The Predictive Value of Myocardial Perfusion Scintigraphy after Stress in Patients without Previous Myocardial Infarction

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Seventy-five patients who had chest pain but no history or ECG evidence of myocardial infarction (MI) underwent myocardial-stress perfusion scintigraphy (MSPS) with thallium-201, treadmill-stress testing (TST), and coronary cineangiography (CA). The sensitivities of MSPS and TST for coronary stenosis ≥75% were 68% and 71%, respectively; their specificities were 97% and 79%, respectively ($0.1 > p > 0.05$). When the character of a patient's chest pain is considered, Bayesian analysis leads to the following conclusions: (a) MSPS can be useful in pre-CA screening of patients with chest pain but no MI if their pain is thought to be of uncertain or nonischemic origin; (b) the sensitivity of Tl-201 MSPS is not sufficient for pre-CA screening of patients without MI who have typical or atypical angina pectoris; (c) the sensitivity of MSPS would have to be approximately 95% in order for the test to be useful in pre-CA screening of patients who have atypical angina pectoris; (d) MSPS may be superior to TST in these applications; and (e) it is not clear that there is any advantage in combining MSPS and TST into a single screening test rather than using MSPS alone.

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One of the most important applications of noninvasive tests for reversible myocardial ischemia is the evaluation of patients who have chest pain but no objective evidence of coronary artery disease. In this context, the goal is to differentiate pain due to coronary artery disease (CAD) from pain of other origin. Exercise-stress testing has been used for this purpose, but its accuracy is less than might be desired, particularly because of poor specificity (*1,2*).

Numerous reports have suggested that myocardial perfusion scintigraphy at rest and with exercise is a sensitive, specific test for CAD in populations that include patients with previous myocardial infarction (MI) (*3–12*). The earliest of these reports, and the availability of thallium-201 for investigative use in humans (*13,14*), prompted the prospective study reported here. Its goal was to estimate the predictive value (*15,16*) of myocardial-stress perfusion scintigraphy (MSPS) alone and in combination with treadmill-stress testing in patients with chest pain but without previous MI. Knowledge of the predictive value of MSPS in these patients was desired in order to gain insight into the clinical application of the test as a screening procedure for coronary cineangiography.

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MATERIALS AND METHODS

Patient selection. Patients were selected from those referred to the Section of Cardiology for coronary cineangiography because of periodic chest pain, thought by the referring physician to be suggestive of CAD. Patients were considered ineligible for the study if they had previous MI or were unsuitable for exercise stress testing by reason of physical disability, prolonged pain at rest, left-ventricular hypertrophy, left bundle-branch block or digitalis therapy. Since the problem addressed was clinical rather than theoretical, "previous MI" was given a clinical definition, i.e., patients were included as having previous MI if they exhibited pathological Q-waves on resting ECG or had been admitted to the hospital at any time for suspected MI. Eligible patients were interviewed in an arbitrary sequence: the first two individuals who gave informed consent each week became volunteer subjects in the experiment.

Exercise-stress testing. Continuous, multi-stage treadmill-stress testing (TST) was carried out on a motorized treadmill. Multiple electrocardiographic (ECG) leads were recorded. Orthostatic changes were noted by recording a 12-lead ECG in the supine, sitting and standing positions. Patients were asked to hyperventilate for 90 sec, during which the ECG and blood pressure were monitored. A 2-min practice walk was performed by the patient to familiarize him with the treadmill and to establish a brisk but comfortable pace. Once the testing procedure was begun, the work load was increased by raising the grade of the treadmill by 3.5% at 3-min intervals. The minimal end points of the TST were the submaximal heart rate according to Lester, Sheffield, and Reeves (*17*), or a 3-min period of chest pain that the patient recognized as his typical symptom. A dose of 15–22.5 μCi/kg of ^{201}TlCl* was injected through an indwelling butterfly needle once the patient had achieved his submaximal heart rate or had experienced his typical pain for 3 min. The patient was then asked to exercise for 2 additional minutes. One millimeter (0.1 mV) or more of flat or downsloping ST-segment depression, 80 msec from the J-point, was taken as a positive (ischemic) response.

