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Adenosine Combined With Dynamic Exercise for Myocardial Perfusion Imaging

DUDLEY J. PENNELL, MA, MD, MRCP, SOPHIE I. MAVROGENI, MD,
SANDRA M. FORBAT, MB, MRCP, STEFAN P. KARWATOWSKI, MD, MRCP,
S. RICHARD UNDERWOOD, MD, MRCP

London, England, United Kingdom

Objectives. **This study investigated whether combining exercise with adenosine would reduce the adverse effects of adenosine vasodilation.**

Background. **Adenosine vasodilation is effective for perfusion imaging but causes frequent unpleasant noncardiac adverse effects, high noncardiac tracer uptake and occasional arrhythmias.**

Methods. **Of 500 consecutive patients referred for thallium-201 myocardial perfusion imaging, 407 were randomized to three study groups: 6 min of adenosine infusion alone; 6 min of adenosine with submaximal exercise; or symptom-limited exercise with continuous adenosine. Minimal detectable differences are presented; a significance level of 0.05 with a power of 80% is assumed.**

Results. **There was no difference among the three groups in sensitivity and specificity (overall 96% and 78%, minimal detectable differences 5.5% and 11%, respectively) for detection of coronary artery disease or stenosis in individual coronary arteries. There was a trend toward improved sensitivity in the combined exercise groups compared with that in the adenosine-only group (98% vs. 93%, $p = 0.07$, minimal detectable difference 6%). Noncardiac side effects were reduced by 43% in the exercise groups ($p < 0.0001$), and major arrhythmias were reduced by 90% ($p < 0.0001$). There was no effect on minor arrhythmias (25% vs. 22%, $p = 0.6$, minimal detectable difference 12%). The heart/background ratios were higher in the exercise groups (all $p < 0.02$). Each ratio was correlated with the exercise level achieved (all $p < 0.001$). The reversibility score increased with exercise ($p = 0.04$), as did the number of patients and segments with reversible defects (both $p = 0.03$).**

Conclusions. **Combining exercise with adenosine infusion reduced the noncardiac side effects of vasodilation and major arrhythmias while improving redistribution and heart/background ratios. These findings may be clinically important. Although maximal exercise with adenosine infusion produced optimal results, the improvement over the submaximal exercise protocol was minor, and this has the advantage of being simple and achievable within the normal 6-min duration of the adenosine infusion.**

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Adenosine is a naturally occurring purine that causes coronary hyperemia comparable in intensity to papaverine in a high proportion of patients at an intravenous dose of 140 μg/kg body weight per min (1). Because of its very short half-life of 4 to 10 s (2,3), adenosine has a rapid onset and cessation of action that make it attractive for the clinical manipulation of coronary flow, most importantly during myocardial perfusion scintigraphy. In addition, it is associated with a low incidence of serious sequelae (4). Numerous studies (5–7) have demonstrated its efficacy in comparison with both exercise stress and coronary angiography. It may be used in patients whose exercise capabilities are impaired for noncardiac reasons to allow confident assessment of coronary arterial function, which otherwise might be suboptimal (8–10). However, there are some drawbacks including specific contraindications (asthma [11,12], sinoatrial disease [13], high grade atrioventricular [AV] block [14]), attenuation of effect (recent caffeine [15–17] or methylxanthine ingestion [18]), potentiation of effect (recent dipyridamole ingestion [19,20]) and high extracardiac tracer uptake, and the high frequency of adverse effects (21). In the present study, we examined the effect of combining dynamic exercise with adenosine infusion for thallium myocardial perfusion imaging to determine whether such a combination could improve image quality and reduce side effects.

Methods

Randomization and stress protocols. Five hundred consecutive patients were considered for inclusion in the study. There were 93 exclusions (19%) for the following reasons: asthma in 30, sinoatrial disease in 1, current participation in a syndrome X study requiring exercise stress only in 26, recent caffeine intake in 22, dipyridamole treatment in 6 and specific physician requests for exercise stress in 8. The remaining 407 patients (81%) were allocated randomly to one of three stress proto-

From the Nuclear Medicine Department, Royal Brompton Hospital, London, England, United Kingdom. This research was supported in part by the Coronary Artery Disease Research Association (CORDA), London and the British Heart Foundation, London, England, United Kingdom.

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Address for correspondence: Dr. Dudley J. Pennell, Magnetic Resonance Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, United Kingdom.

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cols: adenosine only at 140 μg/kg per min for 6 min (adenosine-only group); adenosine at 140 μg/kg per min for 6 min combined with submaximal exercise of 2 min at 25 W and 4 min at 50 W (adenosine with submaximal exercise group); or maximal exercise combined with adenosine at 140 μg/kg per min continued throughout the exercise period (adenosine with maximal exercise group). The subjects were positioned semisupine on a bicycle ergometer with the feet a little below the body, and 80 MBq of thallium-201 (the maximal U.K. permissible dose) was injected 2 min before the end of the stress protocol. Two venous cannulas were inserted into the arm, one for adenosine infusion and one for thallium injection. The electrocardiogram and blood pressure were recorded every 2 min.

