Concordance and Discordance Between Stress-Redistribution-Reinjection and Rest-Redistribution Thallium Imaging for Assessing Viable Myocardium

Comparison With Metabolic Activity by Positron Emission Tomography

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Background. Stress thallium scintigraphy provides important diagnostic and prognostic information in patients with coronary artery disease by demonstrating regional myocardial ischemia. However, if the clinical question being addressed is whether a region is viable and not whether there is inducible ischemia, then it may be more reasonable to perform rest-redistribution imaging rather than stress-redistribution imaging followed by either reinjection or late redistribution. Therefore, we determined whether stress-redistribution-reinjection and rest-redistribution imaging provide the same information regarding myocardial viability.

Methods and Results. Both stress-redistribution-reinjection and rest-redistribution thallium single photon emission computed tomographic imaging was performed in 41 patients with chronic stable coronary artery disease, with quantitative analysis of regional thallium activity. Thallium reinjection was performed immediately after the 3- to 4-hour redistribution images were completed. Of the 155 myocardial regions with perfusion defects on the stress images, 91 (59%) were irreversible on conventional 3- to 4-hour redistribution images. When the outcomes of these irreversible regions were assessed after reinjection and compared with rest redistribution images, there was concordance of data regarding myocardial viability (normal/reversible or irreversible) in 72 of the 91 (79%) irreversible defects. Twenty of the 41 patients also underwent positron emission tomography at rest with $^{18}$F-fluorodeoxyglucose and $^{18}$O-water. In these patients, stress-redistribution-reinjection and rest-redistribution imaging provided concordant information regarding myocardial viability in 427 (72%) of 594 myocardial regions and discordance in 167 regions. However, when irreversible thallium defects were further analyzed according to the severity of the thallium defect in these discordant regions, 149 of 167 (89%) demonstrated only mild-to-moderate reduction in thallium activity (51% to 85% of normal activity), and positron emission tomography verified 98% of these regions to be metabolically active and viable. Thus, when the severity of thallium activity was considered within irreversible thallium defects, the concordance between stress-redistribution-reinjection and rest-redistribution imaging regarding myocardial viability increased to 94%.

Conclusions. These data indicate that one of two imaging modalities, either stress-redistribution-reinjection or rest-redistribution imaging, may be used for identifying viable myocardium. However, if there are no contraindications to stress testing, stress-redistribution-reinjection imaging provides a more comprehensive assessment of the extent and severity of coronary artery disease by demonstrating regional myocardial ischemia without jeopardizing information on myocardial viability. (Circulation. 1993;88:941-952.)

Key Words • coronary artery disease • myocardium • ischemia • scintigraphy • tomography

In many patients with chronic coronary artery disease, impaired left ventricular function at rest is a potentially reversible process that may improve or normalize after myocardial revascularization.1–4 Recovery of regional or global left ventricular function at rest after revascularization suggests that many asynergic myocardial regions represent hibernating myocardium secondary to chronic hypoperfusion.5,6 However, identification of patients with such potentially reversible left ventricular dysfunction has been problematic, since regional dysfunction arising from ischemic myocardium may be clinically indistinguishable from that arising from infarcted myocardium.

Exercise thallium scintigraphy has been used frequently for the assessment of myocardial viability by a number of methods, including early (3–4 hours) or late (24 hours) redistribution imaging.7 Recently, thallium
reinjection after a 3- to 4-hour redistribution or after late redistribution has improved the accuracy in identifying viable myocardium over that achieved by redistribution imaging alone. Rest-redistribution thallium imaging has also been used successfully in the past to distinguish viable from nonviable myocardium. If the clinical question being addressed is whether a region is viable and not whether there is inducible ischemia, then it may be more reasonable to perform thallium scintigraphy at rest rather than during stress. Such an approach, however, will not provide the additional diagnostic and prognostic information gained by evidence of exercise-induced ischemia. Therefore, the aim of this study was to determine whether stress-redistribution-reinjection imaging provides the same information as rest-redistribution imaging for identifying viable myocardium.

Methods

Patient Selection

We studied 41 patients with chronic stable coronary artery disease. The patients ranged in age from 38 to 76 years (mean, 59 years); there were 38 men and 3 women. All patients underwent a history and physical examination, chest x-ray, ECG, thallium single photon emission computed tomography (SPECT), and coronary arteriography. Coronary artery disease was defined as a 50% reduction in luminal diameter of at least one major epicardial coronary artery as determined by coronary angiography. All cardiac medications were withdrawn before exercise studies in 76% of patients. In the remaining 24% of patients, cardiac medications included either one or a combination of nitrates, calcium channel blockers, and β-blockers; one patient was on digoxin and another on amiodarone. We studied only patients with chronic stable coronary artery disease; no patient with recent acute myocardial infarction or unstable angina was included in the study. Thirty-two patients had either a clinical history of prior myocardial infarction or Q waves on the ECG. Fifteen patients had undergone previous coronary artery bypass surgery. Patients were included in the study only if they demonstrated an irreversible thallium defect on postexercise 3- to 4-hour redistribution images. Patients demonstrating “fixed” thallium defects after conventional redistribution images who were eligible for this study then gave informed consent for a second thallium study performed at rest.

