Safety and Clinical Utility of Combined Intravenous Dipyridamole/Symptom-Limited Exercise Stress Test with Thallium-201 Imaging in Patients with Known or Suspected Coronary Artery Disease

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Dipyridamole-induced coronary hyperemia with ^{201}Tl myocardial perfusion scintigraphy can detect ischemic regions in individuals unable to perform adequate exercise, but it has several limitations. Symptom-limited exercise supplementation to intravenous dipyridamole can potentially overcome them, but the safety and diagnostic accuracy for this combination has not been established. Between 1987 and 1991, 441 consecutive patients were assessed for combined symptom-limited exercise test preceded by i.v. dipyridamole. Clinical records could not be obtained for 37 patients, and 40 patients were not exercised because they were unable; therefore 384 patients (mean age 58 ± 9.8 yr, 278 men) underwent symptom-limited exercise preceded by 0.56 mg/kg of dipyridamole and followed by planar ^{201}Tl perfusion scintigraphy. Following dipyridamole infusion, systolic blood pressure fell by 10 ± 14 mmHg and heart rate increased by 8 ± 11 bpm. Adverse effects were experienced by 77 people (dizziness in 44; headache in 11; nausea in 9; syncope in 2 and chest pain in 11). Exercise heart rate was 69% ± 16% of predicted maximum and ST shift was −0.9 ± 0.9 mm. Following exercise, seven patients required aminophylline (four after dizziness, two after headache, one after chest pain), which was uniformly successful. There were no episodes of prolonged chest pain, MI, death or serious arrhythmia. Safety was maintained for people with severe triple coronary artery disease, the elderly (>70 yr) and those with significant pulmonary disease. Sensitivity was 95% for at least one with >70% luminal stenosis and 94% for at least one with >40% luminal stenosis. Specificity was 28% and 53% respectively. The addition of a symptom-limited exercise test to i.v. dipyridamole is safe for all groups of patients referred for ^{201}Tl study.

J Nucl Med 1993; 34:2053–2061

Received Jan. 22, 1993; revision accepted Jul. 1, 1993.

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Perfusion scintigraphy with ^{201}Tl can determine the presence, localization, and extent of myocardial ischemic regions when it is combined with a symptom-limited exercise tolerance test. The sensitivity of ^{201}Tl in detecting coronary artery disease (CAD) is lower with submaximal exercise (*1–3*), as up to 50% of abnormalities occur at heart rates in excess of 85% of the maximally predicted target heart rate (*4,5*). However, a considerable number of patients are unable to achieve maximal exercise and false-negative scintigrams may be found in about 25% of patients (*6–8*). Frequent reasons for suboptimal exercise include pulmonary, musculoskeletal, neurological, vascular and arrhythmic disorders. With the increasing use of beta blockers in the treatment of CAD, pharmacologic effect is by far the most common reason not to have an adequate heart rate response.

Given these limitations to achieve maximal exercise, other means of increasing the sensitivity of this procedure have been sought. In 1978, Gould et al. (*9–12*) were the first to describe ^{201}Tl perfusion imaging after infusion of dipyridamole. It has since become a popular pharmacologic agent to produce hyperemia, but it does not provide additional clinically useful information such as exercise capacity or functional status. About 10% of patients fail to achieve maximal hyperemia and higher doses are associated with a marked increase in side effects (*13,14*). Previous studies have reported interference of dipyridamole with caffeine-containing drinks and with aminophylline-containing drugs. Image quality is reduced because of a lower heart-to-background ratio. Finally, ^{201}Tl kinetics differ from those obtained during exercise, thus precluding the utilization of quantitative image assessment programs calibrated for exercise ^{201}Tl tests.

It has been postulated that exercise supplementation following dipyridamole administration can overcome some

TABLE 1
Study Population

	Incomplete data	Total	Men	Women	Angiography
n	37	384	278	106	281
% Total		100	72	28	73
Age (yr)	57.7 ± 11.6	58.2 ± 9.8	57.7 ± 9.5	59.4 ± 10.5	58.1 ± 9.2
Range (yr)	35–83	33–88	33–88	33–81	38–88
Exercise duration (sec)	485 ± 212	472 ± 295	500 ± 326	399 ± 173†	482 ± 322
Dipyridamole dose (mg)	42.9 ± 6.1	44.6 ± 8.1	46.2 ± 7.8	40.2 ± 7	44.8 ± 8
Mean ST Δ (mm)	−0.8 ± 0.8	−0.8 ± 0.9	−0.8 ± 0.9	−0.9 ± 0.8	−0.9 ± 0.9
Exercise heart rate (bpm)	117 ± 20	115 ± 21	113 ± 22	119 ± 20	113 ± 22
Predicted maximum (%)	67 ± 15	69 ± 13	68 ± 13	72 ± 12	68 ± 13
Following dipyridamole					
Systolic BP Δ (mmHg)	−15 ± 18	−10 ± 14	−10 ± 13	−10 ± 15	−10 ± 14
Diastolic BP Δ (mmHg)	−13 ± 18	−8 ± 9	−8 ± 9	−7 ± 9	−8 ± 9
Heart rate Δ (bpm)	1 ± 12*	8 ± 11	7 ± 11	10 ± 11	8 ± 11