Patient symptoms. Patients were requested to report any symptoms during the stress protocols, and in addition they were asked directly about symptoms every 2 min.

Imaging. Emission tomographic imaging was begun within 5 min of the injection of thallium, and redistribution imaging was performed 4 h later in an identical manner. A Sopha Medical DS7 large field of view gamma camera was used. Thirty-two planar images (64 × 64-pixel matrix, 400-mm field of view, 30 s/image) were acquired over a 180° arc from the right to the left posterior oblique position. The planar images were reconstructed into transaxial tomograms of 1-pixel depth using backprojection and a Ramp-Hanning filter with a 0.75-pixel^{-1} cutoff frequency. From these, oblique tomograms were reoriented in the vertical and horizontal long-axis and short-axis planes.

Image analysis. The myocardium was divided into nine segments representing the anterior, septal, lateral and inferior walls, each with an apical and basal segment, and the apex. Each segment was scored according to its thallium activity: 0 = *normal* (80% to 100%); 1 = *mild reduction* (60% to 80%); 2 = *moderate reduction* (40% to 60%); 3 = *severe reduction* (20% to 40%); 4 = *nearly absent activity* (<20%) (22). Total stress and redistribution scores varied from 0 (normal) to a theoretic maximum of 36. A reversibility score was calculated by subtracting the redistribution score from the stress score. Comparison with the coronary anatomy was achieved by allocating the anterior wall and septum to the territory of the left anterior descending coronary artery, the inferior wall to the right coronary artery and the lateral wall to the left circumflex coronary artery. The apex was assigned to the left anterior descending coronary artery if it occurred alone or in conjunction with an anterior or septal defect; otherwise it was assigned to an inferior or lateral defect as appropriate. Because of the known overlap of the left circumflex and right coronary artery territories (22), comparisons were also made with a combined territory.

Heart/background ratios were calculated by drawing regions of interest on the anteroposterior planar view around the heart, lungs and liver and the abdomen excluding the liver. This was performed for both stress and redistribution images.

Angiographic analysis. When coronary angiography was performed, the angiograms were reported visually without knowledge of the thallium findings. Significant coronary artery disease was defined as at least one narrowing >50% in diameter in a major or branch vessel.

Statistical analysis. All groups were analyzed by intention to treat, and thus a patient unable to exercise who was allocated to an exercise group was analyzed as a member of the relevant exercise group and assigned an exercise performance of zero. Calculation of sensitivity and specificity for detection of coronary artery disease was performed only in patients who had undergone coronary angiography. Comparisons among the three groups were performed using analysis of variance (CSS Statistica 3.1, Statsoft Inc., Letchworth, United Kingdom). Differences between groups were analyzed using the Scheffé F test. When the submaximal and maximal exercise groups were combined to form a single exercise group for comparison with the adenosine-alone group, comparisons were performed using the unpaired t test. Differences between exercise and nonexercise groups for patient symptoms and arrhythmias were analyzed by chi-square analysis. Differences between the patient group baseline characteristics were examined with either analysis of variance or chi-square analysis. The variation in heart/background ratios according to stress level achieved was calculated with linear regression analysis. All calculations of study power quoted for major end points in the text describe the minimal detectable difference in real units detectable with a significance value of $p < 0.05$ and 80% power, given the number of patients studied.

Results

Baseline patient characteristics. The distribution between the groups with regard to age, gender, weight, number of patients with coronary angiography and baseline hemodynamic measurements is shown in Table 1. There were no significant differences in any baseline characteristic between the groups, with the exception of calcium channel blocking agent treatment. Overall, 56% of patients had coronary angiography.

Hemodynamic changes during stress. The changes in heart rate, systolic and diastolic blood pressures and rate-pressure product among the three groups are shown in Figure 1. Adenosine infusion alone caused a significant and progressive increase in heart rate, with a small progressive decrease in systolic and diastolic blood pressures. Overall, rate-pressure product increased by 16%. Additional exercise caused significantly greater increases in heart rate and rate-pressure product than adenosine alone. Systolic and diastolic blood pressures also increased compared with the decrease seen with adenosine alone.

Tolerance to exercise. In the submaximal exercise group (n = 128), exercise was performed to 25 W by 123 patients (96%) and 50 W by 104 (81%). In the maximal exercise group (n = 145), exercise was performed to 25 W by 145 patients (100%), 50 W by 135 (93%), 75 W by 106 (73%), 100 W by 46 (32%), 125 W by 19 (13%) and 150 W by 4 (3%).

