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Independent and Incremental Prognostic Value of Exercise Single-Photon Emission Computed Tomographic (SPECT) Thallium Imaging in Coronary Artery Disease

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Objectives. The objective of this study was to examine the independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in patients with angiographically defined coronary artery disease.

Background. Previous studies showed the importance of exercise thallium-201 in risk stratification. However, most of these studies used planar imaging techniques.

Methods. Follow-up data were obtained in 316 medically treated patients with coronary artery disease. Cox proportional hazards regression models were used to examine the independent and incremental prognostic values of clinical, exercise, thallium and cardiac catheterization data.

Results. There were 35 events (cardiac death or nonfatal myocardial infarction) at a mean follow-up time of 28 months. Univariate analysis showed that gender (chi-square = 5.1), exercise work load (chi-square = 3.1), extent of coronary artery disease and left ventricular ejection fraction (chi-square = 14.8) and thallium variables (chi-square = 22.7) were prognostically important. The thallium data provided incremental prognostic value to catheterization data (chi-square = 33.7, $p < 0.01$). The extent of the perfusion abnormality was the single best predictor of prognosis (chi-square = 14). Patients with a large perfusion abnormality had a worse prognosis than that of patients with a mild or no abnormality (Mantel-Cox statistics = 10.6, $p < 0.001$).

Conclusions. In medically treated patients with coronary artery disease, exercise SPECT thallium imaging provides independent and incremental prognostic information even when catheterization data are available. The extent of the perfusion abnormality is the single most important prognostic predictor.

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Several studies have shown that patients with stable coronary artery disease can be stratified into different risk groups based on demographic, exercise, radionuclide and catheterization information (1–10).

The results of studies using exercise thallium imaging in risk assessment were recently reviewed by Brown (11). These studies were obtained with planar imaging techniques. Compared with planar thallium imaging, single-photon emission computed tomography (SPECT) has a better contrast resolution, a better image quality, is more sensitive in detecting individual diseased vessels and is inherently more quantitative in nature (12,13). However, tomographic imaging with thallium may have a lower spatial resolution and a lower specificity because of artifacts. Tomography may also differ from planar imaging in the method of assessing lung thallium uptake and left ventricular dilation, which have been shown to be prognostically important. The use of SPECT thallium imaging in risk assessment has not been well defined. The purpose of this study is therefore to examine the ability of exercise SPECT thallium imaging to provide independent and incremental prognostic information over that provided by clinical, exercise and cardiac catheterization data in medically treated patients with angiographic evidence of coronary artery disease.

Methods

Study patients. The patients included in this study underwent, within a 3-month period, both exercise SPECT thallium imaging and cardiac catheterization including coronary angiography for the evaluation of a stable chest pain syndrome due to suspected or proved coronary artery disease. Patients were excluded from the study if they had normal coronary angiograms, previous coronary artery bypass surgery, previous percutaneous transluminal coronary angioplasty, recent acute myocardial infarction (within 3 months) and unstable angina pectoris. We also excluded patients who

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underwent coronary revascularization (coronary artery bypass surgery or angioplasty) within 3 months because the results of the catheterization or exercise testing in these patients may have influenced the decision to perform the revascularization procedures. The 316 study patients (mean age 62 ± 10 years) had angiographically defined coronary artery disease (≥50% diameter stenosis of one or more of the major coronary arteries). The follow-up period was 28 ± 15 months (range 1 to 60). There were 109 patients with one-vessel, 114 patients with two-vessel, and 93 patients with three-vessel or left main disease.

Exercise testing. The patients underwent symptom-limited treadmill exercise testing using the Bruce protocol. The test was terminated when there was excessive fatigue, shortness of breath, dizziness or angina pectoris of at least moderate degree, hypotension, ST segment depression ≥2 mm or significant arrhythmia. Cardiac medications were withheld on the morning of the test. At peak exercise, a dose of 3 mCi of thallium-201 was injected intravenously and the patients were exercised for 1 additional min. Images were obtained within 5 min of termination of exercise and 4 h later. All cardiac medications were withheld on the morning of the exercise study.

Tomographic thallium imaging. Our method of SPECT thallium imaging has previously been described (12,13). Three short-axis slices at the apical, mid- and basal levels were selected, each divided into six segments. The apical perfusion pattern was assessed in two segments at the mid-level tomogram of the vertical long-axis plane, yielding a total of 20 segments/patient. A perfusion abnormality in the initial image that demonstrated complete or partial redistribution on the delayed image involving ≥25% of the segment was considered a reversible abnormality. A perfusion abnormality that remained unchanged in the delayed image was considered a fixed abnormality. Perfusion defects in more than one vascular territory were considered a multivessel thallium abnormality.

