Incremental Prognostic Value of Rest-Redistribution $^{201}$Tl Single-Photon Emission Computed Tomography

Tali Sharir, MD; Daniel S. Berman, MD; Howard C. Lewin, MD; John D. Friedman, MD; Ishac Cohen, PhD; Romalisa Miranda, BS; Raluca D. Agafitei, MD; Guido Germano, PhD

Background—The incremental prognostic value of rest-redistribution $^{201}$Tl compared with stress and rest perfusion abnormalities has not been defined.

Methods and Results—We identified 458 patients who underwent rest $^{201}$Tl/stress (exercise or adenosine) $^{99m}$Tc sestamibi single-photon emission computed tomography (SPECT) and had late (18 to 24 hours) $^{201}$Tl imaging, were not revascularized within 60 days of SPECT, and were followed up at >1 year. SPECT images were visually analyzed with the use of a 20-segment model on a scale of 0 to 4. Thirty-seven cardiac deaths (CDs) and 17 nonfatal myocardial infarctions occurred. Univariate Cox proportional hazards analysis showed that the presence of a large amount of rest $^{201}$Tl reversibility (rest-late summed difference score [SDS] of >8) was a significant predictor of CD ($\chi^2=5.77, P=0.02$) and CD or myocardial infarction ($\chi^2=5.3, P=0.02$). The CD rate was 9.3% y$^{-1}$ in patients with rest-late SDS of >8 compared with 3.6% y$^{-1}$ in patients with a mild/moderate amount of rest reversibility (rest-late SDS 3 to 8) and 3.4% y$^{-1}$ in patients with no rest reversibility (rest-late SDS <3) ($P=0.029$). Kaplan-Meier survival analysis demonstrated significantly lower cumulative survival rates in patients with rest-late SDS of >8 ($P=0.01$). Multivariate Cox proportional hazards analysis demonstrated that the presence of a large amount of resting reversibility was an independent and incremental predictor of CD after adjustment for stress and rest perfusion information. Multivariate logistic regression analysis demonstrated that resting reversibility was not an independent predictor of referral to coronary angiography and revascularization.

Conclusions—The identification of a large amount of resting $^{201}$Tl reversibility is an independent predictor of CD over stress and rest perfusion abnormalities. (Circulation. 1999;100:1964-1970.)

Key Words: myocardial perfusion imaging $^{201}$Tl-201 rest redistribution prognosis

Rest-redistribution $^{201}$Tl scintigraphy is widely considered the single-photon nuclear technique of choice for the identification of viable myocardium. This technique has been shown to be highly sensitive but to have low specificity for the prediction of contractile improvement after revascularization$^{1-5}$; however, its prognostic value has not been fully investigated. Although the presence of redistribution on rest $^{201}$Tl single-photon emission computed tomography (SPECT) has been demonstrated to be an independent predictor of cardiac death in patients with left ventricular dysfunction,$^6$ the incremental prognostic value over stress/rest perfusion scintigraphy has not been assessed.

The aim of this study was to determine whether additional, delayed (18 to 24 hours after injection) $^{201}$Tl SPECT adds an incremental prognostic value to rest $^{201}$Tl/stress $^{99m}$Tc sestamibi SPECT and to determine the prognostic value of the amount of resting $^{201}$Tl reversibility for the prediction of coronary events. We also examined the impact of resting $^{201}$Tl reversibility on referral of patients to coronary angiography and revascularization.

Methods

Study Population

We identified 736 patients who underwent dual-isotope rest $^{201}$Tl/stress $^{99m}$Tc sestamibi myocardial perfusion SPECT and had late (18 to 24 hours after injection) $^{201}$Tl imaging between January 1991 and December 1996 at Cedars-Sinai Medical Center. Of these patients, 709 (96.3%) were followed >1 year for cardiac events. Of these 709 patients, 564 who had ≥2 myocardial segments with a moderate perfusion defect (see visual interpretation below) on their initial resting $^{201}$Tl images were included in the study. The 106 patients who underwent coronary revascularization within 60 days of the nuclear testing were excluded from the analysis.$^7$ Thus, the prognostic data are based on 458 patients, of whom 254 underwent exercise stress testing and 204 underwent adenosine stress testing.