Scintigraphic procedure. Using an Anger scintillation camera, imaging of the myocardial distribution of Tl-201 was begun within 10–20 min of termination of exercise. The pulse-height analyzer was set for an interval of about 22 keV centered at about 75 keV. For the first 26 patients, the camera was fitted with a low-energy converging collimator; subsequently, a medium-resolution, low-energy, parallel-hole collimator was used. Images were recorded on Polaroid film in four projections: anterior, 45° left anterior oblique, left lateral, and either 60° left anterior oblique or 30° right anterior oblique. Each image contained 250,000–350,000 counts. Studies were completed within 60 min of the termination of exercise.

Interpretation of the scintigrams. The perfusion scintigrams were inspected for regions of decreased uptake by two observers who had no knowledge of the clinical data, the results of the TST, or of other tests. The observers were allowed to compare the images with Tl-201 myocardial-stress perfusion scintigrams of patients with angiographically normal coronary arteries. After reaching a consensus in the interpretation of each study, the observers indicated their level of confidence that myocardial perfusion was abnormal in terms of the following five rating categories: "definitely abnormal;" "probably abnormal;" "possibly abnormal;" "probably normal;" or "definitely normal." Scintigrams rated "definitely" or "probably" abnormal were called "positive;" those placed in the remaining three categories were called "negative."

Cardiac catheterization and coronary angiography. Cardiac catheterization was performed percutaneously using the Judkins' technique. Left-ventricular end-diastolic pressures were recorded with a transducer positioned at the mid-chest position. The left-ventricular ejection fraction was obtained from a single-plane left-ventricular cineangiogram in the right anterior oblique projection. The minor axis was determined by planimetry using Green's method (*18*). Coronary cineangiograms were recorded on 35-mm film using an Arreflex Camera with a 100-mm lens and a cineradiographic system with image intensification.

Coronary cineangiograms were evaluated for coronary-artery stenoses, which were graded according to the most severe percentage of narrowing of the luminal diameter. Patients with 50% or less were considered "normal." Those with 75% or more were considered to have significant CAD ("abnormal"). Those whose most severe narrowing fell between 50 and 75% were excluded from the study.

Data analysis. The sensitivity—i.e., the conditional probability of a positive test given an abnormal patient [p(T+|D+)] —and the specificity—i.e., the conditional probability of a negative test given a normal patient [p(T−|D−)]—were calculated for MSPS, TST, and a "combined test" that was called positive if either the TST, the MSPS, or both were positive, as follows:

$$p(T+|D+) = \frac{\text{No. of "abnormal" patients with positive tests}}{\text{Total no. of "abnormal" patients}}, \quad (1)$$

and

$$p(T-|D-) = \frac{\text{No. of "normal" patients with negative tests}}{\text{Total No. of "normal" patients}}. \quad (2)$$

The post-test probability of a patient having disease given a positive test [p(D+|T+)], and the probability of disease given a negative test [p(D+|T−)], were calculated for each of the three tests assuming various pre-test probabilities of disease [p(D+)]. Bayes' Theorem (*19,20*) was employed in these calculations as follows:

$$p(D+|T+) = \frac{p(T+|D+)p(D+)}{p(T+|D+)p(D+) + p(T+|D-)p(D-)}, \quad (3)$$

and

$$p(D+|T-) = \frac{p(T-|D+)p(D+)}{p(T-|D+)p(D+) + p(T-|D-)p(D-)}. \quad (4)$$

In the foregoing equations,

$$p(T-|D+) = 1 - p(T+|D+), \quad (5)$$

$$p(T+|D-) = 1 - p(T-|D-), \quad (6)$$

and

$$p(D-) = 1 - p(D+). \quad (7)$$

RESULTS

Seventy-five patients entered the protocol. Six were excluded from the final analysis because they failed to achieve their predicted submaximal heart rates during exercise stress and did not exhibit an ischemic electrocardiographic response. Three additional patients were excluded because they had coronary artery narrowing greater than 50% but less than 75%. The TSTs of two patients were excluded, although their scintigrams were included; one developed left bundle-branch block during exercise and the other had Wolff-Parkinson-White syndrome. The scintigrams of two patients were excluded, although their TSTs were included, because in both cases the Tl-201 was inadvertently injected subcutaneously.

