Prediction of Death, Myocardial Infarction, and Worsening Chest Pain Using Thallium Scintigraphy and Exercise Electrocardiography

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Although used extensively, there is little published information on the prognostic ability of exercise ^{201}Tl scintigraphy. Accordingly, 1 yr after testing we contacted 819 patients without previous MI or CABG seen in our laboratory during a 2-yr period. Events were defined as death from a cardiovascular cause, nonfatal MI, or worsening clinical state requiring CABG. The event rate was 3.9 events per 100 patients per year. There was univariate prognostic information when comparing the highest and lowest categories as risk ratios for chest pain characteristics (2.7), sex (2.3), exercise duration (3.1), ST slope (2.5), and thallium pattern (11.6), intensity of perfusion defect (17.2), and number of abnormal regions (8.7). However, the strongest predictors were also the least common. Prognostic ability was improved by combining the results categorically, as the number of abnormal tests (13.9). The highest risk ratio, 20.5:1, was obtained by combining results through discriminant function analysis. We conclude that exercise thallium scintigraphy provides prognostic information, although the most predictive patterns are uncommon. Combining the results of multiple test results improves the prognostic ability.

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Stress thallium scintigraphy is an effective diagnostic test, and is, therefore, widely assumed to have prognostic value as well. While this assumption is often true for diagnostic tests, there is clearly no systematic relationship between diagnosis and prognosis. Our study is the first large scale follow-up study relating the results of thallium exercise testing to long-term prognosis. Specifically, we followed the 819 patients without known coronary heart disease referred to our laboratory during a 2-year period. The goal of the study was to answer four questions in patients.

1. What is the predictive ability of the individual variables obtained during history and physical?
2. Which stress test results are the most powerful predictors of 1-year risk?
3. How frequently are the most powerful predictors of risk observed?
4. Can multiple results be integrated into an individual risk prediction for every patient?

METHOD

Patient Population

Between January 1, 1979 and January 1, 1981, 1484 people underwent thallium stress testing in our laboratory (Table 1). The 819 individuals in this group with completed follow-up who denied a history of either myocardial infarction or coronary artery bypass surgery, and who also had no clinical evidence of valvular heart disease, form the basis of this report.

Exercise Protocol

All patients were exercised on a Case Marquette treadmill. Electrocardiographic assessment was performed using 3-min recordings of the 12 monitoring leads with continuous display and one minute recording of signal averaged complexes from V1, V5, and aVf. The symptom limited maximal Bruce protocol was employed. We did not remove patients with abnormal electrocardiograms at rest and patients who did not obtain a predetermined heart rate. Rather, we included

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TABLE 1
Patient Inclusion and Exclusion

Total patients having exercise thallium scintigraphy		1,484
Reason for exclusion		
Prior coronary bypass grafting	233	
Prior myocardial infarction	309	
Early CABG after testing	58	
Died from noncardiac cause	10	
Lost to follow-up	55	
Remaining patients		819

all patients as performing a "symptom limited" test and recorded the ST depression as the amount of developed depression. At 1-min prior to the end of the exercise, the patient was given 2 mCi of thallous-201 (^{201}Tl) chloride into a previously placed intravenous line. The patient was placed on a gurney after the stress test and nuclear imaging was begun 5 min after the termination of the test. Between 3 and 5 hr after injection, the patient was again imaged. Imaging was performed in the anterior, 45° LAO and 70° LAO positions using a portable scintigraphic camera with a 1/4 in. parallel hole, high resolution collimator. The polaroid pictures of the analog signal taken from the scintigraphic camera were used for analysis in this study. There was no background subtraction or image enhancement. Images were collected for a total of 200,000 counts per image.

Data Collection and Classification

Historical data for chest pain classification and history of prior infarction were obtained from the patient before testing using a questionnaire with explicit closed ended questions. The history of chest pain was classified by three characteristics: (a) retrosternal location, (b) precipitation by exertion, (c) prompt relief by rest or nitroglycerin. Using these characteristics, four categories of chest pain were established: (a) typical angina: all three characteristics present, (b) atypical angina: any two of the three characteristics present, (c) nonanginal chest pain: 1 or 0 of the characteristics present, (d) asymptomatic: no pain.

The ECG was classified by both magnitude and slope of ST depression. The magnitude of developed ST segment depression was measured at 0.08 msec after the J point and the slope of the ST segment depression was visually defined as upsloping, horizontal, or downsloping. The duration of exercise was determined from the computer printout.