*$p < 0.001$ vs. total.
†$p < 0.001$ vs. men.
Values expressed as mean ± 1 s.d.; BP = blood pressure.

of these problems by decreasing lung uptake and increasing blood flow to large leg muscles, thus improving the heart-to-background ratio. Exercise may further increase coronary blood flow with an increase in myocardial oxygen demand resulting in higher ^{201}Tl uptake in normal myocardium, thus improving sensitivity (*15,16*). Finally, exercise-calibrated quantitative computer programs might still be utilized. Several questions need to be answered. It is not known how much exercise supplementation is enough and whether the combination of dipyridamole and maximal exercise is safe. Furthermore, the diagnostic accuracy of the combination and its relationship to that of either test alone are unknown.

The purpose of this study was:

1. To determine whether the combination of intravenous dipyridamole followed by symptom-limited exercise study is safe for various categories of patients, including people with significant CAD, significant pulmonary disease and the elderly.
2. To correlate patient hemodynamics and clinical responses to this combination.
3. To estimate the sensitivity and specificity of this test for the presence of CAD.

METHODS

Patient Population Description

The study population consisted of 441 consecutive patients referred for dipyridamole ^{201}Tl imaging at the Nuclear Cardiology Laboratory at the University of Alberta Hospitals between July 20, 1987 and June 19, 1991. Retrospective review of their charts was possible for all except 37 patients. Demographic statistics of these groups are in Table 1. Forty patients (20 men, 20 women) with a mean age of 59 yr (range 2–81 yr) were not exercised because the cardiologist performing the test thought them unable to exercise. Three hundred and eighty-four patients underwent a symptom-limited exercise tolerance test after dipyridamole infusion. There were 278 men and 106 women in this group. Three-hundred and forty-three were outpatients and 41 were inpatients. No patient had an episode of unstable angina or myocardial infarction within 6 wk from the time of the study.

Indications for Dipyridamole

Indications for dipyridamole infusion were divided into eight groups:

- pharmacologic (beta-blockade).
- pulmonary (significant lung disease manifesting itself in dyspnea and decreased exercise tolerance).
- musculoskeletal (including arthritides, recent surgical procedure or trauma).
- neurological (including significant sequelae of cerebrovascular accidents, recurrent TIAs or neurological disorders such as muscular dystrophy).
- vascular (peripheral vascular disease).
- arrhythmic (including persons with pacemakers, patients suffering significant arrhythmia or syncopal episodes).
- left bundle branch block (performed until the study by Burns et al. (*17*) showed a decrease in test accuracy when supplemented with exercise).
- "to increase diagnostic accuracy" in other persons not able to exercise to at least 85% of the target heart rate (as shown on a previous stress test, etc.).

The largest group of people were those on beta blockers (252) followed by persons for whom the test was performed to increase diagnostic accuracy (40), then pulmonary (14), vascular (13), musculoskeletal (10), arrhythmic (9), left bundle branch block (6) and neurological (4).

Dipyridamole Exercise Protocol

Patients were asked to refrain from consuming caffeinated beverages after midnight prior to testing. An intravenous line with 5% glucose was established and sitting blood pressure, heart rate and electrocardiogram were recorded at baseline. Dipyridamole (0.56 mg/kg) was infused over 4 min, and blood pressure, heart rate and ECG were obtained at 2-min intervals. A nonspecific enquiry was made about side effects after 2 and 4 min. Answers were grouped

TABLE 2
Systolic Blood Pressure and Heart Rate Changes Following Dipyridamole

	Systolic blood pressure			Heart rate	
	Up	Down	Down >−40 mmHg	Up	Down
n	45	258	4	263	45
Age (yr)	60.1 ± 8.3	58.1 ± 9.6	58.8 ± 9.6	58.1 ± 9.7	58.4 ± 8.5
Range (yr)	41–78	33–88	46–68	33–88	38–71
Exercise duration (sec)	436 ± 183	489 ± 335	489 ± 98	486 ± 331	431 ± 193
Dipyridamole dose (mg)	45.6 ± 9.1	44.9 ± 8.2	46.5 ± 8.0	44.9 ± 8.2	46.8 ± 8.9
Mean ST Δ (mm)	−0.8 ± 0.9	−0.9 ± 0.9	−1.0 ± 0.8	−0.9 ± 0.9	−0.9 ± 0.8
Exercise heart rate (bpm)	112 ± 19	111 ± 22	119 ± 17	116 ± 21	113 ± 20
Following dipyridamole					
Systolic BP Δ (mmHg)	12 ± 9	−15 ± 10	−57 ± 11*	−11 ± 14	−7 ± 13
Diastolic BP Δ (mmHg)	0 ± 9	−10 ± 8	−32 ± 9*	−9 ± 9	−5 ± 9
Heart rate Δ (bpm)	7 ± 10	8 ± 11	15 ± 9†	11 ± 8	−10 ± 10

