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Incremental Prognostic Value of Thallium Reinjection after Stress-Redistribution Imaging in Patients with Previous Myocardial Infarction and Left Ventricular Dysfunction

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This study evaluated the incremental prognostic value of ^{201}Tl reinjection imaging over clinical, exercise and thallium stress-redistribution data in patients with previous myocardial infarction and left ventricular dysfunction. **Methods:** Thallium-201 reinjection after stress-redistribution SPECT was performed in 104 consecutive patients with a first Q-wave myocardial infarction (>8 wk) and left ventricular ejection fraction ≤40%. Follow-up data (mean 22 mo) were available for 98 patients; 16 patients underwent early revascularization procedures within 3 mo after exercise testing and were not considered for the analysis. **Results:** During follow-up there were 13 hard events (cardiac death and myocardial infarction) and 11 soft events (coronary revascularization procedures >3 mo after thallium imaging). With multivariate Cox regression analysis, the sum of defects at stress-redistribution imaging that were reversible or moderate irreversible after reinjection was a powerful predictor of subsequent events. The addition of thallium reinjection imaging data significantly improved the prognostic power of clinical, exercise and stress-redistribution data for the occurrence of hard events ($p < 0.01$). **Conclusion:** In patients with previous myocardial infarction and left ventricular dysfunction, thallium reinjection imaging provides incremental prognostic information over those obtained from conventional stress-redistribution imaging.

Key Words: myocardial infarction; left ventricular dysfunction; viable myocardium; thallium reinjection imaging

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Stress-redistribution ^{201}Tl imaging is widely used to identify coronary artery disease in patients with chest pain (*1,2*). Furthermore, it has been demonstrated that the presence and the extent of transient defects have important prognostic value in coronary artery disease patients (*3–8*).

Thallium-201 reinjection after stress-redistribution enhances the identification of hypoperfused but viable myocardium (*9,10*), and its results are useful for management decisions in patients after myocardial infarction (*10,11*). Stress-redistribution reinjection thallium protocols, providing information concerning both jeopardized and viable myocardium, seem attractive for evaluating prognosis in patients with nonrecent myocardial infarction and left ventricular dysfunction (*11*). However, there are no data as yet available on the prognostic value of thallium reinjection after stress-redistribution in patients with chronic ischemic left ventricular dysfunction. This

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study was designed to evaluate the incremental prognostic value of thallium reinjection imaging in medically treated patients with previous myocardial infarction and left ventricular dysfunction undergoing exercise-redistribution thallium protocol.

MATERIALS AND METHODS

Patients

From January 1992 to December 1993, 104 consecutive patients with a first Q-wave myocardial infarction and left ventricular dysfunction (left ventricular ejection fraction ≤40%) were referred to our nuclear cardiology laboratory for ^{201}Tl reinjection after stress-redistribution SPECT imaging. Left ventricular ejection fraction was assessed by two-dimensional echocardiography (57 patients) or contrast ventriculography (47 patients). Patients with recent myocardial infarction (≤8 wk) and those with unstable angina were excluded. Digoxin, β-adrenergic blocking agents and calcium antagonists were withheld whenever possible for 72 hr, and long-acting nitrates for 48 hr, before the stress test.

Exercise Testing

After an overnight fast, all patients underwent symptom-limited bicycle exercise testing according to a standardized multistage protocol with continuous monitoring of heart rate and rhythm, blood pressure and symptoms. After 2 min of bicycling at 0 load, patients started the test with a 25-W load that was increased by 25 W every 2 min. Twelve-lead electrocardiogram, heart rate and blood pressure were recorded at each minute of exercise and at 1, 3, 4 and 5 min after exercise. At peak exercise, 111 MBq (3 mCi) of ^{201}Tl were injected intravenously, and the patient was encouraged to continue exercise at the same level for an additional 60 to 90 sec before stopping. The test was terminated at the appearance of excessive fatigue, dyspnea, dizziness, angina, hypotension or complex ventricular arrhythmias. ST segment changes were considered ischemic when the ST segment, normal at rest, demonstrated during exercise either horizontal or downsloping depression 1 mm or more below the baseline 0.08 sec after the J point; the response was also considered ischemic if the ST segment was depressed at rest, but the depression increased by 2 mm or more during exercise.

