Whole-Body Imaging of Thallium-201 After Six Different Stress Regimens

Dudley J. Pennell and Peter J. Ell

Institute of Nuclear Medicine, University College London School of Medicine, London, England

There are a number of stress techniques in common use for ^{201}Tl myocardial imaging but few studies have been performed comparing the biodistribution of ^{201}Tl in each case. **Methods:** We studied 36 normal patients after six different stress regimens by whole-body imaging, 40 min after ^{201}Tl injection. The stress regimens were exercise, dipyridamole, adenosine or dobutamine alone in standard doses and exercise combined with a vasodilator (dipyridamole or adenosine). **Results:** Cardiac uptake expressed as a percentage of whole body uptake was greater for the vasodilators compared with exercise ($p < 0.005$), and this difference was unaffected by combining either vasodilator with exercise. Intermediate results were found with dobutamine. Heart-to-liver ($p < 0.01$) and abdomen ($p < 0.05$) ratios were greater for exercise compared with the vasodilators, and this difference was also unaffected by combining the exercise with either vasodilator. Heart-to-lung ratios were highest with any stress involving exercise ($p < 0.05$). The heart-to-background ratios with dobutamine were similar to the vasodilators. **Conclusion:** Vasodilator infusion yields higher cardiac ^{201}Tl uptake than exercise, but when given alone this results in poor heart-to-background ratios. Combining either vasodilator with exercise maintains the high cardiac uptake, but substantially improves the heart-to-background ratios to levels similar to exercise alone. Dobutamine stress produces an intermediate cardiac uptake, and heart-to-background ratios similar to the vasodilators. Therefore, optimal imaging conditions are obtained by stress which combines a vasodilator with exercise.

Key Words: thallium-201; stress; whole body imaging

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Thallium-201 imaging is useful in the noninvasive investigation of coronary artery disease, both in the diagnosis of chest pain, and in the definition of prognosis (*1,2*). Clinical studies have mainly used exercise stress but many other techniques have been used. These fall into two categories: the physical and the pharmacological. Except for dynamic exercise (treadmill or ergometer), physical stresses such as atrial pacing, cold pressor stress and mental pressure have not been widely used, but pharmacological stresses have been extensively investigated. These include the vasodilators, dipyridamole (*3,4*) and adenosine (*5,6*), the vasoconstrictors, angiotensin and ergometrine and the inotropic agents, dobutamine (*7,8,9*) and less commonly adrenaline or isoprenaline. Intravenous dipyridamole has been used in combination with exercise stress (*10–13*). However, there is little comparative data on the distribution of ^{201}Tl produced by the various commonly used stress regimens. The aim of this study is to compare the uptake by the heart and surrounding organs after stress and to attempt to establish which type of stress yields optimal ^{201}Tl distribution for imaging.

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For correspondence and reprints contact: Dr. D.J. Pennell, Magnetic Resonance Unit, Royal Brompton Hospital, Sydney Street, London, U.K. SW3 6NP.

METHODS

Patients

Patients were recruited prospectively from those undergoing routine thallium imaging who had a low pretest likelihood of coronary artery disease (by age, sex and presence of chest pain criteria), in whom unequivocally normal stress tomographic images were found. A total of 36 patients were studied with whole-body imaging after stress. Their mean age and weight was 55 yr and 66 kg, respectively, and 28 were male. There were no significant differences between stress groups for age, weight and male-to-female ratio.

Stress

Six different stress regimens were performed: exercise, dipyridamole, adenosine, dobutamine, exercise with dipyridamole and exercise with adenosine. Exercise was performed on a bicycle ergometer to maximal levels in all cases, with the heart rate reaching >85% of the age-predicted maximum. The protocol consisted of a basal workload of 25 W, increasing every 2 min by 25 W. For the studies using dipyridamole, 0.56 mg/kg was infused intravenously over 4 min and thallium was given 2 min after the end of the infusion. For the studies combining dipyridamole with exercise, the dipyridamole infusion was given in the same way commencing with the start of exercise, and the thallium was given at the maximum exercise level. For the studies using adenosine alone, an infusion was given at 140 μg/kg/min for 6 min, and thallium was given at 4 min. For the studies combining adenosine and exercise, the adenosine infusion began with the start of exercise and thallium was injected at maximum exercise level. For the studies using dobutamine, an infusion was started at 10 μg/kg/min and increasing to a maximum of 40 μg/kg/min according to patient tolerance. At the appropriate time during stress as described above, the UKs recommended dose of 84 MBq of ^{201}Tl was given intravenously.

