Thallium Reinjection Demonstrates Viable Myocardium in Regions With Reverse Redistribution

Jose A. Marin-Neto, MD; Vasken Dilsizian, MD; James A. Arrighi, MD; Nanette M.T. Freedman, PhD; Pasquale Perrone-Filardi, MD; Stephen L. Bacharach, PhD; Robert O. Bonow, MD

**Background.** The clinical significance and pathophysiological mechanisms of reverse redistribution on stress-redistribution thallium-201 myocardial scintigraphy in patients with chronic coronary artery disease are unclear. Recent studies have shown that thallium-201 reinjection is a useful technique for the detection of myocardial viability in chronic coronary artery disease. In this investigation we determined whether thallium reinjection distinguishes viable from nonviable myocardium in regions with reverse redistribution.

**Methods and Results.** We studied 39 patients with chronic stable coronary artery disease (age, 60±10 years), all of whom demonstrated reverse redistribution on standard exercise-redistribution thallium single-photon emission computed tomography (SPECT). Reverse redistribution was defined as ≥10% decrease in relative thallium-201 activity from stress to redistribution images. Thallium reinjection was performed immediately after the 3- to 4-hour redistribution phase. Of 39 regions with reverse redistribution, 32 (82%) showed enhanced thallium-201 activity (≥10% increase) after reinjection. In the other 7 regions (18%), the scintigraphic defect persisted after reinjection. Abnormal Q waves were present in only 8 of 32 (25%) regions with enhanced thallium-201 uptake after reinjection compared with 5 of 7 (71%) regions not responding to reinjection (P<.05). Akinesis or dysskinetic wall motion was present in 3 of 32 (9%) regions showing enhanced uptake after reinjection, in contrast with 5 of 7 (71%) regions not responding to reinjection (P<.01). Critically stenosed or totally occluded coronary arteries supplied 24 of 29 (83%) regions with enhanced thallium-201 uptake after reinjection but only 2 of 7 (28%) regions not showing a positive response to reinjection (P<.05).

Collateral circulation was detected in 23 of 29 (79%) regions with a positive thallium reinjection effect but in only 1 of the other 7 regions (P<.01). Sixteen of the 39 patients also underwent positron emission tomography using 18F-fluorodeoxyglucose (FDG) to assess glucose utilization and H14CO2 to assess regional blood flow. The 14 regions with reverse redistribution that responded to reinjection with enhanced thallium uptake all showed either normal patterns of FDG uptake and flow or an ischemic pattern with increased FDG uptake relative to flow. Reduced FDG uptake and reduced flow values were seen in the two regions not responding to thallium reinjection.

**Conclusions.** These observations indicate that reverse redistribution in chronic coronary artery disease usually reflects viable myocardium, critically dependent upon collateral circulation. (Circulation. 1993;88[part 1]:1736-1745.)

**Key Words** • myocardium • thallium • collateral circulation • coronary artery disease • positron emission tomography

Reverse redistribution is defined as the worsening of a perfusion defect during the redistribution phase of conventional thallium-201 scintigraphy, and includes either the worsening of a defect apparent on the post-stress images or the appearance of a new defect on the redistribution images. No experimental correlates for reverse redistribution have been described in animal models of myocardial ischemia, and the nature and clinical significance of this scintigraphic finding remain controversial in patients with chronic coronary artery disease. For example, its presence in some studies has been associated with severe coronary stenosis, whereas other studies suggest that this phenomenon can occur in the absence of significant coronary artery disease. It is also unclear, both in patients with chronic ischemic heart disease and in patients after thrombolytic therapy for acute myocardial infarction, whether reverse redistribution represents areas of myocardial necrosis or ischemic but viable myocardium. The elucidation of the mechanisms underlying reverse redistribution and the determination of the viability of the involved myocardium might bear rele-
vant implications as to the management of a sizable group of patients with ischemic heart disease.

Recent studies have shown that thallium-201 reinjection after stress-redistribution scintigraphy is a useful technique for the detection of viable myocardium in the setting of chronic coronary artery disease.\textsuperscript{5,10} This investigation was undertaken to observe the effects of reinjection of thallium-201 in patients showing reverse redistribution on conventional stress-redistribution thallium scintigraphy. We hypothesized that improved thallium uptake after reinjection would differentiate viable from nonviable myocardium in regions of reverse redistribution. In a subset of patients, metabolic activity in the regions with reverse redistribution was assessed by positron emission tomography (PET) imaging using \textsuperscript{18}F-fluorodeoxyglucose.