Sensitivity and specificity. The overall sensitivity for detection of coronary artery disease in all patients who had angiog-

Table 1. Baseline Patient Characteristics for the Three Stress Groups

	Aden (n = 134)	AdSub (n = 128)	AdMax (n = 145)	p Value
Age (yr)	57.9	58.6	56.8	0.4
Weight (kg)	73.3	83.8	75.4	0.4
Men/women	100/34	91/37	107/38	0.8
Coronary angiography	75 (52%)	73 (57%)	78 (58%)	0.7
Diseased vessels	1.5 ± 1.1	1.4 ± 1.1	1.6 ± 1.1	0.4
Previous MI	54 (40%)	44 (34%)	50 (35%)	0.5
Rest defect score	3.7 ± 5.5	3.3 ± 5.4	3.0 ± 5.1	0.6
Hemodynamic variables				
SBP (mm Hg)	141	141	141	0.9
DBP (mm Hg)	88.1	85.5	86.6	0.2
HR (beats/min)	73.6	71.5	74.2	0.3
RPP ($\times 10^3$ mm Hg/min)	10.4	10.1	10.5	0.5
Drugs				
Beta-blockers	47 (35%)	46 (36%)	42 (29%)	0.4
Calcium-blockers	58 (43%)	59 (46%)	43 (30%)	0.01
Nitrates	45 (34%)	42 (33%)	40 (28%)	0.5
ACE inhibitors	14 (10%)	12 (9%)	17 (12%)	0.8
Digoxin	7 (5%)	3 (2%)	2 (1%)	0.2
Diuretic agents	22 (16%)	27 (21%)	16 (11%)	0.08
Amiodarone	4 (3%)	3 (2%)	4 (3%)	0.9
Aspirin	43 (32%)	42 (33%)	54 (37%)	0.6

Data presented mean value ± SD or number (%) of patients, unless otherwise indicated. Aden = adenosine only; AdMax = adenosine with maximal exercise; AdSub = adenosine with submaximal exercise; DBP (SBP) = diastolic (systolic) blood pressure; HR = heart rate; MI = myocardial infarction; RPP = rate-pressure product.

raphy was 96% (175 of 181), with a specificity of 78% (35 of 45), but there was no significant difference among the three groups for either variable (Fig. 2) (minimal detectable difference for sensitivity and specificity 5.5% and 11%, respectively). The sensitivity and specificity values for each arterial territory are shown in Table 2. There were no significant differences between the stress groups in detection of disease in the individual arteries except for a borderline significant result for the right coronary artery. When adenosine alone was considered versus adenosine combined with any level of exercise, there was a trend toward a higher overall sensitivity in the combined adenosine and exercise group with borderline statistical significance (98% vs. 93%, $p = 0.07$, minimal detectable difference 6%) but no differences for the individual arteries. In any event, there was no demonstrable decrement in either sensitivity or specificity (minimal detectable difference 12%) by the addition of exercise to adenosine.

Patient symptoms. There was a significant 43% reduction in the incidence of noncardiac side effects in the groups with combined adenosine and exercise (adenosine 57% vs. combined stress 32%, $p < 0.0001$, minimal detectable difference 15%). This improvement was present in both the submaximal and maximal exercise groups, and there were no statistically significant differences in the incidence of adverse effects between the two exercise groups (Fig. 3). There was a relatively small increase in cardiac side effects (dyspnea and fatigue but not chest pain), as would be expected from the additional exercise (adenosine 55% vs. combined stress 67%, $p < 0.02$).

Arrhythmias. Arrhythmias were classified as *major* (supraventricular tachycardia, atrial fibrillation, ventricular tachycardia, second- or third-degree heart block, sinus bradycardia <40/min, sinus arrest and ventricular arrest) or *minor* (ventricular or atrial premature beats, couplets or new bundle branch block). There was a 90% reduction in the incidence of major arrhythmias between the adenosine-only and combined adenosine with exercise groups (11.2% vs. 1.1%, $p < 0.0001$, minimal detectable difference 8% (Fig. 4, Table 3). There was no significant variation between groups for minor arrhythmias (25.4% vs. 22.3%, $p = 0.6$, minimal detectable difference 12%), but overall, all recorded arrhythmias were reduced by 23% in the combined adenosine with exercise group ($p < 0.004$). There was one cardiac arrest, which occurred in the adenosine-only group. The patient became asystolic for ~1 min but made a full recovery. Subsequent 24-h electrocardiography revealed evidence of covert sinoatrial disease (13).

Heart/background ratios. There was significant variation among the three groups for heart/liver and heart/gut ratios, with higher ratios in the combined adenosine with exercise groups (minimal detectable difference in ratio 0.1) (Fig. 5). In addition, the maximal exercise group had higher values than the submaximal group. The heart/background ratio was compared with the exercise level achieved, and there was a significant positive correlation for all three ratios, although with considerable scatter and rather modest overall r values (heart/liver ratio, $r = 0.37$; heart/gut ratio, $r = 0.29$; heart/lung ratio, $r = 0.18$, all $p < 0.001$). After redistribution the difference between the groups was less pronounced, but the heart/liver ratio remained higher in the adenosine with maximal exercise group (minimal detectable change in ratio 0.06).