Thallium SPECT Imaging

All patients underwent exercise thallium SPECT as previously described. After an overnight fast, patients exercised on a treadmill, and 2 mCi of thallium was injected at peak exercise. SPECT thallium images were obtained with a wide-field-of-view rotating gamma camera equipped with a low-energy, medium-resolution, high-sensitivity, parallel-hole collimator (Apex 415, APC-3, Elscint Co, Boston, Mass) centered on the 68-keV photo peak with a 20% window. The camera was rotated over a 180° arc in an elliptical orbit about the patient’s thorax at 6° increments for 30 seconds each. Redistribution images were acquired 3 to 4 hours after exercise. Immediately after redistribution, a 1-mCi additional thallium dose was administered at rest, and reinjection images were acquired 10 to 15 minutes thereafter.

The rest-redistribution study involved 2 mCi of 201TI administered at rest and was performed 1 to 2 weeks after the stress-redistribution-reinjection thallium study. SPECT thallium data were acquired 10 to 20 minutes after the rest-administered dose and 3 to 4 hours later. The reconstructed images of both stress-redistribution-reinjection and rest-redistribution images were read blindly, grading each segment as either normal, reversible, or irreversible. Short-axis tomograms from the five sets of thallium images (stress, redistribution, reinjection, rest, and redistribution) were also analyzed objectively by use of a semiautomated quantitative circumferential profile as previously described.

Quantitative Thallium Analysis

Briefly, for each patient, an operator-defined region of interest was drawn around the left ventricular activity of each short-axis slice on the stress images and the corresponding tomograms of the redistribution, reinjection, rest, and redistribution images. The myocardial activity was subdivided into 64 sectors, each emanating from the center of the tomograms. All 64 sectors were of equal arc and constructed beginning at the 3 o’clock position (medial wall) and proceeding counterclockwise. The sectors from two consecutive, three-pixel-thick, short-axis tomograms representing the midportion of the heart were then grouped and averaged into four myocardial regions: anterior, septal, inferior, and lateral. The sectors from the apical short-axis tomogram were analyzed to assess apical perfusion defects.

Assessment of regional thallium activity on stress images was carried out with reference to mean thallium activity for groups of normal male and female subjects. The normal subjects, who have been previously reported, consisted of 26 male and 24 female volunteers who were screened for coronary artery disease by complete physical examination, ECG, two-dimensional echocardiogram, and exercise treadmill testing. Subjects who had a strong family history of coronary artery disease were excluded from the normal data base. The male subjects ranged in age from 21 to 58 years (mean age, 39 years), and the female subjects ranged in age from 24 to 57 years (mean age, 38 years).

For each of the 41 patients in the present study, the myocardial region with the maximum mean counts per pixel on the stress study was normalized to the value for the corresponding region for normal subjects of the same sex, and this was used as a normal reference region for that patient. The corresponding regions in the redistribution, reinjection, rest, and redistribution thallium studies were identified and used as the reference region for those studies. The thallium activity in all other myocardial regions was then expressed as a percent of the activity measured in that reference region for each of the stress, redistribution, reinjection, rest, and redistribution image series. A myocardial region was considered abnormal in a patient with coronary artery disease if the thallium uptake on the stress image was greater than 2 SD below the mean observed in the same region for normal volunteers of the same sex. On the basis of previous reproducibility measurements in our laboratory, a region with reduced activity on the stress study was considered reversibly ischemic if the increase of normalized thallium uptake on the redistribution or reinjection image exceeded the reproducibility limit for that region. Alternatively, a region with
reduced activity on the stress study was considered irreversibly abnormal if the normalized thallium activity in that region on subsequent images did not increase more than the reproducibility limit for that region. These irreversible thallium defects on redistribution imaging were then subgrouped on the basis of the severity of reduction in thallium activity: mild to moderate (51% to 85% of peak activity) and severe (≤50% of peak) thallium defects. For analysis of individual patients, myocardial regions were grouped for each patient as viable or nonviable on the basis of the severity of reduction of thallium activity and the presence or absence of thallium reversibility.

**Positron Emission Tomography**

Twenty of the 41 patients underwent positron emission tomography (PET) studies to assess regional myocardial perfusion with $^{15}$O-labeled water ($[^{15}$O]H$_2$O) and exogenous glucose utilization with $[^{18}$F]fluorodeoxyglucose (FDG) as previously described.18 Imaging was performed with a whole-body PET camera producing 21 contiguous tomograms spaced 5.1 mm apart with a slice thickness of 13 mm and an in-plane resolution of 6.5 mm. Images were obtained perpendicular to the long axis of the body to create a series of transaxial tomograms. All patients were pretreated with 50 g of oral glucose 1 hour before the study after an overnight fast. After a 20-minute transmission scan to correct for attenuation, two separate bolus injections of 12 to 15 mCi of $[^{15}$O]H$_2$O were administered intravenously 12 minutes apart. Like most PET scanners, our scanner is unable to accurately handle the bolus phase of injection of more than 15 to 20 mCi when the heart is in the field of view. However, since an injection of 15 to 20 mCi of $[^{15}$O]H$_2$O does not give sufficient counts to obtain an accurate value of flow, two $[^{15}$O]H$_2$O studies were performed, back to back. Each study was analyzed separately, and the flow values were averaged together. This resulted in average flow values with SDs comparable to what would have been obtained from a single 30- to 40-mCi injection. The two separate bolus injections of $[^{15}$O]H$_2$O were followed by the administration of 5 mCi of FDG 15 minutes later. Dynamic PET data were acquired continuously for 5 minutes after each $[^{15}$O]H$_2$O injection and for 60 to 75 minutes after the FDG injection. The data acquired at 30 minutes after FDG injection, corresponding to the final 30 to 45 minutes of data acquisition, were reconstructed to create tomographic images of regional myocardial FDG uptake.

