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Long-Term Prediction of Major Ischemic Events by Exercise Thallium-201 Single-Photon Emission Computed Tomography

Incremental Prognostic Value Compared With Clinical, Exercise Testing, Catheterization and Radionuclide Angiographic Data

PIERRE-YVES MARIE, MD, NICOLAS DANCHIN, MD, FACC, JEAN F. DURAND, MD, LUC FELDMANN, MD, ALAIN GRENTZINGER, MD, PIERRE OLIVIER, MD, GILLES KARCHER, MD, YVES JUILLIÈRE, MD, JEAN M. VIRION, MSc, DANIEL BEURRIER, MD, FRANÇOIS CHERRIER, MD, ALAIN BERTRAND, MD

Nancy, France

Objectives. **This study sought to evaluate the prognostic role of exercise thallium-201 (Tl-201) single-photon emission computed tomography (SPECT) in patients with known or suspected coronary artery disease.**

Background. **Compared with planar Tl-201 scintigraphy, Tl-201 SPECT allows enhanced assessment of myocardial perfusion abnormalities. However, the long-term prognostic value of exercise Tl-201 SPECT has not been ascertained and compared with that of other techniques of investigation.**

Methods. **Predictors of ischemic events were sought in 217 patients with known or suspected coronary artery disease who underwent exercise Tl-201 SPECT, coronary angiography and rest radionuclide angiography and who initially received medical therapy. Predictive values were determined using Cox proportional hazards regression models.**

Results. **During a mean (±SD) follow-up period of 70 ± 19 months, 29 patients had a major ischemic event (cardiac death or myocardial infarction). Total extent of exercise defects was the best independent predictor by Tl-201 SPECT of major events ($p < 0.001$) and provided additional prognostic information compared with clinical, exercise testing and catheterization variables ($p < 0.02$). Extent of reversible Tl-201 SPECT perfusion defects provided additional prognostic information compared with extent of irreversible defects ($p < 0.001$) and was the sole Tl-201 SPECT variable providing additional prognostic information compared with radionuclide left ventricular ejection fraction ($p < 0.02$).**

Conclusions. **Total extent of exercise Tl-201 SPECT defects is a powerful long-term predictor of major ischemic events that enhances the prediction provided by clinical, exercise testing and coronary angiographic data. In view of its prognostic significance, extent of reversible Tl-201 SPECT defects might provide original information about improving prognosis by coronary revascularization.**

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Prognostic assessment remains a main clinical goal in patients with coronary artery disease. Coronary angiography allows identification of patients with coronary artery disease and high risk coronary lesions and those whose prognosis might be improved by surgical revascularization (1–3). Certain noninvasive techniques, such as exercise testing (2,4–6), thallium-201 (Tl-201) scintigraphy (7–10) and radionuclide ventriculography (11–14), have been shown to provide useful prognostic information complementary to that obtained with clinical or catheterization variables, or both. Previous reports (7–10) have demonstrated that prognostic information provided by exercise Tl-201 scintigraphy was superior to that from exercise testing alone. In contrast, only very limited data are available on the comparison between prognosis assessment with exercise Tl-201 imaging and that with radionuclide ventriculography (14).

Prognostic information provided by exercise Tl-201 scintigraphy includes extent of stress perfusion abnormalities, extent of redistribution and indirect signs of severe stress left ventricular dysfunction (left ventricular cavitary dilation, increased lung/heart uptake ratio) (7–10). However, compared with the conventional planar technique, three-dimensional single-photon emission computed tomography (SPECT) allows more precise assessment of exercise myocardial perfusion abnormalities (15–18), which might improve prognostic assessment in patients with coronary artery disease.

In two recent studies (9,10), the total extent of exercise Tl-201 SPECT defects (either reversible or irreversible) was found to be a predictor of major ischemic events at 2 to 3 years (9,10). However, no data were available for a longer follow-up period. In addition, to our knowledge no study has compared

From the Departments of Nuclear Medicine; Cardiology; and Medical Computer Science, Epidemiology and Statistics, Nancy, France. This investigation was supported by Projet Hospitalier de Recherche Clinique 1994-A from the Hospital of Nancy, Nancy, France.

