Hemodynamic Indices of Myocardial Dysfunction Correlate with Dipyridamole Thallium-201 SPECT

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Important differences in hemodynamics and tracer kinetics occur with dipyridamole compared to exercise scintigraphy. To better understand the clinical significance of dipyridamole SPECT ^{201}Tl scintigraphy, we examined the relationships between scintigraphy and clinical, and angiographic and hemodynamic variables in patients with CAD. **Methods:** Forty-nine subjects were divided into three study groups. Patients in Groups A (n = 11) and B (n = 20) had a low (<5%) likelihood of CAD. Group A underwent maximal exercise thallium stress testing. Group B underwent thallium dipyridamole scintigraphy. Group C (n = 18) consisted of patients with coronary artery disease who had dipyridamole thallium scintigraphy and cardiac catheterization within 2 wk. Thallium lung-to-myocardial ratio (L/M), left ventricular dilation and perfusion defect site were compared to hemodynamic, clinical and angiographic variables. **Results:** The Group A L/M ratio of 0.23 ± 0.05 (mean ± 1 s.d.) was significantly lower ($p < 0.001$) compared to the Group B L/M ratio of 0.31 ± 0.05. In Group C, the L/M ratio showed correlation with indices of left ventricular dysfunction including lower resting ejection fraction ($p = 0.02$, $r = 0.83$), higher pulmonary capillary wedge pressure ($p = 0.01$, $r = 0.58$) and lower cardiac index ($p = 0.03$, $r = 0.54$). Left ventricular dilation was associated with hemodynamic changes of ventricular failure including lower resting ejection fraction ($p = 0.008$, $r = 0.88$) and higher pulmonary capillary wedge pressure ($p = 0.02$, $r = 0.54$). Immediate and delayed perfusion defect size showed good correlation with lower resting left ventricular ejection fraction $p = 0.02$ ($r = 0.83$, and $p = 0.004$, $r = 0.91$, respectively). **Conclusion:** Lung uptake, left ventricular dilation and perfusion defect size show good correlation to hemodynamic indices of resting left ventricular dysfunction. A combination of these factors may be a better predictor of future cardiac events and prognosis.

Key Words: dipyridamole; thallium-201; SPECT; hemodynamics

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In exercise ^{201}Tl scintigraphy, a number of studies have reported scintigraphic correlates of clinical, angiographic and hemodynamic parameters, primarily with planar imaging (*1–6*). In pharmacologic stress with dipyridamole, the scintigraphic findings may differ due to different stress hemodynamics, tracer kinetics and imaging techniques. Pulmonary transit time, an important determinant of lung uptake, is longer with dipyridamole compared to exercise scintigraphy. In addition, dipyridamole may not induce myocardial ischemia and dysfunction on the basis of increased rate-pressure product. Lung uptake and ventricular dilation may more commonly represent resting rather than dipyridamole induced ventricular dysfunction. Planar and SPECT scintigraphic findings may also have somewhat different characteristics due to differences in timing of data acquisition. Several investigators have noted a lower lung-to-myocardial (L/M) ratio with exercise SPECT compared to exercise planar imaging.

To better understand the clinical significance of dipyridamole ^{201}Tl SPECT findings, we examined the relationships between scintigraphy and clinical, angiographic and resting hemodynamic variables in patients with coronary artery disease.

MATERIALS AND METHODS

Patients

Normal scintigraphic findings for exercise (Group A) and dipyridamole (Group B) SPECT scintigraphy were first examined. This was followed by comparison to a group with known CAD (Group C) and dipyridamole scintigraphy. Group A (n = 11) patients underwent maximal exercise stress ^{201}Tl perfusion scintigraphy under the Bruce protocol and had a low (<5%) likelihood of CAD. Group B (n = 20) patients underwent dipyridamole scintigraphy and also had a low (<5%) likelihood of CAD. Subjects in Groups A and B were referred for routine preoperative evaluation for nonvascular surgery (hysterectomy and salpingo-oophorectomy, bladder resection or repair, colon resection, pituitary adenoma resection, craniotomy, inguinal hernia repair, liver transplant evaluation, renal transplant evaluation, esophageal surgery, orthopedic surgery, renal mass resection, breast nodule removal) and met the following criteria for low likelihood of CAD: (a) asymptomatic patients without a history of typical or atypical chest pain; (b) no EKG evidence of exercise or dipyridamole induced ischemia defined as greater than 1 mm horizontal or downsloping ST segment depression; and (c) no perfusion defect by myocardial perfusion scintigraphy (*7*). In addition, these subjects did not have a history of lung disease. Group C patients underwent dipyridamole ^{201}Tl SPECT scintigraphy and coronary angiography performed within 2 wk. No intervention was performed between studies and patients without angiography or exercise rather than dipyridamole scintigraphy were excluded.

In addition to hemodynamic indices of resting dysfunction, clinical variables assessed included age, sex, prior myocardial infarction, heart failure, chest pain and risk factors (diabetes mellitus, hypercholesterolemia, family history and smoking). Angiographic variables assessed included specific coronary stenosis location, presence of single or multivessel disease, presence of proximal or left main disease, and presence of collaterals. The hemodynamic variables assessed included cardiac index (CI), pulmonary capillary wedge pressure (PCWP) and left ventricular ejection fraction (LVEF).