The ^{201}Tl myocardial scintigrams were visually interpreted by two expert observers unaware of the patient's history or the results of the other tests. Differences in the interpretation were mediated by consensus. The images were divided into three segments per view: anterior view: anterior, apical, and inferior; 45° LAO view: septal, inferoapical, and posterolateral; and 70° LAO view: anterior, apical, and inferior. The magnitude of thallium uptake in each view was quantified as: 0: normal uptake; 1: mildly decreased; 2: moderately decreased; 3: severely decreased. If a segment was represented in more than one view, the most severe defect score was used. The thallium scintigrams were coded as (a) reversible if there was segmental hypoperfusion of at least grade 2 in the stress image which improved to a grade of 0 or 1 in the 4-hr image, (b) nonreversible if there was segmental hypoperfusion of at least grade 2 on the stress image with persistence of grade 2 or 3, (c) normal if there were no defects in the stress image, (d) equivocal if there were defects of only grade 1 in the stress image. For the dichotomous classification of positive or negative ^{201}Tl studies, reversible and nonreversible patterns were considered as positive.

With respect to the number of segments involved, the defects were grouped as follows: defects in the anterior or septal area were considered as LAD distribution, defects in the inferior wall were considered as right coronary artery distribution, and defects in the posterolateral wall were considered as circumflex distribution. Defects in the inferoapical and apical areas were not included in any territory.

Follow-up

All patients were telephoned at least 1 year after testing by a professional interviewer who read a 5–10 min script consisting of closed ended questions. These questions dealt with (a) myocardial infarction, (b) coronary artery bypass surgery, (c) medications, and (d) chest pain characteristics. If the patient died, the family or referring physician were called about the cause of death. For all patients with a history of death or myocardial infarction, we obtained confirmation from death certificates, hospital charts, and/or the referring physician.

Cardiac events were classified into three types. (1) Death from a cardiac cause. These were deaths which were either sudden (<1 hr from the onset of symptoms) or from an obvious cardiovascular cause. Deaths from known noncardiac causes or for unknown reasons were classified as noncardiac and such patients were excluded from analysis. (2) Myocardial infarction. We included only myocardial infarction documented by typical history, ECG, and enzyme changes. (3) Late bypass surgery. We included as events bypass surgery performed more than 60 days after testing. This fixed cut point was chosen for reproducibility, based on a previous study (*1*) in which charts of patients undergoing CABG after exercise stress testing were reviewed to establish whether bypass surgery was based upon the result of the stress test, or was a result of worsening clinical state.

Sixty days represented the best operational discriminator (85% accuracy) which differentiated surgery performed because of test results from that performed because of worsening symptoms. The mean time from testing to surgery in the coronary artery bypass group was 3.0 mo. At the time of this study, the waiting time for elective surgery was 0–2 wk.

There were 32 events in this population, a rate of 3.9 events per 100 patients per year. There were eight cardiac deaths, 11 nonfatal infarctions, and 13 bypass operations secondary to worsening clinical state. The ten patients who died from a noncardiac cause and the 58 patients who had coronary artery bypass surgery within 60 days of stress testing were excluded from all analyses except for Table 3. For graphical representation, patients with death from a cardiac cause or nonfatal myocardial infarction were classified as a hard event, and patients having bypass surgery more than 60 days after testing were considered as a soft event.

For the initial assessment of combinations of variables, we divided exercise duration, electrocardiography, and thallium results using the following boundaries for positive: duration of exercise, <9 min; ECG, 1.5 mm of upsloping ST depression, or 1.0 mm of horizontal ST depression, or 0.5 mm of downsloping ST depression; thallium, fixed or reversible defects.

Statistical analysis was performed on a VAX 11-750 computer using standard computer software (BMDP) (*2*). For univariate comparisons, the Chi Square analysis was performed. For the multivariate comparisons using discriminant function and logistic analysis, the outcome variable was divided into any event, hard or soft, or no event. The discriminant function analysis was performed for both soft and hard events. All variables were forced into the final equation.

RESULTS

Clinical Variables

Table 2 compares the age, sex, and symptom classification in individuals who experienced a cardiac event and those who did not. The character of the chest pain elicited by history and sex were moderately discriminant ($p = 0.0074$, $p = 0.040$, respectively), although age was minimally discriminant ($p = 0.535$). Table 3 presents the raw data including excluded patients for variables in Figs. 2A, 3 and 4.

