JACC Vol. 31, No. 6
May 1998:1280–5

Thallium Reinjection Versus Standard Stress/Delay Redistribution Imaging for Prediction of Cardiac Events

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Objectives. **The purpose of this study was to compare thallium reinjection with standard stress/delay redistribution for the prediction of cardiac events.**

Background. **Although thallium reinjection enhances the detection of viable myocardium, its contribution to prognosis over stress/delay redistribution in a general referral population has not been clearly evaluated.**

Methods. **This retrospective analysis included 366 consecutive patients with coronary artery disease who underwent stress/delay redistribution imaging and thallium reinjection scintigraphy, with a mean follow-up of 33 ± 12 months.**

Results. **Cardiac events occurred in 48 patients (40 deaths, 8 myocardial infarctions). Of the 366 original patients, 159 demonstrated ischemia by stress/delay redistribution, 107 showed ischemia by reinjection only, and 100 showed infarction only. Cardiac events occurred in 20 patients (12.6%) with stress/delay redistribution, 13 patients (12%) with ischemia detected by thallium reinjection only and 15 patients (15%) with infarction only. The size of the reversible thallium defect by either stress/delay redistribution imaging or reinjection scintigraphy did not predict cardiac events. Independent predictors of cardiac events included left ventricular cavity size, the size of the abnormal perfusion defect and patient age.**

Conclusions. **Thallium reinjection does not contribute independent prognostic utility for cardiac events when compared with stress/delay redistribution. Left ventricular dilation and the size of the post-stress defect were predictors of cardiac events.**

(J Am Coll Cardiol 1998;31:1280–5)

Thallium myocardial perfusion imaging has become an important prognostic tool for various clinical subsets of patients with coronary artery disease (CAD) (1–10). This is due in part to the observation that the extent of reversible perfusion defects (as determined by delayed redistribution imaging) has been widely described as an independent predictor of future cardiac events. Most of these studies were based on a conventional stress test and 2 to 4 h of delayed redistribution, either after exercise (1–3,6) or with dipyridamole (7,8) in patients with suspected CAD without a previous infarction.

However, several studies (11–13) have demonstrated that standard thallium stress/delay redistribution imaging underestimates the number of viable "ischemic" segments, based on improved segmental wall motion after revascularization. In addition, the introduction and widespread use of thallium reinjection in patients with fixed defects after stress/delay redistribution can enhance the detection of viable ischemic segments when compared with standard redistribution studies. The utility of the thallium reinjection technique has been demonstrated by its ability to predict wall motion improvement after coronary artery revascularization (14,15).

Although thallium reinjection has proven value in the evaluation of patients with reduced left ventricular (LV) function and significant coronary stenosis, its prognostic utility in a general referral population is unknown. Accordingly, the aim of the present study was to retrospectively assess the prognostic utility of thallium reinjection as compared with stress/delay redistribution in the prediction of future cardiac events in patients with CAD.

Methods

Study patients and follow-up. From January 1991 to July 1994, 404 patients referred to the University of Massachusetts Medical Center for thallium stress/delay redistribution had additional thallium reinjection imaging ordered to evaluate "fixed" perfusion defects. In this group, 15 patients were found to have tissue attenuation or technically limited studies that excluded them from the study. Of the 389 original patients, medical follow-up was available for review in 366 (94%). Follow-up was conducted by telephone contact with the patient or his or her family or by reviewing the medical records. The clinical end points of the study included cardiac death or nonfatal myocardial infarction (MI), and the average follow-up period was 33 ± 12 months.

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Manuscript received November 12, 1996; revised manuscript received December 5, 1997, accepted January 23, 1998.

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0735-1097/98/$19.00
PII S0735-1097(98)00079-5

Abbreviations and Acronyms

CAD = coronary artery disease
LV = left ventricular
MI = myocardial infarction

Twenty-six of these patients (6%) were included in a previous study of thallium lung uptake (16) and 6 (1.6%) in a study of LV cavity size (17).

Stress test protocol. Dipyridamole (n = 193) or exercise (n = 173) thallium scintigraphy was performed according to the protocol of our laboratory, as previously described (10,18), and cardiac medications were not routinely discontinued.