Study Protocols

Subjects in Group A underwent Bruce protocol maximal exercise stress testing and achieved greater than 85% maximal predicted heart rate. At peak exercise, 2.5 mCi of ^{201}Tl was injected intravenously and the exercise was continued for an additional minute. A lower exercise dose of ^{201}Tl was administered to allow for possible re-injection of 1.0 mCi ^{201}Tl if a perfusion defect was present on the stress images. In Groups B and C, dipyridamole

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TABLE 1
Reproducibility of Measurements: Linear Correlation Coefficient (r)

Parameters	Intraobserver	Interobserver
Lung counts	0.98	0.99
Myocardial counts	0.99	0.99
Lung-to-myocardial ratio	0.95	0.96
Perfusion defect size		0.90

subjects underwent scintigraphy after intravenous infusion of 0.56 mg/kg over 4 min. Three mCi of ^{201}Tl was injected 2–3 min after completion of dipyridamole infusion. For both protocols, tomographic images were obtained immediately afterwards and 4 hr after initial injection. The subjects' blood pressure, heart rate, 12 lead EKG and symptoms were monitored throughout the study.

SPECT Data Acquisition and Processing

Initial and delayed SPECT images of the heart were acquired for 180° starting in the 45° right anterior oblique position to the 45° left posterior oblique position. The 32 projection images were obtained for 40 sec per stop. Images were acquired on a 64 × 64 matrix and reconstructed using a Hanning 0.6 sec^{-1} pre-filter and standard filtered back projection. The interpretation of the scintigraphic findings was performed by two experienced readers blinded to the clinical data. Differences were resolved by consensus.

Lung-to-Myocardial Ratio

Lung and myocardial thallium activity quantification was performed similar to methods previously described and validated (*8*). The anterior planar projection image was used for analysis. A 2 × 2 pixel region of interest was placed over the myocardial wall with the greatest count density. The mean myocardial counts per pixel was determined by locating the region with the lowest total count standard deviation which still contained the highest count per pixel within the myocardium. A 5 × 5 pixel region of interest in the left lung was placed at least three pixels above the superior border of the myocardium. The mean lung counts per pixel was obtained from this 25 pixel ROI. The L/M ratio was defined as the mean counts per pixel in the lung ROI divided by the mean counts per pixel in the myocardial ROI.

To determine the intra-operator variability, 19 patient studies were measured by the same operator twice on separate days at least three days apart. To determine the interoperator variability, 19 patient studies were analyzed independently by two operators.

Left Ventricular Dilation

Dilation was assessed as present or absent after viewing projection and tomographic images. Readers were blinded to the clinical data. Objective measurements of peak-to-peak distance from horizontal and vertical profiles through the mid-ventricular short axis slice were obtained for the normals in Group B. These measurements showed a wide variation in ventricular diameter for normal patients, most likely due to normal variation in heart size. This variation resulted in a wide range of left ventricular diameters in normal patients which did not agree with the subjective assessment of dilation. Other investigators have found similar difficulties in objectively quantifying dilation using this and other methods (*9*). Therefore, only the results for the subjective analysis will be reported. Dilation was scored subjectively as either present or absent by viewing the projection and tomographic images. Dilation was judged by the left ventricular size compared to the chest and by the ratio of myocardial wall to myocardial cavity size. Differences in scoring were resolved by consensus.

Perfusion Defect Size

To determine defect size, each myocardial short axis slice was divided into 6 equal sectors and scored individually. The apical portion was evaluated on a mid-ventricular vertical long axis slice in 3 equal sectors. The majority of subjects had 8 short axis slices resulting in a total of 51 sectors scored on each volume. The percentage of normal myocardium was defined as the number of normal segments divided by the total number of scored segments. Defect reversibility was defined as the difference between initial and delayed perfusion defect size. Interobserver variability in defect size was assessed for all Group C studies.

Cardiac Catheterization

Significant stenosis was defined as greater than or equal to 50% luminal narrowing. Percent stenosis was graded subjectively and independently by an experienced cardiologist at the time of catheterization. Cardiac output was measured by the Fick method in 17 of 18 Group C patients. Left ventricular ejection fraction was measured by biplane cineangiography in 7 of 18 Group C subjects. Pulmonary capillary wedge pressure was measured in all patients during catheterization.

Statistical Analysis

Continuous data were expressed as mean ± 1 s.d. The normal values for the exercise and the dipyridamole populations were expressed as mean ± 2 s.d. Differences between groups with nominal data were evaluated for significance ($p < 0.05$) with Fisher's Exact T-test. Differences in groups with small numbers ($n = 7$, for ejection fraction) were confirmed for significance ($p < 0.05$) by Wilcoxon 2 sample t-test. Differences between groups and within groups for interval data were evaluated with the Student's t-test with results expressed as mean ± 1 s.d. Correlations between continuous variables were evaluated by simple linear regression with r representing the Pearson's correlation coefficient. Similarly,

TABLE 2
Clinical Characteristics of Group A and B Subjects

Clinical variables	Group A mean (s.d.)	Group B mean (s.d.)	p value
Age (range)	57 (39–79)	52 (32–83)	ns
Sex	M = 4, F = 7	M = 12, F = 8	ns
Rest hemodynamics			
Heart rate (bpm)	82 (9)	70 (9)	ns
Systolic blood pressure (mmHg)	127 (13)	139 (22)	ns
Diastolic blood pressure (mmHg)	83 (8)	85 (9)	ns
Double product (bpm × mmHg)	10,328 (1224)	10,955 (2321)	ns
Stress hemodynamics			
Peak heart rate (bpm)	154 (12)	90 (12)	<0.001
Peak systolic blood pressure (mmHG)	179 (28)	133 (25)	<0.001
Increase in double product (bpm × mmHg)	17,218 (4375)	1034 (2379)	<0.001