*p < 0.001 vs. rest of systolic BP down.
†p = not significant vs. rest of systolic BP down.
Values expressed as mean ± 1 s.d.; BP = blood pressure.

into five categories: nausea, dizziness, chest pain, shortness of breath and none. Patients then underwent symptom-limited exercise test utilizing either a Bruce or a modified Bruce protocol. In two instances, a bicycle or Naughton protocol was used. Exercise test was considered positive if during exercise patients had at least 1 mm of horizontal or down-sloping ST depression measured 80 msec from the J point. A negative test implied that a patient exercised until reaching at least 85% of his predicted target heart rate (THR—calculated by subtracting the patient's age in years from 225) without reaching at least 1 mm of horizontal or down-sloping ST depression measured 80 msec from the J point. In all other instances, the test was considered inconclusive.

At peak exercise, 81–111 MBq of ^{201}Tl was injected and the patients were asked to continue exercise for a period of up to 1 min. Planar acquisitions were obtained for 10 min in each of the three standard views. If required, treatment with nitroglycerin (for chest pain) or aminophylline (for other adverse effects) was offered at that time. Following stress image acquisition, patients were allowed to recover for about 4 hr (range 3–5 hr), after which further images were acquired. The studies were interpreted qualitatively by consensus of two experienced observers who were not blinded to the clinical history, exercise data, and on occasion, angiographic reports when they were available.

Cardiac Catheterization

Cardiac catheterization and selective coronary angiography were performed in 281 people, but only 170 of them had the catheter study performed within 100 days of the nuclear study (mean 43 ± 28 days). Vessel involvement was quantified by visual assessment as either mild (0%–40% cross-diameter narrowing with respect to the prestenotic segment), moderate (between 40%–70%) or severe (70% to occlusion). Interpretation of angiograms was made by a team of independent observers who were rarely aware of the results of dipyridamole exercise ^{201}Tl. There were 73 patients with severe one-vessel CAD, 42 patients with severe two-vessel CAD and 19 patients with severe three-vessel CAD. Nineteen patients had either normal coronary arteries or mild involvement of at least one artery (<40% stenoses). Thirty-six patients had CAD described as less than severe (<70% stenoses). In total, 107 patients had previous percutaneous transluminal coronary angioplasty (PTCA) and 80 patients had previous coronary artery bypass surgery (CABG).

Statistical Analysis

The continuous variables were compared with unpaired Student's t-test. The results were considered statistically significant when a two-tailed p value was less than 0.05.

RESULTS

Hemodynamic Response to Dipyridamole

Changes were modest in both systole and diastole and were associated with a slight increase in heart rate (Table 2). Systolic blood pressure (BP) rose in 45 patients and fell in 258 patients. In 58 patients, systolic BP fell by more than 20 mmHg and in 17 by more than 30 mmHg. Four patients had a >40 mmHg drop. Their heart rates rose on average by 11 ± 8 bpm in 263 patients, and 45 patients lowered their heart rates on average by 10 ± 10 bpm, with mean systolic and diastolic BP changes of −7 mmHg and −5 mmHg respectively. There was no statistically significant difference in mean age, exercise duration, average dipyridamole dose or average maximum heart rate after exercise with respect to any of the hemodynamic variables.

Adverse Effects of Dipyridamole

Adverse effects were experienced by 77 people (17%). Forty-four of them experienced dizziness, 11 had chest pain, 11 had headache, 9 had nausea and 2 had syncopal episodes. Seven people experienced more than one side effect. There was no statistical difference in hemodynamic parameters between the patients with adverse effects and the others. For the two people who had syncopal episodes (ages 60 and 68 yr), one had no ST depression and the other −2.0 mm after dipyridamole and exercise testing. A fall of 42 mmHg and 48 mmHg in systolic BP and 40 mmHg and 40 mmHg in diastolic BP was noted in these cases. Their

