Regional Thallium Uptake in Irreversible Defects

Magnitude of Change in Thallium Activity After Reinjection Distinguishes Viable From Nonviable Myocardium

Vasken Dilsizian, MD; Nanette M.T. Freedman, PhD; Stephen L. Bacharach, PhD; Pasquale Perrone-Filardi, MD; and Robert O. Bonow, MD

Background. Thallium reinjection immediately after stress-redistribution imaging identifies ischemic but viable myocardium in as many as 50% of the regions characterized by conventional redistribution imaging as irreversibly injured. However, we have previously shown that some regions in which irreversible defects persist despite reinjection are metabolically active, and hence viable, by positron emission tomography. In the current study, we determined whether the severity of reduction in thallium activity within irreversible defects on redistribution images and the magnitude of change in regional thallium activity after reinjection can further discriminate viable from nonviable myocardium in such defects.

Methods and Results. We studied 150 patients with coronary artery disease by exercise thallium tomography using the rest-reinjection protocol. The three sets of images (stress, redistribution, and reinjection) were then analyzed quantitatively. The increase in regional thallium activity from redistribution to reinjection was computed, normalized to the increase observed in a normal region, and termed “differential uptake.” Of the 175 myocardial regions designated to have irreversible thallium defects on conventional 3-4-hour redistribution images, 132 had only mild-to-moderate reduction in thallium activity (51–85% of normal activity), and 43 had severe reduction in thallium activity (≤50% of normal activity). Thallium reinjection resulted in enhanced relative activity in 60 of 132 (45%) of the mild-to-moderate irreversible defects and 22 of 43 (51%) of the severe irreversible defects, leaving roughly half of these defects remaining irreversible after reinjection. However, in regions that appeared to remain irreversible despite reinjection, the magnitude of differential uptake differed between mild-to-moderate (74±14%) and severe (35±16%) irreversible defects (p<0.001). All regions with mild-to-moderate defects demonstrated >50% differential uptake after reinjection. In contrast, all except two of the regions with severe irreversible defects demonstrated differential uptake of <50%. Fifteen patients also underwent positron emission tomography at rest with 18F-fluorodeoxyglucose (FDG) and 15O-water. FDG uptake was present in 91% of regions with mild-to-moderate reduction in thallium activity, and the results of differential uptake and FDG data were concordant in 81% of these regions.

Conclusions. These data indicate that the magnitude of thallium uptake after reinjection differs between mild-to-moderate and severe irreversible defects on standard 3-4-hour redistribution images. The substantial differential uptake of thallium (>50%) after reinjection in mild-to-moderate defects, even when relative thallium activity does not increase appreciably (and the defect appears to remain irreversible), coupled with preserved metabolic activity by positron emission tomography, supports the concept that such mild-to-moderate irreversible defects represent viable myocardium. (Circulation 1992;85:627–634)

In addition to detecting coronary artery stenosis, thallium scintigraphy has played an important role in distinguishing ischemic from infarcted myocardium. Because the uptake of thallium by the myocardial cell is dependent on regional blood flow and an intact sarcolemma, such uptake can be used as
an index of both regional perfusion and myocardial viability.

Numerous studies have shown that irreversible thallium defects on standard exercise-redistribution imaging overestimate both the frequency and severity of myocardial fibrosis. It has subsequently been demonstrated that thallium reinjection detects viable myocardium in as many as 50% of regions that would otherwise be interpreted as scar on the basis of "irreversible" perfusion abnormalities on conventional redistribution imaging. That myocardial regions identified by thallium reinjection represent viable myocardium is supported by improvement in both regional perfusion and regional wall motion after revascularization. Twenty-four-hour delayed imaging after thallium reinjection appears to render no further insights regarding myocardial viability, with the exception of only occasional patients (6% of patients) in whom 24-hour images identify viable myocardial regions (on the basis of late redistribution) that were undetected on the images immediately after reinjection.

By convention, regional thallium activity on exercise and redistribution images is expressed as a percent of the activity in a normal reference region (defined as the region with peak activity on the stress study). This normalization method may be misleading when applied to rest reinjection studies, in that an irreversible defect on redistribution images may appear to remain irreversible after reinjection if the increase in thallium activity in the normal reference region is greater than the increased activity in the region with the thallium defect. Thus, a defect may appear to persist after reinjection even if the underlying myocardium is viable and the increase in actual thallium activity is substantial.