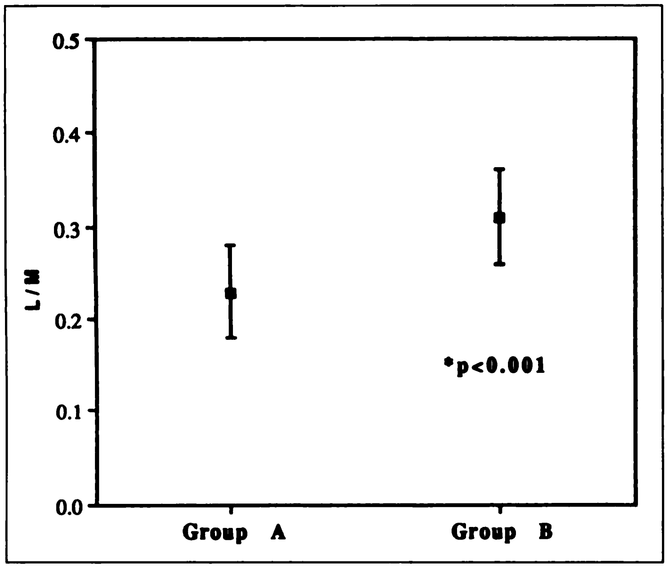

FIGURE 1. Normal L/M ratio (mean ± 1 s.d.) for Group B is significantly higher than for Group A.

intraobserver and interobserver variability were evaluated with simple linear regression.

RESULTS

Variability of Measurements

A summary of the interobserver and intraobserver variabilities is shown in Table 1. Mean lung counts per pixel, mean myocardial counts per pixel, L/M ratio and perfusion defect size showed good reproducibility.

Patients with Low Likelihood CAD

The clinical variables in Groups A and B are summarized in Table 2. There were no significant differences between Groups A and B with respect to age, sex, baseline heart rate, systolic and diastolic blood pressures or double-product. The postinfusion peak heart rate in Group B was significantly lower ($p < 0.001$) compared to exercise peak heart rate in Group A and significantly higher ($p < 0.001$) compared to pre-infusion values. The postinfusion systolic blood pressure for Group B was significantly lower than that for the exercise Group A and significantly lower ($p < 0.02$) compared to pre-infusion values. The mean increase in the double-product for Group B also was significantly lower ($p < 0.001$) compared to the exercise Group A.

The L/M ratios for groups A and B are shown in Figure 1 and are expressed as mean ± 1 s.d. The mean L/M ratio for Group B of 0.31 ± 0.05 (mean ± 1 s.d.) was significantly higher ($p < 0.001$) than for Group A (0.23 ± 0.05).

Patients with CAD

Hemodynamic Characteristics. In Group C, the hemodynamic characteristics determined at angiography included left ventricular ejection fraction (42.1 ± 17.8, range = 19–68), pulmonary capillary wedge pressure (13.4 ± 4.9, range = 6–26 mmHg) and cardiac index (2.6 ± 0.5, range = 1.7–3.4 L/min/m^2).

Lung-to-Myocardial Ratio. The L/M ratio did not correlate with any of the clinical or angiographic variables. Of the hemodynamic parameters, the L/M ratio showed good inverse and linear correlation with resting left ventricular ejection fraction ($p = 0.02$, $r = 0.83$). It showed only weak association with a lower resting cardiac index ($p = 0.03$, $r = 0.54$) and a higher pulmonary capillary wedge pressure ($p = 0.01$, $r = 0.57$). Four of the 18 Group C patients had multivessel disease and L/M ratio greater than 2 s.d. above the mean for Group B.

Left Ventricular Dilatation. None of the clinical variables showed a significant correlation with the presence of left ventricular dilatation. Of the angiographic variables, the presence of collaterals showed weak correlation ($p = 0.05$) with left ventricular dilatation. Of the resting catheterization hemodynamics, correlates included a lower left ventricular ejection fraction ($p = 0.008$) and a higher pulmonary capillary wedge pressure ($p = 0.02$).

Perfusion Defect Size. Of the clinical variables, only a history of prior myocardial infarction showed significant correlation with stress and delayed perfusion defect size ($p = 0.04$ and $p = 0.008$, respectively). Of the angiographic variables, only the presence of collaterals showed a correlation with stress perfusion defect size ($p = 0.002$). Of resting catheterization hemodynamic variables, left ventricular ejection fraction showed good correlation with stress perfusion defect size ($p = 0.02$, $r = 0.83$) and delayed perfusion defect size ($p = 0.004$, $r = 0.91$). A summary of the scintigraphic correlates to clinical variables, angiographic findings and resting catheterization hemodynamics is provided in Tables 3–5. Examples of the scintigraphic correlates of resting left ventricular ejection fraction are shown in Figure 2. L/M ratio, ventricular dilation and perfusion defect size showed correlation with LVEF. Defect reversibility showed no significant correlation.

An example of several L/M ratios from the anterior projection images are shown in Figure 3. In Figure 3A, an exercise subject with a normal L/M ratio of 0.25 was asymptomatic. Maximal exercise stress EKG was normal and thallium scintig-

TABLE 3
Association of Scintigraphic Findings to Clinical Characteristics in Group C (p Values)

Clinical variables	L/M ratio	LV dilation	st nl (%)	dl nl (%)
Age	0.65	0.40	0.94	0.52
Sex	0.15	1.00	0.74	0.73
Chest pain	0.52	1.00	0.10	0.24
Severity heart failure	0.42	0.39	0.28	0.32
History of previous MI	0.63	0.07	0.04	0.008
Risk factors				
Diabetes mellitus	0.49	0.41	0.10	0.20
Hypertension	0.83	0.39	0.87	0.49
Smoking	0.26	0.81	0.47	0.26
Hypercholesterolemia	0.38	0.37	0.62	0.62
Family history	0.94	0.80	0.69	0.30

ST nl (%) = stress perfusion defect size; dl nl (%) = delayed perfusion defect size.

