

Biokinetics of Thallium-201 in Normal Subjects: Comparison Between Adenosine, Dipyridamole, Dobutamine and Exercise

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There are currently four common types of stress used with thallium-201 imaging in the diagnosis of coronary artery disease and risk assessment. The objective of this study was to examine the thallium biokinetics during exercise, adenosine, dipyridamole and dobutamine stress testing in 15 healthy volunteers. **Methods:** Each subject underwent planar ^{201}Tl imaging during maximal treadmill exercise testing, adenosine infusion (140 $\mu\text{g}/\text{kg}/\text{min}$ for 6 min), dipyridamole infusion (142 $\mu\text{g}/\text{kg}/\text{min}$ for 4 min) and dobutamine infusion (40 $\mu\text{g}/\text{kg}/\text{min}$). **Results:** Absolute myocardial thallium activity was greater after pharmacologic testing than exercise, ($p < 0.001$ each). Thus, the activity was 505 counts/pixel with adenosine, 491 counts/pixel with dipyridamole, 517 counts/pixel with dobutamine and 409 counts/pixel with exercise. The myocardial thallium clearance was lower with pharmacologic testing than exercise; 9.7%/hr with adenosine, 9.9%/hr with dipyridamole, 11.3%/hr with dobutamine and 13%/hr with exercise ($p < 0.01$ each). The thallium uptake and clearance in the lung and liver were also greater with pharmacologic stress testing than exercise ($p < 0.05$). **Conclusions:** Thus, thallium biokinetics are different during pharmacologic stress testing with adenosine, dipyridamole and dobutamine than during exercise. Diagnostic criteria for quantitative analysis of myocardial perfusion imaging must therefore be specific for the type of stress used.

Key Words: adenosine; dipyridamole; dobutamine; exercise; thallium-201

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Exercise ^{201}Tl imaging has been widely used in the diagnosis of coronary artery disease and risk assessment (1–4). In patients with exercise limitations, pharmacologic stress testing has been accepted as an alternative method to exercise testing (5–8). There are three pharmacologic agents that are currently used; dipyridamole, adenosine

and dobutamine. Previous studies show that the diagnostic accuracy of thallium imaging with each of these three pharmacologic agents is equivalent to that of exercise thallium imaging (7–12). The mechanism of dipyridamole-induced coronary vasodilation is an increased level of endogenous adenosine due to a decreased cellular reuptake mechanism (10,13). Compared to dipyridamole, adenosine has a more rapid onset of action and a shorter half-life (7,10). Dobutamine is a β_1 -specific agonist which causes increases in heart rate and contractility. Dobutamine is useful in patients who have asthma, severe obstructive pulmonary disease, high-grade atrioventricular block, arterial hypotension or those receiving methylxanthine derivatives or dipyridamole (9,14). The three pharmacologic agents and exercise have also been used with the newer technetium-labeled imaging agents and two-dimensional echocardiography.

The thallium kinetics with pharmacologic stress testing may be different from those with exercise (15–19). The purpose of this investigation was therefore to examine the myocardial and extracardiac thallium uptake and clearance using standard doses of intravenous dipyridamole, adenosine and dobutamine and compare the results to maximal exercise in healthy subjects.

MATERIALS AND METHODS

Study Subjects

The study subjects consisted of 15 healthy male volunteers aged 23–30 yr. These subjects were nonsmokers and took no cardiac medications with no history of cardiovascular disease or other systemic illness. All had normal physical examinations, electrocardiograms and chest x-rays. The protocol was approved by the institutional review board of the University Hospital and each subject signed a written consent form prior to the study. The anticipated whole-body and renal dosimetry for the four thallium tests were 1.2 rem and 8 rem, respectively.

Study Protocol

All 15 volunteers underwent ^{201}Tl myocardial perfusion scintigraphy four times; treadmill exercise testing, adenosine infusion, dipyridamole infusion and dobutamine infusion. The sequence of the tests was variable. All subjects fasted overnight prior to stress

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testing. The mean time interval between two consecutive studies was 15 days (range 7–32 days).