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Address for correspondence: Dr. Pierre-Yves Marie, Service de Médecine Nucléaire, CHU Nancy-Brabois, 54511 Vandoeuvre Cedex, France.

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the predictive value of data from exercise Tl-201 SPECT with those from radionuclide angiography, although rest and exercise left ventricular ejection fraction, as assessed by radionuclide angiography, have been demonstrated (11–13) to be powerful predictors of cardiac death in patients with coronary artery disease.

Therefore, this study sought to assess the long-term (≥5 years) prognostic value of exercise Tl-201 SPECT in patients with known or suspected coronary artery disease and to compare it with comprehensive data from clinical history, exercise testing, coronary angiography and rest radionuclide ventricular angiography.

Methods

Study patients. All patients were retrospectively included if they met the following criteria: 1) presence of known or suspected coronary artery disease and exercise Tl-201 SPECT, coronary angiographic and rest radionuclide angiographic results at our institution from 1982 to 1987 and over a <1.5-month period; 2) no previous history of cardiac surgery or coronary angioplasty, congenital or valvular heart disease (including severe [>2+] mitral regurgitation) or hypertrophic or idiopathic dilated cardiomyopathy; 3) subsequent medical therapy (those for whom a decision of coronary revascularization was taken at the time of hospital discharge or who had undergone a revascularization procedure within the subsequent 3 months were excluded from the study).

Among the 3,755 patients who underwent exercise Tl-201 SPECT from 1982 to 1987 at our institution, 221 (6%) met the inclusion criteria, 4 of whom were completely lost to follow-up. Therefore the remaining 217 (98%) constituted our study group.

Cardiac catheterization. Location and percent diameter reduction of coronary stenoses were determined visually by experienced observers on end-diastolic frames of coronary angiograms (19). Several angiographic variables were analyzed: absence or presence of ≥50% stenosis of the left main and proximal left anterior descending coronary arteries; number of diseased coronary vessels according to the Coronary Artery Surgery Study criterion (20) for stenosis location; and number of diseased coronary segments according to the 15-segment division of coronary vessels of the American Heart Association (21). Number of diseased coronary segments and vessels were calculated using two different cutoff values for significant stenosis: ≥70% and ≥50% diameter reduction. Single-plane X-ray left ventricular ejection fraction was calculated in the 30° right anterior oblique orientation using the area–length method (22).

Exercise testing and Tl-201 SPECT imaging. The exercise test was performed on a bicycle ergometer with the patient in the upright position. The protocol began at 40 W and increased by 30-W increments every 3 min. A 12-lead electrocardiogram (ECG) was recorded at each minute of exercise, and leads V_1, V_5 and aVF were continuously monitored. Exercise end points included physical exhaustion, development of angina pectoris, >2-mm ST segment depression, sustained ventricular tachyarrhythmia, exertional hypotension (≥10 mm Hg decrease in systolic pressure) or achievement of maximal predicted heart rate. For 26 patients (12%) who had a myocardial infarction ≤10 days old, exercise testing was limited to a maximal predicted heart rate of 70%. Whenever possible, antianginal medications were discontinued 48 h before the study. Significant ST segment depression was defined as ≥1-mm horizontal or downsloping depression occurring 0.08 s after the J point compared with baseline values. Exercise testing was judged nondiagnostic in case of left bundle branch block and in patients who did not reach ≥85% of predicted maximal heart rate in the absence of exercise-induced angina or significant ST segment depression.

One minute before the termination of exercise, 37 MBq of Tl-201/25 kg body weight (not >111 MBq) was injected intravenously. Stress imaging was initiated 10 to 15 min later, and redistribution studies were performed 3 to 5 h later. The technique for Tl-201 SPECT imaging and visual analysis has been described elsewhere (23). Analysis of the reconstructed tomographic slices was performed in blinded manner by an experienced observer. Briefly, the left ventricle was divided into four regions from apical to basal slices; the most apical region was analyzed in vertical long-axis slices and the other regions in short-axis slices. Myocardial Tl-201 uptake was scored on a 20-segment division of the left ventricle using a four-point grading system: 0 = normal; 1 = equivocal; 2 = moderate; 3 = severely reduced. Total extent of exercise defects was determined by the percent of segments with an uptake score ≥2 on exercise Tl-201 tomograms, and extent of reversible defects was determined by the percent of segments with exercise defects with a ≥1-point decrease in uptake score at redistribution.