**Regional myocardial FDG uptake.** For each patient, a mean of six transaxial tomograms from the five sets of thallium images (stress, redistribution, reinjection, rest, and redistribution) and the corresponding transaxial tomograms of myocardial FDG uptake from the PET study were visually aligned for direct comparison.18 To compare relative regional FDG uptake and thallium activity objectively, five myocardial regions of interest representing the posterolateral, anterolateral, anteropapical, anteroseptal, and posteroseptal myocardium were drawn on each FDG tomogram and on each of the five corresponding thallium images. FDG and thallium activities were then computed within each region.

In each patient, the myocardial region with the maximum counts on the exercise thallium study was used as the normal reference region for that patient. The corresponding regions in the redistribution, reinjection, rest, and redistribution thallium studies were identified and used as the reference regions for those studies. The thallium activity in all other myocardial regions was then expressed as a percentage of the activity measured in the reference region for each of the exercise, redistribution, reinjection, rest, and redistribution image series. For each exercise study, thallium activity in any myocardial region measuring <85% of the normal reference region was considered reduced and defined as a thallium perfusion defect. Perfusion defects on exercise were defined as irreversible if relative thallium activity was unchanged or increased <10% on the subsequent redistribution study. The myocardial region on the FDG series that corresponded to the normal reference region on the thallium stress image series was used as the normal reference region for relative FDG uptake. FDG uptake in all other myocardial regions was expressed as a percent of the activity in this reference region.

**Regional myocardial blood flow.** Absolute regional myocardial blood flow was computed from the dynamic $[^{15}$O]H$_2$O data as previously described.18 The FDG image series was reviewed for each patient to identify the appropriate tomographic levels in which the left ventricular cavity was well defined. On average, four such tomographic levels were identified per patient. Left ventricular cavity regions of interest were manually constructed on these FDG tomograms and were then applied directly to the corresponding tomographic $[^{15}$O]H$_2$O data to derive a composite ventricular blood pool time-activity curve of the tracer. This ventricular time-activity curve was then used as the $[^{15}$O]H$_2$O arterial input function. Previous studies have demonstrated that the blood pool time-activity curve computed in this manner accurately represents instantaneous arterial concentrations of $[^{15}$O]H$_2$O.19,20 Using the $[^{15}$O]H$_2$O arterial input function, the myocardial $[^{15}$O]H$_2$O time-activity curve, and an assumed partition coefficient for $[^{15}$O]H$_2$O of 0.92, absolute regional myocardial blood flow was computed by a modification of the methods of Libet al21 and Herrero et al22 that automatically accounts for partial volume and spill-over effects.

**Regional FDG uptake relative to blood flow.** Regional FDG uptake was then interpreted in relation to regional myocardial blood flow assessed by $[^{15}$O]H$_2$O. Four groups of myocardial regions were identified: (1) normal (≥80% of activity in the normal reference region associated with normal blood flow), (2) mismatch (reduced myocardial blood flow with FDG:blood flow ratio ≥110% of that of the normal reference region), (3) moderately reduced FDG uptake (50% to 79% of normal reference FDG activity with reduced or normal blood flow and FDG:blood flow ratio <110% of that of the normal reference region), and (4) severely reduced FDG uptake (<50% of normal reference FDG activity with reduced blood flow and FDG:blood flow ratio <110% of that of the reference region). As previously described,23 a region could be defined as showing mismatch if FDG activity was normal, increased, or less than normal, as long as FDG activity was disproportionately increased relative to the reduced regional blood flow. The cutoff for the FDG:blood flow ratio of 110% was derived from previously published data obtained in normal volunteers in whom FDG:blood flow ratio values ranged from 1.02 to 1.12 mg/g per minute,24 which is
similar to the 1.20 cutoff value used by Vanoverschelde et al. 25 We have previously shown that when regions with reduced FDG uptake on PET images are subgrouped on the basis of the severity of reduction in FDG activity, regions with moderately reduced FDG uptake have greater end-diastolic wall thickness and regional systolic wall thickening by gated magnetic resonance imaging than regions with severely reduced FDG uptake. 26 Thus, regions with moderately reduced FDG uptake were interpreted as representing a mixture of viable and fibrotic myocardium, and they were grouped together with normal and mismatch FDG-blood flow patterns as regions with viable myocardium. 18 Regions with severely reduced FDG activity were considered to represent myocardial fibrosis. For analysis of individual patients, regions were grouped for each patient as normal, mismatch, moderately reduced FDG, or severely reduced FDG activity.

