Incremental Prognostic Value of Exercise Thallium-201 Myocardial Single-Photon Emission Computed Tomography Late After Coronary Artery Bypass Surgery

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Objectives. This study assessed the incremental prognostic value of exercise thallium-201 myocardial perfusion single-photon emission computed tomography (SPECT) performed ≥5 years after coronary artery bypass surgery.

Background. Thallium-201 scintigraphy has shown significant prognostic value in a variety of populations with suspected and known coronary artery disease. However, its value in patients with previous bypass surgery remains unknown.

Methods. We studied 294 patients who were prospectively followed up. Cox proportional hazards models for prediction of "hard" events (cardiac death and nonfatal infarctions) were constructed, with variables considered for inclusion in hierarchic order: clinical and exercise data first, followed by scintigraphic information.

Results. Mean (±SD) follow-up duration after scintigraphy was 31 ± 11 months. There were 20 cardiac deaths and 21 nonfatal acute myocardial infarctions. Twenty-nine patients had late (>60 days after thallium-201 SPECT) revascularization procedures or underwent repeat bypass surgery or percutaneous transluminal angioplasty. Shortness of breath and peak exercise heart rate were the most important clinical predictors of hard events. Two scintigraphic variables added significant prognostic information to the clinical model: the thallium-201 summed reversibility score (summation of segmental differences between stress and redistribution scores) and the presence of increased lung uptake of the radiotracer. The global chi-square statistic for this model was twice as high as that for the clinical/exercise model alone (49.7 vs. 24.2). When a second multivariate Cox model was built adding "soft" events (i.e., late revascularization procedures) as outcomes of interest, the summed reversibility score was selected as an independent scintigraphic predictor of events. The global chi-square statistic for this model was 50.7, three times as high as that for the clinical/exercise model alone.

Conclusions. After evaluation of treadmill and exercise data, thallium-201 myocardial perfusion SPECT provided incremental prognostic information in patients late after bypass.

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Stress thallium 201 myocardial perfusion scintigraphy in conjunction with exercise or pharmacologic stress predicts coronary events in a wide variety of patients with known or suspected coronary artery disease (1,2). However, this predictive ability has not been characterized for patients after coronary artery bypass surgery.

Patients with bypass surgery constitute a unique pathophysiologic subset whose outcome is related to a variety of factors, including graft patency, the extent and severity of disease in their native vessels and ventricular function. Angiographic studies have shown that 20% of vein grafts are occluded 5 years after operation and that an additional 5% will show some degree of stenosis (3,4). Also, survival data from large randomized trials have shown a consistent increment in mortality after the fifth postoperative year (5–7).

The goal of this study was to assess the incremental prognostic value (beyond that of historical and treadmill exercise test data) of thallium-201 myocardial single-photon emission computed tomography (SPECT) in patients ≥5 years after bypass surgery.

Methods

Patients. We studied 296 patients with bypass surgery who had routine thallium SPECT testing at least 5 years after bypass surgery at Cedars-Sinai Medical Center from June 17, 1987 to September 27, 1990. They had undergone bypass

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Table 1. Characteristics of the Study Patients

Age (yr)	67.5 ± 9
Male gender	253 (86)
Presenting symptom	
Asymptomatic	105 (36)
Nonanginal chest pain	53 (18)
Atypical angina	46 (16)
Typical angina	74 (25)
Shortness of breath	16 (5)
Prior MI	64 (22)
IMA grafts	43 (15)
No. of grafts	1.94 ± 1.2
Clinical response to exercise	
Normal	187 (64)
Borderline	44 (15)
Abnormal	63 (21)
ECG response to exercise	
Normal	177 (63)
Nondiagnostic	24 (9)
Abnormal	80 (28)
Peak exercise HR (beats/min)	134 ± 21
≥85% maximal predicted	189 (64)
Exercise duration (min)	6.2 ± 2.7

Data presented are mean value ± SD or number (%) of patients. ECG = electrocardiographic; HR = heart rate; IMA = internal mammary artery; MI = myocardial infarction.

surgery between November 12, 1975 and December 27, 1984 and represented 8% of 3,741 patients undergoing bypass surgery at our institution during this interval. From that initial group, two patients underwent repeat bypass surgery within 60 days of SPECT and were excluded from the study. Table 1 summarizes the clinical characteristics of the 294 study patients. Table 2 compares the 294 patients with bypass surgery included in the present study with the 4,186 patients undergoing bypass surgery during the same time interval who did not have thallium-201 scans >5 years postoperatively. Of note, our study included a higher proportion of men and were more symptomatic.