Thallium Imaging

All patients underwent ^{201}Tl SPECT imaging as previously described (*12,13*). Within 5 min of tracer injection, acquisition of tomographic images started using a rotating large field-of-view gamma camera (Elscint SP4HR, Haifa, Israel), equipped with a low-energy, all-purpose, parallel-hole collimator and connected to a dedicated computer system. Briefly, 32 projections (40 sec/projection) were obtained over a semicircular 180° arch extending from the 30° right anterior oblique to the left posterior oblique position. A 20% symmetric energy window centered on the 68-keV peak was used. Filtered backprojection was then performed with a low-resolution Butterworth filter with a cutoff frequency of 0.5 cycles/pixel, order 5.0, to reconstruct transverse axial tomograms 6.2-mm thick per slice, which encompassed the entire heart. Sagittal and oblique tomograms parallel to the long-axis and short-axis of the left ventricle were then extracted from the filtered transaxial tomograms by performing coordinate transformation with the appropriate interpolation (*14*). No attenuation or scatter correction was applied. Four hours later, redistribution images were obtained using identical imaging methods. During the period between exercise and redistribution acquisitions, patients were ambulatory and continued fasting. Immediately after redistribution imaging, all patients received 37 MBq (1 mCi) of ^{201}Tl at rest, and a third acquisition was started 50 to 60 min after the second administered dose using the same imaging protocol.

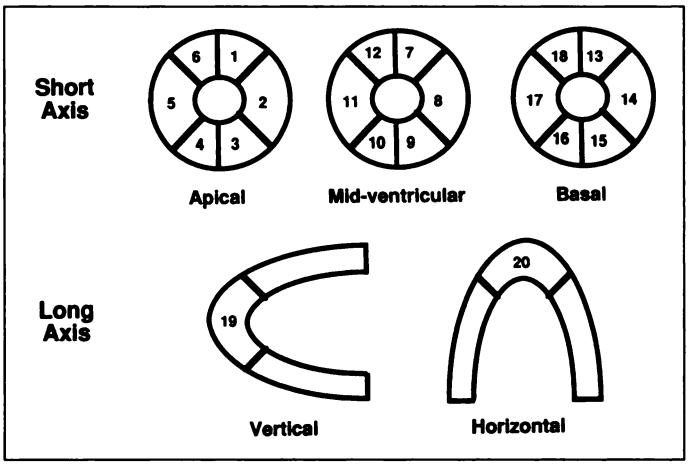

FIGURE 1. Segmentation scheme used for regional quantitative analysis of ^{201}Tl cardiac tomography.

Data Analysis

Thallium-201 exercise, redistribution and reinjection tomographic images were evaluated by direct comparison. For each patient, exercise redistribution images were directly compared. To evaluate the incremental information obtained with reinjection imaging over stress-redistribution data, the ^{201}Tl reinjection images were compared to the redistribution images. For each study, tomograms were divided into 20 myocardial segments (Fig. 1). Regional ^{201}Tl uptake was quantitatively analyzed as previously described (*13,15–17*). Briefly, in each tomogram the myocardial region with the maximum counts was considered as the normal reference region. Thallium-201 uptake in all other segments was then expressed as percentage of the activity measured in the reference region. A myocardial segment was considered abnormal if exercise ^{201}Tl uptake was greater than 2 s.d. below the mean observed in the same region for age- and sex-matched normal volunteers (*9,17,18*). On the basis of previous reproducibility measurements, a segment with reduced activity on exercise ^{201}Tl images was considered reversible if the activity increased by at least 10% on redistribution images; if not, it was considered irreversible (*12,17*). Irreversible ^{201}Tl defects at exercise-redistribution imaging were considered reversible after reinjection if the activity increased by at least 10% on reinjection images. Alternatively, a defect was considered irreversible if the activity did not increase more than 10% or increased by 10% but remained less than 50% on reinjection images.