TABLE 4
Association of Scintigraphic Findings to Angiographic Characteristics in Group C (p Values)

Region	L/M ratio	LV dilation	st nl %	dl nl %
Left main	0.64	0.67	0.76	0.89
Right coronary	0.86	0.20	0.68	0.91
Left anterior descending	0.22	0.37	0.57	0.43
Left circumflex	0.74	0.28	0.10	0.18
Multi-vessel disease	0.78	0.09	0.12	0.28
Proximal or left main	0.91	0.09	0.28	0.81
Collaterals	0.27	0.05	0.002	0.06

raphy showed no perfusion defect. In Figure 3B, an exercise subject with a L/M ratio of 0.39 was evaluated for chest pain (0.33 is 2 s.d. above the mean for the normal group A). The baseline EKG showed old inferior infarction and the exercise EKG was positive with 2mm horizontal ST segment depression V4-V6. Perfusion scintigraphy showed a large predominantly fixed inferior and infero-lateral perfusion defect and a partially reversible infero-apical perfusion defect. In Figure 3C, a dipyridamole subject with a normal L/M ratio of 0.40 was asymptomatic. Electrocardiogram showed no ischemic changes and the thallium study showed no perfusion defects (0.41 is 2 s.d. above the mean for the normal Group B subjects). In Figure 3D, the dipyridamole subject with an abnormally increased L/M ratio of 0.55 complained of chest pain and became hypotensive. The EKG was markedly positive with 3–4 mm ST segment depression in leads II, III, and AVF and V2-V6.

The perfusion study showed transient LV dilatation, and large, severe, predominantly reversible defects in the anterior, septal, inferior and apical regions. The subsequent cardiac catheterization showed a 90% stenosis in the left main, and a completely occluded proximal LAD with good collateral filling. The RCA was completely occluded proximally but also showed filling via collaterals. The circumflex also showed a 50% stenosis in the second marginal branch. The subject who experienced ischemia in Figure 3B has a lower L/M ratio compared to the normal dipyridamole subject; however, the L/M ratio of 0.39 was elevated for exercise reference values. The exercise L/M ratio in 3B was abnormally increased when evaluated qualitatively (lung uptake was higher than background or mediastinal activity) and quantitatively (2 s.d. above the mean for the exercise group is 0.33).

DISCUSSION

Dipyridamole thallium myocardial perfusion scintigraphy is important in the diagnosis and prognosis of known or suspected CAD. It is also a safe, effective means of risk stratification in patients after myocardial infarction (*10*). Important hemodynamic and coronary blood flow differences exist between

TABLE 5
Association of Scintigraphic Findings to Hemodynamics in Group C (p Values)

	L/M ratio	LV dilation	st nl (%)	dl nl (%)
PCWP	0.01	0.02	0.31	0.30
CI	0.03	0.60	0.96	0.82
LVEF	0.02	0.008	0.02	0.004

PCWP = pulmonary capillary wedge pressure; CI = cardiac index; LVEF = left ventricular ejection fraction; st nl (%) = stress perfusion defect size; dl nl (%) = delayed perfusion defect size.

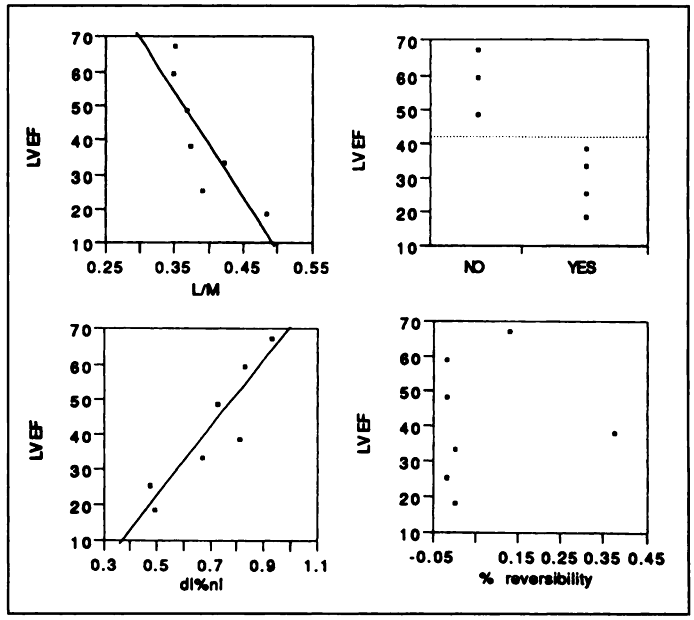

FIGURE 2. Scintigraphic findings correlate with LVEF in Group C (n = 7). (Top left) L/M versus LVEF (r = 0.83, p = 0.02); (Top right) LV dilation versus LVEF (p = 0.008); (Bottom right) % normal myocardium on delayed imaging (dl%nl) versus LVEF (r = 0.91, p = 0.004); (Bottom right) % defect reversibility versus LVEF (p = ns).

exercise and dipyridamole scintigraphy. Indicators of extensive disease and worse prognosis with exercise scintigraphy may have a different significance in dipyridamole scintigraphy. Our findings with dipyridamole showed that increased lung uptake, left ventricular dilation and delayed perfusion defect size correlated with resting hemodynamic indices of myocardial dysfunction.