Thirty-five of the 66 patients who were included in the final analysis had significant coronary artery stenosis. Of these patients, 32 were male and three were female. The mean age of this group was 53.6 yr (±1.2 s.e.). The remaining 31 patients who were ultimately included were considered normal by cineangiography. Twenty-one were male and ten were female. The mean age of this group was 47.5 yr (±1.9 s.e.). All left ventricular ejection fractions were greater than 50%. Seven normal and ten abnormal patients had left ventricular and diastolic pressures (LVEDP) greater than 12 mm Hg. In no case was LVEDP greater than 19 mm Hg.

The scintigrams of 34 patients with significant stenosis were included in the final analysis; 23 (68%) were positive (Table 1). The scintigrams of 30 normal patients were ultimately included; 29 (97%) were negative.

The TSTs of 29 normal patients and 35 patients with significant stenosis were included in the final analysis (Table 1). The TST was positive in 25 (71%) of the abnormal patients and negative in 23 (79%) of the normal patients. Two of the six patients with false-positive TSTs developed ischemic responses during forced hyperventilation at rest (*21*).

In this series the greater specificity of MSPS, as compared with that of TST, is consistent with the observations of others (*10*)†. However, when McNemar's test of paired proportions was applied to the results for the 62 patients whose MSPS and TST were both included, the difference in specificity was not significant ($0.1 > p > 0.05$). The small difference in the sensitivities of the two tests also was not significant ($p > 0.1$).

Both the MSPS and TST of 62 patients were included in the final analysis (Table 1). The combined test was positive in 29 (85%) of 34 abnormal patients and negative in 22 (79%) of 28 normal patients.

The calculated p(D+|T+) and p(D+|T−) for each of the three tests, assuming various values of p(D+), are listed in Tables 3 and 4.

TABLE 1. RESULTS OF MYOCARDIAL-STRESS PERFUSION SCINTIGRAPHY (MSPS), TREADMILL-STRESS TESTING (TST), AND COMBINED TEST IN 66 PATIENTS

Test	MSPS		TST		Combined test	
Degree of stenosis	≥75%	≤50%	≥75%	≤50%	≥75%	≤50%
No. of positive tests	23	1	25	6	29	6
No. of negative tests	11	29	10	23	5	22
Totals	34	30	35	29	34	28
Sensitivity	0.68		0.71		0.85	
Specificity	0.97		0.79		0.79	

DISCUSSION

In a recent editorial in this journal, Parkey has advanced the thesis that Tl-201 myocardial perfusion scintigraphy is now established as a useful clinical tool (*22*). Although this is probably true, a note of caution should be injected. Whereas there is evidence to suggest that Tl-201 myocardial perfusion scintigraphy is useful for specific purposes in well-defined clinical populations, it can be shown to be inappropriate in other situations—particularly, as discussed below, when the p(D+) is very high. Indiscriminate use of the test will inevitably be detrimental.

We were particularly interested in the application of MSPS, alone or in combination with TST, to the screening (prior to coronary angiography) of patients with chest pain but clinically without previous MI. The sensitivity of Tl-201 MSPS in this experiment was less than that reported by others (*3–12*). If this were not the result of chance variation, the sensitivity may have been adversely affected by the 10–20 min delay between the end of exercise and the onset of scintigraphy (*23,24*) or by some other procedural factor not appreciated by us. However, the difference may be due, at least in part, to the fact that other series have included patients with documented previous myocardial infarction, whereas this series did not. Infarcts, which cause fixed perfusion defects, may be easier to detect than reversible ischemia. The incentive for an observer to "detect" reversible ischemia in a patient with a fixed perfusion defect is enormous, since in such a case a "positive" decision almost certainly will be a "true-positive" decision. In any case, the results of this experiment suggest that the sensitivity of MSPS in the detection of CAD may not be as high in populations without previous myocardial infarction as in those that include patients with well-documented infarction.

In order to know how MSPS and TST might be reasonably applied to the screening of patients with chest pain but no myocardial infarction, one must estimate the p(D+|T+) and the p(D+|T−) for each test separately and the two tests in combination. As noted above, estimates of these post-test probabilities of disease may be calculated from the sensitivity and specificity of each test and the pre-test probability of disease in the population being examined. Estimates of p(D+) for patients with various chest-pain syndromes are available from the medical literature (*25,26*). Using these estimates, one can calculate p(D+|T+) and p(D+|T−) of MSPS, TST, and the combined test in patients with the categories of chest pain defined in Table 5. Such an analysis implies that coronary artery disease is essentially the same, regardless of the category of pain with which it is associated.