The differential uptake ratio, which reflects the regional augmentation of thallium after reinjection, is an index of regional blood flow at rest, which may be substantially greater than the blood flow in an ischemic region during exercise. Therefore, the current study was designed to determine whether quantitative analyses of the magnitude of change in regional thallium activity after reinjection rather than relative thallium levels after reinjection, in addition to the severity of reduction in thallium activity within irreversible defects on redistribution images, may further distinguish viable from nonviable myocardium.

**Methods**

**Patient Selection**

We studied 150 patients with chronic stable coronary artery disease. The patients ranged in age from 26 to 79 years (mean age, 58 years); there were 128 men and 22 women. All patients underwent a history and physical examination, chest x-ray, electrocardiography, exercise thallium single photon emission computed tomography (SPECT) and coronary arteriography. Coronary artery disease was defined as ≥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 67% of patients. 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. Twenty-four patients had undergone previous coronary artery bypass surgery.

**Exercise Thallium SPECT Imaging**

All patients underwent exercise thallium SPECT as previously described. After an overnight fast, patients were exercised on a treadmill and 2 mCi of thallium was injected at peak exercise. SPECT thallium images were obtained using 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) 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 3–4 hours after exercise. Immediately after redistribution, a 1-mCi additional thallium dose was administered at rest, and reinjection images were acquired 10–15 minutes thereafter. From the raw scintigraphic data, short-axis tomograms were reconstructed and the stress, redistribution, and reinjection images were then analyzed using a semiautomatic 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 and reinjection 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 (midlateral wall) and proceeding counterclockwise. The sectors were then grouped and averaged into four myocardial regions: anterior, septal, inferior, and lateral. Quantitative data from two consecutive, 3-pixel-thick, short-axis tomograms representing the midportion of the heart were analyzed.

**Relative regional thallium activity.** 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 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 same corresponding regions in the redistribution and reinjection 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, and reinjection image series. The thallium activity assigned to a given region was the lowest regional activity from the two consecutive tomographic slices. Thus, a myocardial region was considered abnormal in a patient with coronary artery disease if the thallium uptake on the stress image was $>2$ 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 activity on the redistribution or reinjection image exceeded the reproducibility limit in that region for either one of the two consecutive tomograms. 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 in both tomograms (Figure 1). These irreversible thallium defects on redistribution imaging were then subgrouped on the basis of the severity of reduction in thallium activity: mild-to-moderate (51–85% of peak activity) and severe (≤50% of peak) thallium defects.

Magnitude of thallium uptake after reinjection. In addition to analyzing the regional thallium activity relative to activity in normal regions for each of the stress, redistribution, and reinjection studies, we also computed the magnitude of increase in absolute regional thallium activity from redistribution to reinjection studies. In each patient, of the myocardial regions determined to be normal on the stress study, the region with the maximum increase in thallium activity from redistribution to reinjection was used as the normal reference region for that patient. The magnitude of increase in thallium activity from redistribution to reinjection in all other myocardial regions was then computed and normalized to the increase observed in the normal reference region. This value, based on increases in absolute thallium activity, was termed "differential uptake."

Positron Emission Tomography

Fifteen of the 150 patients underwent positron emission tomography (PET) studies to assess regional myocardial perfusion with oxygen-15–labeled water ($\text{H}_2^{15}\text{O}$) and exogenous glucose utilization with $\text{F}^{18}$-fluorodeoxyglucose (FDG) as previously described. 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 after an overnight fast. After a 20-minute transmission scan to correct for attenuation, two separate bolus injections of 12–15 mCi of $\text{H}_2^{15}\text{O}$ 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 following each $\text{H}_2^{15}\text{O}$ injection and for 60–75 minutes after FDG injection. The data acquired at 30 minutes after FDG injection, corresponding to the final 30–45 minutes of data acquisition, were reconstructed to create tomographic images of regional myocardial FDG uptake.

Regional myocardial FDG uptake. 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. To compare relative regional FDG uptake and thallium activity objectively, five myocardial regions of interest representing the posterolateral, anterolateral, anteroapical, posteroseptal, and posteroseptal myocardium were drawn on each FDG tomogram and on each of the three corresponding thallium images. FDG activity, thallium activity, and differential uptake of thallium after reinjection 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 and reinjection 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 percentage of the activity measured in the reference region for each of the exercise, redistribution, and reinjection image series. For each exercise study, thallium activity in any myocardial region measuring <85% of the normal reference region was considered reduced and was 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. Differential uptake of thallium was then computed within each region demonstrating an irreversible thallium defect. The myocardial region on the FDG series that corre-
sponded 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.

