Sensitivity and Specificity of Thallium-201 Perfusion Scintigrams under Exercise in the Diagnosis of Coronary Artery Disease

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The specificity and sensitivity of thallium-201 myocardial perfusion imaging (MPI), under exercise, in patients with suspected coronary-obstructive disease was compared with graded exercise ECG tests (GTX) in patients with angiographically normal (N = 34) and obstructed (N = 48) coronary arteries. Of the 34 patients with normal coronaries, only one had a perfusion defect on the MPI (specificity 97%). Of the 48 patients with coronary obstructive disease (>50% obstruction of at least one coronary vessel), MPI was positive in 38 (sensitivity 79%). In contrast, the GTX had a specificity of 62% and sensitivity of 88% if nondiagnostic GTX tests are excluded. When the MPI and the GTX were used in combination, however, the sensitivity of detecting patients with coronary obstructive disease was increased to 94% (p < 0.01). The MPI was particularly useful in the evaluation of the 26 patients with nondiagnostic GTX. In this group, 24 of the 26 patients were correctly identified by the MPI with respect to the presence or absence of coronary-obstructive disease. In the 14 patients with a history of classical angina but with normal coronaries, the MPI was negative in 13 and positive in one, thus suggesting that in the majority of these patients transient transmural myocardial ischemia probably does not occur during exercise. The presence or absence of angiographically demonstrable coronary collateral vessels did not seem to influence the exercise MPI in patients with coronary-obstructive disease. Thus, although the MPI does not correctly identify all patients with either coronary-obstructive disease or normal coronary arteries, it is helpful in patients who have a nondiagnostic GTX. Furthermore, when used in combination with the GTX, the MPI significantly increases the likelihood that significant coronary-obstructive disease is present when both tests are positive, and that coronary disease is absent when both tests are negative.

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Investigations using i.v. injections of potassium-43 have demonstrated the feasibility of obtaining adequate myocardial perfusion images (MPI) for the evaluation of regional myocardial blood flow in patients with coronary-artery disease (*1–5*). More recently, thallium-201 has been introduced for perfusion imaging because its half-life (73 hr), radiation energy, total-body radiation dose, and other favorable physical and biologic properties make it a better MPI agent than potassium-43 (*6,7*). The value of Tl-201 myocardial imaging in the acute phase of both experimental and clinical myocardial infarction has been described (*8,9*). Thallium-201 perfusion

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scintigrams have also been used for the diagnosis of coronary artery disease in ambulatory patients (*10–17*).

The purpose of this investigation was to define further the specificity and sensitivity of the Tl-201 exercise scintigrams in patients with documented coronary-artery disease, and in patients with angiographically normal coronary arteries. In addition, we investigated the effect of collateral circulation on the myocardial perfusion patterns during the exercise.

MATERIALS AND METHODS

Patient population. We studied 82 patients whose coronary arteriograms and left ventriculograms raised the question of coronary-artery disease. Informed consent was obtained from all patients before the study, and the protocol was approved by the Human Use Committee. By angiography, 34 of the patients had normal coronaries or insignificant (<50%) narrowing, whereas the other 48 patients had obstructive coronary-artery disease, as evidenced by greater than 50% obstruction in at least one coronary vessel.

Exercise Electrocardiogram (GTX). A GTX protocol as described by Sheffield (*18*) was used. The exercise tests were considered positive if at least 1 mm of flat or downsloping ST depression persisted 0.08 sec after the J point in three consecutive cycles, during or immediately after the exercise. All the GTX tests were interpreted by one of the observers (M.V.) without the knowledge of the coronary arteriograms or of the myocardial perfusion scintigrams. A normal test required that at least 85% of

TABLE 1. CLINICAL AND GTX FINDINGS IN NORMAL PATIENTS

Case no./ sex/age	History	Graded treadmill exercise ECG				
		Time (min)	Double product	Heart rate	Angina	Result
1/M/56	ACP	9	24.0×10^3	130	+	ND
2/M/46	A	13	25.5×10^3	155	−	+
3/M/45	ACP	5	NA	120*	+	ND
4/M/46	A	15	27.5×10^3	145	−	ND
5/F/55	A, MVP	12	17.8×10^3	108*	−	+
6/M/39	A	17	23.2×10^3	150	−	−
7/M/51	ACP	9	15.7×10^3	150	−	−
8/M/46	ACP	13	24.7×10^3	130*	−	ND
9/F/36	ACP	13	27.5×10^3	167	−	−
10/M/46	ACP	8	15.2×10^3	95†	+	ND
11/F/38	ACP, LBBB	13	24.0×10^3	160*	−	−
12/F/55	ACP	15	30.4×10^3	160	−	−
13/F/52	ACP, LBBB, MVP	12	21.7×10^3	150*	−	−
14/F/52	A	13	28.0×10^3	156	+	−
15/M/63	A	11	23.2×10^3	155	+	−
16/M/56	ACP	7	22.6×10^3	162*	−	−
17/M/44	ACP, MVP	16	32.0×10^3	160	−	−
18/M/66	A	14	15.5×10^3	100*	−	ND
19/M/66	ACP	10	26.6×10^3	140	−	ND
20/M/36	ACP	18	NA	165	−	−
21/M/56	ACP, MVP	16	28.8×10^3	160	−	+
22/M/35	ACP	12	13.2×10^3	110*	−	ND
23/F/39	ACP	9	33.0×10^3	165	−	−
24/F/56	ACP	11	37.5×10^3	150	−	+
25/F/65	ACP, LBBB	4	21.6×10^3	108†	−	ND
26/M/44	A, RBBB	12	25.3×10^3	130*	−	ND
27/M/45	ACP, MVP	13	22.5×10^3	150	−	−
28/M/54	ACP	3	NA	135	+	ND
29/F/56	A	5	27.2×10^3	160	+	+
30/M/37	A	8	16.1×10^3	140	+	ND
31/M/57	A	8	15.6×10^3	120*	+	+
32/F/45	MVP, V TACH	11	17.5×10^3	145	+	ND
33/M/54	A	12	22.4×10^3	140	+	+
34/F/57	A, MVP	11	26.4×10^3	160	−	+