Figure 1 shows the relationship of the exercise duration to annual event rate. In this and all subsequent figures, the x axis represents the level of the independent variable, and the y axis presents the cardiac event rate per 100 patients per year. To enhance comparisons, the scale of the y axis is constant for all figures. The lower portion of each bar depicts the proportion of patients who had hard events (cardiac death or nonfatal myocardial infarction) and the upper portion the additional proportion who had soft events (CABG after 60 days). The number written on each bar indicates the proportion of the population having that level of the independent variable. A strong and consistent correlation existed between event rate and decreasing exercise du-

TABLE 2
Prognosis by Age, Sex, and Symptoms (Events per 100 Patients per Year)

Category	Hard events	Hard + soft events	Occurrence
Sex			
Female	1.2	2.0	30.8
Male	2.8	4.7	69.2
Age			
⇐45	0.7	1.4	17.9
46–55	2.0	4.0	29.8
56–56	2.3	3.5	31.5
>65	4.1	6.4	20.8
Symptom Classification			
Asymptomatic	2.8	3.3	26.8
Nonanginal	0.4	1.9	32.5
Atypical	1.5	4.1	24.0
Typical	6.6	8.8	16.7

TABLE 3
Raw Data for Prognostic Variables

	Alive*	CARD DTH†	Event MI‡	CABG lat§	Othr DTH¶	CABG ERL**	Total
Magnitude of ST Depression							
<1.0	362	4	2	5	6	6	385
1.0–1.9	237	2	4	4	2	18	267
> = 2.0	176	1	5	4	2	34	222
Total	775	7	11	13	10	58	874
Thallium Pattern of Worst Lesion							
Normal	374	0	2	2	3	1	382
Equivocal	187	0	0	1	1	3	192
Fixed	59	2	1	2	1	7	72
Reversible	167	6	8	8	4	47	240
Total	787	8	11	13	9	58	886
Thallium Hypoperfusion							
None	375	0	2	2	3	1	383
Mild	186	0	0	1	1	3	191
Moderate	202	6	8	8	5	43	272
Severe	24	2	1	2	0	11	40
Total	787	8	11	13	9	58	886

* Alive = No event.
† Card DTH = Death from cardiovascular cause.
‡ MI = Nonfatal myocardial infarction.
§ CABG lat = Coronary artery bypass surgery more than 60 days after testing.
¶ Othr DTH = Death from cause other than cardiovascular.
** CABG ERL = Coronary artery bypass surgery no more than 60 days after testing.

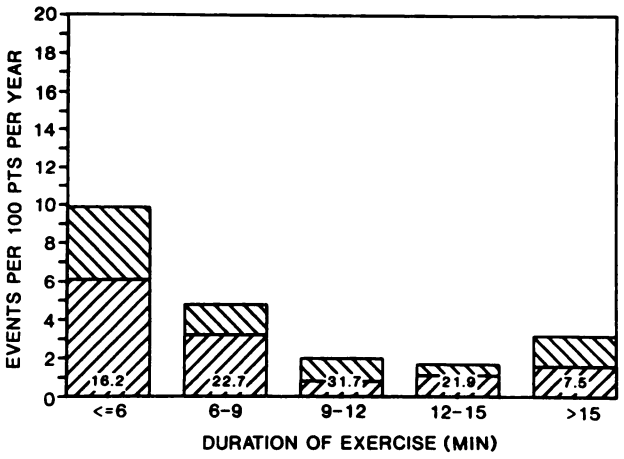

FIGURE 1
In this and all subsequent figures, the x axis represents level of independent variable, and the y axis presents cardiac event rate per 100 patients per year. To enhance comparisons, scale of y axis is constant for all figures. Lower portion of each bar depicts proportion of patients who had hard events (▨) (cardiac death or nonfatal myocardial infarction) and upper portion additional proportion who had soft events (▧) (CABG after 60 days). Number written on each bar indicates proportion of population having that level of independent variable. This figure demonstrates relationship between duration of exercise in minutes on Bruce protocol and event rate. Best representation of data is with log of duration versus event rate (see text)