It has been reported that approximately 95% of patients with typical angina pectoris (Table 5) will

TABLE 2. POST-TEST PROBABILITIES OF SIGNIFICANT CORONARY ARTERY DISEASE FOR MYOCARDIAL-STRESS PERFUSION SCINTIGRAPHY*

Pre-test probability of disease	Probability of disease given positive test result	Probability of disease given negative test result
0.05	0.54	0.02
0.08	0.66	0.03
0.18	0.83	0.07
0.20	0.85	0.08
0.30	0.91	0.12
0.50	0.96	0.25
0.70	0.98	0.44
0.95	1.0	0.86

* Sensitivity = 0.68; specificity = 0.97.

TABLE 3. POST-TEST PROBABILITIES OF SIGNIFICANT CORONARY ARTERY DISEASE FOR COMBINED TEST*

Pre-test probability of disease	Probability of disease given positive test result	Probability of disease given negative test result
0.05	0.18	0.01
0.08	0.26	0.01
0.18	0.47	0.04
0.20	0.50	0.05
0.30	0.63	0.08
0.50	0.80	0.16
0.70	0.90	0.31
0.95	0.99	0.78

* Sensitivity = 0.85; specificity = 0.79.

TABLE 4. POST-TEST PROBABILITIES OF SIGNIFICANT CORONARY ARTERY DISEASE FOR TREADMILL-STRESS TESTING*

Pre-test probability of disease	Probability of disease given positive test result	Probability of disease given negative test result
0.05	0.15	0.02
0.08	0.23	0.03
0.18	0.43	0.07
0.20	0.46	0.08
0.30	0.59	0.14
0.50	0.77	0.27
0.70	0.89	0.46
0.95	0.98	0.87

* Sensitivity = 0.71; specificity = 0.79.

TABLE 5. CLASSIFICATION OF CHEST PAIN*

Typical angina pectoris:
Pain that is
1. clearly precipitated by exertion and relieved by rest.
2. deep visceral pain described as heavy, squeezing, aching, etc.
3. referred to some portion of the sternum.

Atypical angina pectoris:
Pain that has one or two but not all three of the properties of typical angina pectoris as described above, but that all physicians believe to be of ischemic origin.

Nonischemic pain:
Pain that two clinicians agree is not angina pectoris.

Pain of uncertain origin:
Pain that clinicians cannot classify into any of the three groups above or about which two clinicians disagree.

* After Ross and Friesinger: *Amer Heart J* 72: 437–441, 1966.

TABLE 6. CONDITIONAL PROBABILITY OF CORONARY ARTERY DISEASE (CAD) GIVEN A NEGATIVE TEST AGAINST SENSITIVITY OF TEST*

Sensitivity	Probability of CAD
0.99	0.01
0.98	0.02
0.97	0.03
0.96	0.04
0.95	0.05
0.94	0.06
0.93	0.07
0.92	0.08
0.91	0.08
0.90	0.09

Calculated from equation (4) in text.
* Pre-test probability of disease = 0.5; specificity = 0.97.

TABLE 7. POST-TEST PROBABILITIES OF DISEASE FOR A TEST WITH SENSITIVITY = 0.95 AND SPECIFICITY = 0.97

Pre-test probability of disease	Probability of disease given positive test result	Probability of disease given negative test result
0.3	0.93	0.02
0.5	0.97	0.05
0.95	1.0	0.49

be found to have significant CAD at cineangiography (*25,26*). As indicated in Tables 2 through 4, the p(D+|T+) approaches 1.0 for all three tests in such patients. However, given this very high p(D+), the probability of disease is also high if the tests are negative. Hence, the outcome of MSPS, TST, or the combined test should not affect a decision concerning coronary cineangiography in patients with typical angina pectoris.