Acquisition Protocol

All patients underwent separate acquisition, dual-isotope myocardial perfusion SPECT.$^8$ Initially, $^{201}$Tl (3 to 4.5 mCi) was injected...
intravenously at rest, and SPECT imaging was initiated 10 minutes later, with 2 energy windows: 30% centered over the 68- to 80-keV energy peak and 20% centered over the 167-keV energy peak. 99mTc sestamibi (25 to 40 mCi) was then injected at peak stress, and SPECT imaging was initiated 15 to 30 minutes after exercise or 30 to 60 minutes after adenosine stress. Additional SPECT 201TI images were obtained 18 to 24 hours after injection. Acquisitions were performed with a 2-detector (Vertex; ADAC), 3-detector (Prism, Picker, or Multi-SPECT 3; Siemens), or 1-detector (Orbiter, Siemens) camera, with 60 to 64 projections acquired over 180 degrees. Acquisitions times of early and late 201TI were 20 to 35 and 30 to 50 s/projection, respectively, and that of 99mTc sestamibi was 15 to 25 s/projection.

Exercise Protocol
A symptom-limited treadmill exercise test was performed according to standard protocols. Patients received an injection of 99mTc sestamibi at peak exercise and exercised at the same level for an additional 60 seconds and at 1 level lower for 2 additional minutes. ECG response was considered positive when horizontal or downsloping ST-segment depression was ≥1 mm or the upsloping ST-segment depression was ≥1.5 mm at 80 ms after the J point was observed or nondiagnostic when ST/T abnormalities were present at baseline ECG. Failure to achieve 85% of maximal predicted heart rate or ischemic ECG response was followed by conversion to adenosine stress.

Adenosine Protocol
Caffeine-containing products were discontinued 24 hours before the test. Adenosine (140 μg · kg⁻¹ · min⁻¹) was infused over 6 minutes, and 99mTc sestamibi was injected at the end of the 3rd minute. Whenever possible, patients performed low-level treadmill exercise during adenosine infusion.

Image Analysis
Perfusion SPECT images were scored semiquantitatively based on a 20-segment model of the left ventricle⁹ with the use of a 5-point scale in which 0 indicates normal; 1, mildly abnormal; 2, moderately abnormal; 3, severely abnormal; and 4, no uptake. The summed stress score (SSS), summed rest score (SRS), and summed late score (SLS) were calculated by adding the 20 segment scores in the stress, initial resting, and late resting images, respectively. We also calculated the stress-rest summed difference score (SDS), which represents the amount of stress-induced ischemia; rest-late SDS, which represents resting reversibility; and stress-late SDS, which represents the total (stress plus rest) amount of ischemia. Negative segmental score differences (rest score higher than stress score and late score higher than rest score) were set at 0.

Patient Follow-Up
Patient follow-up consisted of scripted and blinded telephone interviews corroborated through the use of objective methods.² The mean follow-up interval was 726±242 days (range 365 to 2141 days).

Prescan Likelihood of Coronary Artery Disease
Prescan likelihood of coronary artery disease (CAD) was calculated with the use of CADENZA,¹⁰ which is based on bayesian analysis of patient data. For patients undergoing exercise stress, the prescan likelihood of CAD included historical and exercise information, whereas for patients undergoing adenosine stress, prescan likelihood was based on historical data only.

Statistical Analysis
Comparisons between patient groups were performed with 1-way ANOVA for continuous variables and a χ² test for categorical variables. Continuous variables were described as mean±SD values. P<0.05 was considered statistically significant.

