Differential Uptake and Apparent $^{201}$Tl Washout After Thallium Reinjection

Options Regarding Early Redistribution Imaging Before Reinjection or Late Redistribution Imaging After Reinjection

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**Background.** Because thallium reinjection enhances the identification of viable myocardium, many laboratories have adopted the routine practice of performing reinjection imaging instead of 3–4-hour redistribution imaging. This approach assumes that the stress-reinjection protocol provides the necessary information regarding both exercise-induced ischemia and myocardial viability. Because apparent “washout” of thallium may occur between redistribution and reinjection studies, we examined the limitations created by eliminating 3–4-hour redistribution images.

**Methods and Results.** We studied 50 patients with chronic stable coronary artery disease by exercise thallium tomography, radionuclide angiography, and coronary arteriography. Immediately after the 3–4-hour redistribution images, 1 mCi thallium was injected at rest, and images were reacquired both 10 minutes and 24 hours after reinjection. The stress, redistribution, reinjection, and 24-hour images were then analyzed quantitatively, and the magnitude of change in regional thallium activity after reinjection was termed “differential uptake.” Of the 127 abnormal myocardial regions on the stress images, 55 (43%) demonstrated either complete or partial reversibility on 3–4-hour redistribution images. After reinjection, 14 of these regions (25%) demonstrated apparent thallium washout due to low differential uptake of thallium, which was only 46±20% of that observed in normal regions. As a result, the relative thallium activity, which was 55±13% during stress (relative to normal regions) and increased significantly to 75±13% on 3–4-hour redistribution studies ($p<0.001$), decreased to only 58±13% after thallium reinjection. At 24 hours, redistribution again developed in all 14 regions, resulting in a relative thallium activity of 71±16% ($p<0.03$), which was similar to that achieved on 3–4-hour redistribution images. Twelve of the 14 regions (86%) exhibiting apparent washout after reinjection were supplied by a totally occluded coronary artery, of which eight (67%) had normal wall motion at rest. In contrast, only 41% of the regions with either improved or unchanged thallium uptake after reinjection were supplied by a totally occluded coronary artery ($p<0.05$).

**Conclusions.** These data indicate that regions with thallium defects that are reversible on 3–4-hour redistribution images may demonstrate apparent washout of thallium after reinjection due to low differential uptake. Although this occurs in only a small fraction of regions (8%) identified as abnormal on exercise images, these regions represent approximately 25% of regions showing redistribution. Such defects would appear irreversible if redistribution imaging is not performed before reinjection. However, these same myocardial regions also redistribute further after reinjection and are identified as reversible on 24-hour images. Thus, one of two imaging options, either stress-redistribution-reinjection imaging or stress–reinjection–24-hour imaging, may be used for a comprehensive assessment of myocardial ischemia and viability. (*Circulation* 1992;85:1032–1038)

**Key Words** • coronary artery disease • myocardial ischemia • $^{201}$Tl scintigraphy

The identification of ischemic but viable myocardium has become an area of intense interest because it would aid in the decision for myocardial revascularization in patients with impaired left ventricular function. Early studies with conventional exercise-redistribution thallium scintigraphy suggested that thallium redistribution is an accurate marker of myocardial viability and that regions with thallium defects that fail to redistribute might represent scarred myocardium. However, subsequent studies have revealed that lack of thallium redistribution may occur frequently in myocardial regions that are severely ischemic or hibernating but viable. The precision for identifying viable myocardium in such irreversible thallium defects can be improved greatly by additional studies such as late redistribution or reinjection imaging. Furthermore, several recent studies suggest that thallium reinjection techniques predict improvement in regional function after revascularization with a positive predictive value of 80–87% and a negative predictive value of 82–100%. These predictive accu-

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racies achieved with reinjection are similar to those reported for metabolic imaging with positron emission tomography.\textsuperscript{13,14}

Although thallium reinjection significantly improves the identification of viable myocardium, the routine performance of thallium reinjection after redistribution imaging may be logistically difficult for a busy nuclear cardiology laboratory. Considering these logistical concerns, several laboratories have adopted the routine practice of performing reinjection thallium imaging instead of 3–4-hour redistribution imaging. However, apparent “washout” of thallium may occur between redistribution and reinjection images, relative to the differential uptake of the reinjected dose,\textsuperscript{9} and important information may be lost if redistribution images are not obtained. In the present study, we examined the limitations created by elimination of 3–4-hour redistribution images.

