Thallium Reinjection After Stress-Redistribution Imaging

Does 24-Hour Delayed Imaging After Reinjection Enhance Detection of Viable Myocardium?

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Background. Thallium reinjection immediately after conventional stress-redistribution imaging improves the detection of viable myocardium, as many myocardial regions with apparently "irreversible" thallium defects on standard 3–4-hour redistribution images manifest enhanced thallium uptake after reinjection. Because the 10-minute period between reinjection and imaging may be too short, the present study was designed to determine whether 24-hour imaging after thallium reinjection provides additional information regarding myocardial viability beyond that obtained by imaging shortly after reinjection.

Methods and Results. We studied 50 patients with chronic stable coronary artery disease undergoing exercise thallium tomography, radionuclide angiography, and coronary arteriography. Immediately after the 3–4-hour redistribution images were obtained, 1 mCi thallium was injected at rest, and images were reacquired at 10 minutes and 24 hours after reinjection. The stress, redistribution, reinjection, and 24-hour images were then analyzed qualitatively and quantitatively. Of the 127 abnormal myocardial regions on the stress images, 55 had persistent defects on redistribution images by qualitative analysis, of which 25 (45%) demonstrated improved thallium uptake after reinjection. At the 24-hour study, 23 of the 25 regions (92%) with previously improved thallium uptake by reinjection showed no further improvement. Similarly, of the 30 regions determined to have irreversible defects after reinjection, 29 (97%) remained irreversible on 24-hour images. These findings were confirmed by the quantitative analysis. The mean normalized thallium activity in regions with enhanced thallium activity after reinjection increased from 57±13% on redistribution studies to 70±14% after reinjection but did not change at 24 hours (71±14%). In regions with irreversible defects that were unaltered by reinjection, mean regional thallium activity did not differ from the reinjection to the 24-hour studies (57±17% and 58±17%, respectively). Twenty-four-hour imaging after reinjection showed improvement in only four of 35 irreversible regions (involving three of the 50 patients).

Conclusions. These data indicate that thallium reinjection at rest after 3–4 hours of redistribution provides most of the clinically relevant information pertaining to myocardial viability in regions with apparently irreversible thallium defects. Hence, thallium reinjection may be used instead of 24-hour imaging in most patients in whom a persistent thallium defect is observed on conventional redistribution images. (Circulation 1991;83:1247–1255)

The distinction between viable, but ischemic, myocardium and irreversibly scarred myocardium is critical in the evaluation of patients with coronary artery disease, especially when invasive interventions are contemplated for myocardial salvage. We recently demonstrated that thallium reinjection after conventional 3–4-hour redistribution imaging results in enhanced thallium uptake within apparently "irreversible" thallium defects, which is compatible with viable myocardium.1–3 Although other methods have been shown to identify viable myocardium within such irreversible thallium defects,4–8 there are practical considerations that may limit their routine application. Eight- to 72-hour delayed thallium imaging is inconvenient and often

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yields poor image quality. Positron emission tomography is very expensive and at present not readily available.

In our previous studies using thallium reinjection,1-3 repeated images were acquired only 10 minutes after the administration of the reinjected dose of thallium at rest. Repeated imaging this soon after reinjection may be too early for the optimal determination of viable myocardium because this imaging protocol does not allow for the further redistribution of the reinjected thallium dose. Thus, the present study was designed to determine whether 24-hour imaging after thallium reinjection provides additional information regarding myocardial viability beyond that obtained by reinjection.

Methods

Patient Selection

We studied 50 patients with coronary artery disease. All patients underwent a history and physical examination, chest radiography, electrocardiography, coronary arteriography, radionuclide angiography, and exercise thallium single-photon emission computed tomography (SPECT). Coronary artery disease was defined as 50% or more 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 70% of patients. These protocol studies were approved by the Institutional Clinical Research Subpanel of the National Heart, Lung, and Blood Institute on October 19, 1988, and all patients gave informed consent. 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. Sixty-six percent of patients had electrocardiographic evidence of previous myocardial infarction. Twelve patients had undergone previous coronary artery bypass surgery. The patients’ ages ranged from 41 to 74 years (mean, 57 years); there were 40 men and 10 women. Patients were included in the study only if they demonstrated a persistent thallium defect on conventional visual interpretation of 3-4-hour redistribution images, which was defined as either partially reversible or irreversible. Selection of patients for this reinjection protocol was done without knowledge of the patients’ coronary anatomy or left ventricular function.