Univariate Cox proportional hazards regression analysis was applied to determine significant predictors of cardiac death and of cardiac death or nonfatal myocardial infarction (MI). The variables tested were prescan likelihood of CAD, history of MI, history of coronary revascularization, type of stress (exercise or adenosine), and perfusion variables: SSS, SRS, SLS, stress-rest SDS, rest-late SDS, and stress-late SDS. The rest-late SDS was converted into a binary variable, which tested multiple thresholds. The value yielding the highest global χ² for the prediction of cardiac death was defined as the best threshold and was selected for further analysis. Stepwise multivariate Cox proportional hazards regression was applied to identify independent variables in the prediction of cardiac death and to assess the incremental value of rest redistribution. A value of P<0.05 was required for entry into multivariate analysis. Variables were removed from the model until all the remaining variables were significant (P<0.05). Kaplan-Meier cumulative survival analysis with stratification by the rest-late SDS was performed. Survival curves were compared with the use of the Wilcoxon test. Determinants of referral of patients to coronary angiography were evaluated through the use of stepwise logistic regression analysis.

Results

Coronary Events
During the follow-up period, 37 cardiac deaths (8.1%) and 17 nonfatal MIs (3.7%) occurred. Forty-one patients (9.0%) underwent late coronary revascularization (>60 days): CABG (n=25, 5.5%) and PTCA (n=16, 3.5%).

Patient Characteristics
Of the 458 patients included in the prognostic analysis, 288 (62.9%) had a history of MI, 119 (26%) had prior coronary angioplasty, and 86 (18.8%) had CABG. Pathological Q waves on baseline ECG were present in 229 patients (50%). Compared with patients with no event, patients who had cardiac death were older, had a higher prescan likelihood of CAD, and underwent exercise test less frequently (Table 1). Patients who had MI had a higher rate of diabetes mellitus than did patients with no event.

Of the 9160 myocardial segments in 458 patients, 1858 demonstrated mild/moderate initial resting perfusion defect (score 1 or 2). Of these segments, 676 (37%) showed redistribution (score difference ≥1) on 18- to 24-hour images. Severe initial resting perfusion defect (score 3) was detected in 1015 segments, of which 226 (22%) demonstrated reversibility. A complete absence of initial resting 201TI uptake (score 4) was observed in 432 segments, of which 105 (24%) were reversible on delayed 201TI images. Although

### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Death (n=37)</th>
<th>MI (n=17)</th>
<th>No Event (n=363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74±10*</td>
<td>70±12</td>
<td>69±11</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>31 (84)</td>
<td>12 (71)</td>
<td>287 (79)</td>
</tr>
<tr>
<td>History of MI, n (%)</td>
<td>28 (77)</td>
<td>10 (59)</td>
<td>225 (62)</td>
</tr>
<tr>
<td>Q wave on ECG, n (%)</td>
<td>18 (49)</td>
<td>10 (59)</td>
<td>188 (52)</td>
</tr>
<tr>
<td>History of angioplasty, n (%)</td>
<td>7 (19)</td>
<td>3 (18)</td>
<td>98 (27)</td>
</tr>
<tr>
<td>History of bypass surgery, n (%)</td>
<td>11 (30)</td>
<td>5 (29)</td>
<td>132 (36)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>22 (59)</td>
<td>11 (65)</td>
<td>173 (48)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (19)</td>
<td>8 (47)*</td>
<td>65 (18)</td>
</tr>
<tr>
<td>Prescan likelihood of CAD</td>
<td>0.49±0.21*</td>
<td>0.53±0.30</td>
<td>0.41±0.28</td>
</tr>
<tr>
<td>Exercise, n (%)</td>
<td>15 (41)*</td>
<td>8 (47)</td>
<td>213 (64)</td>
</tr>
</tbody>
</table>

*P<0.05 vs no event.
Threshold values of >8 yielded less efficient risk stratification (significantly lower global χ²), because patients with a considerable amount of resting reversibility who had cardiac death were classified as having nonsignificant reversibility (below the threshold), reducing the prognostic power of the model.