Imaging

Patients were imaged with tomography in the normal way after stress to determine whether normal myocardial perfusion was present. If so, consent was obtained for whole-body imaging. In all cases, this was started 40 min after stress. A single anterior pass was acquired using a General Electric XCT camera (GE systems, Milwaukee, WI) and a low-energy general-purpose collimator with dual energy settings for thallium (69 and 169 keV with a 20% window). The duration of scanning was approximately 18 min and the number of counts collected was approximately 1 million.

Analysis of Images

The images were transferred to a work station for analysis. All images were reviewed blind to patient details and the stress technique used. The whole-body counts were obtained from a region of interest over the entire image. Counts were also obtained from hand drawn areas of interest over the heart, liver, lungs (excluding the heart) and abdomen (excluding the liver). The percentage of cardiac uptake was calculated as the ratio of cardiac counts to total body counts. Heart-to-liver, -lung and -abdomen ratios were calculated as the ratio of mean cardiac counts to the mean counts in the liver, lung or abdomen.

Statistical Analysis

The data was analyzed using statistical software (Statistica Ltd, Statsoft, Letchworth, Herts, UK). Overall analysis for differences among the 6 groups was performed using analysis of variance. Intergroup differences were analyzed by posthoc analysis using the Newman-Keuls technique. The difference in heart-to-lung ratio between exercise and nonexercise groups was analyzed using the unpaired t-test. Probability values of $p < 0.05$ were considered significant.

RESULTS

Stress

In the exercise group alone, the mean exercise level achieved was 129 W. All patients tolerated the full dose of adenosine and dipyridamole, but the mean tolerated dose of dobutamine was 25 μg/kg/min. In both groups undergoing combined vasodilator and exercise stress, the mean exercise level achieved was 104 W, but this was not significantly lower than that achieved by the subjects undergoing exercise alone.

Cardiac Uptake of Thallium-201

There were significant differences between the groups for the cardiac uptake of thallium (overall $F = 7.0$ $p < 0.0002$, Table 1, Fig. 1). The highest uptake was seen in the vasodilator groups and the lowest uptake in the exercise group. The high uptake seen within the vasodilator groups was not significantly attenuated by the addition of exercise (p = ns in both cases). All 4 stress groups using the vasodilators with or without exercise showed significantly higher cardiac uptake than the group with exercise alone ($p < 0.005$ in all cases). The dobutamine group had higher uptake than the exercise group ($p < 0.05$), but the significance between dobutamine and the 4 stress groups using vasodilators was borderline ($p = 0.04$ versus adenosine, $p = 0.09$ versus dipyridamole with exercise).

TABLE 1
Cardiac Uptake and Heart-to-Background Ratios in Groups of Patients According to Stress Modality

	Cardiac Uptake	Heart/Liver	Heart/Gut	Heart/Lung
Aden	5.40 (0.24)	1.13 (0.15)	1.34 (0.24)	2.58 (0.36)
AdenEx	5.31 (0.25)	1.55 (0.18)	2.00 (0.31)	3.05 (0.30)
Dip	5.40 (0.27)	1.16 (0.28)	1.45 (0.26)	2.34 (0.36)
DipEx	5.15 (0.21)	1.60 (0.30)	1.90 (0.43)	2.85 (0.40)
Dob	4.76 (0.37)	1.15 (0.11)	1.61 (0.26)	2.69 (0.19)
Ex	4.34 (0.26)	1.75 (0.27)	2.07 (0.27)	3.06 (0.53)

The mean (s.d.) is given for each group (abbreviations as in Fig. 1).

Heart-to-Liver Ratio

There were significant differences between the stress groups in the heart-to-liver ratio (overall $F = 8.7$ $p < 0.0001$, Table 1, Fig. 2). The highest ratio was seen in the exercise group, but this was not significantly greater than the ratios for the combined vasodilator and exercise groups. The lowest ratios were seen in the vasodilator and dobutamine groups, and all these ratios were lower than the groups involving exercise ($p < 0.01$ in all cases).

Heart-to-Abdomen Ratio

There were significant differences between the groups in the heart-to-abdomen ratio (overall $F = 6.0$ $p < 0.006$, Table 1, Fig. 3). Again, the highest ratio was seen in the exercise group, but this was not significantly higher than that seen in the vasodilator combined with exercise groups. All three groups involving exercise showed higher ratios than the vasodilator or dobutamine groups ($p < 0.05$). The differences between the stress groups with vasodilator alone and dobutamine was not significant. The differences between the stress groups with exercise and dobutamine were of borderline significance ($p = 0.06$ versus exercise, $p = 0.08$ versus adenosine with exercise).