Rest radionuclide angiography. Multigated equilibrium radionuclide angiography was performed at rest in the supine position using a previously described technique (24). A dose of 740 to 1,110 MBq of technetium-99m pertechnetate was injected intravenously. Gated cardiac imaging was performed with a single-crystal gamma camera with a head that was oriented to maximize ventricular separation, usually 30° to 60° left anterior oblique orientation. Sixteen frames were obtained from the cardiac cycle and a minimum of 250,000 counts/frame were acquired.

All regions of interest were drawn manually, and radionuclide left ventricular ejection fraction was calculated by experienced observers according to the following formula: (EDC − BC) − (ESC − BC)/(EDC − BC), where EDC = end-diastolic counts; ESC = end-systolic counts; and BC = background counts.

Follow-up data. Follow-up data were collected from the patients, their families or attending physicians ≥5 years after the initial hospital period and by means of a mailed questionnaire or telephone interview. Two types of events were considered in the follow-up analysis: 1) *cardiac death*, defined as a death of demonstrated cardiac origin or unknown origin; and

Table 1. Baseline Variables Included in Cox Regression Analysis

Clinical history and rest ECG
Age, gender
Coronary risk factors (diabetes mellitus, hypertension, hyperlipidemia)
History of myocardial infarction, typical angina, angina class ≥III (Canadian Cardiovascular Society)
ECG (Q wave infarction, anterior Q wave infarction, left bundle branch block)
Beta-blocker treatment at discharge from hospital
Exercise testing
Maximal work load
Maximal and increase in heart rate
Maximal and increase in systolic blood pressure
Exercise-induced angina
Maximal (mm) and significant (≥1 mm) ST segment depression
Ventricular arrhythmia
Nondiagnostic exercise test
Cardiac catheterization
Left ventricular ejection fraction
Absence of ≥50% stenosis
No. of ≥50% and ≥70% diseased vessels
No. of ≥50% and ≥70% diseased coronary segments
Presence of ≥50% stenosis of the LMCA
Presence of ≥50% stenosis of proximal LAD
Rest radionuclide angiography
LV ejection fraction
Exercise Tl-201 SPECT
Normal exercise Tl-201 SPECT
Total extent of exercise defects
Extent of reversible exercise defects
Extent of irreversible exercise defects

ECG = electrocardiogram; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; LV = left ventricular; Tl-201 SPECT = thallium-201 single-photon emission computed tomography.

2) *major ischemic event*, defined as the occurrence of either cardiac death or myocardial infarction.

The diagnosis of *myocardial infarction* was always confirmed by a physician, on the basis of prolonged characteristic chest pain and ECG and serum enzyme level changes (increase in serum creatine kinase [CK] level greater than twice the upper limit of normal). For patients who had subsequent cardiac surgery or coronary angioplasty, only the follow-up period preceding the intervention was considered in the analysis (censoring occurred at revascularization). For myocardial infarction followed by cardiac death, the date of the major event was that of the infarction.

Statistical analysis. The Cox proportional hazards regression model (25) (BMDP statistical software [26]) was used for examining relations between occurrence of cardiac death or major ischemic events and initial variables from clinical history, exercise testing, catheterization, radionuclide angiography and Tl-201 SPECT (Table 1). The chi-square value was calculated from the log of the ratio of maximal partial likelihood functions. Variables for which the p value of the univariate chi-square test was <0.05 were considered significant predictors of prognosis.

A stepwise multivariate Cox regression analysis was performed to identify variables providing the best prognostic information. The assumed limit for significance to enter a variable was 0.05, and that to remove a variable was 0.10. Multivariate analysis was performed 1) on the Tl-201 SPECT variables alone to determine the relative prognostic value of each; 2) on available variables from clinical history and all investigations to assess the prognostic value of Tl-201 SPECT data relative to these other variables; and 3) to analyze different clinical situations separately, by assessing the increment in prognosis value relative to Tl-201 SPECT data, if one or several other investigations were already performed. The Cox model was initially only applied to clinical, exercise testing, catheterization and radionuclide angiographic variables separately and in different combinations. In each case, the selected variables were retained in the model, and Tl-201 SPECT variables were then tried at an entrance value of $p = 0.05$ (Table 1).