### Incremental Value of Rest-Redistribution ²⁰¹TI

The addition of the rest-late SDS as a binary variable (threshold for presence of significant rest redistribution of >8) to either the SRS or the SSS resulted in a significant improvement in the prognostic power of the model in the prediction of cardiac death (Figure 2). The best prediction of cardiac death was provided by either of the 2 models: (1) SSS plus rest-late SDS and (2) SRS plus rest-late SDS. These 2 models contained comparable prognostic information (χ²=15.53 and 16.37, respectively; P=NS). Table 3 summarizes the statistical results for these models. The rest-late SDS was an independent predictor of cardiac death after adjustment for rest (SRS) or stress (SSS) perfusion abnormalities. Figure 3 demonstrates the exponential increase in relative risk of cardiac death as a function of the SRS (Figure 3A) and the SSS (Figure 3B) and the increased risk associated with the presence of a large amount of rest reversibility (rest-late SDS >8).

### Kaplan-Meier Survival Analysis: Stratification by Amount of Rest-Redistribution ²⁰¹TI

Figure 4 shows cumulative survival rates with stratification by the amount of rest redistribution of ²⁰¹TI. Patients with a mild/moderate amount of resting reversibility (rest-late SDS of 3 to 8) had a survival function similar to that of patients with no rest reversibility (rest-late SDS of <3). However, patients with a large amount of rest redistribution (rest-late SDS of >8) had significantly lower cumulative survival rates (P=0.01) compared with the other 2 groups. Mean cardiac death rate was significantly higher in patients with a large amount of rest-redistribution (9.3% y⁻¹) compared with patients without (3.6% y⁻¹) or with a small/moderate amount (3.4% y⁻¹; P=0.029) (Figure 5).

### Effect on Referral to Coronary Angiography

One hundred thirty-seven patients were referred to coronary angiography within 60 days of the nuclear test. Univariate logistic regression analysis for the identification of significant predictors for referral to coronary angiography (Table 4) revealed that the stress-rest and stress-late SDSs were the most powerful. The rest-late SDS was also a significant but less powerful predictor. Multivariate analysis demonstrated that the most powerful independent predictor was the stress-late SDS (Wald χ²=19.43, P=0.00001) (Table 5). The amount of resting reversibility (rest-late SDS) was not an independent predictor of referral to coronary angiography as a continuous or binary variable.

### Discussion

In the present study, we assessed the incremental prognostic information gained from additional, delayed ²⁰¹TI imaging compared with conventional rest ²⁰¹TI/stress ⁹⁹mTc sestamibi SPECT. We further defined the relation between the amount...
of rest 201 Tl reversibility and the risk of cardiac events, and we assessed the impact of resting reversibility on referral of patients to coronary angiography.

Mechanism of 201 Tl Rest Redistribution
The initial myocardial uptake of 201 Tl is proportional to the coronary blood flow and depends on intact cell membrane function for active transport against an electrochemical gradient. After the injection of 201 Tl at rest, initial perfusion defects may disappear over time through the process of redistribution. These reversible resting perfusion abnormalities are related to chronic hypoperfusion, in conjunction with preserved cell membrane function. A slower intrinsic clearance rate of 201 Tl from chronically underperfused compared with normally perfused regions appears to result in equalization of 201 Tl concentration in these regions and resolution of perfusion defects. Previous studies have demonstrated that the presence of resting 201 Tl reversibility was related to severe coronary stenosis, which produced chronic hypoperfusion and persistent systolic dysfunction (myocardial hibernation).