Exercise Thallium SPECT Imaging

All patients underwent exercise thallium-201 SPECT as previously described.1 After an overnight fast, exercise thallium scintigraphy was performed according to a standardized multistage treadmill exercise test with continuous monitoring of symptoms, electrocardiogram, heart rate, and blood pressure. Sixty percent of the patients achieved greater than 80% predicted heart rate during exercise. At peak exercise, 2 mCi TI201 was administered intravenously, and the patient continued exercise for an additional 45-60 seconds. After termination of exercise, thallium images were obtained with a wide-field-of-view rotating gamma camera equipped with a low-energy, medium-resolution, high-sensitivity, parallel-hole collimator (Apex 415, APC-3, Elscint Co., Boston) centered on the 68-keV photo peak with a 20% window. The camera was rotated through a 180° arc in an elliptical orbit about the patient’s thorax from 40° right anterior oblique to 40° left posterior oblique at 6° increments for 30 seconds each. Redistribution images were acquired 3-4 hours after exercise. Immediately after redistribution imaging, all patients were then reinjected with an additional 1 mCi TI201 at rest, and images were reacquired within 10-15 minutes of the second dose, with the same imaging protocol as that used for stress and redistribution image acquisition. Twenty-four-hour images were acquired the next day with the same imaging parameters as used for reinjection in the first 28 patients. However, because of suboptimal image quality (despite the additional 1-mCi reinjection dose) and low counts observed on 24-hour studies compared with the stress, redistribution, and reinjection images, the imaging time was subsequently increased to 45 sec/6° increment in the next 22 patients, which is consistent with the acquisition time used in previously published reports of late redistribution imaging without the benefit of the additional 1-mCi thallium boost.5,6

From the raw scintigraphic data, short-axis, vertical long-axis, and horizontal long-axis tomograms were reconstructed, and four consecutive representative slices of each view were selected for interpretation. The reconstructed stress, redistribution, reinjection, and 24-hour images were then analyzed both qualitatively and quantitatively.

Qualitative Thallium Analysis

The distribution of thallium uptake was analyzed qualitatively 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. The stress, redistribution, reinjection, and 24-hour images were all normalized to the region with the maximal myocardial activity in the stress images. 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) and 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 the same abnormal grade on subsequent images. Similarly, a region was determined to be reversible if the assigned abnormal regional grade increased or normalized on subse-
quent images. In regions where both reversible and irreversible adjacent defects were observed in the same vascular territory, the region was assigned to be partially reversible.

**Quantitative Thallium Analysis**

The thallium images were also analyzed with a semiautomatic, quantitative, circumferential profile analysis applied to the short-axis thallium tomograms as previously described. 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 on 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 gravity of the tomograms. All 64 sectors were of equal arc and were constructed beginning at 3 o’clock (midlateral wall) and proceeding counterclockwise. The mean counts per pixel within the myocardial sectors of all redistribution, reinjection, and 24-hour images were normalized to the activity in the sector with greatest thallium activity in the stress images. To facilitate comparison of these data with the qualitative interpretations, the sectors were then grouped and averaged into four myocardial regions as shown in Figure 1.

A myocardial region was considered abnormal in a patient with coronary artery disease if the thallium uptake on the stress image was greater than 2 SD lower than 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 irreversibly abnormal if the normalized thallium activity in that region on subsequent images did not increase more than the reproducibility limit for that region. Alternatively, a region with reduced activity on the stress study was considered reversibly ischemic if the increase of normalized thallium uptake on the redistribution, reinjection, or 24-hour image exceeded the reproducibility limit for that region.

**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 technetium-99m. Imaging was accomplished with a conventional Anger camera equipped with a high-sensitivity, parallel-hole collimator as previously described. 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% with a reproducibility limit of 4%. 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 with the percutaneous femoral technique. Coronary artery stenosis and graft patency were assessed by experienced cardiologists without knowledge of exercise thallium scintigraphy results. Thirty-four percent of the patients had significant one-vessel, 32% had two-vessel, and 34% had three-vessel coronary artery disease. 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**

The quantitative regional thallium uptake for stress, redistribution, reinjection, and 24-hour studies, normalized for peak activity on the stress study, were analyzed with a two-tailed paired t test. Differences between severity of arteriographic narrowing, wall motion abnormality, presence of electrocardiographic Q wave, peak heart rate achieved during exercise, and anginal symptoms in patients with fixed defects that improved after reinjection compared
with those with irreversible defects despite reinjection were performed by \( \chi^2 \) analysis.