Dipyridamole test. Each patient was studied after an overnight fast and the discontinuation of all theophylline-containing medications (for 24 to 36 h) and caffeinated beverages (for 12 h). During continuous electrocardiographic monitoring and frequent blood pressure measurements, intravenous dipyridamole (Boehringer-Ingelheim) was infused at a rate of 0.14 mg/kg body weight per min over 4 min to achieve a total dose of 0.56 mg/kg. Three to four minutes after completion of the dipyridamole infusion, 1.5 to 2.5 mCi of thallium-201 was injected intravenously, followed by a bolus of normal saline solution. All side effects were treated with 75 mg of parenteral aminophylline.

Exercise test. Each patient underwent symptom-limited treadmill exercise testing using the Bruce protocol. The test was terminated when there was excessive fatigue, shortness of breath, significant angina, hypotension, ST segment depression of at least 2 mm or significant arrhythmia. At peak exercise, a dose of 1.5 to 2.5 mCi of thallium-201 was injected intravenously, and the patients exercised for an additional minute.

Thallium scintigraphy. All images were acquired 5 to 10 min after dipyridamole or exercise testing, in three planar views—best septal (left anterior oblique), anterior and left lateral—in a 128 × 128 matrix. A standard Gamma camera was set at 80 keV photopeak with a 20% window and equipped with a high resolution collimator. Each view was collected for 7 min and stored and processed on a Picker PCS Plus II computer system. Similar views were repeated 3 to 4 h later. After completion of the delayed images, an additional injection of 1 mCi of thallium-201 was given intravenously to those patients showing at least one fixed segmental defect. The same views were again collected, as noted earlier, for stress/delay imaging.

Each scan was analyzed by two experienced nuclear cardiologists who divided the myocardium into nine separate segments (18,19). Segments on the immediate post-stress images were compared with those on the delayed images and defined as normal, fixed or reversible defects. In addition, pulmonary thallium uptake was quantitated from the first view of the immediate post-stress images. A region of interest was drawn over the left lung and the peak of myocardial activity to calculate the lung to heart ratio. A ratio >0.51 (16) was considered indicative of increased uptake. A qualitative interpretation of LV dilation was made when the internal cavity diameter was larger than the wall thickness on the left anterior oblique view. In addition, a decrease >10% in the cavity size between stress and delayed images was interpreted as reversible LV dilation (17).

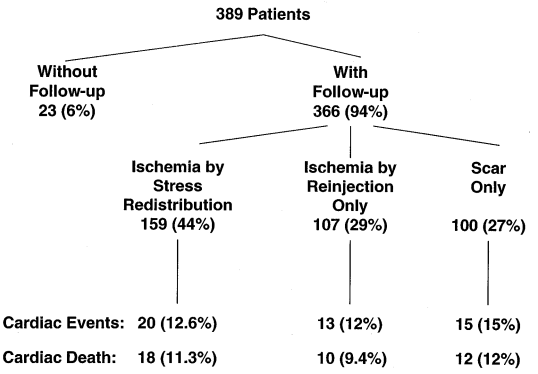


Figure 1. Frequency of cardiac events in 389 patients undergoing stress/delay redistribution and thallium reinjection imaging. There was no difference in the event rate (p = 0.8) or cardiac death rate (p = 0.8) among the three groups.

Statistical analysis. Data are presented as the mean value ± SD, using the chi-square test for comparison of categoric variables and the Student *t* test for continuous variables; $p < 0.05$ was considered statistically significant. Cardiac events were defined as cardiac death and nonfatal MI. Clinical and scan variables that showed univariate association with cardiac events were added to a Cox proportional hazards model using a forward stepwise method to determine their independent contribution to the prediction of the events. Event-free survival curves were calculated using the Kaplan-Meier method, and differences between the curves were assessed using the log-rank test. Statistical calculations were performed using STATA 4.0 (Stata Corp.).

Results

Cardiac events (Fig. 1). Overall, there were 48 events in 366 patients (13%) during the follow-up period of 33 ± 12 months. Forty of the patients (11%) succumbed to cardiac death and 8 (2%) suffered from nonfatal MI. An additional 14 patients who died of noncardiac-related causes were not included in the cardiac event end points (follow-up was censored at the time of noncardiac death). Of the original 366 patients, 159 demonstrated ischemia by stress/delay redistribution and an additional 107 demonstrated ischemia only after reinjection. The remaining 100 patients had fixed defects only. Twenty patients (12.6%) with stress/delay redistribution had cardiac events, compared with 13 patients (12%) with redistribution only after reinjection. Of the patients with only fixed defects, 15 (15%) had cardiac events. The event rate and cardiac death rate did not differ significantly among the groups (Fig. 1).