**Methods**

**Patient Population**

From a series of 262 patients with chronic stable coronary artery disease referred for an exercise thallium study, 39 were selected on the basis of a new scintigraphic defect observed on redistribution images or the worsening of a defect already present in the stress images that was both visually apparent and confirmed by quantitative criteria. There were 32 men and 7 women, with a mean age of 60±10 years (range, 39 to 78). Twenty-five of the patients had a history of previous myocardial infarction. However, no patient had suffered an acute myocardial infarction or had unstable angina within 6 months of the studies. Left ventricular hypertrophy by electrocardiographic and echocardiographic criteria was present in only 2 patients. Twelve patients had undergone previous coronary artery bypass surgery and 6 patients had undergone coronary angioplasty (2 of the patients underwent both interventions); these procedures had been performed at least 6 months before the studies. Exercise thallium scintigraphy was performed after withdrawal of all cardiac medications in 33 (85\%) of the patients. Radionuclide angiography was performed within 3 months of the thallium studies in all patients. Coronary angiography was also performed within 3 months of thallium scintigraphy in 36 of the patients. In a subset of 16 patients, PET was performed using \textsuperscript{18}F-fluorodeoxyglucose (FDG) to assess regional glucose utilization and \textsuperscript{18}O to assess regional blood flow.

**Thallium SPECT Imaging**

Thallium-201 single-photon emission computed tomography (SPECT) was performed in all patients as previously described.\textsuperscript{9} Briefly, after an overnight fast, exercise was performed after a standard or a modified Bruce protocol. At peak exercise, 2 mCi of thallium-201 was injected intravenously, after which the patients continued to exercise for an additional 60 to 90 seconds. Within 10 minutes after termination of exercise, thallium images were acquired with a large-field-of-view rotating gamma camera (Apex 415, APC-3, Elscint, Boston) equipped with a high-sensitivity, low-energy, medium-resolution, parallel-hole collimator centered on the 68 keV photo peak with a 20\% window. A red elliptical 180° orbit was performed by the camera rotating around the patient’s thorax, starting from 40° right anterior oblique to 50° left posterior oblique at 6° increments for 30 seconds each. After the completion of imaging, the patients remained in the fasting state, and 3- to 4-hour redistribution images were acquired. All patients then received an additional 1 mCi of thallium-201 reinjection at rest immediately after the redistribution study, and a third set of images was acquired. The time of imaging was uniform for all three sets of images. From the raw scintigraphic data, tomograms oriented along the three standard orthogonal views (transaxial, sagittal, and short-axis) were reconstructed using constant filtering.

**Quantitative thallium analysis.** A semiautomatic, quantitative, circumferential profile analysis was performed in 23 patients as described previously.\textsuperscript{5,11} An operator-defined region of interest was drawn around the left ventricular activity of each short-axis slice on the stress, redistribution, and reinjection images. The myocardial activity was subdivided into 64 sectors emanating from the center of the left ventricular region beginning at the 3 o’clock position in the mid lateral wall and proceeding counterclockwise in equal arcs. Within each myocardial sector, the mean counts per pixel for the stress, redistribution, and reinjection images were computed. Sectors were then grouped and averaged into four myocardial regions: lateral, anterior, septal, and inferior. Quantitative data from two consecutive, 3-pixel-thick, short-axis tomograms representing the midportion of the left ventricle were analyzed.

The stress images were analyzed with reference to a normal, gender-specific database derived from normal male and female subjects, as previously described.\textsuperscript{9} The myocardial region with the maximum mean counts per pixel on the stress study was scaled to the value for the corresponding region for the normal subjects of the same sex, and this was used as the normal reference region for that patient. The same corresponding regions in the redistribution and reinjection scintigram were used as reference regions for these studies, so that the thallium-201 activity in all other myocardial regions was expressed as a percent of the activity measured in the reference region for each of the stress, redistribution, and reinjection image series. The thallium activity assigned to a given region was the lower of the two values from the corresponding regions in the two consecutive tomographic slices. Thus, for the 23 patients, a total of 92 regions were evaluated in the stress, redistribution, and reinjection tomograms. A myocardial region was considered normal if the thallium activity at stress fell within 2 standard deviations of the mean observed in the same region for normal volunteers of the same sex. On the basis of reproducibility measurements in this laboratory,\textsuperscript{12} a region with normal activity on the stress tomogram was considered as having reverse redistribution if the decrease in normalized thallium activity on the redistribution image exceeded the reproducibility limit for that region, and, in addition, the relative decrease was at least 10\%. Thallium uptake after reinjection was considered to improve if the relative thallium activity increased from redistribution to reinjection by at least 10\%, sufficient to exceed the reproducibility limit for that region (Fig 1).
defined as the highest count density on the stress images. For this analysis, absolute counts in the stress and redistribution images were considered, and washout was defined as \((1 - \text{redistribution counts/stress counts}) \times 100\). Similarly, lung washout rates were measured from absolute counts in the stress and redistribution images, using the same formula. Finally, lung to myocardial count ratios in the stress study were obtained using the regions with maximum absolute counts for both myocardium and lung areas. A ratio of <0.5 was considered normal lung uptake, between 0.5 and 0.6 moderate lung uptake, and a ratio >0.6 severe thallium lung uptake during stress. The lung washout rates and lung to myocardial count ratios were obtained from the raw anterior planar scintigram obtained during the SPECT acquisition.