Results

Baseline characteristics of study patients. At the time of the initial hospital period, the patients had a mean (±SD) age of 53 ± 9 years (range 25 to 72); 188 (87%) were men, and 143 (66%) had history of myocardial infarction that was recent (<1 month) in 62 (29% of the overall cohort). Episodes of chest pain could be documented in 203 patients (94%), and 89 (41%) had class III or IV angina. There were 153 patients (71%) with a history of either myocardial infarction or unstable (class IV) angina. On the rest ECG, 107 patients (49%) had Q waves that were located in the anterior leads in 51; 14 patients (6%) had a left bundle branch block.

Coronary artery disease could be documented in 177 patients (82%): ≥50% stenosis in 167, myocardial infarction with angiographically normal coronary arteries in 10. When the ≥50% reduction in intraluminal diameter criterion was used, 79 patients (36%) had one-vessel disease, 59 (27%) had two-vessel disease, and 21 (10%) had three-vessel disease. Twenty-nine patients (13%) had ≥50% stenosis of the proximal left anterior descending coronary artery. No patient had ≥50% stenosis of the left main coronary artery.

Exercise testing was performed during antianginal treatment in 98 patients (45%), including beta-blocker therapy in 30 (14%). Chest pain occurred during exercise in 38 patients (18%) and ST segment depression in 65 (30%). Exercise testing was judged nondiagnostic in 66 patients (30%). Tl-201 SPECT images showed exercise defects in 184 patients (85%) that were at least partially reversible at redistribution in 123 patients (57% of the overall study group). Radionuclide left ventricular ejection fraction had a mean value of 51 ± 14%; it was abnormal (<50%) in 42% of patients and severely depressed (≤35%) in 11%.

Outcome events. During a follow-up period of 70 ± 19 months, cardiac death occurred in 20 patients and nonfatal myocardial infarction in 9. Ten patients underwent coronary angioplasty and 15 cardiac surgery (13 bypass grafting, and 2 heart transplantation). In all, 29 patients had a major event

Table 2. Estimated Relative Risk for Significant Univariate Predictors of Major Events or Cardiac Death by Cox Regression Analysis of Clinical and Exercise Thallium-201 Single-Photon Emission Computed Tomographic Data

	Prediction of Cardiac Death		Prediction of Major Ischemic Events	
	RR (95% CI)	p Value	RR (95% CI)	p Value
Clinical data				
Age (yr)	1.08 (1.01–1.15)	0.0131	1.08 (1.02–1.13)	0.0036
Q wave MI	2.59 (0.97–6.88)	0.0434	1.77 (0.82–3.80)	0.1326
Anterior Q wave MI	3.62 (1.48–8.87)	0.0021	2.86 (1.35–6.04)	0.0033
Exercise testing				
Maximal work load	0.99 (0.98–1.00)	0.0286	0.99 (0.98–1.00)	0.0056
Increase in HR	0.98 (0.95–1.00)	0.0331	0.98 (0.96–1.00)	0.0259
Exercise angina	1.30 (0.42–4.02)	0.6355	2.51 (1.12–5.64)	0.0188
Extent of Tl-201 SPECT defects (% of LV area)				
Total exercise defects	1.05 (1.03–1.08)	0.0001	1.04 (1.02–1.06)	0.0001
Reversible defects	1.03 (1.00–1.06)	0.0510	1.03 (1.01–1.05)	0.0048
Irreversible defects	1.04 (1.02–1.07)	0.0006	1.03 (1.01–1.05)	0.0019

CI = confidence interval; HR = heart rate; MI = myocardial infarction; RR = relative risk; other abbreviations as in Table 1.

(death or infarction, or both). Kaplan-Meier survival rates, based on cardiac death, were 95%, 91% and 91% at 2, 5 and 8 years, respectively. At the same time points, rates of major event-free survival were 95%, 90% and 81%, respectively.