Stress Thallium Imaging Protocols

The heart rate, blood pressure and a 12-lead electrocardiogram were continuously monitored throughout the procedure. A dose of 2 mCi (74 MBq) of ^{201}Tl was injected during each test. The dose of the thallium was precisely determined with a dose calibrator (Capintec CRC-12, Ramsey, NJ) by measuring the radioactivity in the syringe before and after administration.

Exercise Thallium Imaging

The subjects performed symptom-limited maximal treadmill exercise testing using the Bruce protocol. All subjects achieved at least 85% of the maximum predicted heart rate and the test was stopped because of exhaustion. None had angina or ST segment depression during the test. At peak exercise, ^{201}Tl was injected and the subjects continued to exercise for one additional minute. Imaging was begun within 10 min of the termination of the exercise.

Adenosine Thallium Imaging

Adenosine (adenosine powder, Sigma, St. Louis, MO) was dissolved in 0.9% NaCl and prepared for intravenous use by the pharmacy of the University Hospital in a concentration of 3 mg/ml. Adenosine was administered intravenously using an infusion pump at a rate of 140 $\mu\text{g}/\text{kg}/\text{min}$ for 6 min. At the end of the third minute, ^{201}Tl was injected and imaging was begun within 10 min after thallium injection.

Dipyridamole Thallium Imaging

Dipyridamole was given intravenously at a rate of 142 $\mu\text{g}/\text{kg}/\text{min}$ for 4 min. Three minutes after the infusion was completed, ^{201}Tl was injected intravenously and imaging was begun within 10 min after thallium injection. Supplemental exercise was not used in this protocol.

Dobutamine Thallium Imaging

Dobutamine was infused at an initial rate of 5 $\mu\text{g}/\text{kg}/\text{min}$ for 3 min. The infusion was increased at 3-min intervals until a maximal infusion of 40 $\mu\text{g}/\text{kg}/\text{min}$ was reached. Thallium-201 was injected 1 min after the start of the maximal tolerable dose and infusion was continued for two additional minutes. Imaging was begun within 10 min of thallium injection.

Planar Thallium Imaging

Thallium-201 myocardial perfusion imaging was performed in the anterior, 45° left anterior oblique and 75° left anterior oblique views. The images were recorded for 8 min in each view using a single-crystal gamma camera equipped with a parallel-hole collimator and interfaced with a computer system (Microdelta, Siemens, Hoffman Estates, IL). A 20% energy window was centered at 68–80 keV and a 10% window on the 167 keV peaks of ^{201}Tl . All images were stored in a computer disk in a 128 × 128 matrix. Delayed images were obtained in a similar fashion, 3–4 hr later.

Quantitation of Thallium Uptake and Clearance

Regions of interest (ROIs) were assigned over the myocardium, the lung and the liver in both initial and delayed images. Six myocardial regions were examined; anterior and inferior segments in the anterior projection, septum and posterolateral segments in the 45° LAO projection and anterior and inferoposterior segments in the 75° LAO projection. The mean counts per pixel from a ROI in these areas was determined (Fig. 1). The thallium clearance was

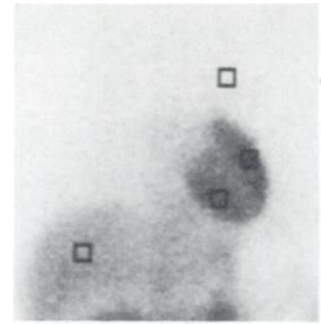


FIGURE 1. ROI assignment in the anterior projection (lung, anterior wall, inferior wall and liver).

measured as follows: (initial counts – delayed counts)/the initial counts. This was then divided by the time between the initial and delayed imaging to yield a clearance rate per hour. The exact time between the initial and delayed images was recorded in each subject.