**Positron Emission Tomography**

Sixteen of the patients underwent PET imaging with FDG and H$_2^{15}$O, as previously described.\(^{10}\) 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 as transaxial tomograms perpendicular to the long axis of the body. All patients received 50 g of oral glucose before the PET studies after an overnight fast. After a 20-minute transmission scan to correct for attenuation, two separate bolus injections of 12 to 15 mCi of H$_2^{15}$O were administered intravenously 12 minutes apart, followed by the administration of 5 mCi of FDG 15 minutes later. Dynamic PET data were acquired continuously for 5 minutes after each H$_2^{15}$O injection and for 60 to 75 minutes after FDG injection. The data collected after 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 thallium and FDG activities.** For each patient, transaxial tomograms from the three sets of thallium images (stress, redistribution, and reinjection) and the corresponding transaxial tomograms of myocardial FDG uptake from the PET study were visually aligned for direct comparison.\(^{10}\) 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 three corresponding thallium images. FDG and thallium activity were then computed within each region. In each patient, the myocardial region with the maximum counts on the stress thallium study was used as the normal reference region for that patient. The corresponding regions in the redistribution and reinjection thallium studies were used as the reference region for those studies. Thallium activity in all other myocardial regions was expressed as a percentage of the activity measured in the reference region for each of the stress, redistribution, and reinjection image series. Myocardial regions were considered normal on the stress study if thallium activity was >85% of the activity in the reference region.\(^{10,13}\) Thallium redistribution, reverse redistribution, and the effect of reinjection were defined using the same criteria.

---

**FIG 1.** Circumferential profile analysis for assessing regional myocardial thallium activity in a patient with reverse redistribution. Short-axis thallium tomograms obtained after exercise, redistribution, and reinjection are shown. On the right, each curve represents thallium activity during stress, redistribution, and reinjection for the 64 sectors that are subdivided into lateral, anterior, septal, and inferior myocardial regions. In this example, reverse redistribution occurs in the anterior region, followed by enhanced thallium uptake after reinjection that reverses the defect.
outlined above for the quantitative analysis of short-axis tomograms. The myocardial region on the FDG series that corresponded to the 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.

FDG uptake relative to regional blood flow. Absolute regional blood flow was computed from the dynamic \( H_2^{18}O \) data in the same regions used for analysis of FDG uptake, as previously described.\textsuperscript{14} Based on previous analysis of myocardial regions with normal thallium activity during stress, redistribution, and reinjection (as defined above) and normal FDG activity (as defined below), a flow value of 0.7 mL·g\(^{-1}\)·min\(^{-1}\) was considered the lower limit of normal.\textsuperscript{13} In these regions the blood flow values ranged from 0.7 to 1.79 mL·g\(^{-1}\)·min\(^{-1}\), with a mean of 1.04±0.24 mL·g\(^{-1}\)·min\(^{-1}\). These values are comparable to those reported in normal human subjects.\textsuperscript{15,16}

Three categories of regions were considered to represent viable myocardium by PET criteria. These were (1) regions of normal blood flow and FDG activity, (2) regions with FDG/blood flow mismatch, and (3) regions with moderately reduced FDG activity in the absence of FDG/blood flow mismatch. On the basis of the variability of FDG uptake reported in normal subjects,\textsuperscript{17} a region was considered normal when FDG activity was ≥80% of the activity in the reference region and blood flow was normal. FDG/blood flow mismatch\textsuperscript{18,19} was defined as a region with reduced blood flow and a relative increase in FDG activity (FDG/blood flow ratio ≥110% of that of the normal reference region)\textsuperscript{13}. The third classification of viable myocardium was based on moderately reduced FDG uptake (50% to 79% of the reference) with normal or proportionately reduced blood flow.\textsuperscript{10,20} Nonviable myocardium (scar) was defined in regions with FDG activity <50% of the normal reference region with blood flow <0.7 mL·g\(^{-1}\)·min\(^{-1}\).