A = angina; ACP = atypical chest pain; LBBB = left bundle branch block; MVP = mitral-valve prolapse syndrome; NA = data not available; ND = nondiagnostic; RBBB = right bundle branch block; V TACH = ventricular tachycardia; + = positive test; − = normal test.

* Patients taking propranolol.

† Patients taking digitalis.

the maximum predicted heart rate be achieved with less than 1 mm of ST depression on ECG. Tests were designated nondiagnostic (ND) if less than 1 mm of depression occurred in the ST segment but 85% of the maximum predicted rate was not achieved. Four patients receiving digitalis, who had abnormal ST depression during GTX, were also designated as ND. Nitrates were not given to any of the patients in the 2 hr preceding the test. The occurrence of exercise-induced pain characteristic of angina pectoris was noted.

Thallium-201 perfusion imaging and its evaluation. MPI tests were obtained with a scintillation camera with a low-energy general-purpose collimator. Counting was done with the dual channel analyzer windows centered at 75 and 167 keV with window widths of 20%. Count density in the region of the myocardium was from 1,500–2,000 counts/cm^2. Each study included an anterior view, a 45° left anterior oblique view, and a left lateral view. The imaging time for each of the views was about 10 min. Thallium-201 (1.5–2.0 mCi) was rapidly injected intravenously during the peak of the GTX through a previously placed catheter in the upper extremity, and was then flushed with 5 cc of saline. The exercise was then continued for an additional 1 min. Peak of exercise was determined by any of the following: 2 mm or more of ST depression, increasing chest pain associated with at least 1 mm of ST depression, incapacitating fatigue or dyspnea. Imaging was usually begun within 15–20 min after completion of the treadmill exercise.

It has been reported (*2–4,10–13*) that MPI done during exercise is much more sensitive than MPI at rest in the diagnosis of coronary-artery disease because perfusion defects present at rest will always be detectable at exercise. Thus, since we were primarily interested in determining the sensitivity and specificity of Tl-201 MPI as a screening test for coronary disease, we performed exercise scintigrams only. The MPI data, without their patient identifications, were interpreted by three of the authors, and were graded as positive or negative. Radiographic films that were not computer-processed were used for the interpretations. MPIs were designated as normal if the distribution of the Tl-201 was homogenous throughout the myocardium. An MPI was designated as positive if a definite area of decreased uptake, by comparison with the surrounding areas, was present in at least one of the three projections. Mild perfusion defects comprising <10% of the left ventricular perimeter were considered normal in the upper third of the posterior wall, apex and upper third of the septum. If the interpretations of the scintigrams were not unanimous (18% of the studies) the interpretation of the two observers in agreement was used.

Angiographic evaluation. All 82 patients were studied with coronary arteriography performed by the method of Judkins, usually the day before or after the MPI. Left ventriculograms were obtained in the 30° right anterior oblique position in all patients, and areas of asynergy were noted visually. Coronary lesions involving greater than 50% of the lumen were considered significant. Collaterals were graded as poor, fair, or good as previously reported from this institution (*19*). Thread-like, barely visible collaterals that produced only a faint distal opacification of the obstructed vessel, were classified as "poor." Large, brightly visible collaterals that opacified the obstructed vessel well were classified as "good," and "fair" collaterals were those in the middle of the spectrum.

Sensitivity was defined by

$$\text{Sensitivity } \% = \frac{\text{No. true-positive tests} \times 100}{\text{No. true-posiitve tests} + \text{No. false-negative tests}}.$$

Specificity was defined by

$$\text{Specificity } \% = \frac{\text{No. true-negative tests} \times 100}{\text{No. false-positive tests} + \text{No. true-negative tests}}.$$

Statistical methods. The sensitivity and specificity of the diagnostic methods were compared by the McNemar test (*20*). In order to compare the sensitivity of GTX and MPI with the combined test, the significance level was adjusted using Bonferroni's inequality, which accepts a p value < 0.0167 as significant (*21*). Student's t test for paired samples was used to compare the GTX findings in the two groups of patients. When appropriate, results are reported as the mean ± one standard error.