Correlates of Lung Uptake

In exercise thallium scintigraphy, increased lung uptake has shown a direct relationship to transiently increased pulmonary

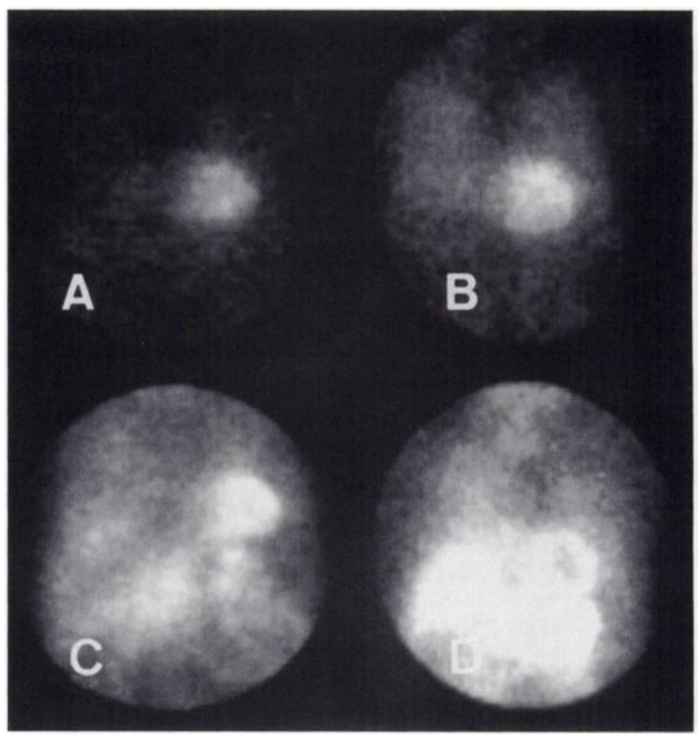

FIGURE 3. (A) EX normal with normal L/M of 0.25. (B) EX subject with CAD and elevated L/M of 0.39. (C) DI normal with normal L/M of 0.40. (D) DI subject with CAD and elevated L/M of 0.55. EX = exercise, DI = dipyridamole.

capillary wedge pressure and increased pulmonary transit time. In an experimental canine model of pulmonary thallium uptake, increases in left atrial pressure or increases in pulmonary transit time have resulted in increased thallium extraction fraction (*2*). Other investigators have shown a linear relationship between increasing interstitial lung water and thallium lung uptake in canine models of pulmonary edema (*11*). In patients with CAD, exercise induced lung uptake has shown direct correlation with transiently increased pulmonary capillary wedge pressure (*1*). In normal volunteers, lung uptake also increases at lower peak heart rates, consistent with increased extraction fraction due to prolonged pulmonary transit time (*14,20,21*).

Clinically, exercise thallium studies have shown the correlation of increased lung uptake with several variables including: a history of prior infarction, greater number of thallium perfusion defects, increased severity and extent of disease, lower resting ejection fraction, greater number of anterior segment defects, multivessel coronary disease, a greater number of asynergic left ventricular segments, less cardiac reserve and a greater prevalence of exercise induced ST-segment depression (*1–6*). Postexercise lung uptake also identifies a subset of patients at high risk for subsequent major cardiac events including death and myocardial infarction (*12–15*).

Our results show that normal lung uptake is higher with dipyridamole compared to exercise scintigraphy. This higher ratio is likely due to the lower peak heart rate and resultant increase in thallium pulmonary transit time and extraction fraction. The increase in heart rate produced by dipyridamole is typically 20%–40% of baseline compared to typically greater than 100% increase with maximal exercise testing. Although the L/M ratio was higher with dipyridamole, the magnitude of this increase may be partially obscured by the relative method of quantification; higher myocardial blood flow and higher myocardial uptake with dipyridamole compared to exercise may decrease the L/M ratio. Higher absolute myocardial uptake, slower early myocardial clearance, higher blood levels of thallium and slower blood clearance (higher splancnic and liver uptake and clearance and lower skeletal muscle uptake) have been previously described with dipyridamole when compared to exercise scintigraphy (*22*). Both lung and myocardial uptake are significantly higher with dipyridamole compared to exercise stress testing when quantified by the planar method (*23*). Another possible mechanism for increased lung uptake is increased pulmonary blood volume with dipyridamole (*24*).

Lung uptake with dipyridamole using planar scintigraphy has been described (*16–18*) but lung uptake measured by SPECT has not been quantified. Previous reports with exercise SPECT quantification from the anterior projection image have shown high reproducibility and good correlation with the planar technique (*8,19*). Our method was very similar to that of Kahn et al. (*8*) and our results for exercise SPECT scintigraphy are comparable to those obtained by others (Table 6). For dipyridamole, the SPECT L/M ratio was also comparable to values obtained for adenosine (*9,19*). Several investigators have noted lower L/M ratios using SPECT and have suggested this difference was due to the difference in time of imaging (*8,19*).

In patients with CAD, the dipyridamole L/M ratio correlated with indices of resting left ventricular dysfunction. The best correlation was with resting left ventricular ejection fraction, but higher pulmonary capillary wedge pressure and lower cardiac index also showed correlation. In our population, lung uptake did not correlate with defect reversibility. Only 1/18 patients had evidence of dipyridamole-induced ischemia with severe hypotension, chest pain and severe ST segment depression on ECG.

TABLE 6
Normal Values for Lung-to-Myocardial Ratio

Author	Study	Method	L/M ratio*
Chin et al.	DI	SPECT	0.31 (0.05)
	EX	SPECT	0.23 (0.05)
Homma et al. (*5*)	EX	PLANAR	0.37 (0.07)
Ilmer et al. (*40*)	EX	SPECT	0.28 (0.05)
Iskandrian et al. (*9*)	AD	SPECT	0.36 (0.05)
Kahn et al. (*8*)	EX	SPECT	0.24 (0.04)
Kushner et al. (*3*)	EX	PLANAR	0.38 (0.08)
Mannting (*41*)	EX	PLANAR	0.36 (not stated)
	EX	SPECT	0.86 (diff method)
Nishimura et al. (*19*)	AD	PLANAR	0.33 (0.06)
	AD	SPECT	0.29 (0.06)
	AD	SPECT	0.30 (0.07) cath
Nordrehaug et al. (*21*)	EX	PLANAR	0.44 (0.08)
Okada et al. (*16*)	DI	PLANAR	0.42 (0.08)
Pennell et al. (*18*)	EX	PLANAR	0.33 (diff method)
	DI	PLANAR	0.43 (diff method)
Villaneuva et al. (*17*)	DI	PLANAR	0.41 (0.05)
	EX	PLANAR	0.39 (0.06)

*normal mean (1 s.d).
AD = adenosine; DI = dipyridamole; EX = exercise.