TABLE 3
Exercise Test Protocols and Their Results

	Bruce protocol				Modified Bruce protocol			
	All	Positive	Negative	Inconclusive	All	Positive	Negative	Inconclusive
n	348	158	48	141	34	12	2	20
% Total	91	41	13	37	9	3	1	5
Age (yr)	57.1 ± 9.4	57.9 ± 8.7	55.1 ± 10.6	56.7 ± 9.8	65.4 ± 9.5*	65.3 ± 8.7	56.5 ± 17.7	66.4 ± 9.3
Range (yr)	33–79	34–78	33–75	33–79	44–83	51–81	44–69	48–83
Exercise duration (sec)	464 ± 184	479 ± 168	542 ± 215	417 ± 180	426 ± 222	407 ± 212	827 ± 130	397 ± 202
Dipyridamole dose (mg)	44.7 ± 8	44.1 ± 6	44.4 ± 10	45.7 ± 9	43.8 ± 11	44.8 ± 12	43 ± 10	43.2 ± 10
Mean ST Δ (mm)	−0.9 ± 0.9	−1.6 ± 0.6	−0.1 ± 0.3	−0.3 ± 0.6	−0.8 ± 0.9	−1.7 ± 0.6	−1.0 ± 1.4	−0.3 ± 0.5
Exercise heart rate (bpm)	116 ± 20	116 ± 19	124 ± 21	113 ± 21	112 ± 24	118 ± 21	152 ± 8	105 ± 23
Predicted maximum (%)	69 ± 12	69 ± 13	73 ± 12	70 ± 12	70 ± 13	74 ± 11	90 ± 4	66 ± 13
Following dipyridamole								
Systolic BP Δ (mmHg)	−11 ± 14	−10 ± 14	−12 ± 10	−10 ± 15	−7 ± 10	−10 ± 7	−2 ± 0	−6 ± 12
Diastolic BP Δ (mmHg)	−8 ± 9	−8 ± 9	−9 ± 7	−9 ± 10	−6 ± 8	−6 ± 4	−12 ± 0	−6 ± 10
Heart rate Δ (bpm)	8 ± 11	9 ± 11	11 ± 12	7 ± 10	3 ± 12	2 ± 8	−40 ± 0	6 ± 9

*$p < 0.001$ vs. all Bruce protocol.
Values expressed as mean ± 1 s.d.

heart rate responses were −5 bpm and 13 bpm respectively. Nausea was experienced by younger people, mean age 52.9 yr, whose hemodynamic data and exercise profile were no different than the rest of the general population. Headache sufferers exercised for shorter durations with a mean ST change of −0.5 mm but had an otherwise similar hemodynamic profile. Dizziness was experienced by 11% of all patients who did not differ from the rest in any screened values. Dizziness was not associated with significant changes in the hemodynamic values compared to the rest of the study group. There was no difference in exercise duration, ST segment change or hemodynamics between chest pain sufferers and the rest with the adverse effects.

Aminophylline

Aminophylline (3 mg/kg) was administered to seven people (2%); four men and three women. One hundred milligrams were given as a bolus with the rest administered as a continuous drip. Four people required aminophylline after complaining of dizziness, two after headache and one after chest pain. Aminophylline was successful in alleviating adverse effects in all patients who received it. Patients who required aminophylline exercised for a shorter duration ($p < 0.01$ versus rest), but other differences were not significant.

Cardiac Side Effects of Combined Dipyridamole and Exercise

Eleven patients experienced chest pain graded mild to moderate (none were severe). Their age, hemodynamic response to dipyridamole and exercise duration were no different in those without chest pain. Their mean ST depression was −0.7 ± 0.9 mm (ns versus the patients without chest pain). All episodes were relieved with sublingual nitroglycerin and/or aminophylline within 20 min. No patient needed hospital admission because of chest pain. There were no myocardial infarctions or deaths in the study group. No patient experienced malignant ventricular arrhythmia (ventricular tachycardia or fibrillation).

Exercise Test Results

Three hundred and forty-eight patients underwent exercise testing according to the Bruce protocol for an average time of 7 min 44 sec with a mean ST shift of −0.89 mm reaching an average of 68.8% of THR (Table 3). One hundred and fifty-eight patients had positive tests for inducible ischemia. Forty-eight patients had negative stress tests, since they were able to exercise for an average of 9 min 4 sec with a ST shift of −0.12 mm, and 141 patients were deemed inconclusive by the Bruce protocol. Thirty-four patients were exercised with a modified Bruce protocol. They were older ($p < 0.001$ versus Bruce), mean age 65.3 yr, and had exercised for 6 min 47 sec to a heart rate of 70.3% THR (ns versus Bruce) with −0.82 mm of ST shift (ns versus Bruce). Twelve had positive tests, 2 had negative tests and 20 were deemed inconclusive.

Effective Medications

Of 240 patients on beta blockers, 24 were on agents with intrinsic sympathomimetic activity. There were 158 patients on calcium channel blockers; 5 on verapamil, 106 on diltiazem and 57 on nifedipine. Ninety-eight patients received nitrates and 31 were on angiotensin-converting enzyme inhibitors. Another eight patients were on centrally acting vasodilators. No significant differences in age, exercise duration, mean ST segment shift or maximal heart rate attained were shown among the various medication groups; they all had similar hemodynamic effects on blood pressure and pulse. Twenty-five patients were on digoxin and 66 on diuretics. One hundred and eighty-nine received acetylsalicylic acid and six were on oral dipyridamole; two received coumadin.