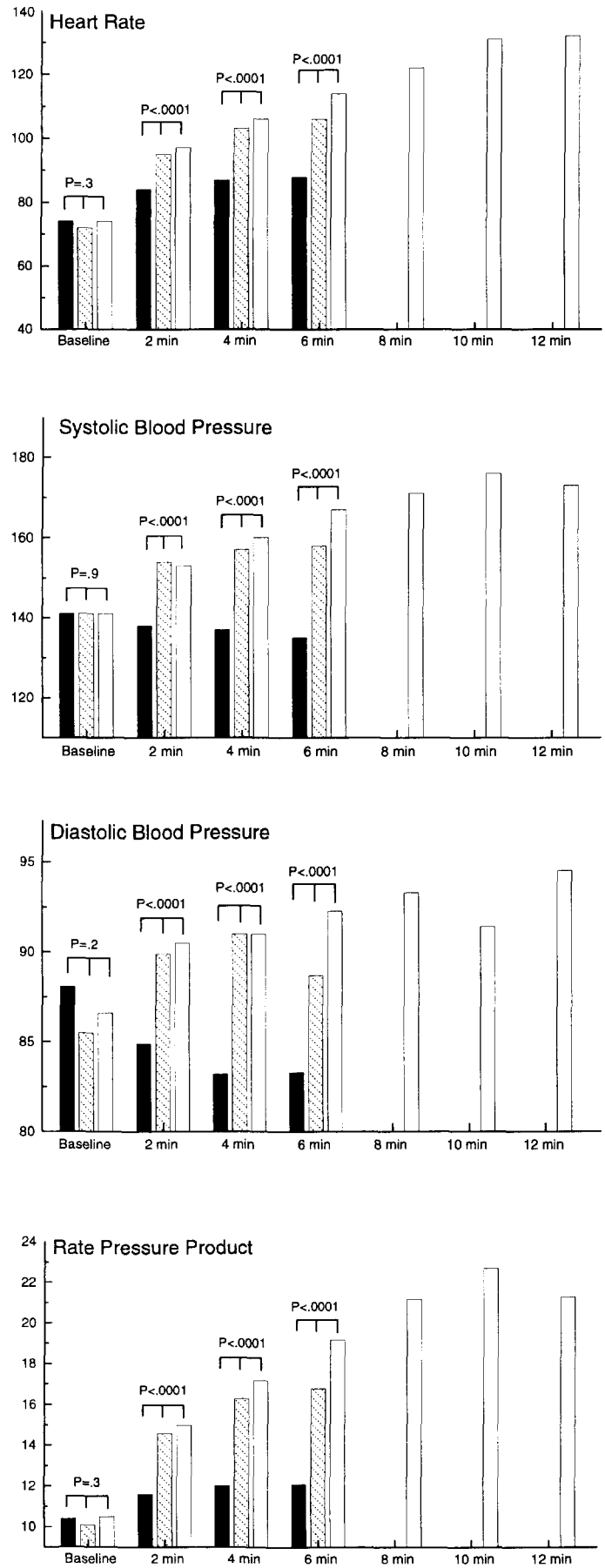


Figure 1. Changes in hemodynamic variables among the three stress groups. The hemodynamic effects typical of exercise dominate those seen with adenosine alone and **(solid bars)** when exercise and adenosine are performed together. **Dotted bars** = adenosine with submaximal exercise; **open bars** = adenosine with maximal exercise.

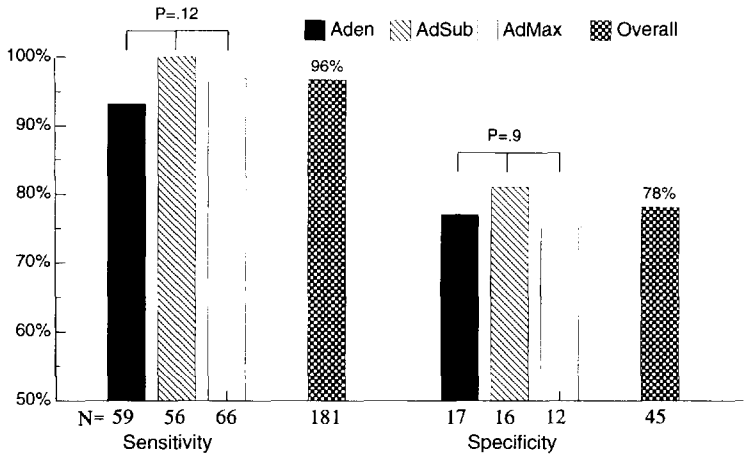


Figure 2. Sensitivity and specificity for the three stress groups and overall results. Aden = adenosine alone; AdSub = adenosine with submaximal exercise; AdMax = adenosine with maximal exercise.