Characterization of Patients Who Underwent PET Studies

When the characteristics of the 20 patients who underwent PET studies were compared with those of the entire group of 41 patients, there was no difference with respect to extent of coronary artery stenosis. Among the 20 patients, 5 patients (25%) had single-vessel disease, 6 (30%) had marked narrowing of two vessels, and 9 (45%) of three vessels. Similarly, among the 41 patients, 12 patients (29%) had single-vessel disease, 11 (27%) had marked narrowing of two vessels, and 18 (44%) of three vessels. The exercise duration on treadmill testing (6.4±3.0 vs 6.6±2.9 minute, P=NS), rate-pressure product achieved during exercise (21±6×10³ vs 22±6×10³, P=NS), and the percentages of patients with anginal symptoms and medical therapy were the same in both groups. There were also no differences between the two groups with respect to the left ventricular ejection fraction or wall motion abnormality at rest. Left ventricular ejection fraction in the 41 patients ranged from 6% to 64% (mean, 32%) and was below the normal range in 31 patients. In the subgroup of 20 patients who underwent PET studies, left ventricular ejection fraction ranged from 6% to 50% (mean, 26%) and was below the normal range in 18 patients.

Radionuclide Angiography

Gated blood pool cardiac scintigraphy was performed to assess left ventricular ejection fraction and regional wall motion at rest by use of red blood cells labeled in vivo with 20 to 25 mCi of ⁹⁹mTc, as previously described. 27 Left ventricular ejection fraction was derived by computer analysis of the scintigraphic data, and regional wall motion was assessed qualitatively by two experienced observers from the images displayed in cineangiographic format. The images were graded on a three-point scale as follows: grade 0, akinetic or dyskinetic; grade 1, hypokinetic; and grade 2, normal. A region was considered to have improved wall motion when the assigned abnormal regional grade increased or normalized after revascularization. The lower limit of normal for resting ejection fraction by our technique is 45%.

Coronary Arteriography

Cardiac catheterization was performed by the percutaneous femoral technique. Coronary artery stenosis and graft patency were assessed by experienced cardiologists without knowledge of exercise thallium results. In patients with bypass grafts, a vessel was considered patent if there was no significant narrowing within the graft or in the native coronary artery distal to the graft anastomosis. For direct comparison of the severity of stress and rest thallium defects with the results of coronary angiography, the five myocardial regions per patient were grouped into the three major coronary vascular territories, with the anterior and septal regions representing the left anterior descending artery territory, the lateral region representing the left circumflex artery territory, and the inferior region representing the posterior descending artery territory. Assignment of the apex to a vascular territory was variable and based on the results of coronary angiography and the presence of adjacent perfusion defects.

Revascularization Studies

Seven patients underwent myocardial revascularization (two percutaneous transluminal coronary angioplasty and five coronary artery bypass surgery). These patients were restudied within a mean of 10 months after revascularization by coronary arteriography, thallium scintigraphy, and radionuclide angiography.

Statistical Analysis

Data are presented as mean±SD. Differences between mild-to-moderate and severe regional thallium uptake in concordant and discordant regions were analyzed by the two-tailed unpaired t test. Group comparisons between stress-redistribution-reinjection and rest-redistribution images were performed by χ² analysis. Differences between the entire group and the subgroup of patients who underwent PET studies with respect to exercise duration, rate-pressure product, symptoms of angina, medical therapy, left ventricular function, wall motion abnormalities, and the extent of coronary artery stenosis were analyzed by either two-tailed unpaired t test or χ² analysis. Changes in left ventricular ejection fraction and regional thallium activity from before to after revascularization were analyzed by the two-tailed paired t test. We did not perform statistical analysis based on the results obtained from an analysis of individual patients. Since many myocardial regions within each patient had different categories of thallium uptake and FDG:blood flow relations, each patient could not be considered an independent unit of observation.

Results

Analysis of Regional Thallium Activity

Among the 41 patients studied, a total of 205 myocardial regions (5 regions per patient) were analyzed. The exercise thallium SPECT study identified 50 regions to be normal and 155 regions to be abnormal during stress. Of the 155 abnormal regions, 91 defects (59%) were irreversible on conventional 3- to 4-hour redistribution images. After the reinjection of thallium at rest, 32 of the 91 regions with irreversible defects (35%) had improved or normalized thallium uptake (suggestive of viable myocardium), and 59 remained irreversible (Fig 1). Similarly, rest-redistribution imaging identified 39 of 91 regions (43%) with irreversible thallium defects on conventional stress-redistribution images to be viable (P=NS) on the
FIG 1. Flow diagram displaying the prevalence of reversible and irreversible thallium perfusion defects by stress-redistribution-reinjection and rest-redistribution studies in the 41 patients studied.

An analysis of regional thallium activity in patients who underwent PET studies

Like the findings obtained in all 41 patients, when stress-redistribution-reinjection and rest-redistribution images were classified as normal/reversible (viable) or irreversible (nonviable) in the 20 patients with PET studies, the two imaging methods provided concordant information in 72% of myocardial regions (Fig 2). Among the 28% discordant regions, 20% were identified to be reversible by stress-redistribution-reinjection imaging and irreversible by rest-redistribution imaging, whereas 8% were identified to be normal or reversible by rest-redistribution imaging and irreversible by stress-redistribution-reinjection imaging.