Prediction of Recovery of Myocardial Dysfunction
Several studies have shown that rest redistribution 201 Tl imaging has high negative predictive value but low positive predictive value for the prediction of recovery of regional myocardial dysfunction after revascularization. Combined analysis of these studies yielded negative and positive predictive values of 92% and 69%, respectively. Thus, a substantial number of patients with rest 201 Tl reversibility do not demonstrate improvement in function after revascularization. However, rest redistribution 201 Tl imaging should not be assessed only as a tool for prediction of short-term improvement in regional wall motion but also, more importantly, for the identification of patients at an increased risk of cardiac death, who might benefit more than others from revascularization.

Rest-Redistribution 201 Tl and Cardiac Death
The prognostic value of rest-redistribution 201 Tl imaging has been previously demonstrated in relatively small patient groups. Gioia et al showed in a group of 80 patients with left ventricular dysfunction that patients who demonstrate redistribution on rest 201 Tl imaging had a higher cardiac death rate than did patients with a similar degree of left ventricular dysfunction but no rest redistribution. Recently, Petretta et al showed in 82 patients with previous MI and left ventricular dysfunction that the combination of rest redistribution 201 Tl and echocardiographic data added incremental prognos-
tic value over clinical data and compared with each technique alone in the prediction of cardiac events.

In the present study, we evaluated the prognostic power of the rest-late SDS, which represents the total amount of complete and partial reversibility of resting perfusion defects over time. We found that this reversibility score was not a predictor of cardiac events when evaluated as a continuous variable; however, when converted into a binary variable, a threshold effect was identified: the presence of rest-late SDS of ≥8 as a significant predictor of cardiac death. This amount of redistribution is substantially large, because translation to number of reversible segments yields mild reversibility (a score difference of 1) in >8 segments or moderate reversibility (a score difference of 2) in >4 segments. Patients who demonstrated a large amount of rest reversibility (>8) were at a higher risk of cardiac death (9.3% ± 2.1%) than were patients with a smaller amount (3.4% ± 1.2%) or with no rest redistribution (3.6% ± 0.8%). Multivariate stepwise analysis demonstrated that the presence of a large amount of rest redistribution was an independent and incremental predictor of cardiac death after the consideration of perfusion data derived from stress and rest images. The increased risk of cardiac death in patients with chronically hypoperfused but viable myocardium might be related to a high rate of fatal ischemic events, malignant arrhythmias, or progressive ventricular dilation and remodeling, leading to heart failure and death. Chen et al.19 demonstrated in an animal study that severe left anterior descending coronary artery stenosis with chronic reduction of ≥40% in resting blood flow induced progressive left ventricular dilation and remodeling in the absence of infarction.

Comparison With Other Techniques

Studies with positron emission tomography have shown that the presence of flow-metabolism mismatch in patients with impaired left ventricular function identified patients at a higher risk of adverse outcome compared with patients with the same degree of ventricular dysfunction but without evidence of myocardial viability.20,21 Di Carli et al.21 found that the extent of mismatch had a negative effect on survival rates. Viable myocardium identified through the use of dobutamine echocardiography has also been demonstrated to be a predictor of cardiac events in patients with left ventricular dysfunction.22 Thus, there is a consensus across various techniques that the presence of viability is a predictor of an adverse outcome in patients with chronic CAD and left ventricular dysfunction.6,18,20–22

Ventricular function was not assessed in the present study, because most of the SPECT acquisitions were not gated. We recently showed that the poststress ejection fraction and the end-systolic volume have incremental prognostic value compared with perfusion in the prediction of cardiac death.23 Future studies will determine whether resting 201 Tl reversibility adds prognostic information to the poststress ejection fraction and the end-systolic volume. Based on previous studies, which demonstrated that patients with left ventricular dysfunction and viability had a higher coronary event rate than did patients with the same degree of dysfunction but without evidence of viability,6,18,20–22 we believe that the presence of a large amount of resting 201 Tl reversibility will demonstrate incremental value over the poststress ejection fraction and will improve risk stratification of patients with ventricular dysfunction. An alternative to rest/24-hour 201 Tl redistribution discussed in the present study might be rest/4-