Perfusion defect scores and reversibility. There was no significant difference between groups in the mean perfusion defect score after stress or redistribution (Fig. 6), but the difference between the scores, which is a marker of reversibility, showed significant variation (F = 3.0, p = 0.04, minimal detectable difference 1.2), with significantly greater reversibility for the maximal exercise group (p = 0.04) and greater reversibility of borderline significance for the submaximal group (p = 0.07) compared with adenosine-alone group. When the data were reanalyzed to exclude patients with normal thallium imaging, in whom reversibility was not at issue, the variability in reversibility between groups increased (F = 4.9, p = 0.008). Linear regression analysis of reversibility in this group against peak heart rate achieved during stress showed a significant relation with greater reversibility with higher heart rate, although once again, considerable scatter was present (r = 0.15, y = 2.5 + 0.03x, p = 0.01). To determine whether this increased redistribution was clinically important, the data were reanalyzed with respect to the number of patients or segments in each stress group who had fixed only (with no reversibility) or reversible perfusion defects (Table 4). The analysis showed significantly more reversible segments and a trend toward fewer fixed segments in the exercise groups. The analysis was significant for both fixed and reversible defects in terms of patients.

Discussion

Symptoms associated with adenosine infusion. Adenosine has a very short half-life, which is useful for limiting the duration of adverse effects, but this also results in an intense onset of coronary hyperemia. The majority of patients therefore experience some symptoms, the most common of which is flushing. The vasodilation and hypotension also cause other problems, such as headache, nausea, dizziness and anxiety, which in some patients are amplified into a morbid fear. Dyspnea is common because of activation of peripheral respiratory centers (probably the carotid body) (23), and chest pain is frequent because of either true myocardial ischemia (redirection of subendocardial blood flow to the subepicardium) (24) or direct activation of myocardial nociceptors, which may occur without ischemia in normal subjects (25,26).

The intensity of such adverse effects is reported as moderate by most patients but can be severe, and a method of reducing their frequency or intensity would be useful. The present study shows that combining adenosine with exercise is effective in reducing these adverse effects. There are several possible explanations: 1) the hemodynamic response is dominated by the exercise component, so that the normal decrease in systolic and diastolic blood pressures is reversed, and this may improve symptoms such as dizziness. 2) The catecholamine drive associated with exercise assists in reducing the splanchnic, cerebral and skin vasodilation that is responsible for symptoms, such as nausea, headache and flushing. 3) There is probably a psychologic component in that concentration on exercise is a distraction, and the patient has less opportunity to appreciate sensations caused by the adenosine infusion. Exercise also brings an element of familiarity to the test and in part helps to satisfy patient expectations.

Table 2. Sensitivity and Specificity for Detection of Disease by Coronary Artery

	Sensitivity					Specificity				
	Aden	AdSub	AdMax	p Value	Overall	Aden	AdSub	AdMax	p Value	Overall
LAD	89%	93%	91%	0.8	90%	83%	77%	65%	0.21	75%
RCA	85%	79%	98%	0.04	81%	64%	71%	59%	0.6	54%
LCx	44%	70%	58%	0.12	46%	79%	93%	76%	0.07	76%
RCA/LCx	85%	86%	95%	0.22	89%	71%	87%	76%	0.4	79%

LAD (LCx, RCA) = left anterior descending (left circumflex, right) coronary artery; other abbreviations as in Table 1.

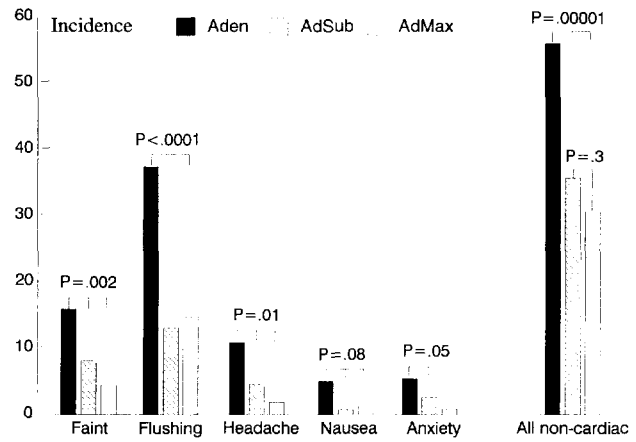
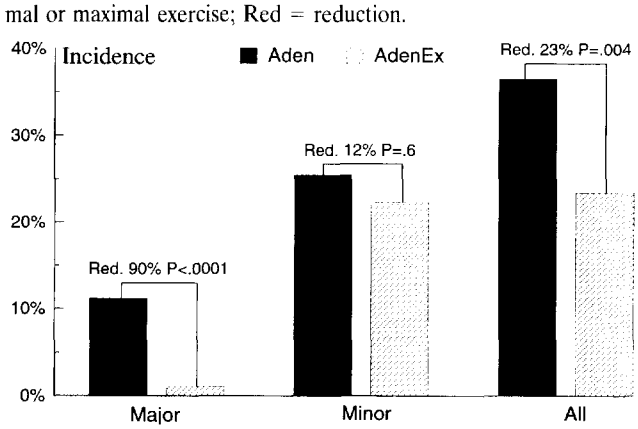


Figure 3. Noncardiac symptoms in the adenosine-alone and combined adenosine with exercise groups. Abbreviations as in Figure 2.