This 28% discordance between the two thallium imaging methods resulted when all irreversible thallium defects were grouped together, without considering the severity of the reduction in thallium activity within the defect. We have previously shown that when irreversible thallium defects on redistribution images are subgrouped on the basis of the severity of reduction in thallium activity, mild-to-moderate (51% to 85% of normal activity) irreversible defects were shown by PET to be metabolically active and viable, whereas regions with severe irreversible thallium defects were shown by PET to be metabolically inactive, and hence scarred.17,18 Thus, we reanalyzed the concordant and discordant myocardial regions after subgrouping the regions according to the severity of thallium activity within irreversible defects.

Myocardial Viability Assessed According to Severity of Thallium Defect

Of the 314 regions with irreversible thallium defects by either stress-redistribution-reinjection or rest-redistribution imaging, 147 regions were determined to be irreversible by both imaging techniques, whereas discordant information regarding reversibility was obtained in the other 167 regions.

Regions with concordant ³¹TI results. Among the 147 regions in which both stress-redistribution-reinjection and rest-redistribution imaging techniques were concordant in demonstrating irreversible thallium defects, 64 had mild-to-moderate reduction in thallium activity (66±10%), and 83 had severely reduced thallium activity (27±12%). PET identified 91% of the regions with mild-to-moderate irreversible thallium defects to be viable. In contrast, only 17% of regions with severe
irreversible thallium defects had preserved metabolic activity. A representative example of a patient demonstrating concordance between PET, stress-redistribution-reinjection, and rest-redistribution images is shown in Fig 3.

Regions with discordant 201Tl results. Among the 167 regions in which the viability information (normal/reversible vs irreversible) was discordant between stress-redistribution-reinjection and rest-redistribution studies, the majority (149 regions, or 89%) had only mild-to-moderate reduction in thallium activity. The relative thallium activity within the mild-to-moderate discordant regions was 69±9%, similar to that observed in mild-to-moderate discordant regions (66±10%, P=NS). PET verified 146 (98%) of these regions to be metabolically active and viable.

Of the 18 discordant regions with severe reduction in thallium activity, 15 were judged to be viable by stress-redistribution-reinjection studies, and 3 were viable by rest-redistribution studies (Fig 4). All 18 regions with severe defects were supplied by totally occluded or critically stenosed coronary arteries. In 14 (78%) of these 18 discordant regions, stress-redistribution-reinjection imaging provided concordant information with PET (12 viable and 2 scarred), whereas rest-redistribution imaging underestimated viable myocardium. These 14 regions represent 15% (14/92) of all (concordant and discordant) severe irreversible thallium defects and only 2% (14/594) of all myocardial regions studied. Although these regions were present in 7 of the 20 patients studied, they represent only 1 to 4 regions (from a mean of 30 regions) per patient. It is noteworthy that the mean thallium activity in these severe defects was 40±7%. Although this meets the criteria we have defined for a severe defect (<50% activity), this level of activity was significantly greater than that observed in the severe defects that were concordant (27±12%, P<.001).

Thallium Activity in Relation to Patterns of PET Viability

The results of PET patterns of viability in relation to stress-redistribution-reinjection and rest-redistribution thallium data, analyzed according to myocardial regions and patients, are shown in Tables 1 and 2, respectively. A total of 594 myocardial regions were evaluated in the 20 patients, of which 209 (35%) had normal FDG uptake and regional blood flow, 188 (32%) had an ischemic pattern with increased FDG uptake relative to reduced regional blood flow, 138 (23%) had moderately reduced FDG uptake, and 59 (10%) had severely reduced FDG uptake. The 59 regions with severely reduced FDG uptake were considered to represent myocardial fibrosis by PET.

Regional analysis. On the basis of the stress-redistribution-reinjection thallium studies (Table 1), 50 of the 59 myocardial regions (85%) with severely reduced FDG uptake by PET had severe irreversible thallium defects. In contrast, only 2% of the normal myocardial regions by PET, 4% of the mismatch, and 13% of the moderately reduced FDG regions had severe irreversible thallium defects. Similarly, on the basis of the rest-redistribution thallium studies (Table 2), 49 of the 59 myocardial regions (83%) with severely reduced FDG uptake by PET had severe irreversible thallium defects, and only 2% of the normal and 5% of the mismatch myocardial regions by PET had severe irreversible thallium defects. However, in regions with moderately reduced FDG uptake, 26% of the regions had severe irreversible defects on the rest-redistribution thallium studies, compared with 13% by stress-redistribution-reinjection studies.

Patient analysis. In this analysis, regions for each patient were grouped as having viable or nonviable myocardium on the basis of relative thallium activity. Similarly, for the PET data, regions were grouped as
normal, mismatch, moderately reduced FDG activity, or severely reduced FDG activity. The results of the patient analysis were similar to those of the regional analysis (Tables 1 and 2). Normal, mismatch, and moderately reduced FDG PET patterns were observed in all 20 patients, whereas a severely reduced FDG pattern was observed in 10 patients. Among these 10 patients with myocardial fibrosis by PET, 8 (80%) were identified to have nonviable myocardium both by the stress-redistribution-reinjection and rest-redistribution thallium studies. In contrast, only 1 of the 20 patients with normal and 2 of the 20 patients with mismatch pattern by PET had severe irreversible thallium defects by the rest-redistribution imaging. However, among the 20 patients in whom regions with moderately reduced FDG uptake were observed, 8 (40%) of the patients were identified to have nonviable myocardium by the rest-redistribution thallium studies, compared with only 3 patients (15%) by stress-redistribution-reinjection studies.