Quantitation. Polar maps were also used to quantitate the size of the perfusion abnormality by comparing each patient's profiles with a gender-matched normal profile. An abnormality was defined if the data points were 2.5 SD below the mean normal limit. The extent of perfusion abnormality was also quantitated visually as the number of segments with abnormal perfusion pattern.

Regions of interest were placed over the myocardium and the left lung, and count densities were derived from the initial postexercise images to derive the lung/heart ratio. A ratio <50% is considered normal in our laboratory. The initial and 4-h images were also assessed subjectively for the presence of left ventricular dilation.

Follow-up study. All follow-up data were obtained from questionnaires and from telephone interviews conducted by the research nurses. Events were verified by reviewing the hospital records and by interviewing family members or treating physicians. Our method has previously been described (14,15).

Statistical analysis. Clinical, exercise, catheterization and SPECT variables considered relevant to the outcome were examined by means of Cox models for survival analysis. The stepwise selection or removal of the variable and estimation of significant probabilities were computed by means of a maximal partial likelihood ratio test. The chi-square value was calculated from the log of the ratio of maximal partial likelihood functions. This model was applied to each of the clinical, exercise, cardiac catheterization and scintigraphic variables alone and in combination. The clinical variables considered included age, gender, presence of typical angina (n = 94), coronary risk factors (hypertension [n = 146], diabetes mellitus and hyperlipidemia), history of prior infarction (n = 166), and cardiac medications. The exercise variables included duration of exercise, exercise work load, peak exercise heart rate, peak systolic blood pressure, presence of ST segment depression (n = 104) and presence of angina during exercise (n = 97). The scintigraphic variables included the presence of abnormal scans (n = 264), the total extent of the perfusion abnormality (fixed and reversible) determined from the polar maps or by the number of segments with an abnormal perfusion pattern, the presence of multivessel thallium abnormality, the presence of redistribution, the extent of the redistribution, the lung/heart thallium ratio and the presence of left ventricular dilation. Finally, the catheterization data included left ventricular ejection fraction and the extent of coronary disease. The Pearson chi-square test was used for comparison of discrete variables and analysis of variance for comparison of continuous variables. A $p < 0.05$ was considered significant. Results were expressed as mean value ± SD, when appropriate.

Results

Pertinent data in patients with (n = 35) and without (n = 281) a cardiac event are shown in Table 1. Univariate analysis showed important differences in several variables between those with and without an event. However, during multivariate analysis, only the following variables were predictors of events: gender (chi-square = 5.1), exercise work load (chi-square = 3.1), extent of coronary artery disease and ejection fraction (chi-square = 14.8) and the extent of total perfusion abnormality, the extent of ischemic abnormality (defined as the number of segments with reversible defects) and left ventricular dilation (chi-square = 22.7). The computer-derived extent of abnormality obtained from the polar maps and the number of abnormal segments assessed by visual analysis were equally important. In the final model, the computer-derived measurements were used. There were 192 patients who achieved 85% of maximal predicted heart rate or had ST depression during exercise. The remaining 124 patients performed submaximal exercise. There were 19 events in patients with adequate exercise and 16 events in those with submaximal exercise (p = NS).

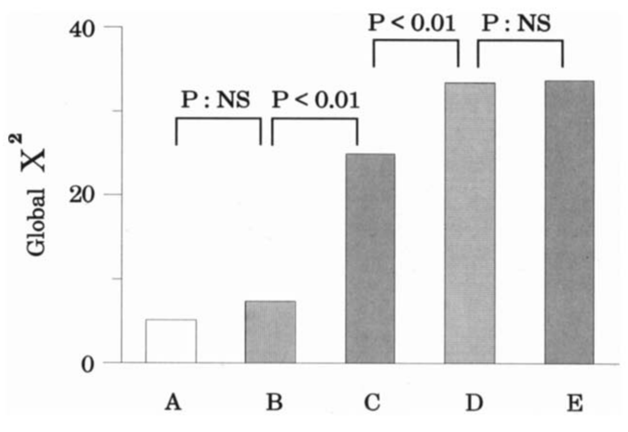
Table 1. Pertinent Data on Patients With and Without a Cardiac Event*