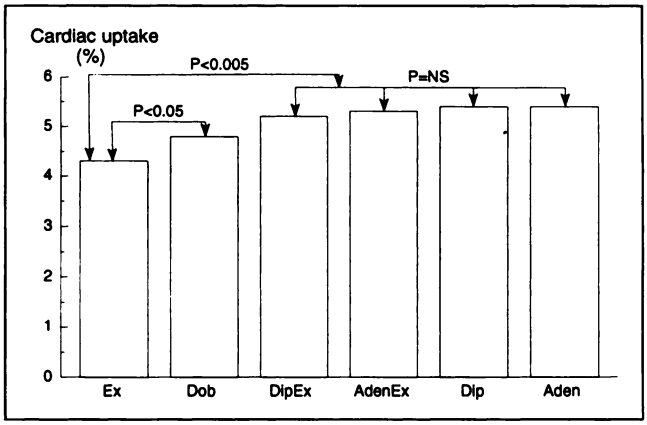

FIGURE 1. Cardiac uptake expressed as the percent of cardiac counts to whole-body counts. Uptake was lowest for exercise and highest for any stress using vasodilators. Dobutamine occupied an intermediate position (Ex = exercise alone, Dob = dobutamine alone, DipEx = dipyridamole with exercise, AdenEx = adenosine with exercise, Dip = dipyridamole alone, Aden = adenosine alone).

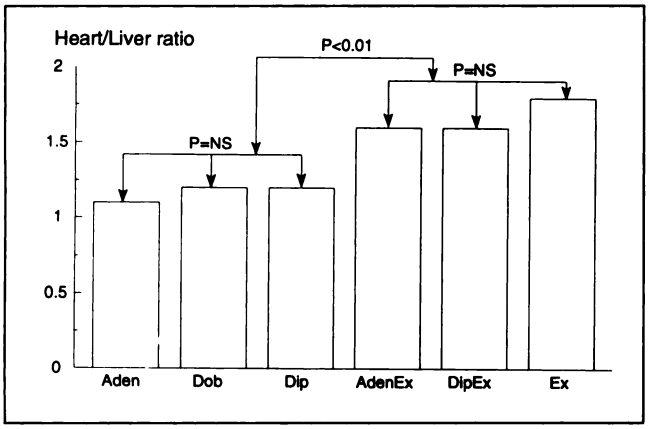

FIGURE 2. The heart-to-liver ratio in the stress groups. There was no significant difference between exercise and exercise combined with a vasodilator, and all these three stress groups were better than vasodilator or dobutamine alone (abbreviation same as Fig. 1).

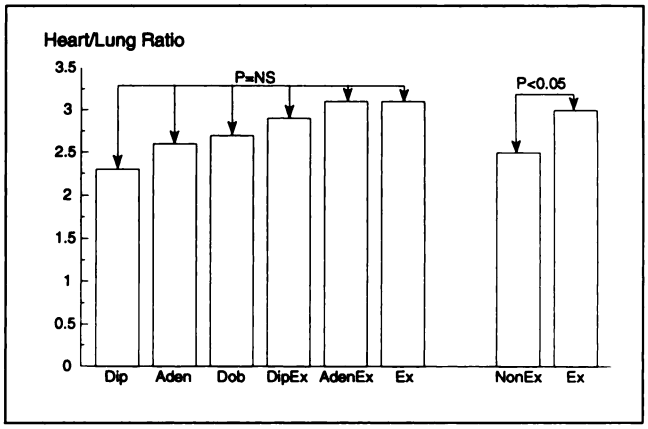

FIGURE 4. The heart-to-lung ratio in the stress groups. Overall, the differences between stress groups failed to achieve statistical significance, but combining the exercise and nonexercise groups together showed higher ratios for any stress involving exercise (abbreviations as in Fig. 1, with NonEx = non exercise stress; Ex = exercise stress).

Heart-to-Lung Ratio

There were no overall significant differences between the 6 groups in the heart-to-lung ratio (overall $F = 1.6$ $p = 0.2$, Table 1, Fig. 4). However, there was a trend favoring the exercise groups, and the data was reanalyzed comparing exercise and nonexercise groups. The exercise groups had a higher heart-to-lung ratio ($t = 2.4$ $p < 0.05$).