Table 1. Comparison of Clinical Variables in Patients With Versus Those Without a Cardiac Event

	No Events (n = 318)	Events (n = 48)	p Value
Age (yr)	62 ± 11	67 ± 12	0.004
Men	221 (70%)	36 (75%)	0.44
Diabetes	62 (20%)	15 (31%)	0.085
Angina	151 (47%)	20 (42%)	0.71
Heart failure	24 (08%)	6 (12%)	0.24
CABG before follow-up	63 (20%)	13 (27%)	0.25
PTCA before follow-up	48 (15%)	5 (10%)	0.39
CABG during follow-up	31 (10%)	2 (04%)	0.21
PTCA during follow-up	13 (04%)	2 (04%)	0.98
Medication			
Digoxin	40 (13%)	9 (19%)	0.24
BBs	113 (36%)	15 (32%)	0.63
CCBs	137 (43%)	22 (46%)	0.72
Nitrates	150 (47%)	19 (40%)	0.33

Data presented are mean value ± SD or number (%) of patients. BBs = beta-blockers; CABG = coronary artery bypass graft surgery; CCBs = calcium channel blockers; PTCA = percutaneous transluminal coronary angioplasty.

Clinical variables. Univariate analysis of the clinical variables in patients without cardiac events (n = 318) and with events (n = 48) is summarized in Table 1. No significant differences were found for any of the clinical variables between these two groups, except for mean age, which was higher in the patients with events. It is of interest that no difference was found between the groups in terms of the proportion of patients who had undergone coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty before or after follow-up, and that only 48 patients (13%) went on to have these type of procedures. This suggests that coronary revascularization was not a major factor and did not bias the cardiac event findings.

Stress testing variables (Table 2). The cardiac event rate in patients who underwent exercise testing (9.8%) was not different from the event rate in patients who underwent dipyridamole (16.1%; p = 0.09). Univariate analysis of the stress test variables (including Bruce protocol and dipyridamole test) showed that cardiac symptoms and ST segment depression were not different between the patients with and without events. However, in those who underwent the Bruce stress test protocol, the exercise duration was shorter (p = 0.005) and the percent maximal predicted heart rate achieved was lower in patients with events (p = 0.04).

Table 2. Comparison of Stress Testing Variables in Patients With Versus Those Without a Cardiac Event

	No Events (n = 318)	Events (n = 48)	p Value
Exercise test (n = 173)			
Exercise time (min)	8.9 ± 3	6.7 ± 3	0.005
% MPHR	81 ± 15	73 ± 15	0.04
ST ↓ (mm)	0.8 ± 1	0.8 ± 1	0.92
ST ↓ ≥1 mm	46%	50%	0.77
Dipyridamole test (n = 193)			
ST ↓ (mm)	0.2 ± 0.5	0.2 ± 0.5	0.96
ST ↓ ≥1 mm	14%	13%	0.84
Cardiac Sx with exercise or dipyridamole stress	27%	19%	0.46

Data presented are mean value ± SD or percent of patients. MPHR = maximal predicted heart rate; ST ↓ = ST segment depression; Sx = symptoms.

Table 3. Comparison of Thallium Variables in Patients With Versus Those Without a Cardiac Event

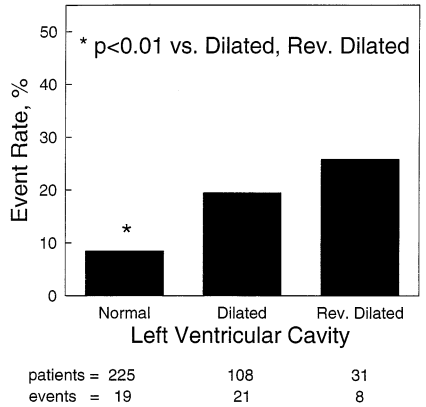
	No Events (n = 318)	Events (n = 48)	p Value
Increased Tl lung uptake	64 (20%)	16 (33%)	0.059
RV dilation	13 (4%)	3 (6%)	0.50
LV dilation			
Transient	23 (7%)	8 (17%)	0.002
Fixed	87 (27%)	21 (43%)	0.002
Abnormal segs	3.8 ± 1.5	4.6 ± 1.6	0.002
Stress/delay redist			
Revers segs	0.8 ± 1.1	0.8 ± 1.3	0.94
Fixed segs	3.0 ± 1.6	3.8 ± 1.5	0.003
Thallium reinjection			
Revers segs	0.9 ± 1.2	1.1 ± 1.5	0.43
Fixed segs	2.1 ± 1.6	2.7 ± 1.9	0.03

Data presented are number (%) of patients or mean ± SD number of segments/patient. LV = left ventricular; redist = redistribution; Revers = reversible; RV = right ventricular; segs = segments; Tl = thallium.