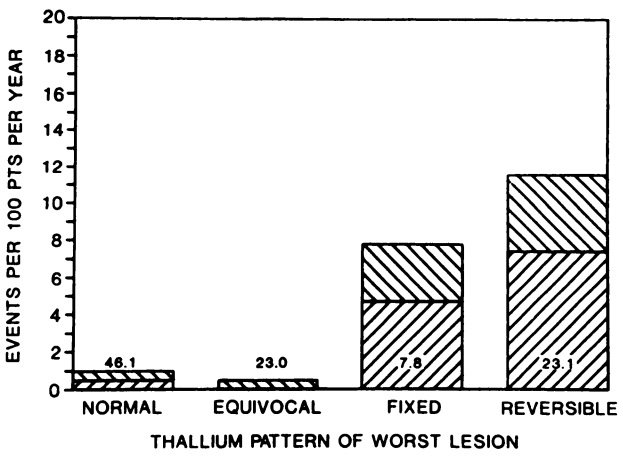

FIGURE 3
Thallium pattern of worst lesion. This figure shows the results of pattern of most ischemic segment on visually interpreted thallium scintigram and event rate. Note that event rate for equivocal category is lower than that of normal category. (▨) Hard events; (▧) Soft events

ration. Considering event rates as the sum of deaths, myocardial infarction, and late surgery, the data show an exponential relationship: the log of the event rate is highly correlated with exercise duration ($x^2 = 0.996$, $p < 0.001$).

ECG Variables

Figures 2A and B show the relationship of event rate to the magnitude and the slope of maximal ST segment depression. The frequency of cardiovascular events increases only slightly with increasing ST segment depression ($p = 0.595$). There is a 1.9-fold increase in the total event rate between the lowest and the highest group of ST segment depression. ST segment slope has predictive value ($p = 0.042$). This analysis is assessed independent of the magnitude of the ST depression. Event rate increases as the slope becomes more downward. There is a 2.5-fold increase in events over the three ST slope categories.

Scintigraphic Variables

Figure 3 shows the predictive ability of stress thallium scintigrams classified as normal, equivocal, fixed, or reversible. As the interpretation of the thallium image becomes more consistent with the diagnosis of exercise induced ischemia, the probability of a cardiac event

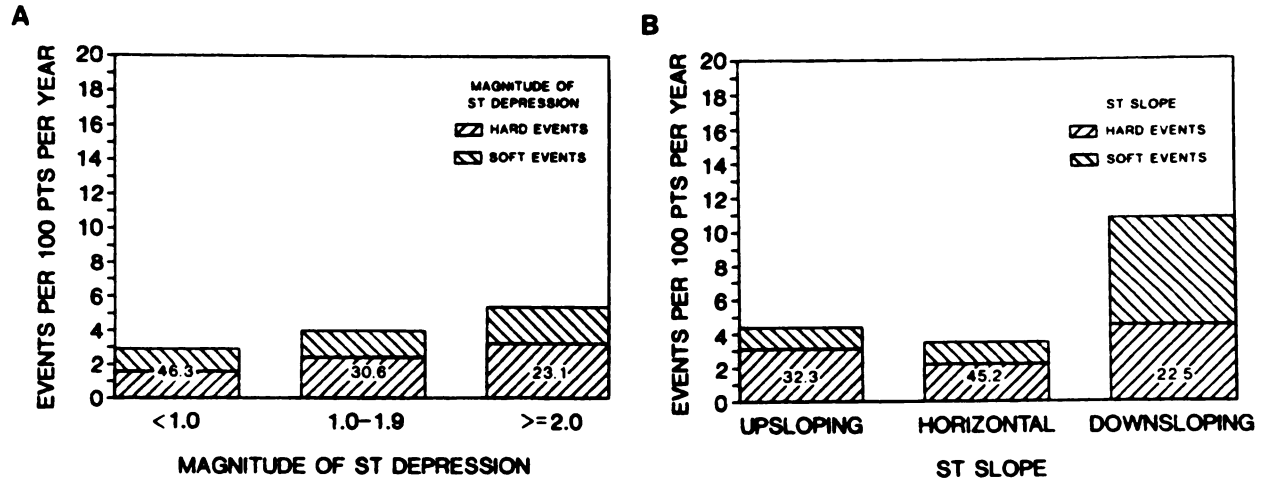

FIGURE 2
Effects of standard exercise electrocardiographic variables, magnitude of ST depression (A), and ST slope (B), on event rate