TABLE 4
Adverse Effects in Selected Population Groups

	Elderly patients (age > 70 yr)				Patients with severe CAD (triple-vessel)		
	All	Men	Women	Adverse effects	All	Adverse effects	Angina after ETT
n	31	17	14	5	28	8	11
Age (yr)	74.9 ± 3.9	75.3 ± 4.7	74.4 ± 2.9	74.0 ± 2.4	61.9 ± 8.6*	60.8 ± 8.9‡	59.5 ± 7.4
Range (yr)	71–88	71–88	71–81	71–77	41–75	44–70	44–70
Exercise duration (sec)	356 ± 198	391 ± 214	314 ± 175	208 ± 94	448 ± 165†	395 ± 142‡	369 ± 169‡
Dipyridamole dose (mg)	43.3 ± 12	45.4 ± 12	40.7 ± 12	48.4 ± 22	42.9 ± 6†	43.6 ± 6	43.3 ± 6
Mean ST Δ (mm)	−0.9 ± 0.8†	−0.6 ± 0.7	−1.3 ± 0.8	−0.7 ± 0.8‡	−1.0 ± 0.8†	−0.9 ± 0.8‡	−0.7 ± 0.8‡
Exercise heart rate (bpm)	102 ± 23	99 ± 26	106 ± 20	101 ± 42	108 ± 15†	105 ± 11	110 ± 16
Predicted maximum (%)	68 ± 15†	67 ± 17	70 ± 13	67 ± 28‡	66 ± 10	64 ± 9	67 ± 11
Systolic BP Δ (mmHg)	−9 ± 15†	−7 ± 15	−11 ± 14	−12 ± 2‡	−10 ± 16†	−6 ± 17‡	−7 ± 16‡
Diastolic BP Δ (mmHg)	−9 ± 9†	−8 ± 11	−10 ± 7	−11 ± 8‡	−6 ± 7†	−5 ± 6‡	−4 ± 8‡
Heart Rate Δ (bpm)	8 ± 6†	6 ± 6	10 ± 7	9 ± 8‡	6 ± 9†	7 ± 8‡	5 ± 7‡

*$p < 0.05$ vs. rest of population.
†Not significant vs. rest of population.
‡Not significant vs. rest of all in the subgroup.
Values expressed as mean ± 1 s.d.; BP = blood pressure.

Thallium Imaging Results

Two hundred and twenty-seven people (59%) had ^{201}Tl scintigraphy interpreted as positive with regards to ischemia only and defined as the presence of reversible ^{201}Tl defects, and 157 (41%) people had no evidence of reversible ischemia. Of those, 75 had findings of myocardial damage with the evidence of fixed defects. Eighty-two people had entirely normal scans.

Subgroup Analysis of Adverse Effects of Dipyridamole

Severe CAD. There were 28 patients with severe triple-vessel CAD (Table 4). They were older ($p < 0.05$) than the rest of the study group and had a trend of less exercise which correlated to more ST segment change. Their hemodynamics were similar to the rest of the study group. Of the patients with severe triple-vessel CAD, eight (29%) complained of side effects (four of dizziness, two of headache, one had nausea and one had chest pain). The patients with side effects were not older, exercised to similar durations to similar ST segment shifts, and had similar changes in BP and heart rate. The four patients who experienced dizziness had a more profound systolic BP drop, a more profound shift in ST segments and were also slightly older. Eleven patients (39%) experienced anginal type of chest pain following termination of their stress test. On average, they exercised for 6 min 9 sec and had −0.74 mm of ST shift (ns versus triple-vessel CAD patients without anginal chest pain on the stress test). All other characteristics were similar.

Significant Pulmonary Disease. Of the 14 people with significant pulmonary disease, only one person, a 58-yr-old male, complained of a headache after dipyridamole administration. Even though this group was able to exercise significantly less ($p < 0.05$ versus rest), differences in ST segment shifts and hemodynamics were nonsignificant. As a group, the patients with pulmonary disease were no different than the rest of general population in incidence of adverse effects. None of the patients experienced bronchospasm attacks.

Elderly Population. There were 31 people (17 men and 14 women) who at the time of the dipyridamole exercise test were at least 70 yr old (8% of the population), with a mean age of 74.9 ± 3.9 yr (Table 4). They received similar dipyridamole doses (with similar BP and heart rate changes) and had −0.9 ± 0.8 mm ST segment shifts after exercising to 68% of THR (ns versus patients less than 70 yr old). Five patients (16%) complained of adverse effects (two had dizziness, two had chest pain and one complained of headache). There were no significant differences in the frequency of the adverse effects between this group and the younger patients.