| Table 4. Univariate Logistic Regression Analysis for Prediction of Referral to Coronary Angiography |
|-----------------------------------------------|-----------------|-----------------|
| Likelihood of CAD                             | 9.64            | 0.002           |
| History of myocardial infarction              | 4.22            | 0.04            |
| History of coronary angioplasty               | 0.001           | 0.97            |
| History of bypass surgery                     | 1.09            | 0.3             |
| Type of stress                                | 0.41            | 0.52            |
| SSS                                           | 2.18            | 0.14            |
| SRS                                           | 4.18            | 0.04            |
| SLS                                           | 0.04            | 0.003           |
| Stress-rest SDS                               | 26.94           | <0.000001       |
| Stress-late SDS                               | 37.34           | 0.238           |
| Rest-late SDS                                 | 4.87            | 0.027           |
| Rest-late SDS >8                              | 2.94            | 0.09            |

| Table 5. Best Model by Multivariate Logistic Regression for Prediction of Referral to Coronary Angiography |
|---------------------------------------------------------------|-----------------|-----------------|
| Stress-late SDS                                               | 19.43           | 0.00001         |
| SLS                                                           | 5.52            | 0.019           |
| Stress-rest SDS                                               | 4.61            | 0.032           |
hour $^{201}$TI redistribution imaging before stress $^{99m}$Tc sestamibi injection or nitroglycerin-augmented rest $^{99m}$Tc sestamibi SPECT.24

Referral to Coronary Angiography and Revascularization

Previous studies have demonstrated the positive correlation between the extent of myocardial viability and postrevascularization improvement in global ventricular function.2,25 Others have shown that patients with left ventricular dysfunction and viability have better survival rates when revascularized compared with patients without viability.20,26,27 The presence of a large amount of dysfunctional but viable myocardium on dobutamine echocardiography identifies patients with dysfunctional myocardium who have the best prognosis after revascularization compared with patients with a small amount or no viability.27 In the present study, we evaluated the impact of the identification of chronically underperfused but viable myocardium on the referral of patients to coronary angiography. We found that stress-induced ischemia and “total” ischemia (stress plus rest) were independent predictors of referral to coronary angiography, resting reversibility was not an independent predictor. Thus, patients with predominantly stress-induced ischemia or combined stress and “resting” ischemia were referred for invasive strategy, whereas patients with predominantly resting reversibility were treated medically. Because the presence of a large amount of resting reversibility is an independent predictor of cardiac death, it appears that this parameter should be incorporated in the decision-making process and favors the referral of patients to invasive procedures, even when the amount of stress-induced ischemia is relatively small.

Study Limitations

In the present study, we did not use a quantitative analysis of myocardial $^{201}$TI uptake. We have previously shown that semiquantitative visual analysis of stress and rest perfusion images provides powerful prognostic information.9 Because our purpose was to examine the incremental prognostic value of delayed $^{201}$TI imaging over rest $^{201}$TI/stress $^{99m}$Tc sestamibi, we used the same method of visual analysis in this study. Quantification of relative rest-redistribution $^{201}$TI uptake has been shown to provide accurate information for the prediction of postrevascularization improvement in systolic function3; however, the importance of quantitative $^{201}$TI uptake in the assessment of prognosis has yet to be defined.

In this study, we assessed only the importance of late redistribution $^{201}$TI.28,29 Whether the same added value of redistribution imaging could be derived from rest and 4-hour redistribution imaging performed before stress testing using a potential practical protocol is a question that was not addressed here.

Conclusions

The presence of a large amount of rest $^{201}$TI reversibility is associated with a high risk of cardiac death and has an incremental and independent prognostic value over conventional rest $^{201}$TI/stress $^{99m}$Tc sestamibi in the prediction of cardiac death. The identification of a large amount of reversibility at delayed $^{201}$TI images ought to influence the decision regarding the referral of patients for invasive treatment strategy.

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