As previously reported (*13,15,18*), ^{201}Tl defects remaining irreversible after reinjection were divided on the basis of the severity of reduction in tracer activity into moderate (>50% of peak activity) or severe (≤50% of peak) defects. Previous studies demonstrated that irreversible defects after standard exercise-redistribution ^{201}Tl imaging that were reversible after reinjection, and those irreversible defects with a moderate reduction of tracer uptake represent severely hypoperfused but still viable myocardium (*10,12*). Therefore, for the purpose of this study, reversible and moderate irreversible defects after reinjection were combined. Finally, ROIs were placed over the myocardium and the left lung, and count densities were derived from the initial postexercise tomographic anterior images to calculate the lung/heart ratio.

Follow-up

Follow-up was obtained by phone contact with patients and by review of hospital or physician records. The mean follow-up period was 22 mo (range 4–40 mo). Death and nonfatal myocardial infarction, whichever occurred first, were considered hard events; if death occurred during hospitalization for myocardial infarction, death was considered as the event. Coronary artery bypass surgery

TABLE 1
Clinical, Exercise and Thallium Variables in Study Patients

Variable	No event (n = 58)	Soft events (n = 11)	Hard events (n = 13)	p value
Clinical				
Age (yr)	55 ± 10	59 ± 7	58 ± 11	ns
Male (%)	76	82	77	ns
Hypertension (%)	21	46	8	ns
Diabetes (%)	14	9	15	ns
Exercise				
Work load (W)	86 ± 22	79 ± 23	79 ± 17	ns
Heart rate at peak exercise (beats/min)	127 ± 22	126 ± 14	130 ± 16	ns
Systolic bp at peak exercise (mmHg)	169 ± 23	168 ± 28	174 ± 28	ns
Double product at peak exercise (heart rate × systolic bp/1000)	21.6 ± 5.4	21.2 ± 4.6	22.6 ± 4.0	ns
Abnormal systolic bp response (%)	12	18	15	ns
Patients with ischemic ST changes (%)	22*	45	54	<0.05
Patients with angina at exercise (%)	15	36	23	ns
Stress-redistribution imaging				
Reversible defects at stress-redistribution (n)	2.4 ± 1.2	3.2 ± 2.1	3.9 ± 2.2*	<0.05
Persistent defects after stress-redistribution (n)	5.6 ± 2.7	6.4 ± 3.2	8.5 ± 3.9*	<0.01
Lung/heart ratio	0.48 ± 0.10	0.50 ± 0.12	0.54 ± 0.13	ns
Reinjection imaging				
Sum of reversible and moderate irreversible defects after reinjection (n)	3.7 ± 2.2	4.1 ± 2.5	6.8 ± 3.1*	<0.001
Irreversible defects after reinjection (n)	1.9 ± 2.5	2.4 ± 2.7	1.8 ± 1.9	ns

*Difference when all three groups are compared.

or angioplasty occurring >3 mo after stress test were considered soft events.

Statistical Analysis

Univariate analysis of categorical data was performed using the chi-square test. Continuous data were expressed as mean ± s.d. and compared with one-way analysis of variance. Multiple comparisons were performed using Duncan's multiple range test. A p value <0.05 was considered significant. Survival curves were constructed using the Kaplan-Meier method and were compared with the log-rank test (*19*).

A multivariate analysis was performed using the Cox proportional-hazards model (*19,20*) to determine which of the clinical, exercise, ^{201}Tl stress-redistribution and ^{201}Tl reinjection variables could predict the occurrence of hard events. For this analysis, patients with soft events were considered censored at the time of the event. The stepwise selection of the variables 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. The additional value of each category of variables added sequentially was evaluated on the basis of the increases in the overall likelihood ratio statistic. The analysis was also performed considering together the occurrence of hard and soft events as endpoints.

The clinical variables considered were age, gender and histories of hypertension and diabetes mellitus. The exercise variables were exercise work load, peak exercise heart rate, peak systolic blood pressure, double product at peak exercise, abnormal blood pressure response, presence of ischemic ST segment changes and presence of angina during exercise. The ^{201}Tl stress-redistribution variables comprised the number of reversible defects at stress-redistribution, the number of persistent defects after stress-redistribution and the lung/heart ratio. The ^{201}Tl reinjection variables were the sum of defects, irreversible after redistribution, that were reversible or moderate irreversible after reinjection, and the number of severe irreversible (fixed) defects also after reinjection.