Follow-up. Since October 1975, a clinical data base has been maintained for all patients undergoing bypass surgery at Cedars-Sinai Medical Center. Prospective follow-up has been performed annually by mail or telephone interview by trained data collection personnel. For the purpose of this study we defined four outcomes of interest, two of them considered "hard" coronary events: 1) cardiac death confirmed by review of the death certificate or hospital chart, or both, and 2) nonfatal myocardial infarction documented by a consistent history, confirmed by elevation of cardiac enzymes (8) or new Q waves on the electrocardiogram (ECG) (9), or both; and two "soft" coronary events: 1) repeated bypass surgery, and 2) percutaneous transluminal coronary angioplasty, when performed >60 days after testing, as proxies for worsening clinical status.

Table 2. Comparison Between Overall Surgical Population and Study Patients

	Study Patients (n = 294)	All Surgical Patients (n = 4,186)	p Value
Mean age (yr)	67	66	0.098
Range	43–89	41–83	
Male gender	86%	75%	<0.001
Symptomatic	64%	57%	0.022
Prior MI	22%	23%	0.747
No. of grafts	3.94 ± 1.2	3.85 ± 1.1	0.178

Data presented are mean value ± SD or number or percent of patients. MI = myocardial infarction.

Exercise stress testing. All patients underwent maximal symptom-limited treadmill exercise testing using the Bruce protocol. Exercise was terminated because of fatigue, claudication, angina, hypotension, shortness of breath [illegible]tricular tachycardia. If their clinical status permitted, pa[illegible]s were instructed to withhold beta-adrenergic blocking agents or calcium channel blocking agents for at least 48 h and long-acting nitrates for 8 h before testing. Heart rate, blood pressure and a 12-lead ECG were recorded every minute during baseline, exercise and a 10-min recovery period. The ECG response was rated normal, nondiagnostic or abnormal. In the presence of a normal baseline ECG response, a test result was considered abnormal if either ≥1 mm of horizontal or downsloping or ≥1.5 mm of upsloping ST segment depression occurred 0.08 s after the J point in response to exercise. ST segment depression was interpreted as nondiagnostic if left bundle branch block, left ventricular hypertrophy or digitalis effect was present. When baseline ST segment depression was present in the absence of any of these conditions, the test result was considered abnormal if >2 mm additional ST segment depression occurred in response to exercise. The clinical response to exercise was categorized as normal, abnormal or borderline. An abnormal response included the presence of angina, anginal equivalent or exertional hypotension. If inappropriate shortness of breath was the only symptom, the clinical response was considered borderline.

Thallium-201 imaging. At near-maximal exercise, 3 to 4 mCi of thallium-201 were injected intravenously, and exercise was continued for another minute. The SPECT imaging began 15 min after exercise, and redistribution images without reinjection were acquired 4 h later. Five-minute anterior planar images were obtained immediately before the SPECT studies. One hundred four patients also underwent 24-h SPECT image acquisition to detect late reversibility of thallium defects still present on 4-h images (10). The SPECT acquisition and processing were performed as previously described (10). For the purpose of scoring, tomograms were divided into 20 segments (Fig. 1). Image interpretation was performed by experienced observers, unaware of clinical history and exercise test results, using a four-point scoring system to express thallium uptake in each segment (0 = normal uptake; 1 = equivocal defect; 2 = moderate defect; 3 = severe defect). Any segment with a score ≥2 at stress was considered abnormal. Reversibility in any given segment was defined as the presence of any of the following scoring combinations: 3/1, 3/0, 2/1, 2/0 in stress/redistribution images, respectively.

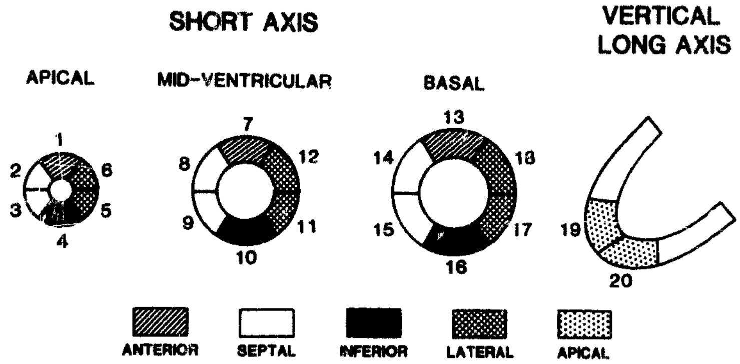

Figure 1. Diagrammatic thallium-201 single-photon computed tomographic images demonstrating the 20 segments analyzed for the presence of perfusion defects, using the apical, midventricular and basal short-axis slices and the midvertical long-axis slice. (Modified from Kiat et al. [10] with permission.)