DISCUSSION

Dipyridamole causes an increase in extra-cellular adenosine concentration, thus producing coronary artery dilatation by increasing cyclic AMP (*13*). Hyperemia is produced in regions supplied by normal epicardial arteries but not in the presence of a coronary artery stenosis. This technique produces a nearly fivefold increase in coronary blood flow (*18*) within 2–4 min which lasts for at least 30 min. The results are reproducible and can be standardized. The sensitivity and specificity are comparable to those reported with exercise studies (*19,20*).

It was proposed that exercise supplementation would overcome certain limitations of pharmacological hyperemia, but most importantly, that it would be safe. The addition of exercise significantly decreases the severity of noncardiac side effects of dipyridamole infusion (*21*) and may increase the occurrence of myocardial ischemia-enhancing diagnostic efficiency (*22*). The first reports of combining dipyridamole with an isometric hand grip pointed

out that the diagnostic accuracy of the combination was maintained and side effects of dipyridamole were reduced (*19*). Supplementation of dipyridamole with low-level exercise has been studied by several investigators (*23–30*) and has been found to be safe. It decreases the incidence of side effects and improves image quality (where hand grips do little). Reports of exercise supplementation usually utilized a bicycle (*24*) or treadmill (*23*) but generally were not symptom-limited. Hurwitz et al. (*27*) reviewed a series of 820 patients of which 158 patients had exercise supplementation (significant in 109 patients and truncated in 49) to intravenous dipyridamole. He found that chest pain and reversible defects were induced more frequently in the exercise supplemented group. Splanchnic background activity was lower in the group with significant amounts of exercise supplementation, and the false-positive rate tended to be lower.

Laarman et al. (*25*) studied 200 patients whose dipyridamole infusion was supplemented with low-level exercise and compared the results to 101 patients who had standard dipyridamole infusion. The likelihood of CAD was the same, and the occurrence of angina was similar in both groups, however, ischemic changes were significantly more frequent in the exercised group despite significantly fewer adverse effects than the dipyridamole group alone. Casole (*26*) found in a group of 100 patients that combined low-level treadmill exercise and intravenous dipyridamole testing is safe, is associated with fewer side effects and has a higher target-to-background ratio with a higher incidence of clinical and electrographic ischemia than dipyridamole alone.

In our study, all patients deemed able to exercise underwent symptom-limited exercise stress tests which allowed us to study specific subgroups of patients who might be at increased risk for major complications.

Hemodynamic Effects

It appears that severe hypotension following dipyridamole is rare. Syncopal episodes occurred rarely or occurred in persons with an inappropriate negative chronotropic response to hypotension. The influence of primary abnormalities in sino-atrial function and neuro-cardiac reflexes cannot be accounted for in this study.

Adverse Effects of Dipyridamole

Adverse effects were elicited in only 17% of all patients, whereas the biggest review suggests the occurrence is as high at 47% (*34*). It is important that questions about adverse effects were asked immediately after dipyridamole infusion and in a nonspecific manner. Not unexpectedly, dizziness was the most frequently experienced problem. It appears that dizziness did not influence the exercise time, but on the other hand, headache sufferers tended to exercise less. Nausea alone seemed to affect the younger population, but it also improved during exercise. We conclude that noncardiac adverse effects subside with exercise and that exercise had no deleterious effect on any of the patients experiencing adverse effects. The mechanism by which exercise influences adverse effects is suspected, at least in part, to be secondary to an increase in cardiac output and systolic BP, thus attenuating dizziness, headache and nausea.

Cardiac Side Effects

All patients experiencing chest pain following dipyridamole infusion graded it as mild to moderate. The addition of exercise did not worsen ST segment shift and on average they were able to exercise for a similar duration as the rest of the general population. All episodes of chest pain improved spontaneously or with sublingual nitroglycerin. Only one patient required aminophylline. We conclude that exercise supplementation is safe and does not produce an increased incidence of cardiac adverse effects. We agree with earlier studies that chest pain following dipyridamole probably does not represent true ischemia (*31*).

Exercise Test Results

In this selective group of patients, who are traditionally considered suboptimal candidates for maximal symptom-limited stress tests, we found that 70 of 384 had positive results and 50 had negative results. Exercise duration was not affected in patients on beta-blocking agents, in patients for whom the test was done to improve diagnostic accuracy or in patients with musculoskeletal problems. On the other hand, patients with bradyarrhythmia, pulmonary, vascular and neurologic indications exercised significantly less. Because of a large number of beta-blocked patients, the maximal exercise heart rate was between 68.8%–70.3% of THR. We conclude that the addition of a symptom-limited exercise test provides a significant amount of clinically useful information with regards to functional capacity and could provide important information relating to the risk of cardiac events (*32*).