Effects of Revascularization

Among the seven patients who underwent myocardial revascularization, six (86%) had an increase in resting left ventricular ejection fraction, from 33±12% before to 39±13% after revascularization (P=.02). Six patients had subnormal ejection fractions at rest (≤45% for our

### Table 1. Relation of Stress-Redistribution-Reinjection Thallium Results to Patterns of PET Viability

<table>
<thead>
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<th>PET</th>
<th>Normal</th>
<th>FDG: blood flow mismatch</th>
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<th>Severely reduced FDG</th>
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<td>No. %</td>
<td>No. %</td>
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<td></td>
<td>Reversible 65</td>
<td>115 61</td>
<td>48 35</td>
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<td></td>
<td>Irreversible Mild-to-moderate 42</td>
<td>28 15</td>
<td>46 33</td>
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<td>2 10</td>
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<td></td>
<td>Nonviable 1</td>
<td>5</td>
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SPECT, single photon emission computed tomography; FDG, [18F]fluorodeoxyglucose; n, number of myocardial regions; N, number of patients in whom the corresponding positron emission tomography (PET) category was observed.
laboratory) before revascularization, of whom five manifested an increase in ejection fraction from 30±8% before to 36±11% after revascularization (P<.04).

A total of 14 regions were identified with abnormal regional wall motion before revascularization, 7 with irreversible thallium defects despite reinjection and 7 with improved thallium uptake after either 3- to 4-hour redistribution or the reinjection study. Three of the 7 reversible defects (43%) were reversible only after reinjection. All 7 regions with irreversible thallium defects on redistribution-reinjection imaging before revascularization (mean, 45±21%) again demonstrated irreversible thallium defects after revascularization (45±20%, P=NS) that were associated with persistent abnormalities in regional wall motion. In contrast, 6 of 7 regions (86%) with improved thallium uptake after redistribution or reinjection studies before revascularization (61±6%) had improved thallium uptake after revascularization (71±8%, P=.04) that were associated with improved regional wall motion at rest on the basis of radionuclide angiography. The remaining one region with persistent wall motion abnormality after revascularization had a reversible thallium defect that was unchanged compared with the prevascularization study. Similarly, when rest-redistribution thallium uptake was assessed among the 14 regions with abnormal regional wall motion before revascularization, 7 had irreversible thallium defects and 7 were either normal or reversible. Six of 7 regions (86%) with irreversible thallium defects on redistribution imaging before revascularization (44±13%) again demonstrated irreversible thallium defects after revascularization (48±25%, P=NS) that were associated with persistent abnormalities in regional wall motion. In contrast, 5 of 7 regions (71%) with normal or reversible thallium defects before revascularization (74±4%) had normal thallium uptake after revascularization (71±8%, P=NS) that was associated with improved wall motion at rest. An example of a patient with three-vessel coronary artery disease in whom global and regional left ventricular function improved after revascularization is shown in Fig 5.

Regional Thallium Uptake Relative to Coronary Anatomy

When the severity of stress and rest thallium defects was compared with the severity of coronary artery stenosis, as anticipated, the stress studies identified more myocardial regions subtended by stenotic coronary arteries than rest studies alone. Of the 205 myocardial regions analyzed, 155 regions (76%) were identified to be abnormal during stress compared with 109 regions (53%) with the rest-redistribution protocol. When the relative thallium activity after the stress and rest injections were assessed in each coronary artery vascular territory, there was a significant association between the severity of thallium uptake during stress and percent coronary artery stenosis. Relative to peak activity, thallium activity in territories with 100% coronary occlusion was 42±14% (mean±SD) compared with 54±20% in territories supplied by 75% to 99% coronary stenosis (P<.01) and 61±19% in territories supplied by 50% to 74% coronary stenosis (P<.003). In contrast, there was no association between severity of thallium uptake at rest and percent coronary artery stenosis. Thallium activity was 54±19% in territories with 100% coronary occlusion, 65±21% in territories supplied by 75% to 99% coronary stenosis, and 64±20% in territories supplied by 50% to 74% coronary stenosis (P=NS).