**Methods**

**Patient Selection**

The 50 study patients formed the basis of a previous report.\textsuperscript{15} In the previous report, we focused on the results of thallium reinjection and 24-hour imaging in myocardial regions with thallium defects that were irreversible on standard 3–4-hour redistribution imaging. In the present study, we evaluate the impact of thallium reinjection in regions with exercise-induced thallium defects that are reversible on redistribution images.

All 50 patients underwent a history and physical examination, chest radiography, ECG, exercise thallium single-photon emission computed tomography (SPECT), radionuclide angiography, and coronary arteriography. The patients’ ages ranged from 41 to 74 years (mean, 57 years); there were 40 men and 10 women. Coronary artery disease was defined as 50% or greater reduction in luminal diameter of at least one major epicardial coronary artery as determined by coronary arteriography. All cardiac medications were withdrawn before exercise studies in 70% of patients. In the other 30% of patients, the severity of anginal symptoms precluded discontinuation of medical therapy. All patients had chronic stable coronary artery disease; no patient with recent acute myocardial infarction or unstable angina was included in the study. Twelve patients had undergone previous coronary artery bypass graft surgery.

**Exercise Thallium SPECT Imaging**

All patients underwent exercise thallium SPECT as previously described.\textsuperscript{9,15} After an overnight fast, patients were exercised on a treadmill, and 2 mCi 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 centered on the 68-KeV 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 imaging, an additional 1-mCi thallium dose was administered at rest, and reinjection images were acquired 10–15 minutes thereafter. Twenty-four-hour images were acquired the next day. The reconstructed stress, redistribution, reinjection, and 24-hour images were then analyzed.\textsuperscript{9,15}

**Qualitative Thallium Analysis**

The distribution of thallium uptake was interpreted visually in the three standard orthogonal tomographic imaging planes as follows: the septal, apical, and lateral regions in the horizontal long-axis (transaxial) view; the anterior, apical, and inferior regions in the vertical long-axis (sagittal) view; and the anterior, septal, inferior, and lateral regions in the short-axis (oblique) view. Four consecutive representative slices of each view were displayed simultaneously for interpretation. The images were graded by two experienced, blinded observers on a 5-point scale from 0 (markedly reduced or absent activity) to 2 (definitely reduced) to 4 (normal). Differences were resolved by consensus. The grade assigned to a given region was the lowest regional score from all tomographic slices and views. A region was determined to be irreversible if the assigned regional grade was abnormal and remained so on subsequent images. Similarly, a region was determined to be reversible if the assigned abnormal regional grade increased or normalized on subsequent images. In regions where both reversible and irreversible adjacent defects were observed in the same vascular territory, the region was considered partially reversible. Regional thallium washout was defined as a decrease in relative thallium activity between the redistribution and reinjection images that makes a reversible defect appear to become irreversible.

**Quantitative Thallium Analysis**

The program used to analyze the thallium data is quantitative only to the extent of assessing counts in a sector and does not represent per-unit quantitative data at depth. From the raw scintigraphic data, short-axis tomograms were reconstructed and four consecutive representative slices were selected for interpretation using a semiautomatic quantitative circumferential profile as previously described.\textsuperscript{9,15}

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, and 24-hour 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. Mean counts per pixel within each myocardial sector on the exercise, redistribution, reinjection, and 24-hour images were computed. The sectors were then grouped and averaged into four myocardial regions: anterior, septal, inferior, and lateral.