Effective Medications

Interestingly, medications did not significantly affect a patient's ability to exercise (when comparing between the groups), nor did they produce differences in ST segment change following exercise. Not unexpectedly, as current standards of practice reserve this class of medications for the elderly and people with vasculopathies, patients treated with beta blockers with intrinsic sympathicomimetic activity had a tendency to exercise less and were slightly older. To conclude, the medications had little effect on the patient's ability to exercise following dipyridamole infusion.

Sensitivities and Specificities

Several studies have found the sensitivity of dipyridamole ^{201}Tl scintigraphy to be between 78%–100%. Our finding of 95% for the combination of symptom-limited exercise and intravenous dipyridamole is similar (Table 5). Specificity for the combination ranged from 28% for the absence of severe CAD up to 53% for the absence of moderate CAD. These numbers compare favorably with other studies. Diagnostic accuracy was maintained between men and women, although the number of female

TABLE 5
Diagnostic Accuracy of Combined Symptom-Limited Exercise and Intravenous Dipyridamole with ^{201}Tl Perfusion Imaging

Variable	Sensitivity n	Sensitivity %	Specificity n	Specificity %	PPV (%)	NPV (%)
Disease* in at least one vessel						
>70%, overall	127/134	95	10/36	28	83	59
>40%, overall	142/151	94	10/19	53	94	53
Disease in at least one vessel >70%						
Men	103/108	95	7/25	28	85	58
Women	24/26	92	3/11	27	75	60
Disease at least 70% in each vessel						
LAD	28/36	78	28/43	65	65	74
LCX	2/9	22	80/87	92	22	92
RCA	20/28	71	53/69	77	56	87
Disease at least 70% in each vessel						
Single-vessel CAD	69/73	95				
Double-vessel CAD	40/42	95				
Triple-vessel CAD	18/19	95				

*Refers to percent of luminal stenosis.
CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; PPV = positive predictive value; NPV = negative predictive value.

patients, especially those undergoing cardiac catheterization was small, perhaps reflecting a "gender bias." A lower number for specificity for CAD may be explained in two ways. First, "referral bias" occurs when a negative result of a well established test usually lowers the post-test likelihood of CAD to below 10%, thus reducing the need for coronary angiography. Of 85 people who had entirely normal ^{201}Tl scintigraphy, 40 had coronary angiography (only 19 had the test within 100 days of the scan). Some of those patients underwent successful PTCA or CABG and had ^{201}Tl scintigraphy performed in follow-up. The findings of the normal scan were considered negative for re-stenosis and not followed by a new angiographic study. Several other patients had atypical symptoms and inconclusive exercise tests, so findings of the normal scan usually lowered the probability of CAD below 10%, thus no further testing was felt to be necessary. Overall, 66 of 85 patients were believed to have a low probability for CAD for the normalcy ratio of 78%.

Second, 38 patients had no records accessible to us, indicating that they had no further cardiac history (at least in our catchment area), again likely representing a low risk group. Multivessel coronary artery detection of 95% for single-vessel disease, 95% for double-vessel disease and 95% for triple-vessel disease is similar to previously reported data.

Our findings of sensitivities and specificities for the presence of any single-vessel CAD are comparable to those reported in the literature. Again, we selected 70% of luminal narrowing as representing severe disease, whereas some studies set a threshold of only 50% as representing significant disease (*33*). It is generally accepted that as CAD becomes more severe, it is easier to visualize scintigraphically.

We conclude that symptom-limited exercise supplementation maintains specificity and sensitivity for the detection of CAD and positive and negative predicted values are not adversely affected. No studies are available to directly compare the diagnostic accuracy of the combined approach to either modality alone.

Subgroup Analysis

Severe CAD. An adverse effect profile for 28 patients with three-vessel CAD is similar to that of a population with less severe disease. Chest pain following dipyridamole infusion occurred in a single instance, indicating that dipyridamole is not an agent that produces profound ischemia, even in this group of patients. Adverse effects did not inhibit patients' ability to exercise and they tolerated the addition of exercise to intravenous dipyridamole well. There were only 11 episodes of anginal chest pain after the stress test (which is surprisingly low in this population and suggests either silent ischemia or aggressive medical therapy). They were not associated with significantly larger ST segment shifts, raising the possibility that at least some of these episodes were nonischemic in nature and instead represented "vascular migraine effect," as suggested by Pearlman et al. (*31*). All episodes of pain following symptom-limited exercise were successfully treated with nitroglycerin before the patients left the laboratory. There were no episodes of prolonged chest pain requiring hospital admissions. There were no myocardial infarctions or ventricular arrhythmia.

Triple-vessel CAD carries an especially adverse prognosis—exercise capacity is often all that is necessary to suspect the diagnosis since scan findings are often nonspecific. Inability to exercise properly may impair the diagnostic value as well as provide a suboptimal scan. It is therefore an important adjunct in this group of patients and can be performed with low risk.