For the construction of the cumulative survival curves, and for possible clinical use, continuous variables that showed prognostic value at multivariate analysis were dichotomized seeking the point that maximized the hazard ratio from a Cox regression model for comparing patients at or below the cutpoint with those above it (*20*).

RESULTS

Of the 104 enrolled patients, 6 (5.8%) were lost at follow up. Of the 98 patients remaining, 16 underwent early revascularization procedures (9 bypass grafting and 7 percutaneous angioplasty) within 3 mo after exercise testing. These latter patients were not considered for the purpose of the study because the results of the test may have influenced the decision to perform coronary revascularization. Thus, the final study population consisted of 82 patients.

During the follow-up period there were 13 hard events (9 cardiac deaths and 4 nonfatal myocardial infarctions) and 11 coronary revascularization procedures >3 months after thallium imaging (9 bypass grafting and 2 percutaneous coronary angioplasty).

Univariate and Multivariate Analysis

The results of univariate analysis performed considering separately patients without events, patients with hard events and patients with soft events are reported in Table 1. Patients who did not experience any event during follow up had a lower incidence of ischemic ST segment changes at stress test, while patients with hard events showed a higher number of reversible and persistent defects at stress-redistribution than the other two groups. Moreover, the sum of defects, irreversible after stress-redistribution, that were reversible or moderate irreversible after reinjection was higher in patients with hard events.

Results of multivariate analysis are reported in Table 2. The significant predictors of hard events for each group of variables were: presence of ischemic ST changes, the number of reversible defects at stress-redistribution, the sum of reversible and moderate irreversible defects after reinjection. The same variables were significant predictors of prognosis when hard and soft events were combined.

The cutoff points that maximized the predictive power for the occurrence of hard events were four for the number of revers-

TABLE 2
Results of Cox Multivariate Analysis for Each Group of Variables

Variable	χ^2	p value
Hard events		
Clinical and exercise		
Presence of ischemic ST changes at exercise	3.9	<0.05
Stress-Redistribution		
Number of reversible defects at stress-redistribution	11.4	<0.001
Reinjection		
Sum of reversible and moderate irreversible defects after reinjection	16.7	<0.001
Hard and soft events		
Clinical and exercise		
Presence of ischemic ST changes at exercise	4.4	<0.05
Stress-Redistribution		
Number of reversible defects at stress-redistribution	8.1	<0.01
Reinjection		
Sum of reversible and moderate irreversible defects after reinjection	8.1	<0.01

ible defects at stress-redistribution imaging and five for the sum of abnormal segments reversible and moderate irreversible after reinjection. The Kaplan-Meier hard event-free survival curves for these two variables are showed in Figures 2 and 3.

Incremental Prognostic Value

Values for the chi-square statistic as an index of the predictive power of the clinical and electrocardiographic stress test data and thallium imaging are shown in Figure 4. In regard to hard events, stress-redistribution imaging provided significant additional information to clinical and ECG stress test data. Moreover, the inclusion of reinjection imaging data improved the prognostic value of the model. When hard and soft events were considered together, stress-redistribution imaging added to clinical and ECG stress test data, but the inclusion of reinjection data did not improve the prognostic value of the model.

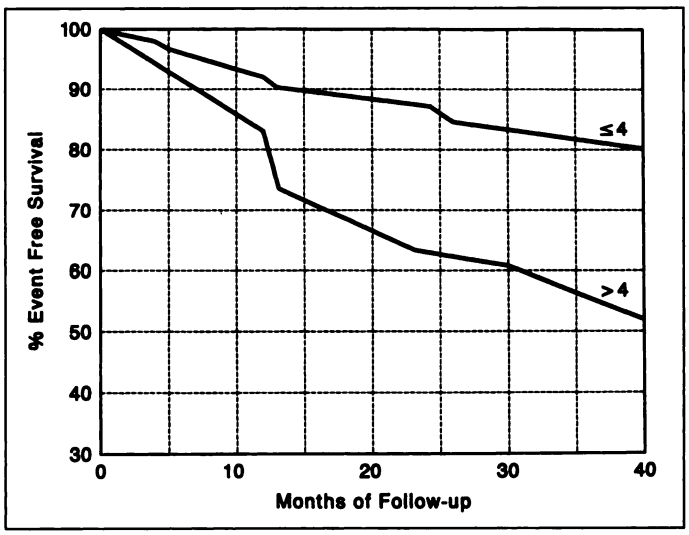

FIGURE 2. Hard event-free survival curves of patients in low and high categories for number of reversible defects at stress-redistribution (≤4 segments = low category; >4 segments = high category). At start of follow up, 64 patients were at or below cutoff point and 18 above it.