Tolerance of exercise during adenosine infusion. It is well established that adenosine infusion alone is a very effective means of manipulating coronary blood flow to produce heterogeneous perfusion in the presence of coronary artery disease and that for this purpose it is as effective as exercise stress (5,6). A major attraction of this and other pharmacologic techniques is that very little patient cooperation is required, allowing confident assessment of stress myocardial perfusion in those patients who are physically or psychologically incapable of adequate exercise. However, even patients with limited exercise capacity are usually able to perform some exercise, as is clearly demonstrated by this study in which only 5 (1.8%) of 273 patients randomized to exercise were unable to exercise at all. Beneficial symptomatic and other improvements may be seen with the lowest levels of exercise, and therefore combined adenosine with exercise stress is likely to be widely applicable.

Sensitivity and specificity. It is important that the sensitivity and specificity of combined exercise with adenosine infusion not be compromised in comparison with adenosine alone. In this study there was no evidence of a decrement in the diagnostic performance of the adenosine infusion with combined exercise at either submaximal or maximal levels compared with adenosine alone (5). Indeed, there was a trend toward a small overall improvement in diagnostic sensitivity with additional exercise. Importantly, there was no loss in specificity, which might have resulted from exercise-related artifacts, such as upward creep (27).

Figure 4. Difference in major and minor arrhythmias between the adenosine-only and combined adenosine with exercise groups. Aden = adenosine alone; AdenEx = adenosine combined with either submaximal or maximal exercise; Red = reduction.



Reduction in major cardiac arrhythmias. The substantial reduction in major cardiac arrhythmias was an important finding of this study (Fig. 4, Table 3). Atrioventricular block is the most common important arrhythmia during adenosine infusion (second degree 4.1%, third degree 0.8%) (4), and this occurs because of activation of A_1 receptors (28). Its incidence in this study was reduced by additional exercise (second- or third-degree block with adenosine alone 4.7%, adenosine combined with exercise 0.4%, p = 0.003). This was probably because of the modulating influence of increased circulating catecholamine levels. Sinus bradycardia/arrest was also less common with additional exercise (adenosine alone 4.7%, adenosine combined with exercise 0.4%, p = 0.003). These reductions are useful clinically despite the finding that the majority of the cases of AV block caused by adenosine are self-limiting because their occurrence may result in the need to stop the adenosine infusion in 8% of patients (4) and may cause considerable alarm to stress technicians and the patient. It is noteworthy that the only life-threatening episode occurred in a patient receiving adenosine only, who developed atrial and ventricular arrest. Sinoatrial disease may have been responsible, as reported elsewhere (13).

Improvement in heart/background ratios. Substantially improved heart/background ratios were seen in the combined adenosine with exercise groups compared with those in the adenosine-alone group. This again results from catecholamines circulating during exercise, which cause a decrease in splanchnic blood flow. Such improvements are clinically useful in reducing difficulties in the interpretation of inferior wall activity. Although the differences in the ratios were diminished after redistribution, the heart/liver ratio remained higher in the maximal exercise group than in the adenosine-alone group. Regression analysis of the ratios against exercise show that considerable interpatient variability exists in the heart/background ratios but that, overall, the greater the exercise level achieved the greater the heart/background ratio. Despite this finding, the improvement in heart/background ratio is present at low levels of exercise, which most patients would be expected to achieve.

Defect scores and reversibility. There was no difference among the groups with respect to stress and redistribution scores for the extent and severity of the perfusion defects found, but it was possible to observe trends favoring the exercise groups for higher stress and lower redistribution scores. The difference between the scores reflects reversibility of the defects, and in this case, the maximal exercise group showed greater reversibility than the adenosine-only group (p = 0.04). The submaximal exercise group also had a higher reversibility score, which was of borderline significance (p =

Table 3. Arrhythmias in the Three Stress Groups

	Ventr. Arrest	Sinus Arrest	3° Ht Block	2° Ht Block	VT	Sinus Brady	AF	SVT	PVC	PAC	Couplets
Aden	1	2	2	4	1	4	1	—	22	11	1
AdSub	—	—	—	1	—	—	—	1	17	7	2
AdMax	—	—	—	—	—	1	—	—	21	14	—
p value	0.3	0.11	0.11	0.04	0.3	0.04	0.3	0.7	0.3	0.5	0.7

AF = atrial fibrillation; Brady = bradycardia; Ht = heart; PAC = premature atrial contractions; PVC = premature ventricular contractions; SVT = supraventricular tachycardia; Ventr = ventricular; VT = ventricular tachycardia; 2° = second-degree; 3° = third-degree; other abbreviations as in Table 1.

0.07). There is no obvious baseline difference between the groups, such as the incidence or size of previous infarction, to explain this difference, and the additional exercise is therefore the most likely cause. This implies that the addition of exercise to the adenosine favorably influences redistribution in the heart such that defects are more likely to be interpreted as reversible rather than fixed. The clinical importance of this was demonstrated by the significantly higher number of patients and segments with reversible defects in the two exercise groups than in the adenosine-alone group.

This probably results from the faster heart rate caused by the additional exercise, which is associated with an increased myocardial washout of thallium (29,30). A significant relation between reversibility score and peak heart rate achieved during exercise was shown in those patients whose stress perfusion defect score was >0, which supports this notion.