**Relative regional thallium activity.** In each patient, the myocardial region with the maximum mean counts per pixel on the stress thallium study was used as the normal reference region for that patient. The corresponding regions in the redistribution, reinjection, and 24-hour 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 that reference region for each of the stress, redistribution, reinjection,
and 24-hour image series. A myocardial region was considered abnormal if the thallium uptake on the stress image was more than 2 SDs 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 subsequent redistribution, reinjection, or 24-hour 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.\(^\text{\textsuperscript{16}}\)

**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 computed the magnitude of increase in absolute regional thallium activity from redistribution to reinjection studies. In each patient, among 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, which is based on increases in absolute thallium activity, was termed “differential uptake.”\(^\text{\textsuperscript{7, 16}}\)

**Radionuclide Angiography**

Gated blood pool cardiac scintigraphy was performed to assess left ventricular ejection fraction and regional wall motion at rest using red blood cells labeled in vivo with 20–25 mCi \(^{99m}\text{Tc}.\) Imaging was accomplished using a conventional Anger camera equipped with a high-sensitivity, parallel-hole collimator, as previously described.\(^\text{\textsuperscript{17}}\) 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 lower limit of normal for resting ejection fraction by our technique is 45%. Left ventricular ejection fraction in the 50 patients ranged from 19% to 69% (mean, 43±12%) and was below the normal range in 25 patients.

**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. Seventeen patients had marked narrowing of one vessel, 16 of two vessels, and 17 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. The quantitative regional thallium activities for stress, redistribution, reinjection, and 24-hour studies were analyzed using the two-tailed paired \(t\) test. Differences in differential uptake between regions with either improved or unchanged thallium uptake after reinjection and regions demonstrating thallium washout were performed using the two-tailed unpaired \(t\) test. Differences between severity of arteriographic narrowing in regions demonstrating a reduction in relative thallium activity after reinjection (i.e., apparent thallium washout caused by low differential uptake) were compared by \(\chi^2\) analysis with those that showed no change or an increase in relative activity after reinjection. Differences between patients with and those without low differential uptake after reinjection with respect to symptoms of angina, duration of exercise, rate-pressure product, medical therapy, left ventricular function, wall motion abnormalities, and the number of narrowed coronary arteries were analyzed by either two-tailed unpaired \(t\) test or \(\chi^2\) analysis.

**Results**

**Qualitative Thallium Analysis**

Among the 50 patients, 127 myocardial regions were graded visually as abnormal by qualitative analysis on the stress images. Of these, 72 (57%) were either completely or partially reversible on 3–4-hour redistribution images, and 55 demonstrated irreversible abnormalities of relative thallium activity. Among the 72 regions with reversible thallium defects, 63 (87%) demonstrated either no change or further improvement after reinjection, and nine (13%) had apparent thallium washout between the redistribution and reinjection studies. These nine regions occurred in seven of 50 (14%) patients. Twenty-four-hour studies obtained after reinjection demonstrated redistribution in all regions with apparent thallium washout.

**Quantitative Thallium Analysis**

A total of 127 myocardial regions were identified as abnormal by quantitative analysis of the exercise studies, a quantity identical to the results of the visual scoring. Of these, 55 (43%) were either completely or partially reversible on 3–4-hour redistribution images, and the remaining 72 (57%) were considered to have persistent defects. After reinjection, relative thallium activity increased in 37 of the 72 regions (51%) with apparently fixed defects, as previously described in these patients,\(^\text{\textsuperscript{15}}\) with an increase in mean regional activity from 57±13% during redistribution imaging to 70±14% during reinjection imaging and no further change after 24 hours (71±14%). Mean regional thallium activity for all 72 regions on stress images was 53±14%.

**Reversible regions on redistribution images.** Of the 55 regions that were either completely or partially reversible on redistribution images, 41 (75%) demonstrated either no change or further improvement after thallium reinjection. The remaining 14 regions (25%) demonstrated the phenomenon of apparent thallium washout due to low differential uptake after rest reinjection. These 14 regions occurred in nine patients and represent only 8% of all abnormal regions identified in these 50 patients.