Gated Blood Pool Cardiac Scintigraphy
Radionuclide angiography was performed in all patients using red blood cells labeled in vivo with 20 to 25 mCi of technetium-99m and a conventional Anger camera equipped with a high-sensitivity parallel-hole collimator. Data were acquired in list mode in a modified left anterior oblique position at rest and during maximal supine bicycle exercise, as previously described.\textsuperscript{21} Regional wall motion in the septal and lateral regions were assessed qualitatively as normal, hypokinetic, akinetic, or dyskinetic by two experienced observers. The left ventricular ejection fraction was calculated semiautomatically by computer analysis of the scintigraphic data after manual construction of ventricular and background regions of interest.

Cardiac Catheterization and Coronary Arteriography
Cardiac catheterization and coronary arteriography were performed by the percutaneous femoral approach in 36 patients. Contrast ventriculography in the right anterior projection was also performed, which permitted the analysis of regional wall motion in the anterior and inferior walls. The severity of coronary artery stenoses supplying regions with reverse redistribution, graft patency, and presence of collateral circulation were evaluated independently by two experienced observers who were blinded to the results of thallium scintigraphy. The severity of a luminal stenosis was graded according to the following ranges: <50%, 50% to 74%, 75% to 99%, and 100%. A discrepancy in the qualitative evaluation of a major coronary artery stenosis by the two reviewers of enough magnitude to alter the range assignment occurred in 6 patients. A quantitative assessment of luminal diameter reduction was then carried out by using a computerized method of semiautomatic edge detection on a cardiac image analysis workstation (ImageComm Systems, Inc, Santa Clara, Calif). Briefly, after optical magnification and digitization of 35-mm cineframes, an arterial segment containing the stenosis was measured in two views. The diameter of the coronary artery catheter was used as a reference after correction for pincushion distortion, allowing the calculation of the maximal percent luminal diameter reduction in the stenotic segment in comparison to the diameter of the normal adjacent segment. Bypass grafts were considered patent only if the graft and the native vessel distal to the surgical anastomosis were free of significant narrowing. Collateral circulation was classified according to the following criteria: grade 1, faint visualization; grade 2, good visualization leading to faint opacification of a major coronary vessel; grade 3, excellent visualization with clear opacification of the recipient major coronary artery.

Statistical Analysis
Data were expressed as mean±SD. Student’s\( t \) tests for paired data were used to compare thallium activities in the stress and reinjection images and to compare left ventricular ejection fraction at rest and stress. Washout rates in normal and reverse redistribution regions were compared by an unpaired Student’s\( t \) test. Fisher’s exact test was used to compare electrocardiographic, radionuclide, and angiographic data between patients with positive or negative thallium reinjection results.

Results
Clinical and Hemodynamic Responses to Exercise
During treadmill exercise in the 39 patients, the heart rate rose from 73±14 beats per minute at baseline to a peak value of 132±23 beats per minute. The rate-pressure product increased from 10.4×10\(^2\)±2.4×10\(^2\) at rest to 22.7×10\(^3\)±7.5×10\(^3\) at peak exercise. Twenty-five of 39 patients (64%) achieved a peak heart rate >85% of the maximum predicted by age and gender characteristics. In the remaining 14 patients, exercise was stopped because of symptoms such as chest pain, dyspnea, or fatigue. Twenty-six patients developed ST-segment depression of >1 mm in at least two leads.

Stress-Redistribution Thallium-201 Scintigraphy
A total of 172 myocardial regions were assessed in the 39 patients. The first 23 patients were studied in the short-axis view, with four regions per patient. The other 16 patients, who were also studied by PET, were studied in the transaxial plane, with five regions per patient. The quantitative analysis of the 172 regions, on the basis of standard stress-redistribution scintigraphy, characterized 50 (29%) regions as normal, 23 (13%) regions with reversible thallium defects, and 60 (35%) regions with irreversible perfusion defects. There were
39 (23%) regions with reverse redistribution. Fourteen of these 39 regions (36%) were considered normal on the initial postexercise images. According to our selection criteria, the region with reverse redistribution by quantitative criteria was also identified by qualitative analysis in every patient. Washout rates in the 39 reverse redistribution regions averaged \(57 \pm 19\%\), a value significantly greater than that obtained for the 50 normal regions \((37 \pm 21\%, \ P < .01)\). The lung washout averaged \(31 \pm 10\%\), and the lung uptake of thallium during stress was abnormal in 5 patients (lung/heart ratios of 0.61 to 0.88).