Significant Pulmonary Disease. Only 14 of 384 patients had significant pulmonary disease. They tolerated exercise to a similar extent as the others and the incidence and severity of adverse effects was low. No episodes of bronchospasm were encountered, but none of the study patients had a history of recent asthma attacks. The majority of patients had a pulmonary diagnosis of chronic obstructive coronary disease. Ranhosky et al. (*34*) have suggested that the group of patients with an asthmatic component to their pulmonary disease may be at high risk for severe and even fatal bronchospasms following dipyridamole infusion. It appears that in the absence of recent exacerbation of a pulmonary process the combination is safe and allows for avoiding the pitfalls of oral theophylline, which reportedly decreases the diagnostic accuracy of dipyridamole alone (*35*) by providing an additional mechanism for increasing myocardial blood flow. We are unable, however, to comment about the safety of this combination for patients with a recent history of bronchospasm.

Elderly Population. Earlier studies by Lam et al. (*36*) indicated that intravenous dipyridamole is a safe, noninvasive method for assessment of older patients and that the adverse effects profile is similar to that seen in younger patients. Gerson et al. (*37*) observed attenuation of the heart rate response and delayed decrease in systolic blood pressure in the elderly population, which he thought explained in part why the drug was so well tolerated in that group. We concur with those findings and conclude that adverse effects were not more common in the elderly population. Furthermore, the elderly tolerated the addition of exercise well and suffered no adverse effects to it.

We conclude that symptom-limited exercise supplementation to dipyridamole-induced hyperemia can be performed safely in patients with severe three-vessel CAD, patients with significant pulmonary disease and in the elderly population.

Limitations

In the 37 patients with incomplete data, the demographic characteristics were quite similar to those of the general population (Table 1). Therefore the loss of these patients is unlikely to influence the data. Six of them had normal ^{201}Tl scans and 12 underwent coronary angiography.

Adverse effects were reported before the patients left the laboratory, whereas side effects were recorded for up to 24 hr following the test in some studies. It is unlikely, however, that the vasodilatory effect of dipyridamole would persist for more than 45 min, the length of the patient's stay in the laboratory.

CONCLUSION

The addition of a symptom-limited exercise test to intravenous dipyridamole does not provide serious additional risks for all groups of patients referred for ^{201}Tl studies. Relative safety is maintained for people with severe CAD, the elderly and probably in the presence of pulmonary disease. We report no major adverse effects in our series. The severity of minor side effects was markedly reduced by exercise supplementation and the need for aminophylline as an intervention was reduced. The diagnostic accuracy of the test was maintained. With earlier studies showing improved image quality for this combination, we conclude that symptom-limited exercise supplementation should be used as frequently as possible for intravenous dipyridamole ^{201}Tl scintigraphy.

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EDITORIAL

Exercise-Dipyridamole Myocardial Perfusion Imaging: The Circle Is Now Complete

The use of vasodilator pharmacologic stress as an adjunct for myocardial perfusion imaging has grown steadily, particularly since FDA approval of the intravenous preparation of dipyridamole. It allows a broader application of a now time-tested approach to evaluating patients with coronary heart disease who are unable to exercise optimally. A growing number of studies have demonstrated that vasodilator pharmacologic-stress myocardial perfusion imaging has comparable value to exercise perfusion imaging for the diagnosis of coronary artery disease as well as for risk stratification across a wide clinical spectrum of patients (*1,2*).

However, along with this increasing use has come recognition of drawbacks and limitations of this approach:

1. *Increased Splanchnic Uptake of Tracer.* Resting dipyridamole-myocardial perfusion imaging is associated with substantial uptake of ^{201}Tl in the liver, spleen and gut which, because of their close proximity to the heart, can confound image interpretation. This phenomenon is particularly problematic with planar imaging where overlap on the inferior wall commonly occurs. However, adjacent, intense uptake of ^{201}Tl can cause difficulty with SPECT imaging as well. Even modest levels of exercise can substantially decrease splanchnic blood flow and, consequently, uptake of ^{201}Tl, which can improve image quality and ease of interpretation. Splanchnic uptake, particularly in the liver, tends to be greater with ^{99m}Tc-sestamibi and although it diminishes with exercise it can remain problematic, especially with planar imaging.
2. *Inability to Evaluate Efficacy of Medications.* One of the drawbacks of vasodilator pharmacologic-stress myocardial perfusion imaging is that any ameliorating effects of anti-anginal medications cannot be evaluated in patients with coronary artery disease because coronary hyperemia is induced independent of myocardial oxygen demand. With exercise myocardial perfusion imaging, anti-anginal medications can blunt the hemodynamic response to exercise and reduce or eliminate stress-induced hypoperfusion. It has become common practice to evaluate the potential efficacy of medications in patients with known coronary artery disease by using symptom-limited exercise myocardial perfusion imag-

Received Aug. 18, 1993; accepted Aug. 24, 1993.
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