Relative regional thallium activity in the 41 regions with either improved or unchanged thallium uptake after reinjection increased from 51±14% on stress images to
72±14% during redistribution imaging and 75±16% after reinjection with no further change after 24 hours (78±15%). In these regions, thallium reinjection resulted in a differential uptake of 74±16% by analysis of changes in absolute thallium activity. In contrast, in the 14 regions demonstrating the phenomenon of apparent thallium washout after reinjection, the differential uptake was only 46±20% (p<0.001). In these 14 regions, the relative thallium activity was 55±13% during stress, increased significantly to 75±13% on 3–4-hour redistribution studies (p<0.001), and then decreased to only 58±13% after thallium reinjection. The individual changes in relative thallium activity in these 14 regions are shown in Figure 1. If the 3–4-hour redistribution images were omitted and the reinjection images alone acquired, these regions would appear (incorrectly) to have irreversible thallium defects.

Twenty-four-hour studies obtained after reinjection in the 14 regions with apparent washout demonstrated redistribution, with an increase in relative thallium activity to 71±16% (p<0.03), which was similar to the mean achieved on the 3–4-hour redistribution images. As apparent in Figure 1, all 14 regions demonstrating redistribution at 3–4 hours and apparent washout after reinjection also showed redistribution at 24 hours. Thus, if the 3–4-hour redistribution study was eliminated, the results of the reinjection–24-hour image sequence would provide information comparable to that obtained from the 3–4-hour redistribution–reinjection image sequence. An example of this effect is illustrated in Figure 2.

Characterization of Patients With Low Differential Uptake

Patient analysis. When the two patient groups—those with and those without low differential uptake—were compared, the patients exhibiting low differential uptake had significantly shorter exercise duration (4±2 versus 7±2 minutes, p<0.01). Despite the reduced exercise tolerance in patients with apparent washout on reinjection, the percentage of patients achieving >80% predicted maximal heart rate (67% versus 57%, p=NS) and the rate-pressure product achieved during exercise (21×10³ versus 24×7×10³, p=NS) were the same in
both groups. There were no differences between the two groups with respect to the number of coronary arteries narrowed, anginal symptoms, medical therapy, left ventricular ejection fraction at rest (44±12% versus 44±12%), or wall motion abnormality at rest.

**Regional analysis.** Of the 14 myocardial regions that demonstrated low differential uptake after thallium reinjection, resulting in apparent thallium washout, 12 (86%) were located in a territory supplied by a totally occluded coronary artery, and two regions were located in the anterior and septal regions of a female patient who had ECG evidence of left bundle branch block. Of the 12 regions supplied by a totally occluded coronary artery, eight (67%) had normal wall motion at rest. Thus, the presence of thallium redistribution coupled with preserved regional wall motion in regions with low differential uptake supports our contention that these regions with apparent thallium washout are viable, despite being supplied by totally occluded coronary arteries. In comparison, among the 41 regions with reversible thallium defects in which relative thallium activity either increased or was unchanged after reinjection, only 17 (41%) were supplied by a totally occluded coronary artery (p<0.05).

**Discussion**

The reinjection of thallium at rest immediately after stress-redistribution imaging identifies viable myocardium in regions that would otherwise be interpreted as scar on the basis of apparently irreversible defects on 3–4-hour redistribution imaging. The uptake of thallium after reinjection represents viable myocardium that has been verified by improved regional perfusion and wall motion after coronary artery revascularization, preserved regional metabolic activity on positron emission tomography, and preserved regional systolic wall thickening by gated magnetic resonance studies. Furthermore, 24-hour delayed imaging after reinjection provides no additional insights regarding myocardial viability in 87–94% of patients with irreversible thallium defects at 3–4-hour redistribution.

The application of thallium reinjection to only selected patients with persistent defects on 3–4-hour redistribution images would reduce the number of reinjection studies that might be required. However, such a procedure would require early identification of patients with irreversible defects and would be difficult to apply in a busy nuclear cardiology laboratory, especially
when a large volume of SPECT studies are performed. To circumvent this practical issue, several laboratories have adopted the routine practice of performing reinjection thallium imaging at 3–4 hours instead of redistribution imaging. This protocol will streamline laboratory procedures and provide the necessary information regarding both exercise-induced ischemia and myocardial viability in the majority of patients. However, our data indicate that there are also important limitations that may result when conventional redistribution studies are eliminated.