In only four patients was death demonstrated to be noncardiac in origin. When follow-up after cardiac intervention was also taken into account, six additional patients had a major event: One had a myocardial infarction 2 years after angioplasty; five had a major event that was directly related to the intervention (perioperative cardiac death in one, perioperative infarctions in three, acute graft rejection after heart transplantation in one).

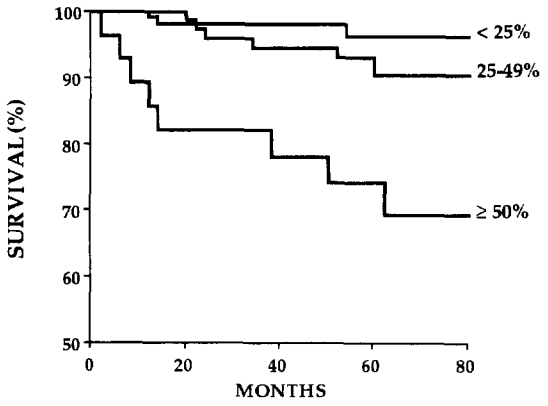
Univariate Cox regression analysis. Significant variables of the univariate analysis are presented in Tables 2 and 3. Among clinical and exercise testing data, age, anterior Q wave on the ECG, maximal workload and increase in heart rate were predictors of major events and of cardiac death; in addition, exercise-induced angina was a significant predictor of major events. Among catheterization variables, left ventricular ejection fraction, presence of significant (≥50%) stenosis and number of ≥50% and ≥70% diseased coronary segments were predictors both of cardiac death and or major events. In addition, number of ≥50% and ≥70% diseased vessels was a predictor of major events, and the presence of stenosis of the proximal left anterior descending coronary artery was a significant predictor of cardiac death.

Among radionuclide methods, radionuclide left ventricular

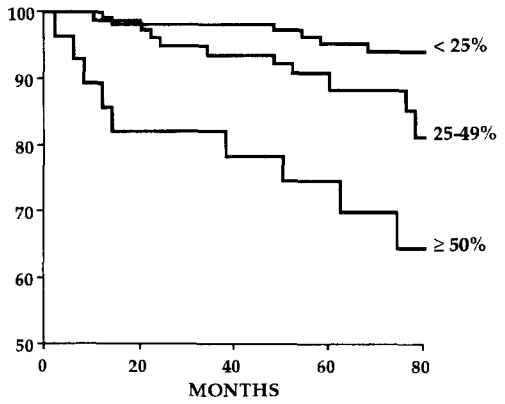
Table 3. Estimated Relative Risk for Significant Univariate Predictors of Major Events or Cardiac Death by Cox Regression Analysis Of Cardiac Catheterization and Radionuclide Angiographic Data

	Prediction of Cardiac Death		Prediction of Major Ischemic Events	
	RR (95% CI)	p Value	RR (95% CI)	p Value
Catheterization				
Absence of ≥ 50% stenosis	0.16 (0.02–1.21)	0.0374	0.10 (0.01–0.80)	0.0067
No. of diseased vessels				
≥50% stenosis	1.54 (0.97–2.25)	0.0582	1.60 (1.09–2.36)	0.0123
≥70% stenosis	1.57 (0.91–2.72)	0.0961	1.96 (1.26–3.08)	0.0021
No. of diseased segments				
≥50% stenosis	1.33 (1.05–1.69)	0.0132	1.30 (1.07–1.59)	0.0061
≥70% stenosis	1.44 (1.06–1.97)	0.0174	1.43 (1.10–1.85)	0.0050
Proximal LAD stenosis	3.11 (1.17–8.26)	0.0144	2.27 (0.95–5.40)	0.0529
LV ejection fraction (%)*	0.96 (0.93–0.99)	0.0027	0.97 (0.95–0.99)	0.0140
Radionuclide angiographic LV ejection fraction (%)	0.93 (0.90–0.96)	0.0001	0.95 (0.92–0.97)	0.0001

*Calculated by catheterization in 210 patients only. Abbreviations as in Tables 1 and 2.