Miller et al. showed a small but significant increase in pulmonary capillary wedge pressure after dipyridamole infusion in a preliminary study of postinfarction patients. Small, transient increases in pulmonary capillary wedge pressure showed correlation with multivessel disease and redistribution, but did not correlate with increased lung uptake (*25*). In a larger study with adenosine, lung uptake showed correlation with resting left ventricular ejection fraction, perfusion defect size, the presence of collaterals and prior myocardial infarction. In agreement with our results, there was no significant correlation with the percent of defect reversibility (*19*). Mild (20%–40%) increases in double product, ''coronary steal'' and subendocardial ischemia (*26–28*) have been described, however, lung uptake may more commonly represent resting ventricular dysfunction. In resting thallium studies of postinfarction patients, Jain et al. showed that increased lung uptake correlated with congestive heart failure, thallium defect score, lower resting left ventricular ejection fraction and peak creatinine kinase levels (*29*). Therefore, increased lung uptake may not necessarily be due to dipyridamole induced left ventricular dysfunction.

Our analysis of clinical and angiographic variables did not show significant correlation with lung uptake. Further investigation in a larger patient population may show correlation of lung uptake with prior myocardial infarction similar to previous studies with adenosine (*19*) and planar dipyridamole (*17*).

Correlates of Left Ventricular Dilation

Scintigraphic left ventricular dilation showed correlation with resting hemodynamics including pulmonary capillary wedge pressure and left ventricular ejection fraction. These findings confirm the association of scintigraphic dilation with the hemodynamic changes of ventricular dilation. Of the angiographic variables, the presence of collaterals and the initial perfusion defect size showed some correlation with ventricular dilation. The clinical variables showed no significant correlation.

Correlates of Perfusion Defect Size

The strongest correlate of delayed defect size was lower resting left ventricular ejection fraction (r = 0.91, p = 0.004). Our findings are in agreement with a study by Stratton et al. which showed a good inverse correlation of delayed perfusion defect size and resting left ventricular ejection fraction in resting ^{201}Tl scintigraphy (*37*). These findings suggest that delayed perfusion defect size may provide a good estimate of regional resting left ventricular ejection fraction. This may potentially provide an accurate measurement of regional ventricular dysfunction and a more accurate method to assess the efficacy of therapy. Planar dipyridamole perfusion defect size and reversible perfusion defects have already shown powerful prognostic value in determining future cardiac events (*34*). Younis et al. have also shown that combined or reversible dipyridamole SPECT defects are powerful predictors of future cardiac events (*38*). These findings are similar to those reported for exercise SPECT scintigraphy which reported defect size as the most powerful prognostic indicator of survival (*39*).

Study Limitations

In Groups A and B it was not feasible to obtain confirmation of normal coronary arteries with cardiac catheterization. The likelihood for CAD, however, was less than 5% for the population with no perfusion defects on thallium scintigraphy assuming a disease prevalence as high as 30% in these asymptomatic subjects (*7*). In Group C (n = 18), the number of patients is relatively small due to exclusion of patients with catheterization and scintigraphy separated by greater than 2 wk. This was necessary to lessen the possibility of large changes in hemodynamics over time. Therefore, weak correlations between scintigraphic findings and clinical or angiographic findings may not have been detected due to lower statistical power.

In addition, medications may influence hemodynamic indices, however, analysis of patients treated with and without nitrates or diuretics showed no significant differences in pulmonary capillary wedge pressure. Large changes in ventricular ejection fraction are less likely within 2 wk without intervention. The results of this study more likely represent the population with extensive coronary artery disease due to selection based on the results of either the catheterization or scintigraphic results. Finally, this study provides observational information, and therefore, the mechanisms which underlie these observations have not been proven.

CONCLUSION

The normal thallium L/M ratio is higher in SPECT scintigraphy with dipyridamole compared to maximal exercise stress testing. This finding is likely related to a longer pulmonary transit time for dipyridamole compared to exercise stress testing. Quantitatively, the upper threshold for normal lung uptake is higher in dipyridamole scintigraphy. Qualitatively, mild lung uptake may be normal. The L/M ratio correlates with lower resting left ventricular ejection fraction, higher pulmonary capillary wedge pressure and lower cardiac index. Left ventricular dilation by scintigraphy correlates with hemodynamic indices of left ventricular failure including lower resting ejection and higher pulmonary capillary wedge pressure. Delayed perfusion defect size also shows high correlation with resting left ventricular ejection fraction. Lung uptake, left ventricular dilation and delayed perfusion defect size provide indices of resting ventricular dysfunction and a combination of these findings may be the best predictor of future cardiac events and prognosis. In addition, defect size may potentially provide a noninvasive regional measurement of ventricular function useful in the assessment therapy.