RESULTS

Clinical data, GTX, MPI, and arteriographic findings are shown in Table 1 (normal group) and Table 2 (coronary-disease group). Table 3 summarizes the results of GTX and MPI in the two patient groups.

Clinical findings. The mean age in the coronary-disease group was 52.9 ± 1.4; 38 were males and ten females. By comparison, patients in the normal group were only slightly younger (48.2 ± 2.05, $p > 0.05$); 22 were males and 12 females. In the coronary-disease group, the commonest indications for coronary arteriography were typical angina (40 patients, or 83%) or atypical incapacitating chest pain (six patients, or 12%). In the two remaining patients, one had a highly positive GTX and a history of previous myocardial infarction; the other had a

TABLE 2. CLINICAL ELECTROCARDIOGRAPHIC, ANGIOGRAPHIC AND MYOCARDIAL PERFUSION FINDINGS IN PATIENTS WITH CAD

			Exercise electrocardiogram					Coronary arteriograms % obstruction					
Case no./ Sex/Age	History	Rest ECG (MI)	Time	Double product $\times 10^{-8}$	Heart rate	Ex angina	Result	RCA	LAD	CX	LV contraction hypo or akinesis	Exercise thallium-201 scintigram	Collaterals
1/F/55	A	—	6′	14.9	115	—	+	90	50	—	—	—	P
2/M/46	A	—	11′	13.6	105	—	+	80	90	90	+ APX	+ AS	F
3/M/35	A	—	15′	18.8	145	+	—	—	50	100	+ ANT, APX	+ POST	G
4/M/57	A, MI	+ INF	12′	21.0	120*	—	ND	70	40	—	+ INF	+ APX	—
5/M/60	A	—	14′	19.5	130*	—	ND	—	100	70	—	—	G
6/F/63	A	—	4′	16.5	110	+	+	100	90	70	+ APX	+ INF	F
7/M/48	A	—	11′	15.4	103*	+	+	—	90	—	—	+ APX	P
8/M/48	A	—	9′	15.8	93*	+	+	100	30	80	+ INF	+ APX	G
9/M/50	MI	+ INF, POST	10′	18.0	120	—	+	—	70	90	+ INF, POST	+ POST	—
10/M/49	A	—	5′	22.5	125	+	+	—	—	90	—	+ POST	G
11/F/40	A	—	12′	22.7	130	+	ND	100	—	—	+ INF	+ POST	F
12/M/61	A	—	12′	19.2	120	+	ND	40	70	70	+ APX	+ APX	F
13/M/59	A, MI	+ INF	9′	15.2	95*	+	+	100	90	70	+ INF, APX	—	G
14/M/53	NS	—	9′	21.8	125	—	+	100	70	80	—	—	G
15/F/58	A	—	4′	11.6	86*	+	+	100	90	80	+ INF	—	G
16/M/37	A	+ INF	8′	24.6	170	—	+	100	40	20	+ INF, APX	+ INF, APX	G
17/F/46	ACP	—	12′	21.6	165	+	—	90	40	—	—	—	—
18/M/51	A	—	17′	21.0	150	—	+	—	30	70	—	—	—
19/M/24	ACP	+ INF	12′	25.5	170	—	—	80	—	—	+ INF	+ APX	P
20/M/56	A	—	9′	18.9	140†	—	ND	100	100	50	+ APX	+ AS	G
21/M/44	ACP	—	14′		155	+	+	—	—	80	—	—	—
22/M/46	A	—	12′	20.5	128*	+	+	80	80	80	—	—	G
23/M/48	A	—	18′	20.4	125*	—	ND	—	100	50	—	+ INF, APX	P
24/M/60	A	—	4′	16.5	100	+	+	—	95	95	—	+ POST, APX	P
25/M/65	A		5′	14.3	100*	—	+	100	90	100	+ INF, APX, ANT	+ INF, POST, APX	G
26/M/58	ACP	—	6′	14.9	93*	—	ND	70	40	80	+ APX	—	—
27/M/56	A	+ INF	8′	15.0	100*	—	+	90	80	100	+ INF	+ LAT, POST	G
28/M/59	A	+ AS	6′	15.0	100	+	+	—	100	—	+ APX	+ APX, INF	G
29/M/50	A	+ INF, POST	14′	12.6	115*	—	+	95	40	—	+ INF	+ INF, POST	—
30/M/59	A	+ INF, POST	4′	13.5	90†	+	ND	100	100	100	—	+ INF, POST	G
31/F/59	A	—	4′	18.0	120	+	+	—	100	80	+ APX	+ APX	—
32/M/61	A	—	9′	21.9	120	—	+	70	90	80	—	+ APX	—
33/M/40	A	—	5′	NA	110	+	+	—	90	—	—	+ APX, ANT, LAT	P
34/M/64	A	+ INF	8′	15.6	92	+	+	100	95	80	+ INF	+ INF, POST, LAT	G
35/F/75	A	—	3′	NA	80	+	ND	100	100	85	+ INF, ANT, APX	+ APX, AS, ANT, LAT	G
36/M/39	A	+ ANT, LAT	15′	20.0	160*	—	—	—	50	—	+ ANT, LAT	+ ANT, APX	—
37/M/61	A	—	6′	21.5	125	+	+	30	90	70	—	+ APX	F
38/F/62	ACP	—	2′	14.5	100	+	ND	95	—	—	—	+ AS	—
39/M/38	A	—	13′	18.0	120*	+	+	70	90	50	—	+ AS	—
40/F/43	A	—	3′	14.0	100*	+	ND	95	75	—	+ INF	+ INF	—
41/F/61	A	—	11′	18.7	120*	—	+	—	50	50	+ ANT	+ APX, LAT, POST	—
42/M/51	A	+ ANT	5′	13.3	95	+	ND	20	50	50	+ ANT	+ AS	—
43/M/50	A	+ INF	11′	18.7	110	+	+	60	50	95	+ INF, POST	+ INF, POST	F
44/M/58	ACP	—	8′	18.6	155	+	+	100	60		—	+ AS	G
45/M/64	A	—	7′	14.5	100	+	+	100	40	80	+ INF	+ LAT, POST	G
46/M/55	A	+ AS	7½′	19.5	115	—	+	60	75	95	+ ANT, LAT	+ POST, LAT, INF	G
47/M/59	A, MI	+ LAT, POST	10′	17.4	120	—	ND	—	80	80	+ ANT	+ ANT, LAT, APX	—
48/M/60	A	—	7′	18.9	96	+	+	100	40	95	—	+ INF, POST	G