	Patients With No Cardiac Event (n = 281)	Patients With a Cardiac Event (n = 35)	p Value
Men/women	217/64	21/14	0.03
Hypertension	122 (43)	24 (69)	0.01
Diabetes mellitus	39 (14)	12 (34)	0.005
Beta-blocker therapy	121 (43)	7 (20)	0.01
Ex work load (METs)	7.4 ± 2.8	6.3 ± 2.8	0.05
LVEF (%)	61 ± 19	53 ± 21	0.07
Extent CAD	2.3 ± 0.9	1.9 ± 0.8	0.01
Thallium images†			
Defect size (polar map)	16 ± 13%	25 ± 10%	0.0001
Abnormal segments (no.)	7.4 ± 5.7	11 ± 5.0	0.0005
Reversible segments (no.)	4.9 ± 5.3	7.8 ± 5.7	0.006
MV abnormality	144 (51)	27 (77)	0.01
LV dilation	49 (17)	13 (37)	0.01
Increased lung uptake	75 (27)	16 (46)	0.03

*Only variables that were statistically significant are shown. †The extent of thallium abnormality is expressed as computer-derived percent abnormality assessed from the polar map and number of abnormal segments by visual assessment. Data are expressed as mean value ± SD or number (%) of patients. CAD = coronary artery disease; DM = diabetes mellitus; EF = ejection fraction; Ex = exercise; LV = left ventricular; LVEF = left ventricular ejection fraction; METs = metabolic equivalents; MV = multivessel.

Incremental value of the diagnostic procedures. Values for the chi-square statistic, as an index of the predictive power of the important variables from the four major categories, are shown in Figure 1. The addition of the exercise work load to gender improved the value to 7.4. The addition of the catheterization data to the clinical and exercise variables improved the value to 25. Finally, the addition of the SPECT variables to the clinical, exercise and catheterization variables improved the chi-square to 33.7. This value was significantly better ($p < 0.01$) than the value achieved with the combined clinical, exercise and catheterization data. In fact, the chi-square of the clinical, exercise and SPECT data—that is, without the catheterization data—was 33.5, which was not significantly different from the chi-square derived from the clinical, exercise, SPECT and catheterization data. When the variables were examined individually, the extent of the perfusion abnormality had the highest chi-square (= 14).

Figure 1. *Independent and incremental prognostic power of clinical, exercise, catheterization and single-photon emission computed tomographic (SPECT) thallium variables. Data shown represent the chi-square statistic of gender (A); of gender and exercise metabolic equivalents (METs) (B); of gender, exercise METs and catheterization data (C); of gender, METs and SPECT thallium data (D) and of gender, METs, catheterization data and SPECT thallium data (E).*



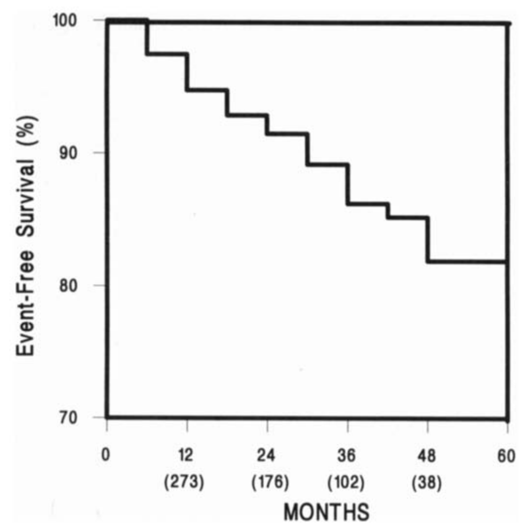


Figure 2. Actuarial event-free survival curve in the study patients. The number of patients at the beginning of each follow-up interval is shown in parentheses at the bottom of the graph.

The event-free survival curve of the 316 patients during the follow-up period is shown in Figure 2. There was a 5%/year incidence rate of hard events (death or nonfatal myocardial infarction) in this patient group. The 4-year event-free survival rate was 86% in men and 66% in women ($p < 0.03$); 87% in patients with an exercise work load of ≥6 metabolic equivalents (METs), and 71% in patients with a work load of <6 METs ($p < 0.04$); 85% in patients with an ejection fraction ≥50% and 79% in patients with an ejection fraction <50% ($p < 0.05$), and it was 88% in patients with one- or two-vessel disease compared with 67% in patients with three-vessel or left main coronary artery disease ($p < 0.001$).