REFERENCES

1. Boucher CA, Zir LM, Beller GA, Okada RD, McKusick KA, Strauss HW, Pohost GM. 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. Canhasi B, Dae M, Botvinick E, et al. Interaction of "supplementary" scintigraphic indicators of ischemia and stress electrocardiography in the diagnosis of multivessel coronary disease. *J Am Coll Cardiol* 1985;6:581–588.
5. Homma S, Kaul S, Boucher C. Correlates of lung/heart ratio of thallium-201 in coronary artery disease. *J Nucl Med* 1987;28:1531–1535.
6. Gibson R, Watson D, Carabello B, Holt D, Beller G. Clinical implications of increased lung uptake of thallium-201 during exercise scintigraphy two wk after myocardial infarction. *Am J Cardiol* 1982;49:1586–1593.
7. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979;300:1350–1358.
8. 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.
9. Iskandrian AS, Heo J, Nguyen T, Lyons E, Paugh E. Left ventricular dilatation and pulmonary thallium uptake after single-photon emission computed tomography using thallium-201 during adenosine-induced coronary hyperemia. *Am J Cardiol* 1990;66: 807–811.
10. Ranhosky A, Kempthorne-Rawson J. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990;81:1205–1209.
11. Slutsky RA, Higgins CB. Thallium scintigraphy in experimental toxic pulmonary edema: relationship to extravascular pulmonary fluid. *J Nucl Med* 1984;25:581–591.
12. 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.
13. Kaul S, Homma S, Leavitt M, Finkelstein D, Okada RD, Boucher CA. Superiority of quantitative exercise thallium-201 variables in determining long-term prognosis in ambulatory patients with chest pain: a comparison with cardiac catheterization. *J Am Coll Cardiol* 1988;12:25–34.
14. Brown KA, Boucher CA, Okada RD, Guiney TE, Newell JB, Strauss HW, Pohost GM. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. *J Am Coll Cardiol* 1983;1:994–1001.
15. Nygaard TW, Gibson RS, Ryan JM, Gascho JA, Watson DD, Beller GA. Prevalence of high-risk thallium-201 scintigraphic findings in left main coronary artery stenosis: comparison with patients with multiple- and single-vessel coronary artery disease. *Am J Cardiol* 1984;53:462–469.
16. Okada RD, Yu-Hua D, 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.
17. 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.
18. Pennell DJ, Ell PJ. Whole-body imaging of thallium-201 after six different stress regimens. *J Nucl Med* 1994;35:425–428.
19. Nishimura S, Mahmarian JJ, Verani MS. Significance of increased lung thallium uptake during adenosine thallium-201 scintigraphy. *J Nucl Med* 1992;33:1600–1607.
20. Brown KA, Boucher CA, Okada RA, 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.
21. Nordrehaug JE, Danielsen R, Vik MH. Physiological inverse relationship between heart rate and thallium-201 lung uptake, clearance and lung/myocardial uptake ratio. *Eur Heart J* 1990;11:628–633.
22. Ruddy TD, Gill JB, Finkelstein DM, Strauss HW, McKusick KA, Okada RD, Boucher CA. Myocardial uptake and clearance of thallium-201 in normal subjects: comparison of dipyridamole-induced hyperemia with exercise stress. *J Am Coll Cardiol* 1987;10: 547–556.
23. Lee J, Chae SC, Lee K, Heo J, Iskandrian AS. Biokinetics of thallium-201 in normal subjects: comparison between adenosine, dipyridamole, dobutamine and exercise. *J Nucl Med* 1994;35:535–541.
24. Wilson RA, Okada RD, Boucher CA, Strauss HW, Pohost GM. Radionuclide-determined changes in pulmonary blood volume and thallium lung uptake in patients with coronary artery disease. *Am J Cardiol* 1981;51:741–748.
25. Miller DD, Scott RA, Riesmeyer JS, Chaudhuri TK, Blumhardt R, Boucher CA, O'Rourke RA. Acute hemodynamic changes during intravenous dipyridamole thallium imaging early ater infarction. *Am Heart J* 1989;118:686–694.
26. Beller GA, Holzgrefe HH, Watson DD. Intrinsic washout rates of thallium-201 in normal and ischemic myocardium after dipyridamole-induced vasodilatation. *Circulation* 1985;71:378–386.
27. Beller GA, Holzgrefe BS, Watson DD. Effects of dipyridamole-induced vasodilatation on myocardial uptake and clearance kinetics of thallium-201. *Circulation* 1983;68: 1328–1338.
28. Becker LC. Effect of nitroglycerin and dipyridamole on regional left ventricular blood flow during coronary artery occlusion. *J Clin Invest* 1976;58:1287–1296.
29. Jain D, Lahiri A, Raftery EB, et al. Clinical and prognostic significance of lung thallium uptake on rest imaging in acute myocardial infarction. *Am J Cardiol* 1990;65:154–159.
30. Leppo JA, O'Brien J, Rothendler KA, Getchell JD, Lee VW. Dipyridamole-thallium-201 scintigraphy in the prediction of future cardiac events after acute myocardial infarction. *N Engl J Med* 1984;310:1014–1018.
31. Boucher CA, Brewster DC, Darling RC, Okada RD, Strauss HW, Pohost GM. Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med* 1985;312:389–394.
32. Leppo J, Plaua J, Gionet M, Tumolo J, Paraskos JA, Cutler BS. Noninvasive