< 25 % :	111	109	108	102	35
25-49 % :	78	77	74	68	18
≥ 50 % :	28	23	21	20	12



< 25 % :	111	109	108	102	34
25-49 % :	78	76	73	67	15
≥ 50 % :	28	23	21	20	11

Figure 1. Actuarial survival curves based on cardiac death **(top)** and major events **(bottom)** for patients stratified by total extent of exercise Tl-201 SPECT defects: <25% of left ventricular area, 25% to 49% of left ventricular area and ≥50% of left ventricular area. **Numbers below abscissa** = number of event-free patients at each 20-month follow-up interval.

ejection fraction, total extent of exercise Tl-201 SPECT defects and extent of irreversible Tl-201 SPECT defects were predictors of major events and cardiac death. In addition, extent of reversible exercise Tl-201 SPECT defects was significantly related to the occurrence of major events.

Multivariate Cox regression analysis. *Analysis of Tl-201 SPECT variables only.* When Cox regression analysis was applied to Tl-201 SPECT data only, the total extent of exercise defects was the only independent predictor of cardiac death and major events. The ability of the total extent of exercise Tl-201 SPECT defects to stratify the risk of cardiac death or major events is illustrated in Figure 1.

If, however, total extent of exercise defects was not entered into the model, the extent of irreversible defects and the extent of reversible defects (expressed as percent of left ventricle), respectively, were independent predictors of major events (relative risk [RR] 1.04, 95% confidence interval [CI] 1.02 to 1.07; RR 1.05, 95% CI 1.02 to 1.08, p = 0.0003) and cardiac death (RR 1.05, 95% CI 1.02 to 1.08, p = 0.0002; RR 1.05, 95% CI 1.02 to 1.09, p = 0.004).

Comprehensive analysis of Tl-201 SPECT and all other baseline variables (Table 4). When the Cox regression analysis was applied to Tl-201 SPECT and all other baseline variables, the best independent predictors of major events were total extent of exercise Tl-201 SPECT defects and age. However, the association of radionuclide left ventricular ejection fraction and age was the best predictor of cardiac death.

Incremental prognostic value of Tl-201 SPECT data with regard to other baseline variables. Incremental prognostic value of data from exercise Tl-201 SPECT with regard to clinical, exercise testing, catheterization and radionuclide angiographic variables separately and in combination is shown in Figure 2. Total extent of exercise Tl-201 SPECT defects provided marked incremental prognostic information with regard to clinical and exercise testing variables. This additional prognostic information was found both for the prediction of major events and cardiac death (both $p < 0.001$).

When clinical, exercise testing and catheterization variables were included in the initial model, the total extent of exercise Tl-201 SPECT defects also provided additional prognostic information, both for major events and cardiac death (both $p < 0.02$).

Compared with the prognostic information provided by the radionuclide left ventricular ejection fraction alone or in association with clinical, exercise testing and catheterization variables, there was no additional prognostic information from Tl-201 SPECT regarding the risk of cardiac death; however, the extent of reversible defects provided additional prognostic information for major events ($p < 0.02$).

Discussion

Prognostic significance of Tl-201 SPECT variables. Compared with planar Tl-201 scintigraphy, Tl-201 SPECT allows more precise assessment of exercise myocardial perfusion abnormalities (15–18), but up to now only limited data were available on its long-term prognostic value (9,10). Our results indicate that exercise Tl-201 SPECT provides important long-term prognostic information in patients with known or suspected coronary artery disease. Among Tl-201 SPECT variables, the total extent of exercise defects (either reversible or irreversible) was the sole best independent predictor of major events and cardiac death. This finding extends to a longer period of follow-up the results of two recent studies (9,10) that demonstrated that total extent of stress defects was the best Tl-201 SPECT predictor of major ischemic events at 2 to 3 years.

In addition, our study provides evidence for the prognostic significance of those exercise defects that are reversible at rest. With regard to prognostic information provided by the extent of irreversible defects, the extent of reversible defects provided

Table 4. Variables Selected by Comprehensive Multivariate Cox Analysis of All Baseline Variables After Exclusion of Thallium-201 Single-Photon Emission Computed Tomographic or Radionuclide Angiographic Data, or Both