A = angina; ACP = atypical chest pain; ANT = anterior; AS = anterior septal; CX = circumflex artery; F = fair; G = good; INF = inferior; LAD = left anterior descending artery; LAT = lateral; MI = myocardial infarction; ND = nondiagnostic; NS = no symptoms; P = poor; POST = posterior; RCA = right coronary artery; + = positive test; — = normal test.

* Patients taking propranolol.

† Patients taking digitalis.

TABLE 3. EXERCISE ECG AND PERFUSION SCINTIGRAMS IN NORMALS AND CAD

Patient group	Exercise electrocardiogram			Perfusion scintigrams	
	Positive	Negative	Nondiagnostic	Positive	Negative
Normals (N = 34)	8 (24%)	13 (38%)	13 (38%)	1 (3%)	33 (97%)
CAD (N = 48)	31 (65%)	4 (8%)	13 (27%)	38 (79%)	10 (21%)

Numbers in parenthesis indicate percentages; N = total number of patients.

strongly positive GTX and Type II hyperlipidemia. Neither of these patients had chest pain.

In the patients with normal coronary arteries, pain characteristic of angina pectoris was present in 14 (41%). The remaining patients had atypical but incapacitating chest pains. Seven patients in the latter group had the syndrome of mitral-valve prolapse.

GTX (see Table 3). *Patients with normal coronary arteries.* In the 34 patients who had either normal coronary arteries or insignificant lesions, the GTX was normal in 38%, falsely positive in 24%, and nondiagnostic in 38%. Table 1 shows the clinical and GTX data for the normal group. The high incidence of nondiagnostic tests was due to the failure to achieve the 85% of maximum predicted rate in all patients. Half of the patients with nondiagnostic GTX tests were on propranolol at the time of this test. The maximum heart rate achieved during the GTX in the patients with nondiagnostic tests was significantly less than that achieved in the patients with diagnostic tests (125 ± 4.7 against 150 ± 3.2, respectively, $p < 0.005$). The peak double product (systolic blood pressure $\times$ heart rate), however, was not significantly different in the patients with nondiagnostic tests compared with those with diagnostic tests ($20,600 \pm 1,600$ vs $25,700 \pm 1,300$, respectively, $p > 0.05$). Exertional chest pain suggestive of angina pectoris occurred during the GTX in 32% of patients without coronary lesions.

Patients with coronary-artery disease (see Table 2). In the 48 patients with coronary-artery disease, the GTX was positive in 65%, falsely negative in 8%, and nondiagnostic in 27%. The false negatives occurred in three patients with one-vessel disease and one patient with two-vessel disease. In the 16 patients with three-vessel disease, the GTX was positive in 13 and nondiagnostic in three. If either exercise-induced angina or abnormal ST depression were considered as a positive GTX test, 83% of the patients with coronary-artery disease would have been identified. Fifteen patients had Q waves in the resting ECG, diagnostic of a previous myocardial infarction. If abnormal Q waves were combined with exercise-induced ST depression as evidence of coronary disease, the total sensitivity of the ECG in diagnosing coronary-artery disease would be comparable to that of the MPI: 77% (37 of 48 patients), which is significantly greater than the 65% sensitivity of the GTX alone ($p < 0.02$). In the patients with coronary-artery disease and nondiagnostic GTX, the maximal heart rate was not significantly different from that of the other patients in the coronary-disease group (111 ± 5.2 and 118 ± 3.4, respectively, $p > 0.05$). The peak double products in the two groups were also not different ($17,400 \pm 900$ and $17,800 \pm 500$, $p > 0.05$).