evaluation of cardiac risk before elective vascular surgery. *J Am Coll Cardiol* 1987;9:269–276.
33. Younis LT, Byers S, Shaw L, Barth G, Goodgold H, Chaitman BR. Prognostic value of intravenous dipyridamole thallium scintigraphy after an acute myocardial ischemic event. *Am J Cardiol* 1989;64:161–166.
34. Hendel RC, Layden JJ, Leppo JA. Prognostic value of dipyridamole thallium scintigraphy for evaluation of ischemic heart disease. *J Am Coll Cardiol* 1990;15:109–116.
35. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging. *Circulation* 1991;83:363–381.
36. Chouraqui P, Rodriques EA, Berman DS, Maddahi J. Significance of dipyridamole-induced transient dilation of the left ventricle during thallium-201 scintigraphy in suspected coronary artery disease. *Am J Cardiol* 1990;66:689–694.
37. Stratton JR, Speck SM, Caldwell JH, et al. Relation of global and regional left ventricular function to tomographic thallium-201 myocardial perfusion in patients with prior myocardial infarction. *J Am Coll Cardiol* 1988;12:71–77.
38. Younis LT, Byers S, Shaw L, Barth G, Goodgold H, Chaitman BR. Prognostic importance of silent myocardial ischemia detected by intravenous dipyridamole thallium myocardial imaging in asymptomatic patients with coronary artery disease. *J Am Coll Cardiol* 1989;14:1635–1641.
39. Iskandrian AS, Chae SC, Heo J, et al. Independent and incremental prognostic value of exercise single-photon emission computed tomographic thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993;22:665–670.
40. Ilmer B, Reijs AE, Fioretti P, Reiber JH. Comparative study of three different approaches on the estimation of the lung-heart ratio in thallium-201 scintigrams in relation to the extent of coronary artery disease and left ventricular function. *Eur J Nucl Med* 1991;18:252–258.
41. Mannting F. A new method of quantification of pulmonary thallium uptake in myocardial SPECT studies. *Eur J Nucl Med* 1990;16:213–222.

Generator-Produced Copper-62-PTSM as a Myocardial PET Perfusion Tracer Compared with Nitrogen-13-Ammonia

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The purpose of this study was to determine the suitability of ^{62}Cu-pyruvaldehyde bis(N^4-methylthiosemicarbazone) (^{62}Cu-PTSM) for estimating myocardial blood flow (MBF) over a wide range of flow by comparison with ^{13}N-ammonia ($^{13}NH_3$). **Methods:** PET studies using ^{62}Cu-PTSM and $^{13}NH_3$ were performed at rest and after pharmacological vasodilatation in 9 normal subjects and 13 patients with coronary artery disease (CAD). According to the microsphere method, values for the product of the extraction fraction and MBF (ExMBF) were calculated using both tracers. In static images, the percent uptake (normalized to the peak count) of each tracer was measured in patients with CAD. **Results:** The myocardial tracer distribution in the normal subjects was significantly higher in the inferior wall in the ^{62}Cu-PTSM studies and lower in the lateral wall in the $^{13}NH_3$ studies. The ExMBF values showed linear correlation for both tracers in a low flow range. In a high flow range, however, the ExMBF values for ^{62}Cu-PTSM were nonlinearly proportional to the increase of those for $^{13}NH_3$ ($y = 1.1x–0.21x^2$, $r = 0.81$). The percent uptake for both tracers at baseline well correlated linearly ($y = 10.4 + 0.88x$, $R = 0.91$). After pharmacological vasodilatation underestimation of blood flow with ^{62}Cu-PTSM was noted compared to that with $^{13}NH_3$ at high flows ($y = 31.8 + 0.63x$, $r = 0.76$). **Conclusion:** These results suggest that the MBF estimates using ^{62}Cu-PTSM in a low flow range may be as accurate as those with $^{13}NH_3$. In a high flow range, however, the extraction fraction of ^{62}Cu-PTSM is considered to be lower than that of $^{13}NH_3$, and this may limit the estimation of MBF with ^{62}Cu-PTSM after pharmacological vasodilatation.

Key Words: PET; myocardial blood flow; copper-62-PTSM; nitrogen-13-ammonia

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Noninvasive evaluation of myocardial blood flow (MBF) is one of the most important aspects in cardiology. MBF can be quantitatively assessed by: PET using ^{13}N-ammonia ($^{13}NH_3$) (*1–5*) or ^{15}O-water (*6–8*) produced by cyclotron, and ^{82}Rb-chloride (*9*) produced by a generator.

Positron-emitting radionuclides produced by a generator could potentially expand the application of PET to centers that do not have an in-house cyclotron. Several studies have shown that ^{82}Rb, in combination with pharmacologic stress, enables the accurate detection of coronary artery disease (CAD) (*10–12*). PET imaging with ^{82}Rb have relatively low intrinsic resolution because ^{82}Rb emits a high-energy positron that travels a long distance before colliding with an electron to produce two gamma photons (*13*). In addition, generation of ^{82}Sr requires a high-energy cyclotron, which makes this generator expensive. Therefore, alternative generator-produced radiopharmaceuticals for PET have long been desired. The ^{62}Zn/^{62}Cu radionuclide generator is a potential source of radiopharmaceuticals for PET. Copper-62-pyruvaldehyde bis(N^4-methylthiosemicarbazone) (^{62}Cu-PTSM) has been introduced as a new generator-produced perfusion tracer.

Previous investigations suggested that ^{62}Cu-PTSM represented a promising radiopharmaceutical for the evaluation of myocardial perfusion in animals and when applied to the normal human heart (*14–22*). This study was designed to determine the suitability of ^{62}Cu-PTSM for evaluating MBF in patients with CAD as well as in normal subjects over a wide range of flow by comparison with $^{13}NH_3$ (*23*).

MATERIALS AND METHODS

Tracer Preparation

Zinc-62 was obtained by ^{63}Cu(p,2n)^{62}Zn nuclear reaction using natural copper (^{63}Cu, 69.2%) as a target material. A ^{62}Zn/^{62}Cu generator was prepared with $^{62}ZnCl_2$ aqueous solution (1.1GBq, pH 5.0) by the method as previously reported (*24*). In this