Thallium imaging variables (Table 3). Univariate analysis of scintigraphic results showed that increased pulmonary thallium uptake was of borderline significance in the patients with cardiac events. However, LV dilation (either reversible or fixed) was more frequent in patients with events as compared with those without events. Figure 2 shows the higher event rate for patients with a dilated LV cavity (either reversible or fixed), compared with those with a normal LV chamber size ($p < 0.01$).

Using univariate analysis to compare the number of segments with ischemia, scar or an abnormal pattern, we found there was no difference between the number of ischemic

Figure 2. The cardiac event rate was higher in patients with dilated or reversibly dilated (Rev. Dilated) left ventricles than in those with a normal LV cavity size ($p < 0.01$).



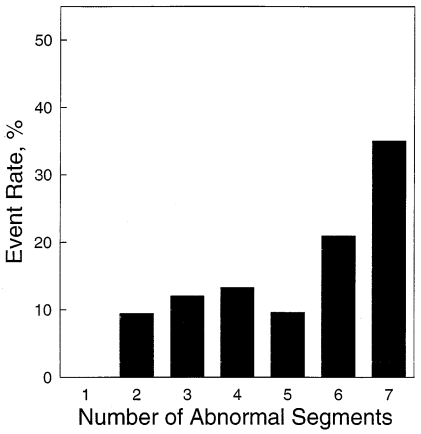


Figure 3. The cardiac event rate increased with the number of abnormal perfusion segments ($p < 0.05$). Patients with six or more abnormal segments had more events than patients with fewer perfusion abnormalities ($p < 0.01$).

segments, either by stress/delay redistribution or thallium reinjection, and the prevalence of cardiac events. However, as shown in Table 3, patients with cardiac events had more abnormal (fixed and transient) segments and more infarct-related segments as compared with patients without events. The frequency of cardiac events was related to the number of abnormal segments ($p = 0.02$), as shown in Figure 3. We then subclassified the patients with abnormal segments into three groups according to the extent of abnormality (1 or 2, 3 to 5 and ≥6 abnormal segments, classified as groups 1, 2 and 3, respectively), and a life-table analysis was performed. The results are shown in Figure 4, and demonstrate that those patients with large perfusion defects (group 3) had a significantly lower event-free survival rate than those with small or moderate abnormalities (groups 1 and 2) ($p < 0.01$).

Prognostic value. Stepwise Cox regression analysis was performed to evaluate the prognostic significance of clinical, stress test and scintigraphic variables (Tables 1 to 3) and their contribution to the prediction of cardiac death or MI. Independent predictors of cardiac events included LV size ($p < 0.004$), patient age ($p < 0.006$) and abnormal perfusion defect size ($p < 0.03$).

Proportional hazards analysis was also performed separately for patients who underwent the Bruce protocol or the dipyridamole test. The independent predictors for the 173 patients who underwent exercise testing were increased thallium lung uptake ($p < 0.001$) and exercise duration ($p < 0.02$). The predictors for the 193 patients who underwent the dipyridamole test were LV dilation ($p < 0.013$) and abnormal perfusion defect size ($p < 0.05$).

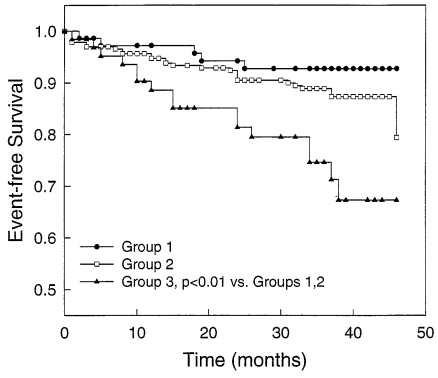
Discussion

Impact of thallium reinjection. It is now well established that the use of thallium reinjection can increase the detection of "ischemic" myocardium that would have been classified as infarct with standard stress/delay redistribution imaging (14). Most studies of thallium reinjection have focused on the evaluation of myocardial viability. Preserved thallium uptake or redistribution is associated with preserved myocardial glucose metabolism (as assessed by ^{18}F-deoxyglucose imaging) and, more importantly, recovery of regional wall motion after coronary revascularization. When thallium imaging demonstrates multiple viable segments, LV function is also likely to improve after revascularization (20,21).