Model	Prediction of Cardiac Death			Prediction of Major Ischemic Events		
	Selected Variable	RR (95% CI)	p Value	Selected Variable	RR (95% CI)	p Value
All variables used	Radionuclide LVEF (%)	0.93 (0.90–0.97)	0.00006	Tl-201 TDE (% of LV)	1.05 (1.02–1.07)	0.00005
	Age (yr)	1.07 (1.01–1.14)	0.032	Age (yr)	1.07 (1.02–1.13)	0.008
Radionuclide LVEF excluded	Tl-201 TDE (% of LV)	1.06 (1.03–1.08)	0.0001	Tl-201 TDE (% of LV)	1.05 (1.02–1.07)	0.00005
	Age (yr)	1.07 (1.01–1.14)	0.026	Age (yr)	1.07 (1.02–1.13)	0.008
Tl-201 data excluded	Radionuclide LVEF (%)	0.93 (0.90–0.97)	0.00006	Radionuclide LVEF (%)	0.95 (0.92–0.97)	0.0001
	Age (yr)	1.07 (1.01–1.14)	0.032	Age (yr)	1.07 (1.01–1.12)	0.010
Radionuclide LVEF and Tl-201 data excluded	X-ray LVEF (%)	0.96 (0.93–1.00)	0.020	Anterior Q wave	2.64 (1.23–5.68)	0.012
	Anterior Q wave	2.70 (1.09–6.72)	0.028	Exercise angina	2.77 (2.21–6.34)	0.014
	Age (yr)	1.07 (1.01–1.14)	0.030	No. of diseased vessels with ≥70% stenosis	1.79 (1.07–3.02)	0.024
				Age (yr)	1.06 (1.00–1.12)	0.028

EF = ejection fraction; TDE = total exercise defect extent; other abbreviations as in Tables 1 and 2.

additional prognostic information. It is likely that with the current use of late acquisitions, especially the Tl-201 rest–reinjection technique, assessment of exercise defect reversibility would be enhanced (27,28) and might have further increased the prognostic value of the extent of reversible defects.

Age dependence of prognostic significance of Tl-201 SPECT variables. Of all the variables, total extent of exercise Tl-201 SPECT defects and age were the best independent predictors of major events. They were also the best independent predictors of cardiac death when radionuclide left ventricular ejection fraction was excluded from the analysis. The poorer prognosis of elderly patients has been clearly documented in studies (12,29–32) of patients with coronary artery disease and in those with a history of myocardial infarction or severe left ventricular dysfunction. Our data show that the predictive value of age is independent of severity of cardiac disease documented by either radionuclide left ventricular ejection fraction or extent of exercise Tl-201 SPECT defects.

Incremental prognostic value of Tl-201 SPECT variables. In clinical practice, prognostic assessment by means of exercise Tl-201 SPECT depends mainly on whether the data can supplement those obtained with other routine methods of cardiac investigation. In a recent report by Iskandrian et al. (9), Tl-201 SPECT data were found to improve prediction of major events at 2 to 3 years relative to clinical, exercise testing and catheterization variables. Our study confirms and extends these results. The additional prognostic value of Tl-201 SPECT remained significant for a much longer follow-up period and was documented as predicting both major events and cardiac death.