### Regional Wall Motion Analysis

Among the 166 regions that were analyzed visually at rest by radionuclide (septal and lateral regions) and contrast angiography (anterior and inferior regions), 79 (48%) showed normal wall motion, 62 (37%) had hypokinesis, and 25 (15%) had akinetic or dyskinetic wall motion. In the 39 regions showing thallium-201 reverse redistribution, wall motion was normal in 18 (46%), hypokinetic in 13 (33%), and akinetic/dyskinetic in 8 (21%) regions. In 27 of the 39 regions with reverse redistribution, wall motion was also analyzed during exercise. Nineteen regions had normal wall motion at rest, of which 17 developed hypokinesis during exercise and 2 remained normal. Five hypokinetic regions and 2 akinetic regions at rest were not altered by exercise, and 1 hypokinetic region became akinetic with exercise. The left ventricular ejection fraction was \(39 \pm 16\%\) at rest (range, 8% to 68%). During supine exercise, the ejection fraction decreased to \(33 \pm 15\%\) \((P < .05)\). All patients demonstrated either no change or a decrease in ejection fraction during exercise.

### Coronary Angiography

In all 36 patients undergoing coronary arteriography, a significant narrowing \((>50\%\) reduction in luminal diameter) was found in at least one major coronary artery. Twelve of the patients had significant stenoses in 2 of the major coronary arteries and 15 had significant stenoses in 3 major coronary arteries. One patient had a 90% narrowing in the left main coronary artery. The reference region selected on the basis of maximum thallium uptake during exercise was supplied in 11 patients by native arteries without significant stenosis \((<50\%\) reduction in luminal diameter), in 10 patients by patent bypass grafts, and in 15 patients by arteries with significant stenoses.

Of the 36 patients who underwent coronary arteriography, 26 (72%) had critical stenosis \((>75\%\) luminal diameter reduction) or total occlusion of the coronary artery supplying the region with reverse redistribution (Table 1). In 21 of these 26 regions, well-developed collaterals (grade 2 or 3) were present, and 5 were also supplied by a patent bypass graft. Bypass grafts supplied another 4 regions with critical stenoses and grade 0 or 1 collateral circulation. Among the 10 patients without critical stenosis of the artery supplying the region of reverse redistribution, none had angiographically demonstrable collateral vessels.

### Effect of Thallium Rejection

Reinjection of thallium-201 after redistribution imaging resulted in significant tracer uptake in regions with reverse redistribution in 32 of the 39 patients, according to the quantitative criteria outlined above (positive reinjection effect). An example of this effect is shown in Fig 1. In the regions with reverse redistribution in the other 7 patients, the perfusion defect on the redistribution image persisted after reinjection (negative reinjection effect). Relative thallium-201 activities by quantitative analysis on stress, redistribution, and reinjection images in regions with reverse redistribution for each of the 39 patients are shown in Fig 2. In the patients with a positive reinjection effect, the mean regional activity increased from 67 ± 10% after redistribution to 84 ± 13% after reinjection, a value comparable to the activity during stress imaging of 81 ± 12%. In contrast, the mean activity in the other 7 patients was unchanged between the redistribution (58 ± 9%) and reinjection images (59 ± 9%), both values being significantly lower \((P < .05)\) than the value on the stress images (70 ± 8%).

Fig 3 summarizes the comparison between patients with a positive and a negative effect of thallium-201 reinjection in regions with reverse redistribution, with respect to electrocardiographic Q waves, regional wall motion, and coronary angiographic findings. Only 8 of 32 (25%) patients with enhanced thallium-201 uptake after reinjection had Q waves compared with 5 of the 7 patients (71%) not showing a positive reinjection effect \((P < .05)\). Akinetic or dyskinetic wall motion was identified in only 3 of 32 patients (9%) responding positively to reinjection as compared with akinetic wall motion in 5 of the 7 patients (71%) showing no thallium uptake after reinjection \((P < .01)\). Among the patients with angiographic data, totally occluded or critically stenosed coronary arteries \((>75\%\) reduction in luminal diame-
ter) supplied 24 of 29 (83%) regions with enhanced thallium-201 uptake after reinjection; in contrast, only 2 of 7 (28%) regions not responding to reinjection were supplied by a critically stenotic artery (P<.05). Grade 2 or 3 collateral circulation was observed in 23 of 29 (79%) reverse redistribution regions with a positive thallium reinjection effect compared with only 1 of the 7 regions (14%) with negative effect of thallium-201 reinjection (P<.01).