As many as 30–50% of patients with atypical angina pectoris (Table 5) have significant CAD (*25,26*). Since the p(D+) for these patients is in the range of 0.3–0.5, the p(D+|T−) is 0.12–0.25 for MSPS, 0.08–0.16 for combined testing, and 0.14–0.27 for TST (Tables 2–4). These p(D+|T−) ranges are undoubtedly too high to serve as the basis for deferring coronary angiography. Hence, MSPS is of limited value in patients with atypical angina pectoris. This conclusion is at variance with that of Botvinick and his colleagues (*10*), who found MSPS "extremely reliable" in patients with atypical chest pain. They reported both the sensitivity and the specificity to be 0.91 for MSPS with rubidium-81. The p(D+) of patients with atypical chest pain was 0.33 in their series. Thus, the p(D+|T+) and p(D+|T−) of MSPS were 0.83 and 0.05 respectively for these patients. The series, however, included patients with documented previous myocardial infarction.

It has been reported that 8–18% of patients with chest pain thought to be of uncertain or nonischemic origin (Table 5) have significant CAD (*25,26*). Hence, given the sensitivity and specificity of MSPS suggested by the results of this experiment, the p(D+|T+) would be approximately 0.66–0.83 (Table 2)—high enough to recommend that such patients undergo coronary cineangiography. The p(D+|T−) would be only 0.03 to 0.07, probably low enough to indicate that cineangiography need not be performed. Thus it seems reasonable to use MSPS to determine whether or not patients with chest pain thought to be of uncertain or nonischemic origin should undergo coronary cineangiography.

The sensitivities of MSPS and TST were similar in this experiment: 0.68 for MSPS against 0.71 for TST. Although not quite significant at the 0.05 level in this small series, the specificity of MSPS was greater than that of TST: 0.97 against 0.79. The effect of the observed difference in the specificities is apparent from inspection of Tables 2 and 4. The p(D+|T−) is about the same for the two tests, for all p(D+), whereas the p(D+|T+) is higher for MSPS than TST. Assuming that the specificity of MSPS is indeed greater than that of TST, a larger number of normal patients would undergo unnecessary coronary cineangiography if decisions were based on TST rather than MSPS. This assumption seems reasonable, given the experience of others (*10*).

It is not clear whether the combined test has any advantage over MSPS alone in the evaluation of these patients; the sensitivity of the combined test

(0.85) was greater than that of MSPS alone (0.68), but the specificity of MSPS was greater (0.97 against 0.79). As a result, p(D+|T+) is much higher for MSPS, but p(D+|T−) is lower for the combined test (Tables 2 and 3).

It might have been possible to increase the sensitivity of perfusion scintigraphy in this series (without lowering specificity) by the use of image processing (*27,28*) or by use of a pharmacological stimulus rather than exercise stress. Improvement in the sensitivity of perfusion scintigraphy without a decrease in specificity might allow extension of the test to the screening of patients with atypical angina pectoris, as suggested by Botvinick et al. (*10*). The sensitivity would have to be very great indeed however, for the test to be reasonably applied in this way. As noted above, patients with atypical angina may have a p(D+) as high as 0.5. Assuming that the p(D+) is 0.5 and the specificity is 0.97, the sensitivity would have to be 0.95 in order to reduce the p(D+|T−) to 0.05 (Table 6). Whether or not this can be achieved with Tl-201 MSPS without reducing specificity, in patients without prior myocardial infarction, remains to be seen. Even if a sensitivity of 0.95 and a specificity of 0.97 could be achieved, MSPS would not be applicable to the screening of patients with typical angina pectoris. Since these patients have a p(D+) of about 0.95, the p(D+|T−) would be quite high (Table 7).

FOOTNOTES

* Activity of Tl-201 in units as redefined by the National Bureau of Standards, 1977.

† Signal-detection theory tells us that the sensitivity and specificity of a test vary monotonically with the decision criterion level. Hence, no statement can be made about the relative inherent detectability of disease with two tests if, as in this case, one appears more specific but less sensitive than the other. Since the MSPSs were read in terms of a five-category rating scale, we can determine that the p(T+|D+) and p(T+|D−) for MSPS at the "strictest" criterion level implied by the five-category scale were 0.53 and 0.0 respectively. The p(T+|D+) and p(T+|D−) of TST at criterion levels of 0.1 mm, 0.2 mm, and 0.3 mm or greater ST depression were 0.71 and 0.21, 0.51 and 0.14, and 0.29 and 0.0 respectively. When these data are plotted as receiver operating characteristic (ROC) curves, it is apparent that the greater specificity of MSPS is not simply an artifact of the decision criterion levels chosen for the two tests; the ROC plot suggests that the inherent detectability of CAD is greater with MSPS than with TST.

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