In patients with coronary artery disease, rest and exercise

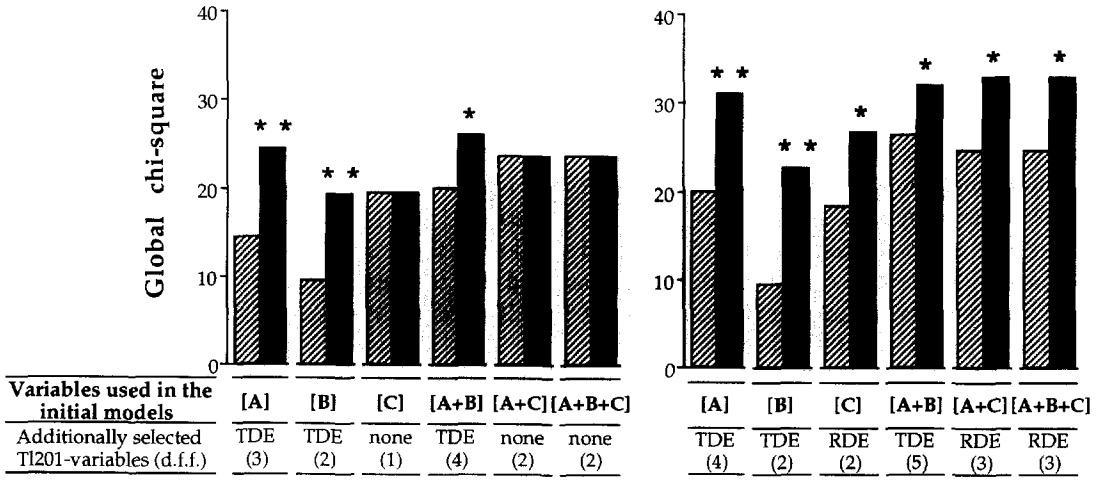


Figure 2. Multivariate analysis for prediction of cardiac death (**left**) and major events (**right**). Incremental prognostic value of exercise Tl-201 SPECT data relative to those provided by clinical history and exercise testing [A], catheterization [B] and radionuclide angiography [C], alone and in combination. Total chi-square values are shown for initial models obtained before the addition of Tl-201 SPECT data (**hatched bars**) and final models obtained after the addition of Tl-201 SPECT data (**solid bars**). d.f.f. = degrees of freedom for the final models; RDE = reversible exercise defect extent; TDE = total exercise defect extent. *$p < 0.02$ and **$p < 0.001$, before versus after addition of Tl-201 SPECT data in the models.

radionuclide left ventricular ejection fractions are powerful predictors of cardiac ischemic events, especially cardiac death (11–13). To date, no SPECT study, and only one planar scintigraphic study (14), has compared the prognostic value of exercise Tl-201 imaging with that of radionuclide cardiac angiography in patients with coronary artery disease. The previous report failed to demonstrate a significant improvement in prognosis determination by Tl-201 variables with regard to radionuclide angiographic data. In our study, when Tl-201 SPECT data were compared with rest radionuclide left ventricular ejection fraction data, no Tl-201 SPECT data provided additional predictive information for the risk of cardiac death; however, extent of reversible defects provided additional predictive information for the risk of major events. This finding might be relevant given that reversible exercise Tl-201 SPECT defects might be corrected by therapeutic measures such as myocardial revascularization (33–36).

Study limitations. Compared with a general population of patients referred for known or suspected coronary artery disease, our study cohort represents a small, retrospectively selected subgroup, and this might limit the generalizability of our results. In particular, the hierarchy of the prognostic values of the different investigations may vary according to both characteristics of the study patients and nature of the analyzed events.

To analyze "spontaneous outcome," we selected only those patients who were initially treated medically. Therefore, few patients at high risk by angiographic criteria were included in our study (left main stenosis 0%; three-vessel disease [≥50% stenosis] 10%), which might partly explain the relatively limited predictive value of coronary angiography. Another possible explanation is that our results did not take into account events related to subsequent cardiac interventions (cardiac surgery or angioplasty). The decision to perform such interventions is subjective and generally strongly influenced by the results of initial investigations (especially coronary angiography for subsequent bypass grafting). Similarly, we did not take into account major events that occurred during or after cardiac interventions because all but one were directly related to the interventions themselves (cardiac graft rejection, perioperative infarction or death). However, our results would not have been modified by the inclusion of these additional events.

There was a high prevalence of coronary artery disease (82%) and history of myocardial infarction (66%) in our study group. This is most likely a result of the retrospective selection of the patients on the basis of comprehensive cardiac investigations usually performed when there is a strong suspicion of coronary artery disease. The high prevalence of patients with a history of infarction could explain the high number of cardiac death among the subsequent major events (69%), as well as the very powerful prognostic value of left ventricular ejection fraction (37,38).

Conclusions. Our study provides evidence that exercise Tl-201 SPECT provides major prognostic information in patients with known or suspected coronary artery disease. Moreover, it offers additional prognostic information over that of routine clinical, exercise testing and catheterization variables. Compared with radionuclide left ventricular ejection fraction, Tl-201 SPECT allows the detection and quantification of viable ischemic myocardium, a potential therapeutic "target." Our data suggest that the reduction of the extent of reversible exercise defects by appropriate therapeutic measures, such as myocardial revascularization, might result in improved clinical outcome. This possibility might be worthy of future prospective, randomized studies.

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