Among patients with enhanced thallium-201 activity after reinjection in the regions with reverse redistribution, 30% of all myocardial regions had normal thallium uptake during exercise, 36% had reversible defects, 25% had reverse redistribution, and 9% had irreversible perfusion defects (Fig 4). In the patients with no thallium-201 uptake after reinjection in regions with reverse redistribution, a comparable proportion of regions had normal activity (27%) and reverse redistribution (23%); however, these latter patients had significantly fewer regions with reversible (17%) defects and a greater proportion of irreversible defects (33%) compared with patients with a positive effect of thallium reinjection (P<.05).

**FDG/Flow Patterns in Regions With Reverse Redistribution**

Among the 16 patients studied by PET, 11 exhibited normal FDG/flow patterns in the regions with reverse redistribution. Three other patients showed a pattern of FDG to blood flow mismatch, and the remaining 2 patients showed severely reduced FDG uptake (<50% of the reference region) with concomitant reduction in blood flow (Table 2). The 14 patients with normal or mismatch patterns of FDG uptake and flow in the regions of reverse redistribution all showed enhanced thallium activity with reinjection. Only the 2 patients with severely reduced FDG uptake failed to demonstrate enhanced thallium activity after reinjection in the regions of reverse redistribution (Table 2).

**Discussion**

The results of this investigation in patients with chronic stable coronary artery disease demonstrate that thallium reinjection results in enhanced thallium activity in the majority (82%) of regions with reverse redistribution. Regions with reverse redistribution and improved thallium uptake after reinjection were associated with absence of electrocardiographic and functional indices of myocardial necrosis such as pathological Q waves and akinetic or dyskinetic wall motion. In addition, normal or mismatch patterns of FDG uptake and blood flow were observed by
PET imaging in such regions. Conversely, regions with reverse redistribution in which thallium reinjection failed to increase relative thallium activity were associated with Q waves, severely impaired wall motion, and severely reduced FDG uptake and regional blood flow by PET.

Our results confirm previous reports that reverse redistribution may occur in areas supplied by occluded or severely stenosed coronary arteries as well as in regions served by patent native or grafted vessels. However, our data also indicate that not all regions demonstrating the phenomenon of reverse redistribution are alike. Myocardial viability assessed by thallium reinjection and confirmed by PET criteria was detected in areas of reverse redistribution that were supplied by critically stenosed or totally occluded vessels but not in several regions in which there was no angiographically apparent restriction to flow. Furthermore, the development of prominent collateral circulation was strongly associated with improved thallium uptake after reinjection and PET evidence for myocardial viability within regions of reverse redistribution.

Previous studies using thallium reinjection after stress-redistribution imaging have shown that thallium uptake after reinjection in regions with irreversible defects on redistribution images is a reliable marker of viable myocardium. This is supported by improvement in regional wall motion after revascularization procedures as well as by preserved metabolic activity by PET. The results of this study also show good concordance between enhanced thallium uptake after reinjection and FDG uptake in regions with reverse redistribution, thus demonstrating myocardial viability in the majority of regions with this type of defect.

It might be argued that if thallium uptake is normal during stress, it should constitute sufficient evidence for myocardial viability in regions with reverse redistribution. However, in the context of chronic coronary artery disease as well as in patients recovering from an acute myocardial infarction, reverse redistribution of thallium has been reported to represent regions of apparently necrotic myocardium, as reflected by impaired wall motion.