Previous studies combining vasodilation with exercise. There have been a number of studies examining the role of combined exercise with dipyridamole vasodilation, but we believe this to be the first study to examine the role of exercise

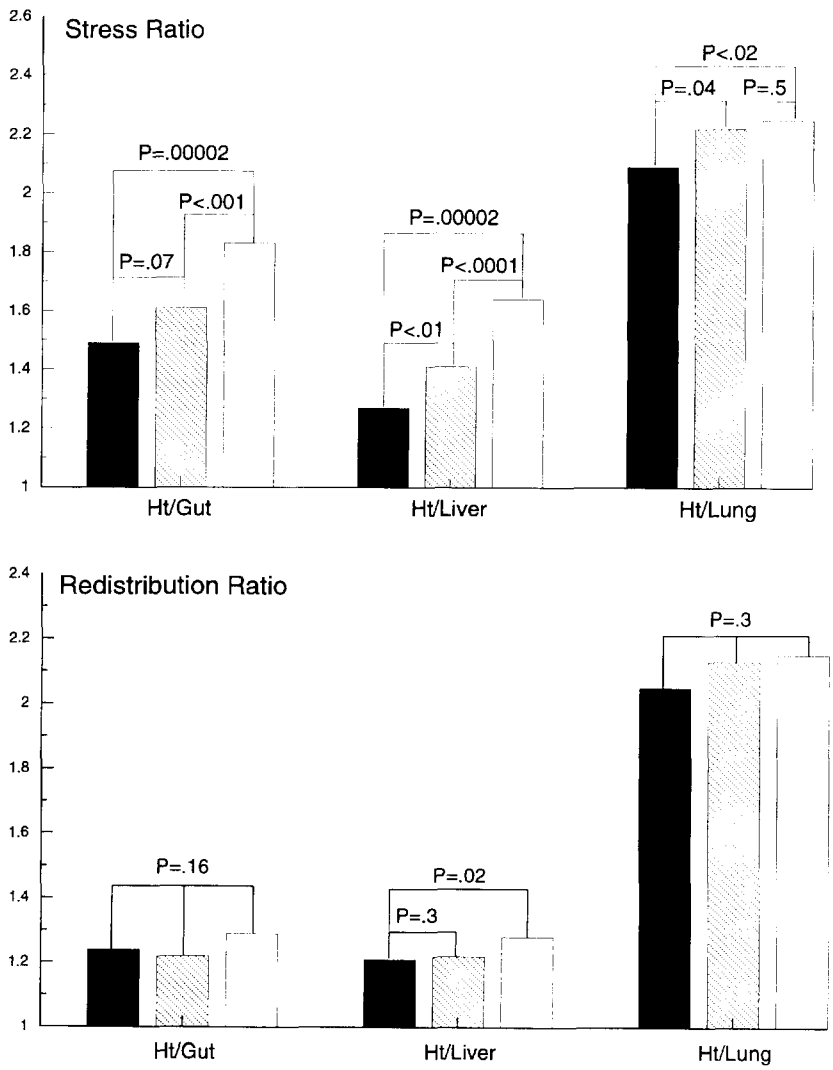


Figure 5. Heart (Ht)/background ratios in the three stress groups after stress and after redistribution. **Solid bars** = adenosine alone; **hatched bars** = adenosine with submaximal exercise; **open bars** = adenosine with maximal exercise.

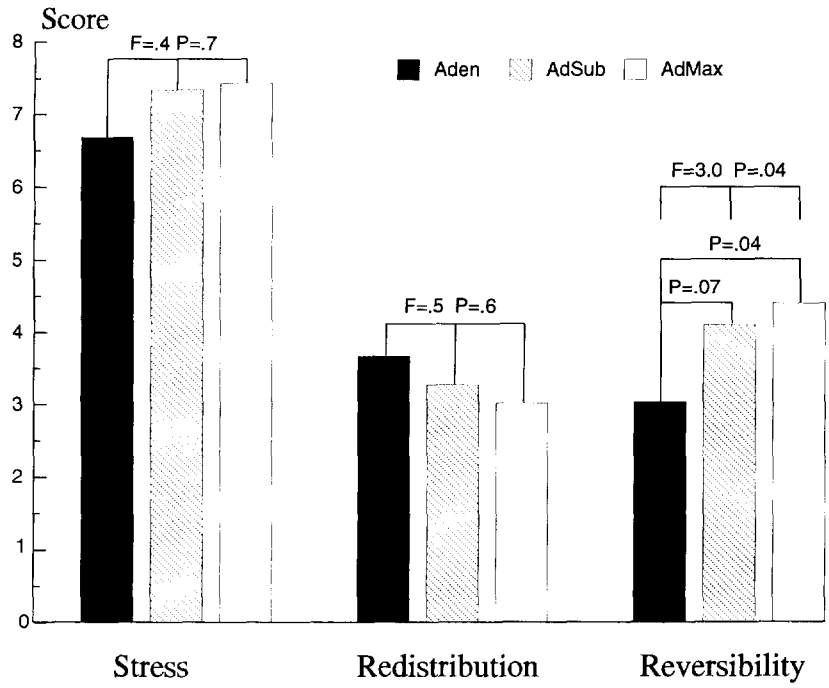


Figure 6. Mean thallium perfusion defect scores in the three groups after stress and redistribution and differences among them, which may be taken as a marker of reversibility. Abbreviations as in Figure 2.