Lung uptake of thallium-201 was evaluated visually from the 5-min planar images as normal, equivocal or definitely abnormal. Similarly, stress-induced enlargement of left ventricular cavity, or transient ischemic dilation, was evaluated visually as absent, equivocal or present.

Definition of semiquantitative scintigraphic indexes. For each patient, the following semiquantitative descriptors were calculated from the thallium-201 SPECT scores (Table 3): 1) The *summed stress score* describes the combined effects of the extent and severity of defects on the stress images and reflects both ischemia and previous infarction. This conglomerate descriptor was obtained by adding the scores of all 20 segments on the stress image. 2) The *summed reversibility score* is the summation of the segmental differences between stress

Table 3. Cox Proportional Hazards Model: Univariate Screening

	Overall (n = 294)	Hard Events (n = 41)	p Value	Hard/Soft Events (n = 68)	p Value
Male gender	253 (86)	32 (78)	0.12	56 (82)	0.45
Median age (yr)	66	68	0.09	68	0.86
Range	39–89	46–84	<0.001	43–89	<0.01
Symptoms					
Asymptomatic	105 (36)	4 (10)		12 (18)	
Atypical	46 (16)	10 (24)		13 (19)	
Nonanginal	53 (18)	6 (15)		12 (18)	
Typical	74 (25)	15 (37)		25 (37)	
SOB (as only symptom)	16 (5)	6 (15)		6 (9)	
IMA graft	43 (15)	7 (17)	0.56	8 (12)	0.48
No. of grafts	3.21 ± 1.9	3.8 ± 1.7	0.33	3.9 ± 1.9	0.26
Clinical response to exercise			0.13		0.02
Ischemic	63 (22)	12 (29)		24 (35)	
Nonischemic	218 (74)	25 (61)		40 (59)	
Abnormal due to SOB	13 (4)	4 (10)		4 (6)	
Peak HR (beats/min)	134 ± 21	110 ± 19	<0.001	103 ± 22	<0.01
ECG response to exercise			0.49		0.56
Normal	17[illegible] (63)	21 (52)		38 (56)	
Abnormal	80 (28)	10 (24)		20 (29)	
Nondiagnostic	24 (9)	10 (24)		10 (15)	
Summed scintigraphic scores					
Summed stress score	12.3 ± 10.3	13.1 ± 11.8	<0.001	11.7 ± 10.0	<0.001
Summed reversibility score	6.1 ± 5.9	9.1 ± 4.3	<0.001	8.7 ± 3.6	<0.001
Summed redistribution defect score	1.1 ± 2.0	1.0 ± 1.7	0.09	1.2 ± 3.1	0.29
Transient ischemic dilation			<0.001		<0.01
Absent	251 (85)	28 (69)		54 (79)	
Equivocal	22 (8)	3 (7)		3 (4)	
Definite	21 (7)	10 (24)		11 (16)	
Tl-201 lung uptake			0.03		0.48
Normal	221 (77)	27 (66)		52 (76)	
Equivocal	43 (15)	8 (20)		9 (13)	
Definitely abnormal	23 (8)	8 (15)		7 (10)	

Data presented are mean value ± SD or number (%) of patients. SOB = shortness of breath; Tl = thallium; other abbreviations as in Table 1.

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and redistribution. This represents the amount of viable myocardium at risk. 3) The *severe redistribution defect score* is the number of segments with a score >3 in redistribution images. It reflects the extent of nonreversible (and, by inference, nonviable) defects.

Late acquisition images, when available (n = 104), were used for calculation of redistribution and reversibility indexes.

Statistical analysis. The Cox proportional hazards model was used to perform the multivariate survival analyses. All variables (historical, exercise, ECG and scintigraphic) analyzed in this study (Table 1) were first assessed by univariate analysis (Table 3) to determine their ability to predict subsequent coronary events. Those variables that showed a significant association with the outcome in question ($p < 0.10$) were included in the multivariate Cox model in a stepwise fashion. First, the best prediction model using clinical and treadmill variables was obtained; then the incremental value of scintigraphic variables was evaluated by their addition to the clinical model. The added value of the scintigraphic variables when incorporated into the clinical model was considered significant when the difference in log-likelihood associated with each model (adjusted for differences in degrees of freedom) corresponded to $p < 0.05$ (11). Two Cox models were generated. The first considered "hard" outcomes only (cardiac death and acute myocardial infarction). The second, "hard" plus "soft" events (cardiac death, myocardial infarction, bypass surgery and percutaneous transluminal coronary angioplasty).