Despite experimental evidence that an acute ischemic or hypoxic insult to the myocardial cell (sufficiently severe as to cause cell death) will result in reduced myocardium extraction of thallium, other studies have shown that, under specific conditions of reperfusion after an acute ischemic insult, even reversibly damaged myocardium may have initial thallium-201 uptake. Furthermore, in vivo and in vitro experimental data suggest that an accelerated clearance of thallium from reperfused myocardium after ischemia is a reliable indicator of nonsalvaged myocardium despite normal initial thallium-201 uptake. It is important to note that these observations in experimental models of acute myocardial ischemia, suggesting that normal initial uptake of thallium-201 does not necessarily indicate normal cellular function, may not pertain to many of the clinical conditions in which reverse redistribution appears. This would be the case particularly in patients with chronic stable coronary artery disease. Although the exact mechanism of the redistribution of thallium-201 after injection during stress has not been fully elucidated, the concept that thallium redistribution is associated with cellular functional integrity in jeopar-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normalized Thallium Activity</th>
<th>Normalized FDG Activity</th>
<th>Blood Flow, mL·g⁻¹·min⁻¹</th>
<th>FDG/Flow Pattern</th>
<th>Coronary Angiography</th>
<th>% Stenosis</th>
<th>Collaterals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>60</td>
<td>85</td>
<td>0.83</td>
<td>Normal</td>
<td>Normal</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>98</td>
<td>84</td>
<td>96</td>
<td>0.97</td>
<td>Normal</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>99</td>
<td>69</td>
<td>99</td>
<td>1.08</td>
<td>Normal</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>77</td>
<td>88</td>
<td>1.35</td>
<td>Mismatch</td>
<td>&gt;75%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>52</td>
<td>53</td>
<td>0.63</td>
<td>Scar</td>
<td>&gt;75%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>93</td>
<td>81</td>
<td>91</td>
<td>1.08</td>
<td>Normal</td>
<td>&gt;75%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>96</td>
<td>62</td>
<td>97</td>
<td>0.95</td>
<td>Normal</td>
<td>&gt;75%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>90</td>
<td>72</td>
<td>103</td>
<td>0.74</td>
<td>Normal</td>
<td>100%*</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>85</td>
<td>72</td>
<td>85</td>
<td>1.73</td>
<td>Normal</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>85</td>
<td>65</td>
<td>81</td>
<td>0.55</td>
<td>Mismatch</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>78</td>
<td>65</td>
<td>68</td>
<td>0.60</td>
<td>Scar</td>
<td>100%*</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>91</td>
<td>75</td>
<td>99</td>
<td>0.78</td>
<td>Normal</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>99</td>
<td>77</td>
<td>98</td>
<td>0.85</td>
<td>Normal</td>
<td>&lt;50%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>91</td>
<td>81</td>
<td>94</td>
<td>0.74</td>
<td>Normal</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>90</td>
<td>81</td>
<td>90</td>
<td>0.73</td>
<td>Mismatch</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>79</td>
<td>67</td>
<td>88</td>
<td>1.30</td>
<td>Normal</td>
<td>&gt;75%</td>
<td></td>
</tr>
</tbody>
</table>

PET indicates positron emission tomography; Redist, redistribution; Reinj, reinjection; and FDG, ¹⁸F-fluorodeoxyglucose. See text for definition of PET imaging patterns.

*Regions supplied by patent grafts.

It is important to note that these observations in experimental models of acute myocardial ischemia, suggesting that normal initial uptake of thallium-201 does not necessarily indicate normal cellular function, may not pertain to many of the clinical conditions in which reverse redistribution appears. This would be the case particularly in patients with chronic stable coronary artery disease. Although the exact mechanism of the redistribution of thallium-201 after injection during stress has not been fully elucidated, the concept that thallium redistribution is associated with cellular functional integrity in jeopar-
dized regions is firmly established.\textsuperscript{24,33-35} Thus, reverse redistribution is a condition that might be interpreted as clearly challenging this principle. The findings of the present investigation are relevant to the issue of distinguishing viable and nonviable myocardium in areas of reverse redistribution. This issue is particularly important concerning clinical decisions about further evaluation and alternative management strategies of patients undergoing exercise thallium-201 scintigraphy.

The scintigraphic pattern of reverse redistribution probably represents the composite effect of several distinct and complex mechanisms, as this pattern has been described in association with different types of stress protocols and also with rest redistribution scintigraphy.\textsuperscript{1-8} One possible explanation for reverse redistribution is the relative nature of the perfusion information provided by thallium-201. Changes in relative thallium activity are analyzed in comparison to the other adjacent, apparently normal myocardial regions. In patients with severe multivessel disease, abnormal flow conditions during stress may prevail in many myocardial regions, making it difficult to appreciate subtle regional differences in thallium-201 availability and uptake. This concept is highlighted by the coronary angiographic data of the 36 patients in whom coronary angiography was performed. The reference region for "normal" thallium uptake on exercise (defined as the region with maximal thallium activity) was supplied by native arteries with significant stenoses in 15 patients and by bypass grafts in 10 patients. In addition, in the 11 patients whose thallium reference region was supplied by arteries without significant stenoses and in the 10 with bypass grafts, extensive involvement of these vessels in supplying collaterals to other myocardial regions was noted. Therefore, flow to the region with reverse redistribution may have actually been restricted during exercise but may have appeared normal relative to a reference region that itself had an impairment in blood flow with exercise. At rest, absolute regional flow values measured by PET in the regions with reverse redistribution were usually within normal limits (11 of 16 patients). Only 3 patients showed an FDG to blood flow mismatch pattern, indicative of myocardial ischemia at rest, in the regions with reverse redistribution.

Another possible mechanism for the appearance of reverse redistribution is thallium washout in normal territories. As ischemic areas may show a net positive uptake of thallium-201 during the redistribution period, this could give rise to the appearance of accelerated washout and reverse redistribution in normal territories. However, our data do not support this simple explanation. In comparison to the normal regions, regions with reverse redistribution had an intrinsically faster washout rate during the redistribution period.