Statistical Analysis

Data were expressed as mean \pm standard deviation when appropriate, and were compared using analysis of variance, Student's t-test and chi-square analysis using the SPSS/PC statistical software program (SPSS Inc., Chicago, IL). A p value of <0.05 was considered statistically significant.

RESULTS

Hemodynamic Responses

The exercise duration in the 15 healthy subjects was 12.9 \pm 1.7 min and the workload was 12.1 \pm 1.3 METS (Table 1). The baseline measurements of heart rate, blood pressure and double product were comparable with the four interventions. Maximum heart rate was higher with exercise than with pharmacologic testing. Similarly, the peak heart rate was higher with dobutamine than with adenosine and dipyridamole. There was no difference in the heart rate response between adenosine and dipyridamole. The systolic blood pressure increased during exercise and dobutamine infusion, but did not significantly change during adenosine or dipyridamole infusion. The double product was significantly higher during exercise than dobutamine.

Side Effects During Pharmacologic Stress Testing

There were no serious side effects. No subject required a specific antidote for reversal of side effects during any of the pharmacologic stress tests. Premature termination of the dobutamine before achieving the maximum dose occurred in one subject. The infusion was terminated at a rate of 30 $\mu\text{g}/\text{kg}$ because of ventricular premature beats. This arrhythmia subsided without treatment within 3 min after the infusion was discontinued. Common side effects are listed in Table 2. Most patients graded the side effects as mild and transient. First degree atrioventricular block appeared in one subject during adenosine infusion. More subjects preferred adenosine than dipyridamole or dobutamine (60% versus 27% versus 13%, $p < 0.05$). More subjects reported that dobutamine was the most intolerable agent, followed by adenosine and dipyridamole (67% versus 20% versus 13%, $p < 0.05$).

TABLE 1
Hemodynamic Responses in 15 Healthy Subjects

	Exercise	Adenosine	Dipyridamole	Dobutamine
Heart rate (bpm)				
Baseline	64 ± 7	63 ± 8	64 ± 11	62 ± 8
Peak	186 ± 12 ^{†*}	79 ± 19	82 ± 11	92 ± 29 [‡]
p-value	<0.001	<0.001	<0.001	<0.001
Systolic blood pressure (mmHg)				
Baseline	109 ± 11	112 ± 7	115 ± 10	110 ± 10
Peak	162 ± 14 [*]	109 ± 10	111 ± 10	175 ± 27 [‡]
p-value	<0.001	NS	NS	<0.001
Diastolic blood pressure (mmHg)				
Baseline	67 ± 9	70 ± 9	71 ± 8	69 ± 8
Peak	83 ± 8	65 ± 5	70 ± 9	81 ± 16
p-value	<0.001	<0.05	NS	<0.01
Double product (×10 ³)				
Baseline	70 ± 10	71 ± 12	73 ± 15	68 ± 8
Peak	301 ± 25 ^{*‡}	87 ± 25	91 ± 16	154 ± 25 [‡]
p-value	<0.001	<0.001	<0.001	<0.001

*p < 0.001 exercise versus adenosine and dipyridamole.

†p < 0.01 exercise versus dobutamine.

‡p < 0.001 dobutamine versus adenosine and dipyridamole.

§p < 0.001 exercise versus dobutamine.

There were no significant differences between adenosine and dipyridamole.

Myocardial and Extracardiac Thallium Uptake

These results are shown in Table 3. None of the normal subjects had perfusion abnormalities during any of the four interventions (Fig. 2). The myocardial thallium activity was higher during pharmacologic testing than exercise. In the anterior projection, the mean activity was 409 counts/pixel with exercise, 506 counts/pixel with adenosine, 491 counts/pixel with dipyridamole and 517 counts/pixel with dobutamine (p < 0.001 versus exercise, each) (Fig. 3). There were no differences between the three pharmacologic agents. The extracardiac activity in the lung and liver was higher during pharmacologic testing than exercise (Table 3).