As assessed by SPECT thallium imaging results, the extent of perfusion abnormality was the best prognostic predictor; however, the extent of reversible abnormality and left ventricular dilation further enhanced the prognostic value (chi-square = 22.7 vs. 14.0). Patients with a large perfusion abnormality (≥15% of the myocardium) had a worse prognosis than those with no or a mild abnormality. The event-free survival rate was 95% in those with a small or no defect and 75% in those with a large defect (Mantel-Cox statistic = 10.6, $p < 0.001$ [Fig. 3]). Patients with a more extensive reversible defect or left ventricular dilation also had a worse prognosis ($p < 0.004$ each). When considered

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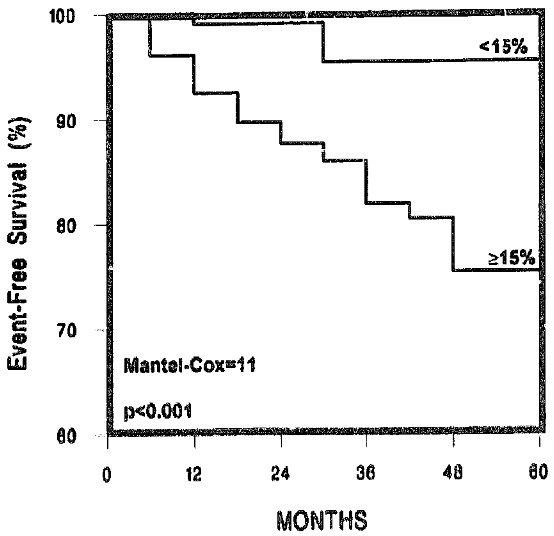

Figure 3. Actuarial event-free survival curves in patients with a perfusion defect ≥15% or <15% of the left ventricular myocardium.

separately, both the number of deaths and the number of nonfatal myocardial infarctions were too small to allow for separate analysis of the predictors of each of these two events.

Discussion

The results of this study show that in medically treated patients with coronary artery disease, exercise SPECT thallium imaging provides independent and incremental prognostic information over that obtained from clinical, exercise treadmill and catheterization data. The size of the perfusion abnormality was the single most important prognosticator; patients with a large abnormality had an 11-fold higher event rate than that of patients with a small or no abnormality. Patients with coronary artery disease who underwent revascularization procedures were excluded from this study because the results of exercise testing may have influenced the decision-making process. These patients may also have had more severe coronary disease. Our results are applicable only to patients with angiographic evidence of coronary disease who are managed medically.

The main features of this study that differed from those of prior studies were the use of tomographic imaging, the documentation of coronary artery disease by coronary angiography and the presence of a sufficient number of combined objective events (cardiac death and nonfatal myocardial infarction) to allow meaningful conclusions to be drawn.

Prior studies. The results of thallium imaging in predicting prognosis have been well documented (1,3–5,11). The thallium predictors of poor prognosis include the presence of redistribution, increased lung thallium uptake, left ventricular dilation, the extent of the thallium abnormality and the presence of multivessel thallium abnormality. These factors were also found to be important predictors in this study.

The nature of the thallium abnormality that is prognostically important in a given study may depend on patient selection and end points. For example, if most end points are ischemic events, such as unstable angina or nonfatal acute myocardial infarction, thallium redistribution (which reflects the presence of ischemia) is probably the most important predictor. In contrast, if most events are due to cardiac deaths, then the total perfusion abnormality (fixed and reversible) is the most important predictor (16). Furthermore, the predictive value of fixed defects would be more apparent in patients with than in patients without a prior infarction. Because most, but not all, fixed defects reflect the presence of myocardial scar, the extent of fixed defects is a rough measure of the ejection fraction at rest, which has an independent prognostic value. In a previous study from our laboratory, 14 of 93 patients with a first acute myocardial infarction died during a follow-up period of 1 year. The extent of the thallium abnormality at rest was a stronger predictor of death than was the ejection fraction at rest (17). Recent data using 24-h delayed imaging or the reinjection technique have shown that roughly 50% of fixed defects on conventional 4-h delayed imaging may show partial or complete redistribution, which is yet another important clue to why fixed defects are important predictors of events (18–20). In this study, as in our previous reports, the total extent of the perfusion abnormality (fixed and reversible) was the single most important predictor of events.

In some studies (3,21,22), the lung thallium uptake has been found to be a strong predictor of events. In our laboratory the lung thallium uptake is measured during tomographic acquisition from the anterior image, which occurs ≈10 min after the start of imaging. This procedure may explain why the lung thallium uptake was not the strongest predictor on multivariate analysis in our study. Nevertheless, prior studies have shown a good correlation between the lung/heart thallium ratio obtained with tomographic imaging, and that obtained with planar imaging (23). Previous studies that showed the importance of lung thallium uptake were done with planar imaging. It is possible that with SPECT thallium imaging, which allows detection of more abnormal segments and vascular territories, thallium lung uptake is not as strong a predictor as the extent of the perfusion abnormality. Therefore, this may be an important difference between planar and tomographic imaging.