Thallium-201 MPI (see Table 3). *Patients with normal coronary arteries.* The specificity of the Tl-201 perfusion scintigrams was found to be 97% in the 34 patients with normal coronaries. Figure 1A

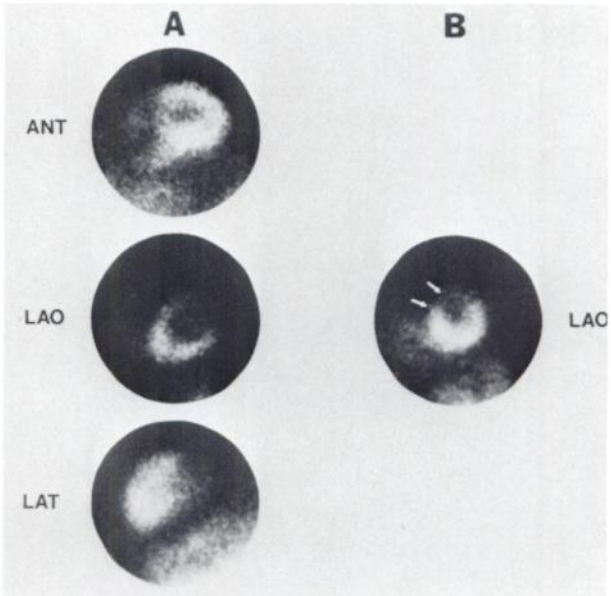

FIG. 1. (A) Normal MPI in patient with clinical diagnosis of unstable angina, a negative GTX, and normal arteries and left ventriculogram. (B) Normal variant MPI. There is apparent decrease in perfusion of upper third of interventricular septum (arrows). This patient had normal GTX, normal coronaries and left ventricle. ANT = anterior; LAO = left anterior oblique (40°); LAT = lateral view.

shows a normal MPI in a patient with clinical diagnosis of unstable angina, negative GTX, and normal coronary arteries. Thirteen of 14 patients with the clinical syndrome of angina and normal coronaries also had normal MPI. In five of the 34 patients, diminished perfusion of the upper third of the intraventricular septum was observed in the left anterior oblique view. This, however, was considered a normal variant, possibly due to anatomic variation of the membranous interventricular septum, to the spatial orientation of the upper septum, or to the overlapping pulmonary- or aortic-valve structures. Figure 1B shows an example of this normal variant in a patient with normal coronary arteries and normal left ventricle.

Patients with coronary-artery disease. The sensitivity of the thallium MPI in the 48 patients with coronary-obstructive disease was 79%. Thus, 21% of the patients had a false-negative MPI (see Table 3). The peak heart rates achieved in the patients with false-negative MPI were not significantly different from those with positive MPI (124 ± 8.6 and 117 ± 30.7, respectively, $p > 0.05$). The peak double products in these two subsets of patients with coronary disease were also similar (17,900 ± 1,200 and 17,800 ± 500, $p > 0.05$). In patients with one-, two- or three-vessel coronary-artery disease, the MPIs were positive in 61%, 83%,and 76%, respectively. An example of a positive scintigram in a patient with coronary-artery disease is shown in Fig. 2.

Fifteen patients with coronary disease had ECG evidence of transmural myocardial infarction. The sensitivity of MPI in patients with previous myocardial infarction was 93%. In patients without previous MI, the sensitivity was 70%.

There was no correlation between the angiographically visible collateral circulation and the pattern of the MPI. For example, 15 of 37 patients with positive scintigrams had good collaterals to obstructed vessels ($p > 0.05$), whereas five of ten false-negative scintigrams occurred in patients with poor or no collaterals ($p > 0.05$) (see Table 2).

Sensitivity and specificity of MPI and GTX (Fig. 2). The specificity of the MPI was 97% in this series. In contrast, the specificity of the GTX was significantly lower (62%; $p < 0.01$) if the nondiagnostic GTX tests are excluded. If the nondiagnostic GTX tests are counted as negative, the specificity of the GTX would be 76%.

The sensitivity of the MPI in this series was 79%. This is similar to the sensitivity of the GTX test (88%) if the nondiagnostic GTX tests are excluded. If the nondiagnostic GTX tests are counted as negatives, the sensitivity of the GTX tests would be 65%.