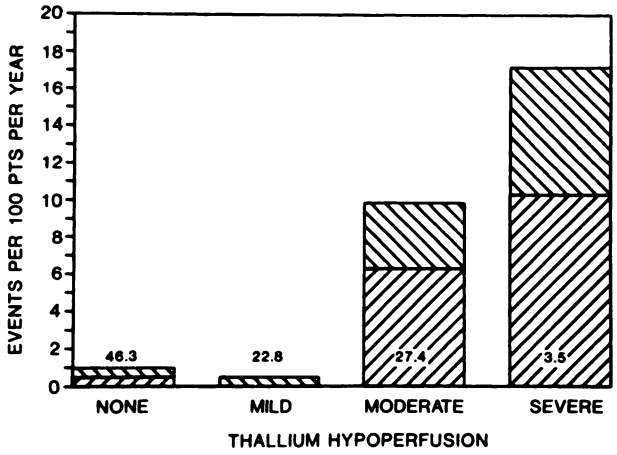

FIGURE 4
Relationship between magnitude of thallium hypoperfusion on most ischemic segment and event rate. (▨) Hard events; (▧) Soft events

increases (p = 0.0001). This effect is also consistent in the different cardiac event groups.

Figure 4 shows the intensity of the most abnormal segment at thallium scintigraphy plotted against the event rate. As the magnitude of hypoperfusion increases, so does the event rate (p = 0.0001). In 69% of the population, with the highest regional score of 0 or 1, the average event rate was 0.88%. In the remaining 31% of the patients, with one or more regional scores of 2 or 3, the average event rate was 10.7%. The graph, however, tends to conceal a serious limitation in what would seem to be an important finding; only 3.5% of the people actually had severe hypoperfusion. This problem is a general one: for any single test parameter, the prediction of high risk occurred very infrequently.

Figures 5A and B correlate cardiac events with the number of myocardial territories exhibiting a perfusion defect. Figure 5A indicates the number of areas with any defect, and Fig. 5B indicates the number with reversible defects. Although the probability of an event did increase with the number of abnormal territories in both analyses (p = 0.0001, p = 0.0001, respectively), the most important discrimination was the presence of any defect. As with severity of thallium hypoperfusion, however, identification of high risk was uncommon: only 7.6% of scintigrams had defects of any kind in more than one territory. Both multiple ^{201}Tl defects, and severe defects, are more common than suggested by the data base under analysis, however, since they occurred in 47% and 57.5% respectively of the excluded patients undergoing early CABG.

Multivariate Methods

Figures 6 and 7 illustrate integration of the univariate characteristics described in the preceding illustrations. The simplest method of integrating results is to separate the test results into positive or negative and count the number of abnormal test results as shown in Fig. 6. The impact of such dicotomy on exercise duration, electrocardiography, and thallium results is an increase in the probability of an event with an increasing number of positive tests. When compared with the previous univariate analyses, there is now a higher event rate in the highest category and a better distribution of the patients among groups. This method, however, still places relatively few patients in the groups at higher risk. Specifically, only 9.0% of the population is in the highest risk group.

Discriminant function analysis, which allows the distribution of patients into four equal groups is shown in Fig. 7. There were no deaths or myocardial infarction in the first quartile, whereas in the fourth quartile, the