The present study is the first to evaluate the incremental prognostic value of thallium reinjection scintigraphy over stress/delay redistribution imaging in a routine consecutive series of patients who had predominately fixed defects after standard delayed imaging. In contrast to most reports (14,15) on thallium reinjection, only 13% of our patients underwent revascularization procedures, and the presence and size of reversible defects (on either delayed or reinjection images) were not significant predictors of future cardiac events. Overall, it appears that the detection of additional reversible (ischemic) segments by thallium reinjection does not enhance the prognostic value of thallium stress scintigraphy in patients with predominantly fixed perfusion defects.

Although many previous studies have consistently demonstrated that patients with an abnormal thallium scan have a higher cardiac event rate than patients with a normal scan, the prognostic significance of redistribution on stress/delay imaging appears to depend on the specific patient group under investigation. Although redistribution has been shown to predict cardiac events in patients with unstable angina (22) and patients undergoing noncardiac surgery (10,23), other studies have indicated that "fixed" thallium defects are most predictive of cardiac events (24,25). In a discussion of this issue, Iskandrian and Verani (26) have suggested that thallium redistribution may be more predictive of events such as angina and recurrent MI, whereas fixed defects may predict cardiac death. Because cardiac deaths comprised a large majority of the events in our study, the observation that these events were

Figure 4. Life-table analysis comparing the event-free survival in groups 1 and 2 with mild (1 or 2 segments) and moderate (3 to 5 segments) abnormal defect size, respectively, with group 3 with severe (6 or 7 segments) abnormal defect size. Event-free survival was significantly reduced in group 3 ($p < 0.01$).



predicted by abnormal perfusion and fixed defect size is consistent with this hypothesis.

The fact that the majority of future events in this patient group were cardiac deaths resulted in a correlation between clinical and stress testing variables that reflect LV function. These factors, including LV dilation, pulmonary thallium uptake, fixed defects and treadmill duration, achieved better prognostic utility than those associated with myocardial ischemia, including reversible defects, ST segment depression or cardiac symptoms. It is also important to note that the choice of stress modality (exercise or pharmacologic) resulted in different predictors.

Study limitations. An important limitation of this study is the lack of quantification of the severity of fixed thallium defects. Recent studies of thallium reinjection show that mild or moderate "fixed" thallium defects probably indicate viable myocardium (20). During the period of this study, the planar images were not routinely analyzed with software to quantify thallium uptake.

Unlike some institutions, we did not routinely reinject all patients. Thallium reinjection was performed in patients in whom stress/delay redistribution imaging showed predominantly infarct. As discussed earlier, the predictors of events (mainly cardiac death) in this group of patients may differ from those in patients with multiple reversible defects on standard stress/delay redistribution imaging.

The lack of single-photon emission computed tomographic imaging may also be viewed as a limitation of our study. However, our overall observations and conclusions are consistent with those of recent studies (27,28) that used quantitative single-photon emission computed tomographic analysis.

In addition, angiographic data were not included in this study because most patients did not later have revascularization procedures. In contrast, our use of hard end points (death and infarction) was also not influenced by invasive interventions.

Clinical implications. Patients who are referred for thallium scintigraphy for risk stratification and prediction of long-term prognosis may not need routine thallium reinjection and reimaging. The prolongation of examination time and increased cost of thallium reinjection may not be warranted, unless the critical question is myocardial viability before coronary revascularization (14,15,29). As we have shown, because thallium reinjection is not more contributory than stress/delay redistribution imaging for the prediction of cardiac events, patients referred for evaluation before vascular or other major noncardiac surgery, or even for risk stratification after MI, might be able to forego this additional imaging procedure. However, this last issue still requires clarification. Further investigations to evaluate the potential prognostic value of routine thallium reinjection in clinical subgroups such as predischarge postinfarction patients or in preoperative cardiac risk assessment are warranted.

We appreciate the secretarial assistance of Harriet Kay in the preparation of the manuscript.

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