Combining the results of the GTX and the MPI led to considerable improvement in sensitivity, which was significant at the $p < 0.01$ level of confidence. Thus, 45 of 48 patients (94%) with coronary disease had either a positive GTX, a positive MPI, or both tests were positive (see Fig. 3). Since both tests were simultaneously positive in only 50% of the patients, it is clear that the two procedures are not always positive in the same patient population (Fig. 4). When the results of a GTX and an MPI are considered together, although the sensitivity is increased, the specificity is markedly decreased because of the

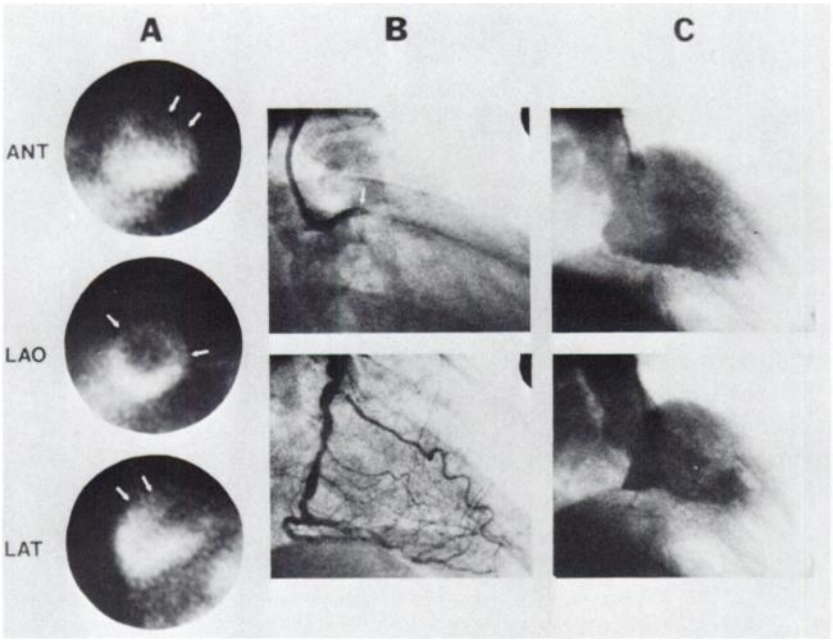

FIG. 2. (A) Abnormal Tl-201 scintigram in patient with severe coronary-artery disease, showing diminished perfusion of anterolateral and high posterolateral walls (arrows). (B) Coronary arteriograms in RAO view, showing total occlusion of main left coronary artery (arrow) and diffuse, severe right coronary lesions. (C) End-diastolic (upper) and end-systolic (lower) frames of left ventriculogram showing severe hypokinesis of antero-lateral wall. (Abbreviations as in Fig. 1.)

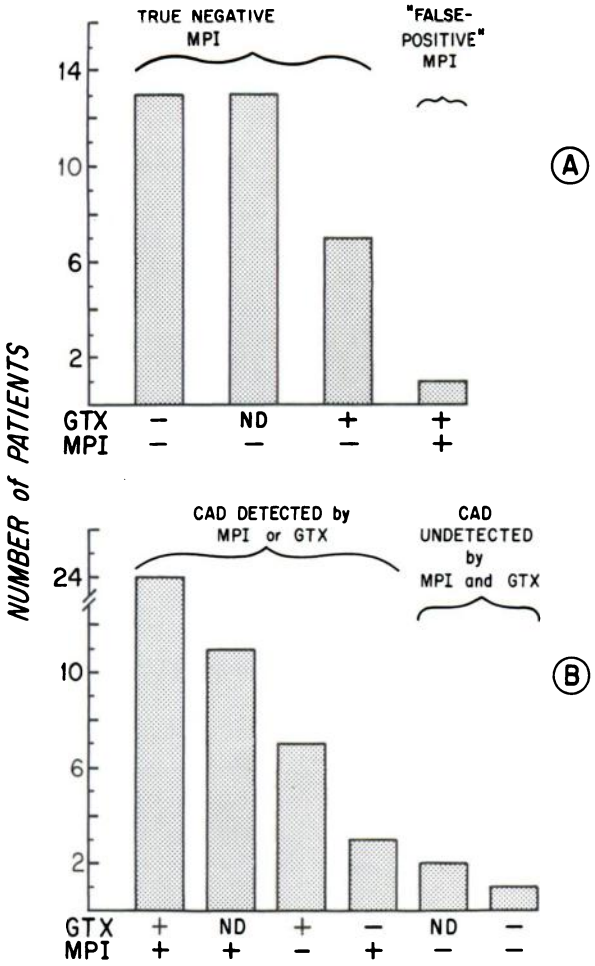

FIG. 3. (A) Results of Tl-201 scintigrams and GTX in subjects with normal coronaries. Note that all patients with nondiagnostic GTX were correctly identified by thallium scintigrams. Only one patient had GTX and MPI simultaneously positive. (B) Results of thallium scintigrams and GTX in patients with coronary disease. Only three patients were not identified by either GTX or MPI. GTX = graded treadmill exercise ECG; MPI = myocardial perfusion imaging; ND = nondiagnostic GTX.

large number of false positives (24%) with the GTX test.

Thirteen of 48 patients with coronary disease had a nondiagnostic GTX; the MPI correctly identified 11 of these patients. Thirteen of 34 patients with normal coronary arteries had nondiagnostic GTX; the MPI correctly identified all thirteen of these patients (see Fig. 3).