We developed these retrospective models only for the descriptive purpose of identifying the important predictors of outcome in a particular group of patients, not for the prescriptive purpose of estimating the outcome of individual patients. Their application to the task of individual patient prediction requires prospective validation.

Results

Clinical outcome. Follow-up duration after thallium testing was 31 ± 11 months. The frequency of hard events was 14% (41 of 294). There were 20 cardiac deaths and 21 acute myocardial infarction. One patient had an acute myocardial infarction and died subsequently, and the event date considered in his case was that of the acute myocardial infarction. Soft events occurred in 10% of patients: 29 underwent coronary angioplasty or had repeat bypass surgery late (>60 days) after exercise thallium testing. Two patients underwent late revascularization and subsequently had an acute myocardial infarction. Thus, the total coronary event rate (hard or soft) was 23% (68 of 294).

Prediction of hard events. *Prognostic value of clinical and treadmill exercise variables.* Univariate analysis identified age, peak exercise heart rate, history of shortness of breath and chest pain classification as significant predictors of cardiac death and acute myocardial infarction (Table 3). Cox proportional hazards analysis selected shortness of breath and peak exercise heart rate as independent predictors. The global chi-square for this model was 24.2 ($p < 0.001$). Sixteen patients had a history of shortness of breath, and the frequency of hard events in this subgroup was 15 ± 9%. A history of typical angina was a significant univariate predictor ($p = 0.01$), but it lost significance after the inclusion of shortness of breath in the multivariate model ($p = 0.07$).

Table 4. Proportional Hazards Model for Prediction of Hard Events

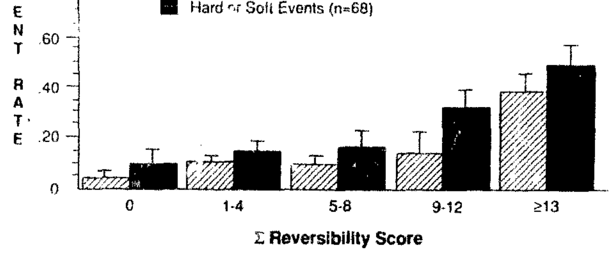
Variable	Odds Ratio (99% CI)	p Value
Clinical/Exercise Model		
Peak exercise HR*	0.786 (0.68, 0.90)	<0.001
Hx of shortness of breath	3.527 (1.45, 8.60)	<0.001
Scintigraphic Variables With Incremental Value		
Summed REV score*	1.130 (1.07, 1.19)	<0.001
Lung uptake	1.767 (1.14, 2.73)	<0.001

*Per unit increase. CI = confidence interval; HR = heart rate; Hx = history; REV = reversibility.

Scintigraphic analysis. Four scintigraphic variables were significant univariate predictors of cardiac death and nonfatal acute myocardial infarction (Table 3). In the multivariate models, two variables were shown to significantly enhance the predictive ability of the clinical model: the summed reversibility score (odds ratio 1.13, $p < 0.001$) and the presence of stress-induced increased lung uptake of thallium-201 (odds ratio 1.77, $p = 0.016$). All other SPECT variables failed to add significant information after the inclusion of these two. Table 4 summarizes the Cox proportional hazards analysis for prediction of hard events. The global chi-square for this model was 49.7 ($p < 0.001$), twice as high as that for the clinical/exercise model alone.

Figure 2 illustrates the relation between coronary events and the summed reversibility score. Figure 3 depicts the relation between coronary events and lung uptake, the second scintigraphic variable selected by the multivariate analysis, and that between coronary events and transient ischemic dilation of the left ventricle. For the purpose of this analysis, patients with segmental total ischemic dilation of the left ventricle or lung uptake were grouped with those patients with definite abnormal findings. Of note, the presence of increased thallium-201

Figure 2. Event rate as a function of the summed (Σ) reversibility score.