**Coronary Arteriography**

Cardiac catheterization was performed using the percutaneous femoral technique. Coronary artery stenosis and graft patency were assessed by experienced cardiologists without knowledge of exercise thallium results. Fifty-seven patients had marked narrowing of one vessel, 42 of two vessels, and 51 of three vessels. 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.

**Statistical Analysis**

Data are presented as mean±SD. Differences between mild-to-moderate and severe irreversible defects and the change in thallium uptake after reinjection were analyzed using the two-tailed unpaired t test. The comparison of regional FDG uptake to relative thallium activity and differential uptake of thallium was performed with χ² analysis.

**Results**

**Analysis of Relative Regional Thallium Activity**

In the 150 patients studied, a total of 432 myocardial regions were identified as abnormal on the stress images, of which 175 defects (40%) were irreversible on conventional 3-4-hour redistribution images. Of these 175 regions, 132 had mild-to-moderate reduction in thallium activity (ranging from 51% to 85% of peak normal activity), and 43 had severe reduction in thallium activity (≥50% of peak normal activity). After thallium reinjection, 60 of 175 (45%) of the mild-to-moderate irreversible defects and 22 of 43 (51%) of the severe irreversible defects demonstrated increased relative thallium activity (Figure 2). Thus, when relative thallium activity was assessed, increased thallium activity after reinjection occurred in a similar percentage of mild-to-moderate and severe irreversible defects. We then assessed the magnitude of differential uptake in these mild-to-moderate and severe irreversible defects.

**Analysis of Regional Increase in Thallium Activity After Reinjection**

There was a gradual but significant decline in the mean differential uptake from normal regions (94±8%) to mild-to-moderate (79±14%) to severe (50±22%) irreversible defects (p<0.001).

**Mild-to-moderate irreversible defects.** The mean relative thallium activity was significantly lower than the mean differential uptake in regions with mild-to-moderate irreversible defects (71±11% versus 79±14%, p<0.001). The individual data representing the magnitude of differential uptake after reinjection in the 132 regions with mild-to-moderate irreversible defects on redistribution images are shown in Figure 3. Thallium reinjection resulted in an increase in thallium activity that was >50% of the increase in normal territories in all regions with mild-to-moderate thallium defects. The magnitude of this increase varied depending on the results of reinjection on relative thallium activity; the mean differential uptake was greater for those regions that appeared to improve after reinjection by relative analysis (85±16%) compared with those regions that appeared to remain fixed by relative analysis despite reinjection (74±14%, p<0.001). The mean relative thallium activities within regions that appeared to improve after reinjection (79±8%) and those regions that appeared to remain fixed (66±9%) were significantly lower than the values of differential uptake in the respective regions (both p<0.001).

**Severe irreversible defects.** The magnitude of differential uptake of thallium in the 43 regions with severe irreversible defects is also shown in Figure 3. The mean differential uptake was 70±15% in severe irreversible regions that showed improvement after reinjection by relative analysis, similar to the mean observed in mild-to-moderate irreversible defects. However, the absolute increase in thallium activity in severe irreversible defects that remained unchanged after reinjection was only 35±16% of the increase in normal territories (p<0.001), with all except two of the regions demonstrating differential uptake of thallium <50%. Examples of patients with mild-to-moderate and severe irreversible thallium defects are shown in Figure 4.

**Comparison of Differential Uptake With Metabolic Activity by PET**

Among the 15 patients who underwent PET studies, a total of 435 myocardial regions were evaluated...
(averaging 29 per patient), of which 169 (39%) were identified as having irreversible defects on redistribution imaging. The frequency of FDG uptake in these regions with irreversible thallium defects depended on the severity of the thallium defect. FDG uptake occurred in 112 (91%) of the 123 regions with only mild-to-moderate reduction in thallium activity and in only 23 (50%) of the 46 regions with severe reduction in thallium activity (p<0.001). Among the myocardial regions with irreversible thallium defects and severe reduction in thallium activity, the results of thallium reinjection and FDG imaging were concordant in 35 regions (76%), with 17 (49%) identified as viable and 18 (51%) identified as scar. In the 11 regions (24%) with discordance between the thallium reinjection and FDG uptake, six regions had FDG uptake alone and five regions had thallium uptake alone after reinjection. We then examined the pattern of differential uptake of thallium in these mild-to-moderate and severe irreversible defects on redistribution images.