In this study, SPECT imaging was used to define reverse redistribution. Therefore, no background subtraction is involved, and uniform filtering during reconstruction excludes spurious reverse redistribution.\textsuperscript{36,37} It is also unlikely that spillover from adjacent lung tissue and underestimation of background could be responsible for the appearance of reverse redistribution\textsuperscript{36} because the majority of the patients in this study showed no increased lung uptake of thallium-201 during stress and the lung washout rates were not fast in comparison with the myocardial washout rates measured in the regions with reverse redistribution.

Several mechanisms could contribute to an explanation of reverse redistribution. First, the thallium clearance rate is faster in regions with expanded interstitial space.\textsuperscript{36} Second, collateral circulation may have peculiar regulatory mechanisms, and it is possible that regions supplied by collaterals may exhibit higher flow rates at rest, a condition associated with faster thallium-201 washout rates.\textsuperscript{34} Third, impairment in the myocardial retention of thallium may exist in regions with reverse redistribution. Accelerated thallium-201 efflux resulting from acute ischemic insults has been demonstrated in experimental conditions and after reperfusion\textsuperscript{25,31} and can be a contributory mechanism leading to reverse redistribution in viable myocardium after reperfusion by thrombolytic therapy.\textsuperscript{6-8}

Although extraction and washout disturbances are reportedly avoided as long as irreversible sarcolemmal membrane injury is prevented in experimental models of acute ischemia,\textsuperscript{26} the efflux of potassium analogues that is detected during myocardial injury is not a definitive marker of cell death, because early revascularization is capable of restoring potassium homeostasis.\textsuperscript{38} Whether such factors may also affect thallium washout in chronic ischemic heart disease is uncertain. However, other disease states such as cardiomyopathy and ventricular preexcitation syndromes also may show reverse redistribution in the absence of detectable coronary artery disease,\textsuperscript{39,40} suggesting that the rapid washout of thallium-201 also may be caused by an impaired ability to retain the tracer and not only by a defect in perfusion. In the reverse redistribution defects of our study population, in which the majority of the regions were supplied by vessels with severe stenoses, both mechanisms are conceivably operative.

In regions with reverse redistribution that do not improve after reinjection and that are supplied by noncritically stenosed coronary arteries or by patent surgical grafts, an admixture of some viable myocardium and predominant fibrotic tissue is the most likely explanation. Since patients who show this scintigraphic pattern have 2- or 3-vessel coronary artery disease, the consequence may be uniformly reduced thallium uptake in all myocardial regions during stress, with consequent overestimation of thallium uptake in a region that may have predominantly scarred myocardium mixed with some viable tissue. This concept is supported by the large proportion of adjacent irreversible defects present in patients not responding to reinjection. The predominant scarred tissue is unmasked during redistribution because the intermingled viable myocardium will sustain a faster thallium washout rate, in keeping with its relatively high flow,\textsuperscript{34} as compared with areas supplied by critically stenosed vessels, which will show slower tracer clearance rates. The intriguing finding that only 5 of 7 such regions showing no improvement on thallium reinjection were supplied by arteries without critical stenoses may be the result of late revascularization after a previous acute ischemic episode, resulting in open vessels directed toward necrotic zones.
The data from this study clearly are not applicable to other clinical conditions showing reverse redistribution on thallium scintigraphy, such as patients showing acute refraction after acute reperfusion. Also, because of the relatively small number of patients, further studies in patients with chronic coronary artery disease are warranted before definitive clinical conclusions are drawn. Finally, although several plausible hypotheses have been discussed, a precise definition of its causative mechanisms for the phenomenon of reverse redistribution cannot be provided by the available data.

Conclusions

In summary, our data demonstrate that the majority of myocardial regions manifesting reverse redistribution have substantial uptake of thallium with reinjection of the tracer at rest. That this uptake of thallium represents viable myocardium is supported by preserved regional wall motion in the majority of such regions and by preserved myocardial metabolism as reflected by FDG uptake by PET imaging in a subset of patients. These findings provide evidence that thallium reinjection may be useful for distinguishing viable from nonviable myocardium in regions with reverse redistribution.

Acknowledgments

Dr Marin-Neto was supported by the Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (90/1066.1).

References


Thallium reinjection demonstrates viable myocardium in regions with reverse redistribution.

Circulation. 1993;88:1736-1745
doi: 10.1161/01.CIR.88.4.1736
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/4/1736

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/