**Results**

**Qualitative Thallium SPECT Data**

Among the 50 patients with exercise-induced defects, a total of 127 myocardial regions were graded as abnormal on the stress images by qualitative analysis, of which 13 (10\%) were completely normal on the conventional redistribution images. Of the remaining 114 regions with persistent thallium abnormalities, 59 showed partial reversibility on the redistribution image, and 55 demonstrated irreversible abnormalities of relative thallium uptake (or irreversible defects).

**Partially reversible regions on redistribution images.** Of the 59 regions determined to be abnormal on the initial stress with only partial reversibility on the redistribution images, 47 (80\%) showed further improvement of thallium uptake after reinjection, of which 30 (64\%) were completely normal. At the 24-hour study, 57 of the 59 regions (97\%) with previously improved thallium uptake showed either no further improvement or washout. Because partially reversible thallium defects on conventional redistribution images connote ischemic, but viable, myocardium, it is in regions with irreversible thallium defects that viability is a clinical concern. Thus, we directed our attention to the 55 regions that were designated to be irreversible on redistribution images (Figure 2).

**Irreversible regions on redistribution images.** After thallium reinjection, 25 of the 55 regions (45\%) with previously irreversible defects on the 3-4-hour redistribution study demonstrated improved thallium uptake, suggestive of viable myocardium, of which seven were completely normal. At the 24-hour study, 23 of the 25 regions (92\%) with previously improved thallium uptake immediately after reinjection showed either no further increase in relative thallium activity or reduced thallium activity (washout). Similarly, of the 55 regions determined to be irreversible after reinjection, 29 (97\%) remained irreversible on 24-hour images. In Figure 3, examples are shown of a patient with an apparently irreversible inferior defect on redistribution that improved after reinjection and did not change after 24 hours; in Figure 4, examples are shown of a patient with extensive lateral, inferior, and inferoseptal thallium abnormalities during stress that persist on redistribution and reinjection images and that do not change after 24 hours.

Thus, in most regions with irreversible thallium defects on conventional redistribution images, there was concordance of 24-hour imaging and reinjection data, in that 92\% of regions that were identified as viable and 97\% of regions that were determined to be scar after reinjection showed no further improvement in relative thallium activity after 24-hour studies. Twenty-four-hour imaging after reinjection showed improvement in three of 55 irreversible regions (involving three of the 50 patients), of which only one region that was determined to be viable on 24-hour imaging was missed by reinjection (Figure 5). Patients exhibiting fixed defects that improved after reinjection did not differ from those with defects that remained fixed despite reinjection with respect to the severity of arteriographic narrowing, electrocardiographic Q waves, wall motion abnormality at rest, anginal symptoms, or the peak heart rate achieved during exercise.

**Quantitative Thallium SPECT Data**

A total of 127 myocardial regions were identified to be abnormal by quantitative analysis, of which 72 (57\%) were determined to have fixed defects by redistribution imaging. Reinjection imaging showed

![Flow diagram displaying the fate of "irreversible" thallium defects on 3-4-hour standard redistribution studies after reinjection and at 24 hours.](http://circ.ahajournals.org/)
that 37 of the regions with apparently fixed defects (51%) had improved or normal thallium uptake, with an increase in mean regional uptake from 57±13% during redistribution imaging to 70±14% during reinjection imaging and with no further change after 24 hours (71±14%). The mean regional thallium uptake for all 72 regions on stress images was 53±14%. In the 37 regions demonstrating enhanced uptake of thallium after reinjection, the mean regional uptake on stress was 52±13% compared with 55±15% in 31 regions determined to be irreversible after reinjection (p=NS). Thus, the defects showing enhanced thallium uptake after reinjection could not be predicted on the basis of the severity of the initial thallium defect during exercise. In 35 regions identified by reinjection imaging to have persistent defects, 24-hour imaging after reinjection showed improvement in four of 35 irreversible regions (involving three of the 50 patients). Thus, in the 35 regions identified by reinjection imaging to have persistent defects, the mean regional uptake of thallium remained unchanged (redistribution, 57±17%; reinjection, 57±17%; and 24-hour imaging, 58±17%).