TABLE 2

Side Effects of Pharmacologic Interventions in 15 Healthy Subjects

	Adenosine	Dipyridamole	Dobutamine
Chest pains	10	7	5
Flushing	8	8	3
Headaches	5	8	4
Choking	5	3	2
Dizziness	2	0	1
1° AV block	1	0	0
Epigastric pain	1	1	0
Dyspnea	6	1	0
Palpitations	0	0	5
Facial numbness	0	0	3
Nausea	0	0	3
Anxiety	0	0	2
Arrhythmias	0	0	1
Chills	0	0	3
Any symptom	13 (87%)	12 (80%)	11 (73%)

Myocardial and Extracardiac Thallium Clearance

These results are shown in Table 4. The myocardial thallium clearance was lower with adenosine, dipyridamole and dobutamine than exercise (Fig. 4). Also, lung thallium clearance was higher with adenosine and dipyridamole than exercise. The thallium clearance during dobutamine infusion was intermediate between exercise and adenosine or dipyridamole. Finally, the liver thallium clearance rates were higher with adenosine, dipyridamole and dobutamine than with exercise but again, there were no differences among the three pharmacologic agents (Fig. 4).

DISCUSSION

Thallium-201 Imaging With Adenosine, Dipyridamole and Dobutamine

Adenosine is a potent vasodilator in most vascular beds with the exception of the kidney (20,21). The coronary vasodilation is thought to be due to activation of purine A₂ receptors. Wilson et al. and Rossen et al. reported a maximal or near maximal coronary hyperemia with an intravenous dose of 140 µg/kg/min (22,23). The primary mechanism of action of dipyridamole is by inhibiting the cellular reuptake of endogenous adenosine and thus, increasing the interstitial adenosine concentration (7,24). The dipyridamole dose used in the United States with thallium imaging is 142 µg/kg/min for 4 min although higher doses are used in Europe, especially with echocardiography (25). Rossen et al. compared the hemodynamic effects of adenosine and dipyridamole and showed that the decrease in coronary vascular resistance was greater with adenosine but the increase in coronary blood flow velocity was similar with both agents (23). Dobutamine is a synthetic sympathomi-

TABLE 3
Thallium Activity in Six Myocardial, Lung and Liver ROIs (mean counts/pixel) in 15 Healthy Subjects

	Exercise	Adenosine	Dipyridamole	Dobutamine
Anterolateral	408 ± 58	501 ± 94 [†]	477 ± 103 [‡]	501 ± 78
Inferior	410 ± 54	510 ± 96	504 ± 113 [‡]	544 ± 81 [†]
Posterolateral	387 ± 47	508 ± 89 [†]	493 ± 95	537 ± 92 [†]
Septum	389 ± 52	531 ± 109 [†]	518 ± 108 [†]	558 ± 99 [†]
Anterior	340 ± 42	497 ± 95 [†]	456 ± 75 [†]	460 ± 89 [†]
Inf-Post	362 ± 39	524 ± 94 [†]	503 ± 77 [†]	526 ± 75 [†]
Lung	115 ± 14	192 ± 21 [†]	191 ± 25 [†]	183 ± 20 [†]
Liver	109 ± 20	442 ± 76 [†]	440 ± 79 [†]	504 ± 46 [†]

*p < 0.001 versus exercise.

[†]p < 0.01 versus exercise.

[‡]p < 0.05 versus exercise.

Inf-Post = inferior-posterior.

metic amine with predominant β_1 -agonist activity resulting in increased myocardial contractility and myocardial oxygen consumption (26, 27). At higher doses (>20 $\mu\text{g}/\text{kg}/\text{min}$), dobutamine produces a β_2 and alpha-adrenergic effect resulting in increases in heart rate and blood pressure. The pharmacokinetic profile of dobutamine is favorable; the tissue half-time is about 2 min and the mean duration of action is less than 10 min. Doses of up to 40 $\mu\text{g}/\text{kg}/\text{min}$ have been used safely for imaging purposes (9).

