease on pulmonary uptake of thallium-201. *Am J Cardiol* 1980;46:821–826.
3. Kushner FG, Okada RD, Kirshenbaum HD, Boucher CA, Strauss HW. Pohost GM. Lung thallium-201 uptake after stress testing in patients with coronary artery disease. *Circulation* 1981;63:341–347.
4. Gibson RS, Watson DD, Carabello BA, Holt ND, Beller GA. Clinical implications of increased lung uptake of thallium-201 during exercise scintigraphy 2 weeks after myocardial infarction. *Am J Cardiol* 1982;49: 1586–1593.
5. Brown KA, Boucher CA, Okada RD, Strauss HW, Pohost GM. Quantification of pulmonary thallium-201 activity after upright exercise in normal persons: importance of peak heart rate and propranolol usage in defining normal values. *Am J Cardiol* 1984;53:1678–1682.
6. Liu P, Kiess M, Okada RD, et al. Increased thallium lung uptake after exercise in isolated left anterior descending coronary artery disease. *Am J Cardiol* 1985;55:1469–1473.
7. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. *N Engl J Med* 1987;317:1485–1489.
8. Albro PC, Gould KL, Westcott RJ, Hamilton GW, Ritchie JL, Williams DL. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation. III. Clinical trial. *Am J Cardiol* 1978;42:751–760.
9. Leppo J, Boucher CA, Okada RD, Newell JB, Strauss HW, Pohost GM. Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenoses and relationship to regional wall motion. *Circulation* 1982;66:649–657.
10. Ruddy TD, Dighero HR, Newell JB, et al. Quantitative analysis of dipyridamole-thallium images for the detection of coronary artery disease. *J Am Coll Cardiol* 1987;10:142–149.
11. Taillefer R, Lette J, Phaneuf D, Leveille J, Lemire F, Essiambre R. Thallium-201 myocardial imaging during pharmacologic coronary vasodilation: comparison of oral and intravenous administration of dipyridamole. *J Am Coll Cardiol* 1986;8:76–83.
12. Borges-Neto S, Mahmarian JJ, Jain A, Roberts R, Verani MS. Quantitative thallium-201 single photon emission computed tomography after oral dipyridamole for assessing the presence, anatomic location and severity of coronary heart disease. *J Am Coll Cardiol* 1988;11:962–969.
13. Okada RD, Dai Y, Boucher CA, Pohost GM. Significance of increased lung thallium-201 activity on serial cardiac images after dipyridamole treatment in coronary artery disease. *Am J Cardiol* 1984;53:470–475.
14. Iskandrian AS, Heo J, Nguyen T, Lyons E, Paugh E. Left ventricular dilatation and pulmonary thallium uptake after single-photon emission computer tomography using thallium-201 during adenosine-induced coronary hyperemia. *Am J Cardiol* 1990;66:807–811.
15. Villanueva FS, Kaul S, Smith WH, Watson DD, Varma SK, Beller GA. Prevalence and correlates of increased lung/heart ratio of thallium-201 during dipyridamole stress imaging for suspected coronary artery disease. *Am J Cardiol* 1990;66:1324–1328.
16. Kahn JK, Carry MM, McGhie I, Pippin JJ, Akers MS, Corbett JR. Quantitation of postexercise lung thallium-201 uptake during single photon emission computed tomography. *J Nucl Med* 1989;30:288–294.
17. Strauss HW, Pitt B. Noninvasive detection of subcritical coronary arterial narrowings with a coronary vasodilator and myocardial perfusion imaging. *Am J Cardiol* 1977;39:403–406.
18. Leppo J, Rosenkrantz J, Rosenthal R, Bontemps R, Yipintsoi T. Quantitative thallium-201 redistribution with a fixed coronary stenosis in dogs. *Circulation* 1981;63:632–639.
19. Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. *Circulation* 1990;82:80–87.
20. Mahmarian JJ, Boyce TM, Goldberg RK, Cocanougher MK, Roberts R, Verani MS. Quantitative exercise thallium-201 single photon emission computed tomography for the enhanced diagnosis of ischemia heart disease. *J Am Coll Cardiol* 1990;15:318–329.
21. Mahmarian JJ, Pratt CM, Cocanougher MK, Verani MS. Altered myocardial perfusion in patients with angina pectoris or silent ischemia during exercise as assessed by quantitative thallium-201 single-photon emission computed tomography. *Circulation* 1990;82:1305–1315.
22. Homma S, Kaul S, Boucher CA. Correlates of lung/heart ratio of thallium-201 in coronary artery disease. *J Nucl Med* 1987;28:1532–1535.
23. Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. *J Am Coll Cardiol* 1990;15:459–474.
24. Ogilby JD, Untereker WJ, Nguyen T, et al. Disparate effects of adenosine on myocardial performance and perfusion [Abstract]. *Circulation* 1991; 84(suppl):II–510.
25. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. *Circulation* 1978;57:1103–1110.
26. Patterson RE, Kirk ES. Coronary steal mechanisms in dogs with one vessel occlusion and other arteries normal. *Circulation* 1983;67:1009–1015.
27. Abreu A, Mahmarian JJ, Nishimura S, Boyce TM, Verani MS. Tolerance and safety of pharmacologic coronary vasodilation with adenosine in association with thallium-201 scintigraphy in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1991;18:730–735.
28. Chouraqui P, Rodrigues EA, Berman DS, Maddahi J, Significance of dipyridamole-induced transient dilation of left ventricle during thallium-201 scintigraphy in suspected coronary artery disease. *Am J Cardiol* 1990; 66:689–694.
29. Nishimura S, Mahmarian JJ, Verani MS. Comparison of lung thallium-201 uptake and transient left ventricular dilatation during adenosine and exercise scintigraphy in coronary artery disease [Abstract]. *J Nucl Med* 1991;32:1030.