This quantitative method was then applied to the 25 myocardial regions with irreversible thallium defects, according to redistribution imaging criteria, that were judged to be viable after reinjection imaging on the basis of qualitative analysis. Enhanced thallium uptake after reinjection was confirmed by quantitative analysis in the 25 regions, with an increase in mean regional thallium uptake from 53±15% on the 3–4-hour redistribution study to 63±18% after reinjection (p<0.01), with no further change after 24 hours (62±19%). Examples of patients with increased regional thallium activity after reinjection that did not change after 24 hours are shown in Figures 6 and 7. Similarly, quantitative analysis confirmed the visual readings in the 30 regions that were judged to be irreversible after reinjection by qualitative analysis, in which the mean regional thallium uptake from redistribution (57±22%), reinjection (54±20%), and 24-hour (59±22%) imaging did not differ.

**Discussion**

Thallium myocardial imaging has been established as a clinically important adjunct to exercise testing
for detecting coronary artery disease and evaluating its physiological impact on myocardial blood flow.\textsuperscript{11,12} In addition, because thallium uptake by myocardial cells is an active process, it has become an important index for assessing myocardial viability.

In clinical studies, reduced initial (postexercise) thallium uptake that redistributes on delayed 3–4-hour images is considered to represent ischemic myocardium, and the converse, the absence of initial thallium uptake and subsequent lack of redistribution on the delayed images, connotes myocardial scar. However, more recent studies demonstrated that many exercise-induced thallium perfusion defects in ischemic myocardium do not normalize on the redistribution images, even when the underlying myocardium is viable rather than infarcted.\textsuperscript{1–8,13–15} In 1981, Rozanski and coworkers\textsuperscript{13} reported that 26% of myocardial segments with both akinetic wall motion and irreversible thallium defects after 3–4-hour delayed images in preoperative studies had normal wall motion after coronary artery bypass surgery. This was followed by several other clinical studies showing that nearly half to two thirds of persistent thallium defects on 3–4-hour delayed images may normalize after revascularization,\textsuperscript{14,15} indicating that the preoperative irreversible defect underestimated the amount of viable, but compromised, myocardium.

In 1983, Gutman and coworkers\textsuperscript{5} were first to report that when a third scan was obtained 18–24 hours after exercise, 21% of the segments with irreversible thallium defects on 3–4-hour delayed planar images showed redistribution on the late images. This was confirmed by two subsequent studies using tomographic imaging, in which up to 61% of segments with irreversible thallium defects on 3–4-hour delayed images demonstrated late redistribution when a third scan was obtained 8–72 hours after exercise.\textsuperscript{5,6} A possible explanation for late redistribution is that the initial uptake of thallium during exercise is sufficiently reduced in certain ischemic myocardial regions that it continues to mimic the appearance of scarred myocardium even after 3–4 hours. However, if a greater time is allowed for redistribution, then a greater number of viable myocardial regions may be distinguished from fibrotic or scarred myocardium. Nevertheless, late delayed images are inconvenient and often yield poor image quality with low target to background counts, making the interpretation of the images either impractical or unreliable.

An alternative explanation for lack of thallium redistribution after 3–4 hours in regions with viable myocardium is that thallium redistribution depends not only on the severity of the initial defect but also on its continuing thallium input function as reflected by the serum thallium concentration.\textsuperscript{6} Hence, if the serum thallium concentration remains the same or increases slightly during the serial imaging interval, a viable defect should fill in. On the other hand, if the serum thallium concentration continues to decrease, thallium delivery may be insufficient, and the defect may persist even though the underlying myocardium is not infarcted.\textsuperscript{16} This suggests that some ischemic segments never redistribute, even with late imaging. Based on this hypothesis, we recently demonstrated that irreversible thallium defects on 3–4-hour redistribution images in regions with viable myocardium reverse if the delivery of thallium is augmented by reinjection of an additional 1 mCi thallium at rest immediately after 3–4 hours of redistribution.\textsuperscript{1–3} Nearly 50% of myocardial regions interpreted as having irreversible thallium abnormalities on the conventional redistribution images were identified as viable by thallium reinjection. This was supported in a subgroup of our patients by postangioplasty improvement in regional thallium uptake during exercise as well as improvement in regional wall motion.\textsuperscript{1} Furthermore, when the results of thallium reinjection were compared directly with metabolic imaging with positron emission tomography and

\begin{figure}
\centering
\includegraphics[width=\textwidth]{stress_redistribution_reinjection_24_hour}
\caption{Stress, redistribution, reinjection, and 24-hour thallium tomogram images. Enhanced regional thallium uptake at 24 hours in a defect that remained irreversible after reinjection. There are extensive anterior and lateral thallium abnormalities during stress, which persist on redistribution and reinjection images but which improve at 24 hours. Only one of 50 patients showed such changes.}
\end{figure}
In keeping with these observations, a recent report by Kayden et al.\textsuperscript{18} who performed late (24-hour) thallium reinjection after stress, 2–4-hour redistribution, and 24-hour redistribution studies, revealed that myocardial sectors in the inferior and low lateral regions that were abnormal during exercise demonstrate partial reversibility on the redistribution study and improve further after reinjection but show no further improvement after 24 hours.