Predictors of prognosis. Although several clinical variables were significantly different between patients with and without a cardiac event, gender was the only important one by multivariate analysis. Recent studies have emphasized differences in the utilization of invasive tests and management between men and women (24,25). It is possible that there are gender-related differences in the accuracy of noninvasive techniques. In a recent study from our laboratory (26), both the exercise electrocardiographic (ECG) changes and the tomographic thallium results had less diagnostic accuracy in women than in men. However, because there were three times as many men as women in this study, the small sample size of women may have also contributed to the gender-related difference in survival.

Exercise work load, or a similar measure of exercise performance such as peak heart rate or exercise duration, has consistently been an important independent predictor of prognosis in previous studies (2). We (26) have previously reported that SPECT thallium imaging at submaximal, compared with maximal, exercise in patients with coronary artery disease tends to underestimate the presence and extent of this disease and of myocardial ischemia.

The catheterization data—specifically, the extent of coronary artery disease and left ventricular ejection fraction—have been well accepted as important predictors of prognosis (7,8). Nevertheless, the important message from this study is that even when these data are available, the exercise thallium data add incremental information. Previous studies (27,28) showed considerable variability in the extent of jeopardized myocardium in patients with one-vessel or multivessel disease assessed by exercise thallium imaging or imaging during balloon occlusion at the time of balloon angioplasty or of acute myocardial infarction. The independent and incremental prognostic value of exercise thallium imaging has also been documented by other investigators. For example, Pollock et al. (29) have shown that inclusion of lung thallium uptake in the analysis of the thallium images yielded incremental prognostic information to that provided by clinical, exercise and catheterization data. Their study was done with planar imaging, whereas our study was done with SPECT imaging. These previous studies are also concordant with the experience reported by Lee et al. (30), who showed that exercise left ventricular ejection fraction provided incremental and independent prognostic information over that provided by cardiac catheterization.

In this study, the size of the perfusion abnormality was the strongest single predictor of events. In previous studies from our laboratory using exercise testing or pharmacologic stress testing combined with tomographic thallium imaging (31–33), a multivessel thallium abnormality pattern was the strongest predictor of left main or three-vessel coronary artery disease. These observations again suggest that it is the size rather than site or sites of the abnormality that determines prognosis.

Limitations of the study. As discussed earlier, our results may not be applicable to all patients with coronary artery disease. It is possible that patient selection may have affected the results; the high risk patients underwent early revascularization. The number of events did not permit us to analyze data in patients who had coronary angiography before or after exercise testing to determine whether there was an additional selection bias. We also included patients with and without prior myocardial infarction, but 53% of patients without an event and 51% of patients with an event had a prior infarction ($p = NS$). The number of patients in each group was too small to allow separate analysis. Although the chi-square statistic was used in this and other studies of this nature (29,30), it may not be the best method; an alternative method is the use of receiver operating characteristic curve areas. Also, we do not know why medical therapy was used in patients at high risk based on the results of this and prior studies. We can only speculate that nonsuitable coronary anatomy, associated medical problems, patient refusal or physician bias may have been important. Finally, we excluded from our analysis 102 patients with no or insignificant disease as determined by angiography. In these patients the SPECT thallium images were normal in 63 patients (62%), the extent of thallium abnormality was only $3 \pm 5\%$ and there were no cardiac events. We believe the inclusion of these patients would have further strengthened the conclusion of this study. In fact, the 4-year event-free survival rate was 75% in patients with a large defect and 95% in patients with a small or no defect if these patients were included (Mantel-Cox statistic = 18.8, $p < 0.0001$).

Clinical implications. Our results show that in medically treated patients with coronary artery disease exercise SPECT thallium imaging provides independent and incremental prognostic information over that obtained from clinical data, exercise treadmill testing and cardiac catheterization. It is clear that patients at high risk identified by exercise SPECT thallium imaging require cardiac catheterization for consideration for revascularization. Cardiac catheterization is obviously also indicated in patients who are severely symptomatic despite optimal medical treatment even if they are in a low risk group because revascularization in these patients is performed to alleviate symptoms rather than to improve survival. In this study, none of 140 patients with coronary artery disease and a thallium abnormality <15% had severe symptoms (probably because of selection bias) and only 15 of 102 patients with no coronary artery disease had a large (15%) thallium abnormality. Therefore, 176 (92%) of 191 patients with a ≥15% thallium abnormality had coronary artery disease. In many other patients, cardiac catheterization is unnecessary once the exercise SPECT thallium data are available. Such a policy restricting the use of catheterization to those at high risk and those with severe symptoms is important in limiting the escalating cost of health care in this country.

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