in combination with adenosine. Submaximal exercise has been reported to result in a reduction in the side effects of dipyridamole (31) and a higher heart/background ratio (31,32). This combination has been shown to be a more effective stress than submaximal exercise alone (33). Studies with dipyridamole and maximal exercise have been few (34,35), but these also point to similar advantages from the combined stress. However, previous studies with dipyridamole and exercise have not demonstrated a reduction in the incidence of major arrhythmias or an improvement in redistribution. This may relate to a difference between adenosine and dipyridamole stress or to the fact that the present study has shown improvements by virtue of its size.

Cardiac uptake and heart/background ratios have been compared using whole-body imaging after six different stress regimes, including the vasodilators combined with exercise (36). Cardiac uptake was greatest with the vasodilators than with exercise or dobutamine, and this effect was not attenuated by combining the vasodilator with exercise. Heart/background ratios were higher with exercise than with the vasodilators alone, and a combined vasodilator with exercise regime was similar to exercise alone. Therefore, the combined vasodilator and exercise regime has the advantages of providing good cardiac uptake of thallium and good heart/background ratios.

Table 4. Fixed and Reversible Defects

	Aden	AdSub	AdMax	p Value
Segments*				
Reversible	30.8%	33.8%	37.1%	0.03
Fixed	13.9%	12.3%	10.6%	0.13
Patients†				
Reversible	76.7%	87.4%	90.1%	0.03
Fixed only	23.3%	12.6%	9.9%	0.03

*Fixed or reversible segments in those patients with abnormal findings on thallium scan. †Patients with abnormal findings on thallium scan with reversible or only fixed defects. Abbreviations as in Table 1.

Limitations of the study. The strongest design for a comparison of stress techniques is to perform each stress in every patient such that each patient acts as his or her own control. Because we chose to examine two levels of exercise stress, this would have imposed an unacceptable radiation burden on the patients and was not considered ethical. This results in a comparison of different patients within each study group. However, the sample size is sufficiently large that variations between the groups should be small. This is supported by the analysis of the baseline characteristics of the groups, which fails to show statistical differences between them except for minor variation in the use of calcium antagonists. Referral bias is another important point that was probably responsible for the high sensitivity for coronary artery disease seen in this study. A pretest referral bias results from the nature of the referral practice to our institution as a tertiary cardiac referral center, and a posttest referral bias occurs with angiography being performed in those with significantly abnormal thallium results.

There is another source of possible bias in the results that occurs as a result of considering all consecutive patients for inclusion in the study. This resulted in trial patients whose exercise capacity would probably be higher than those patients most likely to receive adenosine stress in the clinical setting. Exercise appears to be beneficial in this study, and the greater exercise capacity may have amplified its merits. However, the actual levels of achieved exercise in the two exercise groups

were relatively modest, and only a rather poor correlation between increasing benefit and higher stress levels was observed. This suggests that the higher levels of exercise achieved in the maximal group would bias the results less strongly than might be thought. Another issue of interpretation is that of the lack of a rest injection to identify segments with slow redistribution. It was clearly not appropriate to administer a reinjection in all cases, and in our institution we use a separate-day rest injection and redistribution protocol when the clinical determination of viability is required. This prevented any analysis of the effects of reinjection and whether the delayed redistribution in the adenosine only group would have been successfully unmasked.

This study was conducted with the exercise performed semisupine on a bicycle ergometer, but many departments routinely perform their stress on a treadmill. We have no experience of combined stress using a treadmill and preferred the supine position because there is little danger of patient collapse resulting in immediate physical injury. It would be possible to use the treadmill, but a useful precaution might be to commence walking before starting the adenosine infusion. Combined vasodilator and treadmill exercise has been performed successfully with dipyridamole (31,32).

The power of this study was limited by the number of patients, such that the standard difference detectable between groups was only ~0.3 with 80% power at a significance level of $p < 0.05$. The result of this relatively low study power may have been that some real but small intergroup differences were missed.

Clinical implications. This study suggests that the combination of adenosine with exercise has a number of advantages over adenosine infusion alone. Most patients in whom adenosine stress is being proposed are able to perform some limited exercise, and this is beneficial in reducing noncardiac thallium uptake, the noncardiac side effects of adenosine and important arrhythmias while favorably influencing reversibility. All these effects are clinically useful, but the reduction in arrhythmias and the improvement in reversibility may prove clinically important. There was little difference between the maximal and submaximal exercise protocols, but the latter is preferable because it can be incorporated into the standard 6-min adenosine infusion regime with no time penalty. Exercise also proved popular with the patients because they take an active rather than passive role during the test. It could potentially be used routinely whenever adenosine infusion is planned.

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