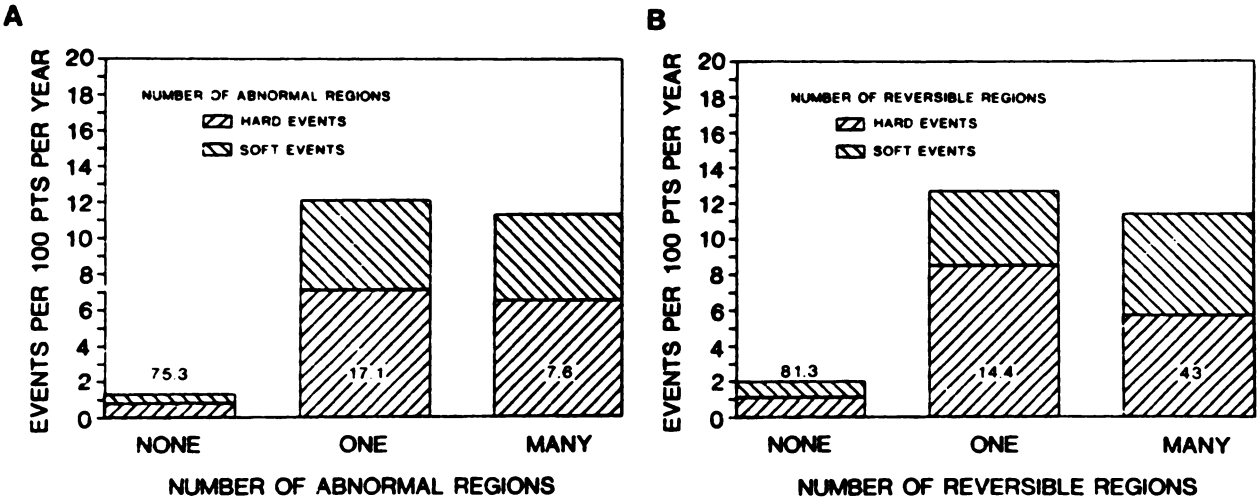

FIGURE 5
This figure demonstrates relationship between number of coronary artery territories indicating thallium perfusion defects and event rate. A identifies territories with fixed or reversible defects, and B identifies only territories with reversible defects. There is no striking difference in results between two panels

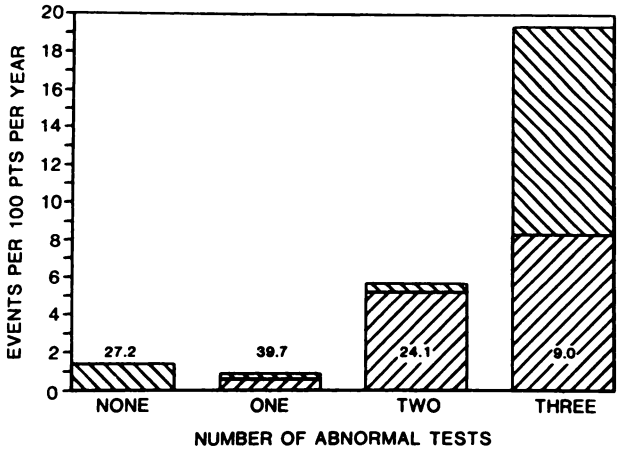

FIGURE 6
Relationship between number of abnormal test results and event rate. The three test results used are exercise duration, ST segment depression, and thallium scintigraphy (see text for cut points). (▨) Hard events; (▧) Soft events

event rate was 17.1%. Between the first and fourth quartile, the risk of a cardiac event increased 20.5 times. The frequencies in Fig. 7 refer only to the occurrence rate of the discriminant function score quartiles. The analysis was performed using any event versus no event. The display in Fig. 7 is to show the results, as in the other figures, of dividing the events into hard and soft.

DISCUSSION

Our study demonstrates the value of individual exercise ^{201}Tl scintigraphic variables in predicting cardiac events over the first year after testing. There are a large number of potential variables with some predictive

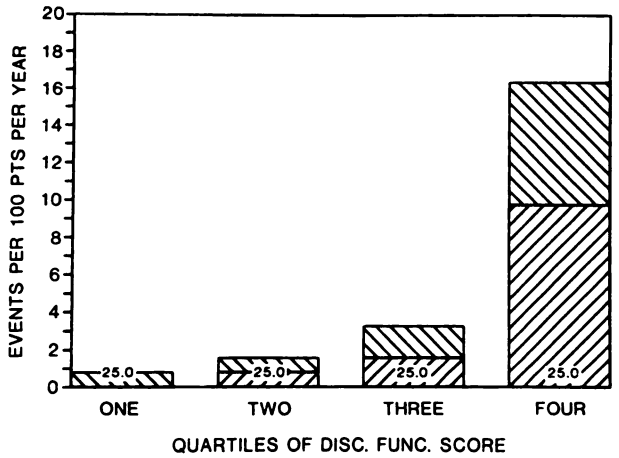

FIGURE 7
Relationship between quartiles of risk as determined by discriminant function analysis and event rate. Frequencies refer only to occurrence rate of discriminant function score quartiles. Analysis was performed using any event versus no event. For this analysis, all variables discussed were included in equation. (▨) Hard events; (▧) Soft events

value. The historical variables of male gender and typical angina and the stress electrocardiographic variables of exercise duration, slope and magnitude of ST depression had weak prognostic value, with risk ratios ranging between 2:1 and 5:1 for highest and lowest risk categories. In contrast, there was major prognostic information in the pattern of thallium perfusion defects. Patients with thallium images read as equivocal had a prognosis similar to those read as normal. There was an increasing event rate as the severity of hypoperfusion increased and as the number of perfusion defects increased. There was no prognostic value in the analysis of perfusion defects by anatomic location. The most powerful individual predictor of cardiac events was severe hypoperfusion. The risk ratio associated with this finding was 17:2. Nevertheless, this apparently important finding is diminished in impact by its infrequency: only 3.5% of patients exhibited this finding.