In the 15 patients in whom both tests were positive, 14 had coronary disease. Of the 14 patients with both tests normal, 13 did not have coronary disease. Thus, when the two tests are positive in the same patient, it is very likely that the patient has coronary disease (probability 93%). In contrast, when both tests are negative in the same patient, it is unlikely that the patient has coronary disease (probability 7%). Nonetheless, the overall specificity of the combined GTX and MPI is low, as noted above.

One patient with typical angina and a 3-mm ST depression during the GTX (Patient 2, Table 1) had diminished perfusion of the whole posterior wall of the left ventricle (Fig. 5). The MPI was repeated at a later date and was again positive both with exercise and 3 hr following exercise. This suggested a myocardial scar as the probable explanation for the abnormal perfusion. The resting ECG, coronary arteriography, and left ventriculography were normal in this patient.

DISCUSSION

The significant findings in this investigation are the following.

1. The specificity of the Tl-201 MPI (97%) has been defined in a group of 34 middle-aged patients with angiographically normal coronary arteries.
2. Thallium-201 MPI has been shown to be particularly useful for the diagnosis of coronary disease in patients who have nondiagnostic GTX tests.
3. When the exercise MPI and the GTX are used in combination, the sensitivity is high—that is, 94% of patients with coronary-obstructive disease will be identified. If both tests are negative it makes significant coronary disease a very unlikely possibility (7%). If both tests are positive, it makes coronary disease a very likely possibility (93%). Unfortunately, when the GTX and MPI are used in combination, the specificity decreases because of the frequent occurrence (24%) of the false-positive GTX tests.
4. Most patients with the clinical syndrome of exertional angina and normal coronary arteries were

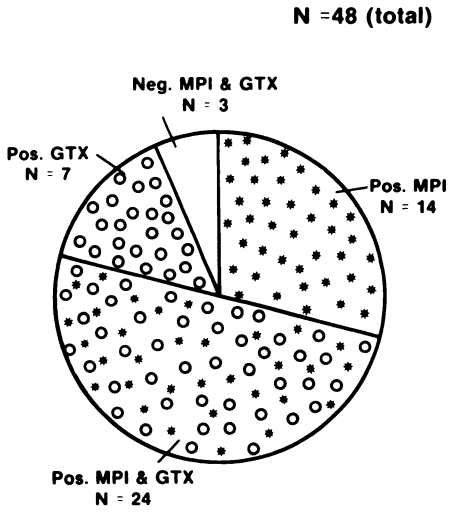

FIG. 4. Results of GTX and MPI in the coronary disease group. Only three patients were not identified by GTX or MPI. (Abbreviations as in Fig. 3.)

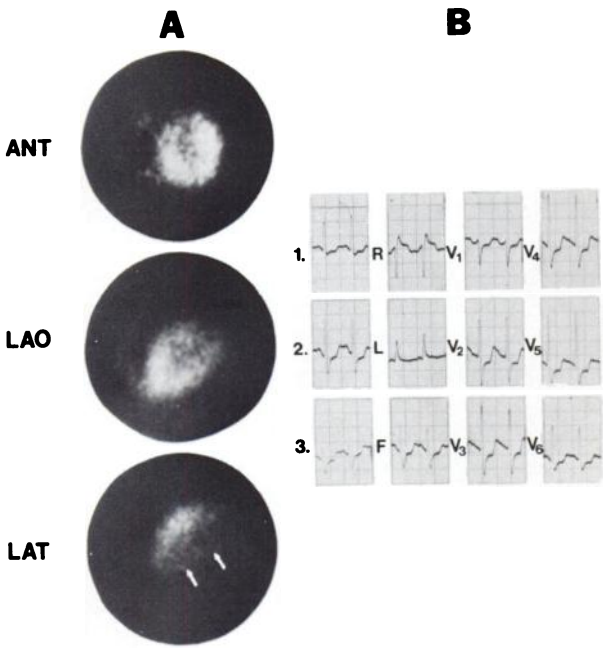

FIG. 5. (A) Abnormal Tl-201 scintigram in patient with angina, showing diminished perfusion of posterior wall of left ventricle. (B) Markedly positive exercise ECG (immediately off exercise). This patient had normal coronary arteries and left ventriculogram. (Abbreviations as in Fig. 1.)

shown to have normal exercise MPI, which suggests that this syndrome may not be explained on the basis of transient transmural regional myocardial ischemia.