Discussion

Stress-redistribution 201Tl scintigraphy provides important diagnostic and prognostic information in patients with coronary artery disease. However, conventional stress-redistribution imaging does not always distinguish between regions of ischemic or scarred myocardium. Thallium reinjection immediately after stress-redistribution imaging identifies ischemic but viable myocardium in 31% to 49% of myocardial regions that appear irreversible on conventional 3- to 4-hour redistribution images.8,9,28,29 However, elimination of the 3- to 4-hour redistribution images and reliance on reinjection images alone may incorrectly assign 8% to 10% of thallium defects identified on stress images to be irreversible and scarred.8,30 These regions represent
Fig 5. $^{201}$Tl scintigraphy and radionuclide angiography studies from a patient with significant three-vessel coronary artery disease before and after coronary artery bypass surgery (CABG). Top, two consecutive short-axis tomograms of preoperative (pre-op) stress (S), redistribution (RD), reinjection (RI), and rest (R)-redistribution images with corresponding postoperative (post-CABG) stress and reinjection tomograms. The preoperative thallium stress-redistribution images (on the left) reveal reversible anterior and minimally reversible inferior defects (shown by the arrowhead) that normalize after reinjection of thallium at rest. Rest-redistribution images identified reversible anterior and minimally reversible inferior defects. After revascularization (on the right), stress-reinjection images reveal normal thallium uptake in the anterior and inferior regions. Global and regional left ventricular function at rest, before and after operation, is shown in the bottom panel. Left ventricular ejection fraction (LVEF) was calculated from end-diastolic (ED) and end-systolic (ES) frames in the left anterior oblique view. Before operation, the left ventricular contraction was diffusely hypokinetic with a calculated ejection fraction of 40%. After revascularization, left ventricular contraction significantly improved with an increase in ejection fraction to 54%.

19% to 25% of myocardial regions that would be reversible on 3- to 4-hour redistribution images. This results from a disproportionately smaller increment in regional thallium activity after reinjection in some ischemic regions compared with the uptake in normal regions, a phenomenon we have called “differential uptake.”

Because of the logistical problems in performing three sets of thallium images in all patients, as well as the problem in interpreting the results if only one set of images is obtained after the stress images (either redistribution without reinjection or reinjection without redistribution), it would be reasonable to perform thallium imaging with resting injections of the isotope if the clinical question to be addressed is one of myocardial viability, not exercise-induced ischemia. In 1979, Gewirtz et al.\textsuperscript{11} reported that thallium defects may occur on resting images in patients with severe coronary artery disease in the absence of an acute ischemic process or previous myocardial infarction. They also recognized that many of these resting perfusion defects redistribute over the next 2 to 4 hours, especially in regions with normal or hypokinetic wall motion. Since this initial report, three other studies evaluated the efficacy of rest-redistribution imaging in predicting the outcome of myocardial regions after revascularization.\textsuperscript{12-14} Berger and coworkers\textsuperscript{12} investigated the outcome of rest-redistribution thallium abnormalities in 22 patients undergoing coronary artery bypass surgery. Among the 48 regions with reversible defects before surgery, 37 (77%) had completely normal thallium uptake after surgery and 10 had persistent reversible defects. However, 12 of 18 regions with irreversible thallium defects before surgery (67%) also showed normal thallium uptake after surgery. These data suggest that although rest-redistribution thallium imaging identifies viable myocardium in the majority of reversible regions, it may underestimate viable myocardium in irreversible regions. The second study, by Iskandrian and colleagues,\textsuperscript{13} examined the value of rest-redistribution thallium imaging in predicting improvement in left ventricular ejection fraction after coronary artery bypass surgery. In 14 patients with left ventricular dysfunction at rest and normal or reversible thallium abnormalities, 12 (86%) showed improvement in left ventricular function after surgery. In contrast, among the 9 patients with left ventricular dysfunction and irreversible perfusion defects on rest-redistribution imaging, only 2 (22%) showed improvement in left ventricular function after surgery ($P<.01$). The third study, by Mori et al.,\textsuperscript{14} showed that although 79% of asynergic regions with thallium redistribution had improved wall motion after revascularization, 38% of asynergic regions without thallium redistribution before surgery also showed improved wall motion after surgery. These three studies were consistent in demonstrating that the majority of regions (77% to 86%) with reversible thallium defects before surgery have normal thallium uptake and/or improved left ventricular function after surgery. However, these studies were also consistent in
showing that 22% to 67% of regions with irreversible defects also improve after revascularization. Hence, the available data suggest that although rest-redistribution thallium imaging identifies viable myocardium in the majority of reversible regions, it may underestimate viable myocardium in up to two thirds of irreversible regions.

However, it should be emphasized that none of the three studies used quantitative thallium scintigraphic methods for assessment of the severity of the irreversible thallium defects. Thallium defects in each of these studies were classified as being reversible, partially reversible, or irreversible. More recently, improved results were obtained with quantitative analysis in which the severity of reduction in thallium activity was considered within irreversible rest-redistribution thallium defects. When myocardial viability was defined as thallium activity >50% of activity in normal regions, 57% of severely asynergic regions that were viable by thallium demonstrated improved wall motion after surgery, compared with only 23% of severely asynergic regions that were considered to be nonviable by thallium.

The results of the present study indicate that in patients with chronic stable coronary artery disease, stress-redistribution-reinjection and rest-redistribution imaging provide concordant information in 72% of irreversible defects when regions are classified simply as either normal/reversible or irreversible thallium defects. This suggests a relatively high rate of discordance (28%) between the two methods of thallium imaging. However, these results can be improved considerably by analyzing irreversible defects further according to the severity of the thallium defect. Of the discordant regions, 89% demonstrated only mild-to-moderate reduction in thallium activity. We have previously demonstrated that regions with mild-to-moderate irreversible thallium defects represent predominantly viable myocardium compared with PET17,18,20 and have substantial uptake of thallium (using the differential uptake ratio) after reinjection17 and preserved regional systolic wall thickening and end-diastolic wall thickness by magnetic resonance imaging.20 These findings are also supported by data reported by Gibson and colleagues81 in patients before and after revascularization using planar thallium scintigraphy. Thus, the finding of only mild-to-moderate reduction in thallium activity within irreversible regions connotes predominantly viable myocardium and appears to be independent of whether one is performing a stress study or a rest-redistribution study. In our series, this quantitative approach increased the concordance between stress-redistribution-reinjection and rest-redistribution imaging regarding myocardial viability to 94%.