**Mild-to-moderate irreversible defects.** There was an excellent correlation between differential uptake of thallium and the results of FDG imaging. Compared with regions that appeared to remain fixed by relative analysis despite reinjection, regions that improved after reinjection showed greater differential uptake (81±15% versus 63±16%, p<0.001) and greater FDG uptake (89±14% versus 83±21%, p<0.05). Among the 123 regions with only mild-to-moderate reduction in thallium activity, differential uptake of ≥50% occurred in 109 (89%) of the regions and FDG uptake of ≥50% occurred in 112 (91%) of the regions. The results of differential uptake and FDG data were concordant in 100 regions (81%), with all regions (except one) identified as viable. In the 23 regions (19%) with discordance between differential uptake and FDG uptake, 13 regions had FDG uptake alone and 10 regions had differential uptake of ≥50% alone.

**Severe irreversible defects.** Similar to the mild-to-moderate irreversible defects, there was a good correlation between differential uptake of thallium and the results of FDG imaging within severe irreversible defects. The mean differential uptake and FDG uptake were greater for those regions that improved after reinjection by relative analysis (61±19% and 66±16%, respectively) compared with those regions.
that appeared to remain fixed by relative analysis despite reinjection (35±21% and 39±15%, p<0.0010, respectively). Among the 46 regions with severe reduction in thallium activity, differential uptake of ≥50% occurred in 21 (46%) regions, of which 15 (71%) were identified as viable by thallium reinjection using the relative regional thallium analysis. Similarly, FDG uptake was preserved in 23 of the 46 regions (50%) with severe reduction in thallium activity. The results of differential uptake and FDG data were concordant in 31 regions (67%), with 14 (45%) identified as viable and 17 (55%) identified as scar. In the 15 regions with discordance between differential uptake and FDG uptake, nine regions had FDG uptake alone and six regions had differential uptake of ≥50% alone.

**Discussion**

Reinjection of 201TI at rest immediately after stress-redistribution imaging provides evidence of myocardial viability by demonstrating thallium uptake in regions with apparently “irreversible” defects on the standard redistribution images.7-11 That these regions indeed represent viable myocardium has been supported by improvement in both regional perfusion and regional wall motion after revascularization and by evidence of preserved metabolic activity on PET.7,9,12 In addition, gated magnetic resonance studies indicate that myocardial regions with irreversible thallium defects that improve after reinjection demonstrate preserved regional systolic wall thickening that is not significantly different from normal segments but is significantly greater than regions that do not improve after reinjection.13

However, we have also observed evidence of metabolic activity, and hence viability, in regions in which thallium defects remain irreversible despite reinjection by using analysis of relative regional thallium activity; this is particularly the case in regions with only mild-to-moderate reduction in thallium activity.12 The results of the current study demonstrate that a substantial increase in thallium activity may occur after reinjection in thallium defects that appear irreversible, and that the magnitude of increase in thallium activity in regions that appear to remain irreversible despite reinjection is significantly greater in mild-to-moderate defects than in severe irreversible defects (Figure 3). All regions with mild-to-moderate defects demonstrated ≥50% differential uptake after reinjection. The substantial uptake of thallium after reinjection in these mild-to-moderate irreversible defects, even though relative thallium activity may not appear to increase, suggests that these regions represent viable myocardium. This is confirmed by the PET data; in regions with mild-to-moderate reduction in thallium activity, FDG uptake was preserved in 91% of the regions and the results of differential uptake and FDG uptake were concordant in 81% of the regions. The substantial differential uptake of thallium after reinjection in mild-to-moderate irreversible defects, coupled with excellent concordance between the differential uptake and FDG uptake, suggest that most mild-to-moderate irreversible defects represent viable, metabolically active myocardium. These findings are also sup-
ported by the data reported by Gibson and coworkers\(^1\) in patients before and after revascularization. Using conventional stress-redistribution quantitative planar imaging, 57% of mild-to-moderate irreversible thallium defects in their study had improved thallium uptake after coronary artery bypass surgery, in contrast to only 21% of severe irreversible defects.

Among severe irreversible defects in our study, those regions that showed improvement after reinjection by relative analysis had a mean differential uptake of thallium (70±15%) that was similar to that observed in mild-to-moderate defects (Figure 3). However, the mean differential uptake in severe irreversible defects that remained unchanged by relative analysis after reinjection was only 35%, with all except two of these regions demonstrating differential uptake of thallium <50%.