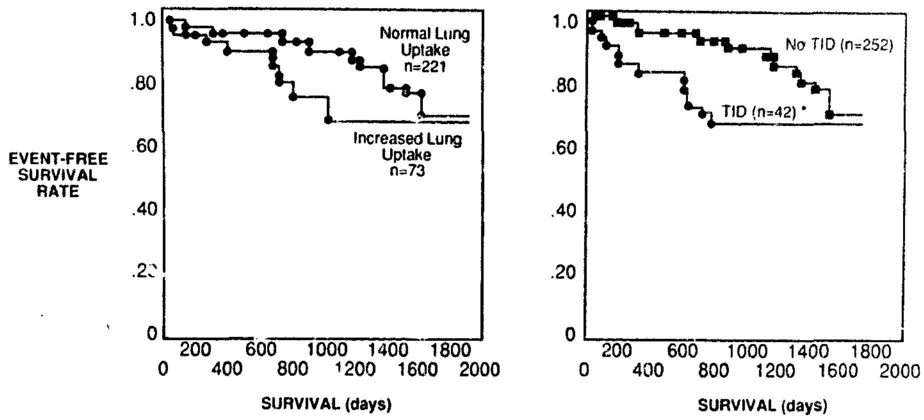


Figure 3. Event-free survival rate as a function of the presence or absence of increased lung uptake (**left**) or transient ischemic dilation (TID) of left ventricle (**right**).

lung uptake indicated a significantly higher risk, even when the relatively small number of patients with that abnormality (8%) was considered.

Prediction of hard and soft events. *Clinical and exercise data.* When revascularization procedures (bypass surgery and coronary angioplasty) performed at least 60 days after scintigraphy were added to the hard events, the stepwise multivariate procedure again selected peak exercise heart rate as one of the two components of the optimal clinical model (Table 5). However, the clinical response to exercise was now selected as the accompanying variable because it performed better than a history of shortness of breath. The global chi-square for this model was 16.1 ($p < 0.001$).

Added value of thallium SPECT. The addition of scintigraphic data to the clinical/exercise model selected the summed reversibility score again as a significant independent predictor (odds ratio per unit increase 1.11, 95% confidence interval 1.06 to 1.15). However, lung uptake and transient ischemic dilation were no longer significant (Table 5). The twofold improvement in the chi-square for hard events alone and the threefold improvement for hard plus soft events indicate that the added value of thallium SPECT was clinically important as well as statistically significant.

Discussion

It is now well accepted that the clinical utility of any test should be determined within the same hierarchic order in which it is used in clinical practice (12–16). According to this scheme, conventional historical information should be considered first, followed by each of the candidate tests in order of increasing technical complexity and cost. We believe that the present study is the first to assess the prognostic utility of myocardial perfusion scintigraphy late after coronary artery bypass surgery within this context. We thereby determined that myocardial perfusion scintigraphy contributed a statistically significant increment in prognostic information over that provided by the clinical history and exercise electrocardiography.

Our group previously reported (17) the incremental prognostic value of planar myocardial perfusion scintigraphy in patients with suspected coronary artery disease. In that study, semiquantitative assessment of the number of segments with reversible hypoperfusion (i.e., extent), degree of the hypoperfusion (i.e., severity) and achieved heart rate were independent predictors of coronary events over the subsequent year. In the present study, we used SPECT, which more accurately quantifies defect extent (18), and we created a new semiquantitative variable—the summed reversibility score—reflecting a combination of both the extent and severity of reversible hypoperfusion. This new variable was the single strongest scintigraphic predictor of coronary events in our group of patients with bypass surgery and had incremental prognostic value when added to clinical and exercise data. Moreover, for both types of outcome (hard vs. hard or soft event), there was an increase in event rate proportional to the summed reversibility score (Fig. 2), thereby providing further confirmation of the clinical canon that patients with severe myocardial ischemia are at increased risk for subsequent coronary events.

Transient ischemic dilation of the left ventricle induced by exercise or pharmacologic stress is a well recognized marker of severe and extensive coronary artery disease (19–22). Increased lung uptake of thallium-201 has been correlated with abnormally high pulmonary capillary wedge pressure and poor left ventricular function and is a prognostically meaningful finding (14,23,24). In our patients, both total ischemic dilation of the left ventricle and increased lung uptake were significant univariate predictors of hard events (Fig. 3). However, total ischemic dilation of the left ventricle failed to show indepen-

Table 5. Cox Proportional Hazards Model for Prediction of Hard/Soft Events

Variable	Odds Ratio (95% CI)	p Value
	Clinical/Exercise Model	
Peak exercise HR*	0.876 (0.78, 0.98)	0.002
Clinical response to exercise	1.442 (1.10, 1.88)	0.001
	Scintigraphic Variables With Incremental Value	
Summed REV score*	1.105 (1.06, 1.15)	<0.001

*Per unit increase. Abbreviations as in Table 4.

dent value in the multivariate analysis, whereas the presence of increased lung uptake significantly increased risk of hard events alone. The reasons for these observations are not apparent.