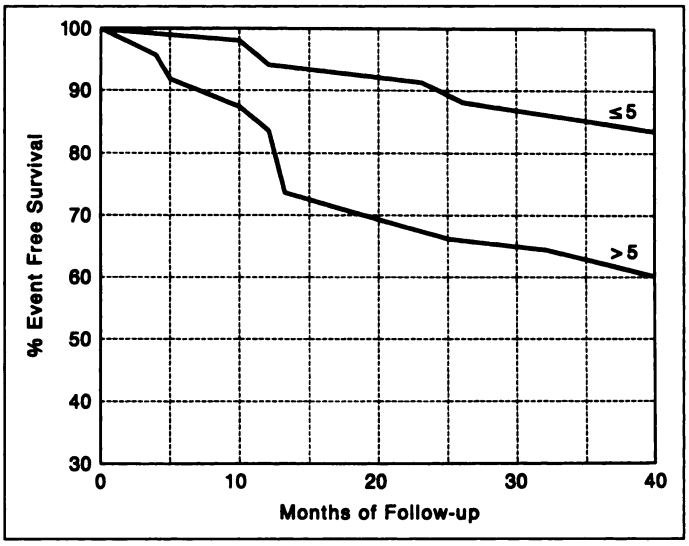

FIGURE 3. Hard event-free survival curves of patients in low and high categories for sum of defects reversible or moderate irreversible after reinjection (≤5 segments = low category; >5 segments = high category). At start of follow up, 58 patients were at or below cutoff point and 24 above it.

DISCUSSION

In several reports, the amount of myocardial hypoperfusion at exercise thallium scintigraphy was the best predictor of future cardiac events in patients with coronary artery disease (*3–5*). Our study confirms previous observations (*6–8*) that redistribution on delayed imaging give incremental prognostic information to clinical and exercise stress test data, and indicates that 4 (20% of the myocardium) is the dichotomizing cutoff point for the number of reversible defects at stress-redistribution that provides the greatest difference in hard event rates (Fig. 2).

Incremental Prognostic Value of Reinjection Imaging

Thallium-201 reinjection imaging improves the detection of viable myocardium (*12,18*). This finding is clinically relevant. In fact, it has been demonstrated that patients with impaired left ventricular function and evidence of viable myocardium appear to benefit most from revascularization procedures (*21–23*).

The prognostic contribution of thallium reinjection in addition to stress-redistribution imaging in medically treated patients has not been clearly defined. To our knowledge, only two preliminary studies have addressed this issue, and they gave conflicting results. Zafrir et al. (*24*) reported that thallium reinjection does not contribute to the prediction of cardiac events over stress-redistribution. On the other hand, Pieri et al. (*25*) found that the strongest predictor of hard events was the number of fixed defects that remained fixed after reinjection, while the presence of defects that became reversible after reinjection did not identify patients at higher risk. However, it must be considered that Zafrir et al. (*24*) included in their study consecutive patients with coronary artery disease and not only patients with previous myocardial infarction and left ventricular dysfunction. In Pieri's study (*25*) of the 10 hard events that occurred during follow up, six were myocardial infarctions, so that it is difficult to explain the mechanism by which the number of irreversible thallium defects, usually considered nonviable myocardium, could predict the occurrence of subsequent infarctions. In our study, thallium reinjection imaging gave incremental prognostic information to clinical, exercise and thallium stress-redistribution data (Fig. 4), and the sum of abnormal segments that were reversible and moderate irreversible after reinjection was strongly predictive of hard events at follow up. Piérard et al. (*26*) demonstrated that, in patients after