A possible explanation for the observed differences between the conventionally defined relative activity method and the magnitude of thallium uptake by the differential uptake method within irreversible thallium defects may relate to the disproportionate increase in thallium uptake after reinjection relative to the distribution of thallium on redistribution images. The differential uptake ratio, which reflects the regional augmentation of thallium after reinjection, is an index of regional blood flow at rest relative to normal regions, which may be substantially greater than the relative blood flow in an ischemic region during exercise. Thus, given the high likelihood of coronary artery narrowing in the vessel supplying the defect zone, it is likely that the ratio of the increase in thallium activity in the defect zone to the increase in normal regions after reinjection will be disproportionate to the ratio of thallium activities in these regions on redistribution images. In many circumstances, this will result in a measurable increase in the thallium activity ratio between the defect zone and normal zones (and will be viewed as a reversible defect after reinjection), but in other circumstances, the defect may appear to remain irreversible despite a substantial differential uptake ratio. For example, after a stress-redistribution study, if the absolute thallium activity in a region with irreversible thallium defect is 60 and the absolute thallium activity in the normal reference region is 100, the relative regional thallium activity in the defect zone is 60%. After thallium reinjection at rest, if the absolute increase in thallium activity was 30 in the region with irreversible thallium defect and 40 in the normal reference region, then the total thallium activity will be 90 (60+30) in the defect zone and 140 (100+40) in the normal zone. Using the conventionally defined relative uptake method, the relative regional activity after reinjection is 90/140=64%. Thus, when compared with the prereinjection study (60%), the defect zone will appear to be irreversible after reinjection (64%). However, using the differential uptake method, the magnitude of change in regional thallium activity relative to the normal zone is 30/40=75%. Therefore, it should not be surprising to find regions with apparently irreversible thallium defects by the conventionally defined relative uptake method that have substantial increases in the magnitude of thallium activity by the differential uptake method. Based on the current study, myocardial regions demonstrating differential uptake of >50% represent zones with predominantly viable myocardium, which was confirmed by the FDG activity using PET in a subgroup of our patients.

It is also important to note that detection of residual viable myocardium is not equivalent to detection of reversible ischemia. That is, a myocardial segment can be a mixture of scar and viable myocardium that is not rendered ischemic during exercise. Therefore, if the magnitude of increase in thallium uptake from redistribution to reinjection is either proportional to or less than that computed in the defect region (differential uptake equal to or less than relative defect ratio), then that region probably represents a mixture of scar and viable myocardium without ischemia. However, if the magnitude of increase in thallium uptake from redistribution to reinjection is greater than that computed in the defect region (differential uptake greater than relative defect ratio), that region probably represents viable myocardium with inducible ischemia, as the regional blood flow at rest relative to normal regions is greater than the relative blood flow during exercise in that region.

In summary, by demonstrating that there is substantial uptake of thallium in many regions with irreversible thallium defects (using the differential uptake ratio), our data support previous data suggesting that not all irreversible thallium defects indicate scarred myocardium. The observation that irreversible thallium defects with only mild-to-moderately reduced thallium activity almost uniformly demonstrate substantial differential uptake (>50%) after reinjection, coupled with the finding of preserved metabolic activity by PET, supports the concept that the level of thallium activity alone in such regions may be used as evidence of myocardial viability. Thus, if the clinical question is one of viability and not inducible ischemia, our findings show that the majority of mild-to-moderate irreversible defects represent predominantly viable myocardium; therefore, further investigation such as thallium reinjection or PET may not be necessary. However, in regions with severe irreversible defects, when myocardial viability is a clinically relevant issue, thallium reinjection yields important diagnostic insights. In these regions, the results of thallium reinjection and PET appear to provide comparable information.

References
imaging and its fate after myocardial revascularization: Does it represent scar or ischemia? Am Heart J 1985;110:996–1001

KEY WORDS • coronary artery disease • myocardial ischemia • myocardial viability • thallium scintigraphy • positron emission tomography
Regional thallium uptake in irreversible defects. Magnitude of change in thallium activity after reinjection distinguishes viable from nonviable myocardium.

V Dilsizian, N M Freedman, S L Bacharach, P Perrone-Filardi and R O Bonow

Circulation. 1992;85:627-634
doi: 10.1161/01.CIR.85.2.627

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 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/85/2/627