Previous studies. Our findings are consistent with those of others reporting the incremental prognostic value of stress thallium-201 testing in various patient groups. For example, Pollock et al. (14) showed that planar exercise thallium scintigraphy contributed a statistically significant increment of prognostic information over that provided by clinical history, exercise electrocardiography and coronary angiography among 503 patients with suspected coronary artery disease over a mean follow-up of 4.4 years. Similarly, Osterhuis et al. (16) showed that planar scintigraphy contributed a significant increment of information over that provided by clinical and exercise ECG data for diagnosis of multivessel disease among 191 patients with known or suspected coronary artery disease and that quantitative analysis of the images was superior to visual assessment in this regard.

Study limitations. Although our follow-up was performed prospectively, this remains a retrospective study. We studied a consecutive sample of patients who had undergone bypass surgery ≥5 years before their referral to the nuclear cardiology laboratory. Because only referred patients were tested, not all eligible patients (all those who had undergone bypass surgery ≥5 years ago at our center) were included in the study group. As noted in Table 2, patients referred to our laboratory had a higher frequency of symptoms and were predominantly male. Whether symptoms or gender played a significant role in the referral cannot be determined through retrospective analysis. However, this pattern might indicate that our study patients were significantly sicker (and therefore more symptomatic) than the general postbypass population.

Given the size of our study group and the number of observed events, the multiple logistic regression models were developed in the same group in which the clinical efficacy of the model was tested. This can result in an overestimation of the predictive values of the variables being studied because the regression variables are optimized for the characteristics of the study group. However, this "upward effect" can be expected for all the analyzed variables. Therefore, it does not invalidate the presence of an incremental value of the thallium scan when added to the other variables, although it might affect its magnitude to an unknown extent.

We performed two different survival analyses: one based only on hard events (death or myocardial infarction) as the outcome of interest and another based also on a soft event (referral for revascularization >60 days after testing) that served as a proxy for worsening clinical status (17,25). Although this practice may lead to an overestimation of the true event rate, the consideration of hard events alone may result in its underestimation. The pair of survival analyses taken together therefore serve as a sensitivity analysis with respect to the reliability of our conclusions. In this regard, both methods of analysis resulted in the identification of the summed reversibility score as the most important scintigraphic predictor.

Late redistribution studies evaluate defects that appear as fixed at 4 h and can improve the detection of viable myocardium (10,26). Because it is likely that this underperfused, viable myocardium is at risk, the scores from late acquisition images were used whenever available for calculation of redistribution/reversibility indexes. However, the limited number of patients with late acquisition (n = 104) does not permit a direct comparison between 4- and 24-h acquisitions. Moreover, left ventricular ejection fraction, a predictor with recognized prognostic value (27,28), was unavailable for analysis in the majority of patients.

All our semiquantitative scintigraphic variables were based on visual assessment of the perfusion images (in particular, heart/lung ratios were not quantified). Automated quantitation methods are now available that might substantially improve the reproducibility of our approach by decreasing its subjectivity (29,30).

Finally, further research is warranted to determine the clinical relevance of our findings. There are no studies assessing whether, and to which degree, the identification of high risk groups in the postbypass population can lead to improvement in survival by means of therapeutic interventions. Therefore, it remains to be determined whether the increment in information that we observed justifies the cost of thallium scans in these patients.

Conclusions. We summarized thallium-201 SPECT information by creating semiquantitative scores that reflect the extent and severity of myocardial hypoperfusion. The resultant summed reversibility score was a strong predictor of outcome, providing incremental information with regard to clinical and exercise data in patients who had undergone bypass surgery ≥5 years before testing. Our findings suggest that thallium-201 SPECT may play an important clinical role in the long-term evaluation of symptomatic patients after coronary artery bypass surgery. However, the particular prediction model that we used in this study requires formal prospective validation before clinical application. Additional studies must be performed to define the cost-effectiveness of this approach and to determine whether the current findings can be extrapolated to the prognostic assessment of patients who remain asymptomatic after bypass surgery.

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