Our study shows that integration of the multiple test results obtained during exercise thallium scintigraphy allows identification of quartiles with a 20.5-fold difference in subsequent risk for a cardiac event at one year. The key to this process is the integration of a number of weakly predictive individual variables. Specifically, these individual variables are history, exercise duration, magnitude and slope of maximal ST depression, magnitude of thallium hypoperfusion defect, and reversibility of the perfusion defect.

One limitation of our analysis is the 5.8% of patients lost to follow-up. This percentage compares favorably with all large follow-up programs in the United States, but nevertheless becomes potentially significant when the percent lost to follow-up is similar to the event rate. Because there were no differences in any of the demographic or test results between those successfully and unsuccessfully followed up, we assume that the lost patients are an unbiased sample of the original population.

The second potential limitation of our analysis is the classification of referrals to CABG after 60 days as a "soft event." In the ideal circumstance for the statistician, no patients would be sent to surgery. Since we assume that CABG may modify the subsequent cardiac event rate, it is inappropriate to ignore this intervention in assessing the prognostic value of the test. On the other hand, we cannot consider CABG an event, since the test results are often used as criteria for the need for CABG. One would therefore predict a higher prevalence of stress test abnormalities in the early CABG group. This prediction is confirmed by our data since the frequency of multiple ^{201}Tl defects and severe ^{201}Tl defects, the strongest predictors of events, were 47% and 57.5%, respectively. Because of the exclusion of the early surgery group, one does not get a true picture of the prognostic value of thallium scintigraphy. The absolute risk of a cardiac event after stress testing cannot

be established, since a segment of the higher risk patients have been eliminated from analysis. On the other hand, our analysis can be taken to indicate the 1-year risk of a cardiac event in those patients not treated surgically for at least 60 days after the stress test.

Even though the event rate increased as the test responses became more ischemic, there was a large number of events in the nonischemic response group (Table 3). This low sensitivity of the test responses may be improved by newer techniques such as quantification of the thallium images and single photon emission computed tomography (SPECT).

Our data also provide a critical insight for the use of stress testing for prognostication, involving the often overlooked distinction between relative and absolute risk in testing. The mean 1-year event rate was 3.9%. Therefore, a blanket prediction to each nonsurgically treated patient that he would not have a cardiac event would be correct 96.1% of the time. Identification of an apparently enormous risk ratio of 20.5:1 may still be questioned as establishing "high risk," when the actual event rate in this group was only 16.4%, after those at highest risk had been extracted for early CABG.

There have been a number of prior studies relating ^{201}Tl stress scintigraphy to prognosis in patients after myocardial infarction. Each study was limited by the relatively small number of patients followed up, the low event rate in the population, and the soft endpoints. The largest study, by Smeets et al. followed 224 patients shortly after myocardial infarction. They found that ST segment depression during exercise and an abnormal thallium scintigram predicted future events, although the majority of their events were bypass surgery (*3*). Dunn found that the size of the thallium defect during infarction was predictive of future events, although most of their "events" were continuation of pre-existing angina or left ventricular failure (*4*). Becker (*5*, *6*), Silverman (*7*), Botvinick (*8*), Gibson (*9*), and Tomoda (*10*) all have reported that the size and location of resting thallium defect in patients with acute myocardial infarction predicted mortality over the next year. This body of evidence indicates that thallium stress scintigraphy does have predictive value in patients with prior infarction.

There is no previous study in a large uncatheterized population typical of that referred to a nuclear stress laboratory. The only comparable data is that of Brown (*11*) who studied 100 patients without previous myocardial infarction with stress thallium scintigraphy. He found that the number of myocardial segments with transient ^{201}Tl defects was the only statistically significant predictor of future cardiac events. In contrast to Brown, we found a number of demographic, exercise, ECG, and scintigraphic results to be predictive of outcome, and that integration of these results was a more powerful predictor than any single variable.

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