DISCUSSION

Study Aims

Exercise stress has been used extensively for thallium imaging, but problems occur when the patient is unable to achieve his or her exercise potential because of physical or psychological problems. Although there are no surveys of the size of this problem, estimates have suggested that perhaps a third of patients fall into this category. Unfortunately, the use of submaximal exercise for thallium imaging has been shown to result in lower sensitivity for the detection of coronary artery disease, and therefore adequate assessment may be compromised (*14–16*). The use of pharmacological agents as an alternative to exercise has grown in popularity because of the reduced need for patient cooperation, and comparisons between exercise and stress with dipyridamole, adenosine and dobutamine have shown similar clinical results. However, there have been very few direct comparisons of the biodistribution of thallium with these agents. This study was designed to compare cardiac uptake and heart-to-background ratios in six stress groups: exercise alone; dipyridamole, adenosine, or dobutamine alone; and combined exercise with dipyridamole or adenosine. We used whole-body imaging to determine the distribution of thallium after stress and to determine relative cardiac uptake (*17*). While such a method has no role to play in the detection of coronary artery disease, it is useful to determine the biodistribution of thallium.

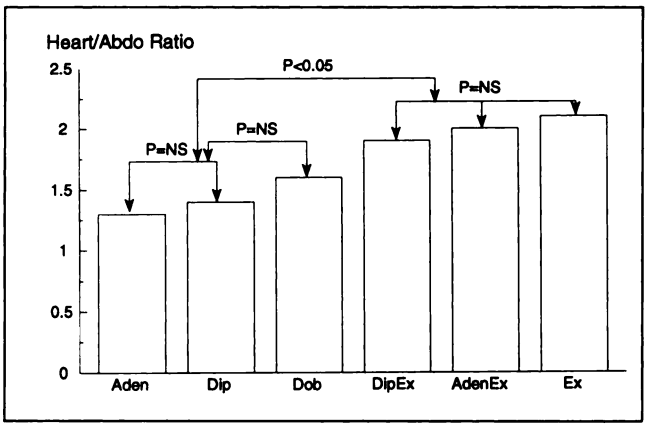

FIGURE 3. The heart-to-abdomen ratio in the stress groups. The results are very similar to those in Figure 2 (abbreviation same as Fig. 1).

Comparison of Stress Modalities

The results show that cardiac uptake is highest with the vasodilators, and lowest with exercise alone. This may result from the higher coronary blood flow that results from the use of vasodilators which may reach 4–6 times baseline (*18,19*) compared with the estimated 2–4 times basal flow seen with exercise alone (*20,21*). Dobutamine occupied an intermediate position producing a higher uptake than exercise alone, with the differences between dobutamine and any stress involving the vasodilators being of borderline statistical significance. The increase in coronary flow with dobutamine is not well studied but has been reported as 2.1 times baseline for 10 μg/kg/min (*22*) and 2.9 times baseline at 40 μg/kg/min (*23*). There was no significant difference between cardiac uptake with the vasodilators and combined vasodilators with exercise. This implies that changes in coronary flow are dominated by the vasodilator action, and that no significant detriment in cardiac counts occurs with combined vasodilator and exercise stress. Although previous studies have noted higher cardiac uptake with

dipyridamole (*24*) and adenosine (*25*) infusion compared with exercise alone, these did not use whole-body imaging and did not examine the effect on uptake of combining the vasodilator with exercise.

Combined Vasodilator with Exercise

The heart-to-background ratios were invariably optimal for imaging using exercise alone, and generally poor using the vasodilators or dobutamine alone. The addition of exercise to either dipyridamole or adenosine significantly improved heart-to-background ratios, such that they were not significantly different from the results obtained by exercise alone. The finding that combined exercise and dipyridamole stress improves heart-to-background ratios has been shown before in comparison with intravenous dipyridamole alone (*10,11*), but there are few comparisons with exercise alone (*13*). We believe this is the first confirmation of a similar effect with the use of adenosine. Dobutamine produced heart-to-background ratios that were similar to those produced using vasodilators alone. Thus, although dobutamine has important effects on the double product during infusion which makes it similar to exercise stress (*7*), it causes extra-cardiac vasodilatation which is more comparable to the vasodilators.

Study Limitations

Imaging was performed with a single anterior pass, but if a dual-headed system had been available this would have been ideal for preventing underestimation of renal thallium activity. This suggests that the heart-to-whole body ratios may be overestimated. In addition, whole-body imaging was performed 40 min after stress at which time heart activity ratios would have differed from those immediately following stress. This occurred because the patients were recruited on the basis of their normality by tomography, and it was considered unethical to perform the study by repeated stress and thallium injection.

CONCLUSION

Cardiac uptake is optimal when vasodilators are used, but poor heart-to-background ratios result. The addition of exercise to either the standard infusion regimens of dipyridamole or adenosine improves the heart-to-background ratios so that they are similar to those produced with exercise alone, and therefore incorporation of exercise to the standard vasodilator regimens results in optimal distribution of ^{201}Tl for cardiac imaging.

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