That reversible or normal thallium uptake on stress-redistribution-reinjection and rest-redistribution studies represents viable myocardium is substantiated by improved regional and global function in the small subgroup of patients undergoing revascularization. Although the findings in these patients do support our conclusion, we acknowledge that the number of patients and myocardial regions submitted to revascularization is small. However, it is also important to point out that the thallium reinjection protocol used in this study has been shown to predict the functional recovery of regions with apparently irreversible defects on conventional stress-redistribution imaging6,28,32 with an accuracy similar to that reported when FDG imaging with PET was used.33-37 Thus, there are a number of prerevascularization and postrevascularization studies to date that support the findings of FDG uptake on PET and thallium uptake after reinjection as reliable and accurate markers of viable myocardium.

In regions with severely reduced thallium activity, rest-redistribution imaging appears to underestimate viable myocardium in 15% of irreversible thallium defects compared with stress-redistribution-reinjection imaging and PET. These severe discordant defects occurred in 2% of all myocardial regions studied, representing only 1 to 4 regions from a mean of 30 regions per patient. Hence, the clinical relevance of these regional differences for an individual patient is likely to be negligible. Moreover, among these severe defects, the mean thallium activity in the discordant regions (27±12%) was significantly lower than the activity within the discordant regions (40±7%). It is likely that within the range of thallium activity from 40% to 50% of normal activity, there is some overlap of information regarding myocardial viability.

Another possible explanation for the underestimation of viable myocardium by rest-redistribution imaging in some discordant regions may relate to a rather severe reduction in regional blood flow even under resting conditions. Such myocardial regions, supplied by totally occluded or critically stenosed coronary arteries, may exhibit severely reduced thallium uptake at rest and remain irreversible on the redistribution study. However, exercise stress may produce even greater regional myocardial blood flow heterogeneity. When followed by augmentation of the serum thallium levels with reinjection after 3 to 4 hours, the magnitude of improvement in thallium uptake from stress to reinjection will differentiate ischemic and viable myocardium from scarred myocardium. Hence, it is not surprising that a small number of regions with severely reduced and irreversible thallium defect on rest-redistribution images may be identified as ischemic rather than fibrotic myocardium on stress-redistribution-reinjection imaging.

In most cases, the identification of inducible myocardial ischemia is a much more important clinical variable in terms of patient management and risk assessment than the knowledge of myocardial viability. The influence of exercise stress in differentiating an asynergic region with admixture of scarred and viable myocardium from a region with underperfused but viable (hibernating) myocardium is outlined in Fig 6. A hypococontractile segment may represent either an admixture of scarred and viable myocardium that is nonischemic or a completely viable but hibernating myocardium. These two hypocontractile segments may be differentiated by demonstrating exercise-induced ischemia (reversible thallium defect) in the case of hibernating myocardium and absence of ischemia (irreversible thallium defect) in the case of the admixture of fibrotic and viable myocardium. Accurate distinction between these two hypocontractile segments has important clinical implications, since impaired regional function is a potentially reversible process in the case of hibernating myocardium but not in regions with admixture of viable and scarred myocardium.

Preliminary data regarding the frequency of late (18- to 72-hour) redistribution imaging after the injection of thallium at rest suggest that 13% to 30% of patients
studied for myocardial infarction, unstable angina, or heart failure had additional redistribution on late imaging.\textsuperscript{38,39} However, the frequency of late redistribution in our study population with chronic stable coronary artery disease is unknown.

Thallium reinjection imaging is a composite of resting perfusion superimposed on a stress-redistribution image. Although initial rest thallium images (without exercise) detected only 56\% of the regions determined to be viable by stress-redistribution-reinjection, they identified 7 additional viable regions among the 59 regions determined to be irreversible (and therefore interpreted to be scarred) by stress-redistribution-reinjection imaging. Since reinjection of thallium after stress-redistribution imaging does not provide the same information as a rest thallium study (without exercise), the terms reinjection and rest-injected thallium should not be used interchangeably. Redistribution images acquired 3 to 4 hours after the initial rest thallium study identified an additional 14 viable regions, of which 8 were identified to be viable by stress-redistribution-reinjection regions. Therefore, our results are consistent with previous reports indicating that 3- to 4-hour redistribution images after initial rest images are required to differentiate viable from nonviable myocardium.\textsuperscript{11-15}

In conclusion, one of two imaging modalities, either stress-redistribution-reinjection or rest-redistribution imaging, may be used for identifying viable myocardium. However, if there are no contraindications to stress testing, stress-redistribution-reinjection imaging provides a more comprehensive assessment of the extent and severity of coronary artery disease by demonstrating regional myocardial ischemia without jeopardizing information on myocardial viability.

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