\textbf{FIGURE 6.} Plots of quantitative regional thallium activity and comparison to the normal range, represented as the shaded area. Top panel: Stress, redistribution, and reinjection curves. Bottom panel: Reinjection and 24-hour curves. In this patient, myocardial sectors in the anterior and high lateral regions that were abnormal during exercise (that is, below the normal range) remained irreversible on the redistribution and reinjection studies and did not change at 24 hours. Myocardial sectors in the inferior and low lateral regions that were abnormal during exercise remained unchanged on the redistribution study but improved further after reinjection.

\textbf{FIGURE 7.} Plots of quantitative regional thallium activity. Myocardial sectors in the anterior and inferior regions remain irreversible on the redistribution study but improve after reinjection and do not change at 24 hours. In addition, anterolateral and inferolateral regions demonstrate partial reversibility on the redistribution study and improve further after reinjection but show no further improvement after 24 hours.
that 14 of the 27 patients (52%) with irreversible thallium defects even at 24 hours had enhanced thallium uptake after reinjection. These data support our hypothesis that irreversible thallium defects in regions of viable myocardium may remain irreversible, even with late imaging, unless the delivery of thallium is augmented.

In our previous studies, the reinjection images were acquired 10 minutes after the administration of $^{201}$Tl at rest. It is conceivable that this time period between reinjection and imaging is too short because this imaging protocol does not allow for further redistribution of the reinjected thallium dose. Thus, the present study was designed to determine whether 24-hour imaging after thallium reinjection provides additional information regarding myocardial viability beyond that obtained by reinjection.

The results of the present study, involving a different series of patients, are consistent with our previous experience with thallium reinjection,1,3 in that nearly 50% of the regions with irreversible thallium defects on conventional redistribution images had further uptake of thallium after reinjection at rest. In such irreversible thallium defects, there was significant concordance of the subsequent data obtained at 24-hour imaging and data obtained immediately after reinjection, in that 92% of regions identified as viable and 97% of regions determined to be scar after reinjection showed no further improvement at the 24-hour study (Figure 2). Thus, the 24-hour study did not provide additional information beyond that obtained by reinjection except for four myocardial regions, involving three of the 50 patients. This represents only 6% of the patients included in this investigation.

A possible explanation for the observed advantage of thallium reinjection immediately after redistribution images is that it provides an opportunity to assess relative myocardial perfusion under stress and resting conditions. Furthermore, by augmenting blood concentration of the isotope, it facilitates the redistribution process of uptake of thallium by viable myocardial cells. Late imaging without reinjection improves detection of viability in some myocardial regions by allowing longer time for redistribution, which results in diminution of ischemic to nonischemic defect ratio. However, despite the longer time rendered, some irreversible thallium defects in viable zones may remain irreversible unless the delivery of thallium (as manifested by serum thallium concentrations) is augmented.18 Thus, thallium reinjection may provide a more accurate, efficient, and convenient method for assessing myocardial viability compared with late imaging alone.

It may be argued that the additional 1-mCi dose of $^{201}$Tl results in a higher radiation exposure at an increased cost for an individual patient. Although at first, this may seem to be a limitation of the reinjection technique, the protocol we used involves the administration of only 2 mCi $^{201}$Tl at stress followed by the additional 1-mCi dose immediately after 3–4-hour redistribution imaging. Because many nuclear cardiology laboratories performing SPECT studies routinely use 3–4 mCi $^{201}$Tl at peak exercise (to improve image quality and maximize count statistics at 24 hours), the proposed reinjection protocol will add neither to the cost nor to the radiation burden for patients undergoing evaluation of myocardial viability. In addition, because we recommend thallium reinjection only for patients with a persistent thallium defect on conventional redistribution images, the reinjection protocol may actually reduce the cost and radiation exposure in most patients undergoing thallium SPECT imaging.

In summary, our findings in patients with chronic stable coronary artery disease indicate that thallium reinjection detects most of the clinically relevant information pertaining to myocardial viability in regions with persistent thallium defects. Hence, thallium reinjection may be used instead of 24-hour imaging in most patients in whom a persistent thallium defect is observed on conventional 3–4-hour delayed images.

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