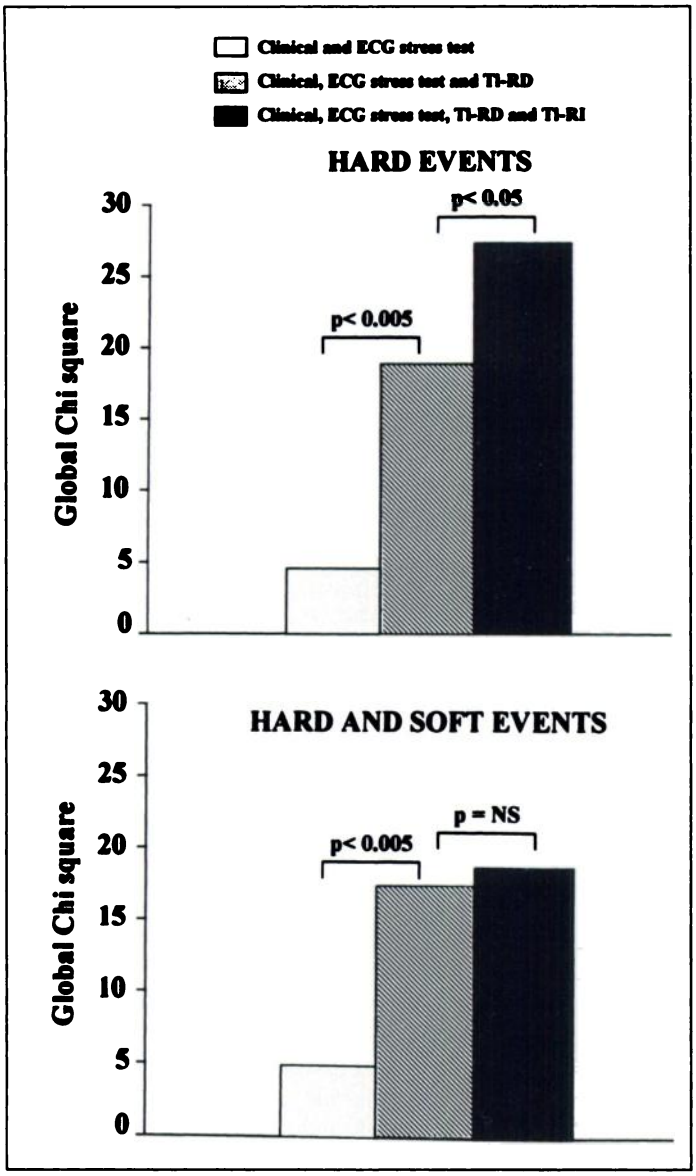

FIGURE 4. Incremental prognostic value (global chi-square values on y-axis) of clinical and ECG stress test data, thallium stress-redistribution (Tl-RD) and thallium reinjection (Tl-RI) imaging for hard events (top) and for hard and soft events combined (bottom).

acute myocardial infarction, the presence of hypoperfused but still viable myocardium may be followed by necrosis. It is also conceivable that chronically hypoperfused myocardium may become necrotic. Moreover, episodes of further ischemia in chronically hypoperfused but viable regions may trigger fatal arrhythmias and may explain the higher event rates observed.

The Kaplan-Meier survival curves for the sum of defects, irreversible after redistribution, that were reversible or moderate irreversible after reinjection, demonstrate that five segments (25% of the myocardium) better separate patients into high- and low-risk categories (Fig. 3). These findings suggest that not only the presence but also the amount of viable myocardium seem critical in affecting prognosis. Interestingly, the difference in survival curves is evident for the first 15 mo of follow up, while thereafter the two curves do not separate further. Thus, the prognostic power of reinjection seems particularly good for up to 15 mo.

When soft events were included as endpoints, thallium reinjection was unable to provide incremental prognostic information. A possible explanation is that stress-redistribution thallium imaging (*1*) and exercise-induced ST segment depression (*27*) are useful in predicting revascularization procedures after myocardial infarction.

Rest-Redistribution Imaging

Many laboratories have recently switched to rest-redistribution thallium imaging to identify dysfunctional hypoperfused but viable myocardium (*28–30*). This technique may be suggested as a practical approach when the clinical issue to be addressed is whether systolic dysfunction may improve after coronary revascularization (*31*). However, with this technique the prognostic information contained in exercise ECG and stress-redistribution imaging is not available.