Hemodynamic Responses

The hemodynamic responses in this study were similar to those reported by others (26–29). Dobutamine increased the heart rate, blood pressure and double product (28). Adenosine and dipyridamole caused much smaller increases in heart rate and double product and an insignificant decrease in blood pressure. The double product was higher during exercise than any of the pharmacologic agents. Mannerling et al. compared the effects of 20 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine to exercise in patients 3 wk after myocardial infarction (29). They suggested that ischemia produced by dobutamine is predominantly caused by an increase in inotropy rather than an increase in heart rate as it occurs with exercise.

Side Effects

Side effects were frequent during pharmacologic stress testing, but were well tolerated and short-lived. No specific

antidote was needed in any of the subjects. In only one subject was maximal dobutamine dose not achieved because of ventricular arrhythmias. Dobutamine has been known to increase the risk of ventricular tachyarrhythmias, especially at higher doses, because of acceleration of diastolic depolarizations (30). The incidence of side effects was not significantly different among the three agents.

Thirteen subjects had at least one symptom during adenosine infusion, 12 during dipyridamole infusion and 11 during dobutamine infusion. These results are similar to those seen in patients with suspected coronary artery disease. Although the sample size is small, more patients preferred adenosine than dipyridamole or dobutamine. In fact, more patients ranked dobutamine as the most intolerable pharmacologic agent. These results are different from those observed by Martin et al. which showed that most patients preferred dobutamine than adenosine or dipyridamole (28). Several studies have reported the use of mild exercise along with dipyridamole (31–35). Compared to dipyridamole alone, there was a significant increase in peak heart rate and blood pressure associated with supplemental exercise.

FIGURE 2. Examples of myocardial images in the anterior projection during exercise (left upper quadrant), adenosine (right upper), dipyridamole (left lower) and dobutamine (right lower).

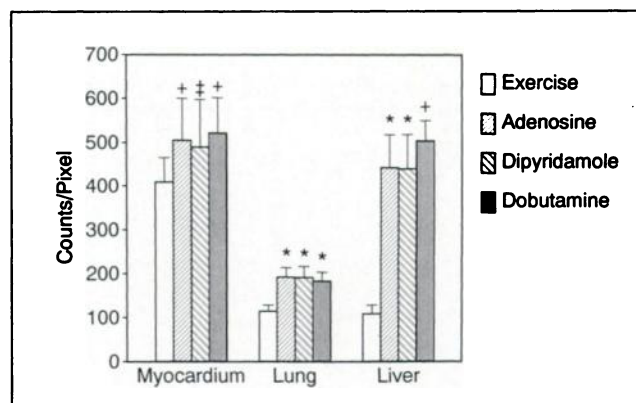
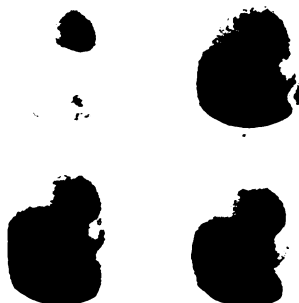


FIGURE 3. Average count densities from the myocardium, lung and liver during exercise, adenosine, dipyridamole and dobutamine stress testing. *p < 0.001, [†]p < 0.01 and [‡]p < 0.05 versus exercise, respectively.