In general, this study confirms many of the observations recently reported by Bailey et al. (*10*). It also extends their work because the specificity of the MPI was defined in a large group of middle-aged patients with angiographically normal coronary arteries. In our patients with coronary disease, the most striking difference between our data and that reported by Bailey was that the Tl-201 MPI was not particularly sensitive in detecting perfusion abnormalities in patients with three-vessel disease. In our study only 76% of patients with three-vessel disease had an abnormal MPI, whereas in the study reported by Bailey, 93% of patients with three-vessel disease were positive if the results of their rest and exercise perfusion scintigrams are considered together. In our study, however, all patients with three-vessel disease had either a positive GTX or a positive MPI. In Ritchie's series (*12*), the specificity of the Tl-201 MPI (92%) was closely comparable with ours (97%) and the overall sensitivity of the combined GTX and MPI—if the results from rest and exercise ECG and perfusion scintigrams are combined—was 91%. In our series, combining only exercise ECG and perfusion scintigrams yielded a sensitivity of 94%. In comparison with Ritchie's report (*12*), our work adds new data regarding the patients with nondiagnostic GTX, and patients with angina but normal coronaries.

In our group of patients with positive MPI, we cannot distinguish transient myocardial ischemia from a myocardial scar because we performed only exercised MPI. In order to make that distinction, a resting MPI would be required. This necessitates two i.v. injections of Tl-201 at least 3 days apart, which would markedly increase the cost of the procedure. Recently it has been suggested that rescanning the patients with positive exercise MPI 2 or 3 hr later may make it possible to distinguish between ischemia and scar (*15*). Nonetheless, neither doing MPI at rest nor rescanning 3 hr postinjection would have altered the overall sensitivity or specificity of the MPI in our patients.

A significant number of false-negative thallium MPI (21%) occurred in this series. A number of factors may be invoked to explain these false negatives. First, although Tl-201 is the best currently available myocardial imaging radionuclide, it is not an ideal imaging agent because its uptake by the myocardium is not always directly proportional to myocardial blood flow. Although at low flow rates (<100 ml/min · 100 g) the distribution of Tl-201 and coronary blood flow are almost perfectly correlated (*7*), at high flow rates (>200 ml/min · 100 g) such as might be expected with exercise, Tl-201 significantly underestimates coronary blood flow*. Second, the three-dimensional geometry and the location of the ischemic area are of importance. Thus, areas of ischemic myocardium closer to the camera —such as the anterior wall, transmural regions, and ischemic regions located in the center rather than at the edge of the image—will be more easily identified than ischemic regions with less favorable locations (*8*). Third, since the Tl-201 MPI is dependent on the relative distribution rather than absolute coronary blood flow, coronary-obstructive lesions that involve all three major coronary vessels and cause a homogeneous decrease in the uptake of Tl-201, may not be identified as abnormal. Of the four patients in this series with three-vessel coronary-obstructive disease and a negative Tl-201 MPI, three had obstructive lesions of similar severity in all three coronary vessels. Fourth, it is conceivable that some false-negative MPIs could occur in patients who did not exercise sufficiently. Finally, patent coronary vessels do not necessarily imply normal myocardial perfusion, and vice versa.

The functional importance of angiographically visible coronary collateral vessels remains a controversial subject (*19,22*). The perfusion scintigrams

obtained in this study did not indicate that well-developed coronary collateral vessels normalize regional myocardial perfusion during stress. Our data showed that about half of the positive scintigrams occurred in patients who had well-developed coronary collaterals in the region distal to the obstructed coronary artery, and half of the false-negative scintigrams occurred in patients with poor or absent coronary collaterals. The failure of the exercise Tl-201 MPI to correlate with the extent of angiographically visible coronary collateral vessels, however, does not detract from the possibility that these collateral vessels may be important in maintaining a normal resting perfusion. Since we did not do resting studies, we cannot confirm this possibility.

In the present study we found a "false-positive" perfusion scintigram in only one of 34 patients with angiographically normal coronary arteries. Potential causes for false-positive results are: (a) infiltration or fibrosis of the myocardium unrelated to coronary-obstructive disease; (b) the relatively broad range of normal Tl-201 uptake by areas of normal myocardium (*6,8*); (c) coronary obstructions that were not visualized in conventional angiographic projections (*23*); and (d) myocardial ischemia not due to atherosclerotic coronary disease, such as has been shown to occur during coronary spasm (*24*).

The number of false-positive GTX tests in this series (24%) was relatively high. This is due in part to a tendency of referring physicians to request coronary arteriography when a routine GTX test yields an unexpected strikingly positive result. It also reflects the relative prevalence of coronary disease in the population of patients being subjected to the GTX test (*25*). In other series, the number of false-positive GTX tests has varied from 8 to 65% (*26–29*).

The low incidence of false-positive MPIs in this series in part reflects careful attention to the normal variability of the Tl-201 perfusion scintigram. In this study we noted that the upper ⅓ of the interventricular septum in the left anterior oblique view, or the apex of the left ventricle in the left lateral anterior view, could be slightly decreased in normal patients. If these scintigrams were read as positive, it would markedly increase the apparent incidence of false positives.

The practical implications of this study are that an exercise Tl-201 MPI in combination with the GTX significantly increases the number of patients with coronary obstructive disease who can be identified. In addition, the MPI helps to identify false-positive GTX tests, and provides further evidence of normality in patients with negative GTX.

FOOTNOTE

* K. Lance Gould, personal communication.

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