Lung/Heart Ratio

In our study the lung/heart ratio was unable to predict subsequent events. Our data are in agreement with those of Iskandrian et al. (*33*) who failed to demonstrate an independent and incremental prognostic value for quantitatively assessed lung thallium uptake. Differently, Kaul et al. (*32*) found that the lung/heart ratio was the most important predictor of future cardiac events in patients with chest pain. In our study, the selection of patients with reduced ejection fraction could have lessened the predictive power of an index, the lung/heart ratio, which is an indirect measure of left ventricular function.

CONCLUSION

This study demonstrates that in patients with previous myocardial infarction and left ventricular dysfunction, ^{201}Tl reinjection imaging provides incremental prognostic information over those obtained from clinical, ECG exercise and conventional stress-redistribution thallium data. The extent of viable regions at thallium reinjection is an important prognostic predictor of subsequent hard events.

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Exercise-Rest Same-Day SPECT Sestamibi Imaging to Detect Coronary Artery Disease

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This study examined the results of exercise-rest same-day SPECT protocol in 193 patients, of whom 132 had coronary artery disease (CAD) by angiography (≥50% diameter stenosis), and 61 had a low pretest probability of CAD. **Methods:** The rest study was combined with first-pass radionuclide angiography using the multicrystal gamma camera in 72 patients. **Results:** The sensitivity of SPECT was 76% (25/33 patients) in patients with one-vessel, 84% in patients with two-vessel (38/45) and 98% in patients with three-vessel CAD (53/54) (P = 0.01 versus one- or two-vessel CAD). The sensitivity of SPECT in patients with CAD was higher than ST depression (88% versus 28%, P = 0.001). The exercise was submaximal in 53 patients (40%). The perfusion defects were reversible (complete or partial) in 80 patients and fixed in 36 patients. The left ventricular ejection fraction was 50 ± 12% in patients with reversible defects (n = 44) and 39 ± 9% in patients with fixed defects (n:19) (P = 0.0004). The normalcy rate in subjects with a low pretest probability of CAD was 95% (53 of 61 subjects). **Conclusion:** The exercise-rest same-day sestamibi protocol provides high diagnostic accuracy for CAD detection. The protocol may eliminate the need for rest studies in patients with normal exercise images, help improve laboratory throughput and lower costs.

Key Words: coronary artery disease; sestamibi; single-photon emission computed tomography

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Currently in the U.S. approximately 30%-40% of perfusion studies are performed with ^{99m}Tc-sestamibi using one of several protocols: two-day protocol, same-day stress-rest and same-day rest-stress protocol (*1–7*). Each of these protocols has advantages and limitations. The two-day or, more precisely, separate-day protocol is used primarily in overweight patients because of the need for higher doses of sestamibi (20–30 mCi or 740-1110 MBq) for each of the stress and rest studies. For the same-day protocol the rest-stress sequence is more commonly used than stress-rest. One advantage of rest-stress is that the higher dose (30 mCi) is used with the stress study. A high dose is necessary to obtain high-quality images and gating. It also has been suggested, based on limited experience, that the rest-stress protocol is better than the stress-rest protocol for detecting reversible defects (*2,3*). The main disadvantage of the rest-stress protocol is the requirement to perform the rest study on every patient, the need to perform the stress studies later in the day and the contamination of the stress images by the tracer activity from the rest study. This study describes our experience with the same-day exercise-rest protocol in detecting CAD.

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MATERIALS AND METHODS

Patients

We studied 670 patients in our laboratory between July 1993 and August 1994. Of those, 132 patients had CAD by coronary angiography within 3 mo of the exercise study and 61 patients had low pretest probability of CAD on the basis of clinical presentations and coronary risk factors (*8*). The demographics of patients with and without CAD are listed in Table 1. Coronary angiography was performed in multiple projections using standard techniques. Significant CAD was defined as ≥50% diameter stenosis in any one of the major coronary arteries or their branches. The degree of stenosis was assessed by two angiographers unaware of the scintigraphic findings.

Exercise Testing

All patients underwent symptom-limited exercise testing using the Bruce protocol. The endpoints of exercise were: angina of at least moderate severity, excessive fatigue, weakness, shortness of