TABLE 4
Thallium Clearance from Cardiac and Extracardiac ROIs

	Exercise	Adenosine	Dipyridamole	Dobutamine
Anterolateral	12.9 ± 1.0	9.8 ± 1.7*	9.7 ± 2.2†	11.0 ± 1.9
Inferior	13.0 ± 1.3	9.7 ± 1.7†	10.1 ± 2.3†	11.6 ± 1.7†
Posterolateral	12.4 ± 1.1	10.3 ± 1.5†	10.4 ± 2.3†	11.3 ± 1.5‡
Septum	12.0 ± 1.0	10.3 ± 1.9†	10.5 ± 2.3	11.4 ± 1.6‡
Anterior	11.7 ± 1.2	11.0 ± 1.9	10.8 ± 1.9	11.3 ± 1.8
Inf-Post	11.7 ± 1.2	10.7 ± 1.6	11.0 ± 1.6	11.5 ± 1.3
Lung	7.9 ± 1.7	9.8 ± 1.2‡	10.4 ± 1.2†	8.7 ± 1.5
Liver	-3.0 ± 5.5	12 ± 2.6*	12.5 ± 3.7*	11.5 ± 1.7†

*p < 0.001 versus exercise.

†p < 0.01 versus exercise.

‡p < 0.05 versus exercise.

Inf-Post = inferior-posterior.

Noncardiac side effects were less with combined exercise and dipyridamole.

Myocardial Thallium Uptake

Myocardial uptake of ²⁰¹Tl in normal subjects was greater after pharmacologic testing than exercise. The average myocardial activity was 1.3 times greater with adenosine, 1.2 times greater with dipyridamole and 1.4 times greater with dobutamine (see Table 3 and Fig. 3). There were no significant differences in the myocardial activity among the three pharmacologic agents. The myocardial thallium uptake depends on flow, extraction and clearance. Based on Saperstein's fractionation principle, myocardial thallium activity is related to coronary blood flow as a percent of the cardiac output (36). The ratio of the coronary blood flow-to-cardiac output is greater during adenosine or dipyridamole infusion than exercise because the increase in coronary blood flow is more, while the increase in cardiac output is less (10). The similar myocardial thallium activities with adenosine and dipyridamole, however, do not necessarily prove that the coronary blood flow was also similar because the extraction fraction of ²⁰¹Tl tends to

level off at a flow rate above 2.5 times the baseline flow level (1).

Previous studies have shown a higher myocardial-to-background ratio resulting in visually superior thallium images when dipyridamole protocol was supplemented with low-level exercise (31-35). Brown et al. found a 68% increase in coronary sinus flow with supplementation of an isometric handgrip as compared with dipyridamole alone (32). However, Rossen et al. demonstrated no significant change in coronary flow reserve as measured with a coronary Doppler catheter (33). They suggested that their results differed from Brown et al. because of limitations intrinsic to coronary sinus thermodilution technique. Furthermore, they proposed that the addition of an isometric handgrip to dipyridamole testing might well improve the accuracy of the technique as a result of factors other than a change in coronary flow such as increase in double product, and adrenergic stimulation.

Dobutamine produced hemodynamic changes similar to exercise. In patients with and without coronary artery disease, dobutamine results in a dose-dependent increase in coronary blood flow, cardiac output and left ventricular contractility and, to a lesser extent, in heart rate and mean arterial blood pressure (37-40). Meyer et al. (41) and Stephen et al. (39) reported that during infusion of dobutamine at a rate of 8-10 µg/kg/min, patients with a normal coronary angiogram had a 130%-150% increase in coronary perfusion. Also dobutamine produced a twofold increase in cardiac output at a dose of 32 µg/kg/min in dogs and patients with coronary artery disease (41, 42).

Our thallium data suggest that the increase in coronary blood flow was probably greater than the increase in cardiac output with dobutamine at a dose of 40 µg/kg/min. It is, however, possible that because of a greater increase in myocardial oxygen demand, the thallium extraction with dobutamine may differ from that from dipyridamole and adenosine, and further studies are necessary to measure the coronary flow and cardiac output during these interventions. Weich et al. found a logarithmic decrease in