In our previous studies, we focused on identification of viable myocardium and hence directed our attention to the outcome of reinjection in irreversible thallium defects. It was in regions with irreversible thallium defects that viability was of clinical concern, because reversible thallium defects on 3–4-hour redistribution imaging connotes ischemic but viable myocardium. Therefore, a reversible thallium defect on 3–4-hour redistribution images was considered to be viable independent of the outcome after reinjection.

However, we have also reported that approximately 10% of thallium defects on stress images develop apparent thallium washout after reinjection of thallium.9 These regions represented 19% of myocardial regions that were reversible on 3–4-hour redistribution. This apparent washout 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 termed “differential uptake.”9,10 Unlike conventional redistribution imaging, in which washout reflects an actual net loss of thallium activity between stress and redistribution imaging, it is the low differential uptake of thallium after reinjection that is responsible for the appearance of washout. Realizing this phenomenon, it is therefore important to determine the ideal cardiac imaging options with thallium reinjection. That is, it is unclear whether all three images (stress, 3–4-hour redistribution, and reinjection) are necessary for a comprehensive assessment of myocardial ischemia and viability or whether late 24-hour imaging after reinjection can provide information comparable to 3–4-hour redistribution images within regions demonstrating the phenomenon of reduced differential uptake.

The results of the current investigation, involving a different series of patients, are remarkably similar to those of our original report9 in that 8% of thallium defects identified on stress images demonstrated apparent thallium washout due to low differential uptake of the tracer. These regions represented 25% of myocardial regions that were reversible on 3–4-hour redistribution; these would have been incorrectly interpreted to be irreversible defects if only stress-reinjection images were acquired. Twenty-four-hour images obtained after reinjection demonstrated further redistribution, resulting in relative thallium activities that were indistinguishable from those observed on the 3–4-hour redistribution images. Therefore, these data indicate that elimination of the 3–4-hour redistribution images and reliance on reinjection images alone would incorrectly designate 25% of ischemic myocardial regions as scar. However, these data also suggest that if such isolated reinjection images were followed by 24-hour studies, the results of the 24-hour studies provide information comparable to those acquired at 3–4 hours.

We have previously shown that when reinjection is performed after 3–4-hour redistribution imaging, very few irreversible defects after reinjection show further redistribution at 24 hours.15 This has subsequently been confirmed by Dae and associates.20 Thus, 24-hour images are not required to further investigate irreversible defects after reinjection when reinjection follows 3–4-hour redistribution studies. However, if reinjection imaging is performed in isolation without the intervening 3–4-hour redistribution study (which has become routine practice in several nuclear cardiology laboratories), then a much larger number of apparently irreversible defects after reinjection will show late redistribution at 24 hours, giving the false impression that 24-hour imaging is necessary after thallium reinjection. The mechanism for this apparent discrepancy is apparent from our data as depicted in Figure 1. If the 3–4-hour redistribution images are not obtained, regions with low differential uptake after reinjection (with apparent thallium washout) appear to have irreversible defects on the reinjection images, with redistribution only on late imaging. It is also apparent in Figure 1 that 11 of the 14 myocardial regions (79%) demonstrating low differential uptake and apparent thallium washout could have been predicted to be viable on the basis of the severity of the reduction in thallium activity on the initial images alone (>50% of peak normal activity).16,18 However, information regarding exercise-induced myocardial ischemia would have been lacking if only stress-reinjection images were acquired.

In summary, apparent thallium washout due to low differential uptake of the tracer may occur after thallium reinjection. Although regions demonstrating this phenomenon represent only a small fraction of regions identified as abnormal on exercise images (8%), they represent a sizeable percentage of regions (25%) that are reversible on 3–4-hour redistribution images. Late (24-hour) redistribution images identify the same reversibly ischemic myocardial regions with low differential uptake after thallium reinjection that would be detected on 3–4-hour redistribution images. Thus, two imaging options appear to provide comparable information for identifying most of the ischemic but viable myocardial regions. In those patients with persistent irreversible defects on stress-reinjection studies, 24-hour imaging after reinjection appears to be a reasonable alternative to stress–3–4-hour redistribution–reinjection imaging.

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