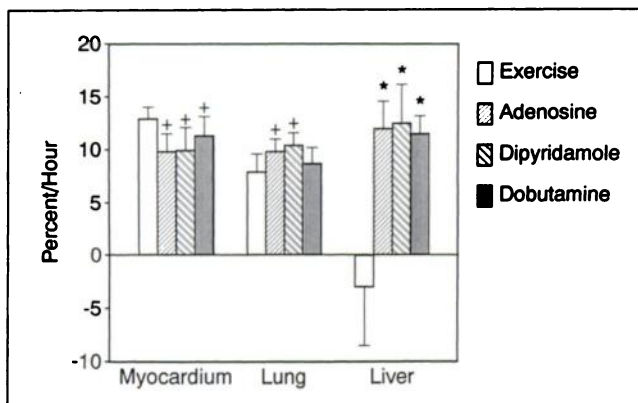


FIGURE 4. Thallium-201 washout from the myocardium, lung and liver after exercise, adenosine, dipyridamole and dobutamine stress testing. *p < 0.001 and †p < 0.01 versus exercise, respectively.

thallium uptake when coronary blood flow was increased in excess of oxygen demand (43).

Myocardial Thallium Clearance

The myocardial thallium clearance was slower with pharmacologic interventions than exercise (see Table 4 and Fig. 4). There were no significant differences between the three pharmacologic agents. Of note, in the 75° left anterior oblique projection, the differences between the pharmacologic interventions and exercise was not visible. This projection is the last projection to be obtained almost 20 min after completion of the exercise.

The myocardial clearance with exercise was slightly lower than that observed in the anterior and 45° left anterior oblique projection. Myocardial clearance with dobutamine was slightly but insignificantly higher than that of dipyridamole and adenosine, and was somewhat intermediate between the clearance rates of these two agents and exercise. Lower myocardial thallium clearance with pharmacologic intervention rather than exercise, despite a higher initial thallium activity, may be due to a lower gradient (myocardium to blood pool). The lower gradient is probably related to higher blood pool activity caused by a higher liver clearance as shown in this study (see below). Previous studies have also suggested differences in clearance rates in rest, pharmacologic and exercise thallium studies. Even in exercise studies the clearance is lower in patients with submaximal than maximal stress (15-17, 44, 45).

Extracardiac Thallium Activity and Clearance

The lung and liver thallium activities were higher with pharmacologic interventions than exercise, but again there were no significant differences between the three pharmacologic agents (see Table 4 and Fig. 4). The differences in regional thallium activity between pharmacologic tests and exercise are probably related to differences in regional blood flows (46). With exercise, the increase in oxygen delivery to exercising muscle is mediated by increases in cardiac output, oxygen extraction and redistribution of the cardiac output from the liver and splanchnic tissue to the exercising muscles. In contrast with pharmacologic vasodilatation with adenosine and dipyridamole, there are no important changes in regional flow distribution.

The lung uptake of thallium after pharmacologic tests was also greater than after exercise. This may be related to a slower pulmonary transit time caused by a lower heart rate facilitating thallium extraction. A decrease in pulmonary vascular resistance may also enhance lung thallium uptake. This decrease has been observed with adenosine and with dobutamine (47). The lung thallium clearance was faster with adenosine and dipyridamole than with exercise. Also, the liver clearance rate of thallium was higher with adenosine, dipyridamole and dobutamine than with exercise. These differences might be due to higher thallium activity in the lung and liver in the initial images with pharmacologic agents than with exercise (see Tables 3 and 4 and Figs. 3 and 4).

In conclusion, there are important differences in the myocardial and extracardiac uptake and clearance of ²⁰¹Tl between pharmacologic stress testing and exercise testing. These differences suggest the need for stress-specific normal files when quantitative analysis is used to examine the myocardial perfusion. In a previous study, we observed that if the file obtained during exercise is used with adenosine studies, the defect size is overestimated (48). Finally, the differences in cardiac and extracardiac activities combined with differences in clearance rates are important parameters that may affect the accuracy of quantitative analysis when interpolative background subtraction methods are used.

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