Immediate Thallium-201 Reinjection Following Stress Imaging: A Time-Saving Approach for Detection of Myocardial Viability

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Thallium-201 reinjection following 3–4-hr redistribution imaging improves the detection of viable myocardium but considerably prolongs the total investigation time. We compared the results of immediate ^{201}Tl reinjection with 3-hr redistribution imaging in 120 consecutive patients who were evaluated for myocardial ischemia. Thallium-201 was reinjected immediately following the postexercise study. The images were acquired 1 hr later and reacquired at 3 hr redistribution. A total of 960 segments per imaging series were evaluated, of which 320 (33%) segments showed perfusion defects on the postexercise images. On the 1-hr images, 220 (69%) segments demonstrated enhanced thallium uptake, 97 (30%) segments did not change and 3 (1%) segments showed reverse redistribution. Of the 100 (97 + 3) persistent defects, only 12 (4%) segments showed fill-in of ^{201}Tl on 3 hr redistribution images. A total of 49 (15%) segments showed reverse redistribution. Defects on postexercise images were seen in 95 patients (79%) of whom 9 (10%) showed no change on immediate reinjection images. In only 1 (1%) patient was the diagnosis changed from myocardial necrosis to myocardial ischemia after analysis of the 3-hr redistribution images. These data indicate that immediate postexercise reinjection of ^{201}Tl followed by 1-hr image acquisition may be superior to 3-hr redistribution imaging in identifying viable myocardium in patients evaluated for myocardial ischemia. This protocol eliminates the need for an additional series of 3–4-hr redistribution images and offers the advantages of reduced total imaging time, improved convenience for the patient and increased patient throughput.

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Conventional ^{201}Tl stress-redistribution imaging may underestimate the presence of ischemic but viable myocardium (*1–7*). Several recent studies have reported the value of ^{201}Tl reinjection imaging in order to identify viable myocardium in irreversible perfusion defects on conventional 3–4-hr redistribution images (*8–10*). Furthermore, it has been shown that the ^{201}Tl reinjection technique predicts improvement in regional function after revascularization with a predictive accuracy similar to that reported for metabolic imaging with positron emission tomography (PET) (*11–13*). Although the ^{201}Tl reinjection technique significantly improves the identification of viable myocardium, the routine performance of ^{201}Tl reinjection following 3–4-hr redistribution imaging prolongs the total investigation procedure by approximately 1 hour and necessitates a second venipuncture. This procedure is suboptimal from the standpoint of patient convenience and may be logistically impractical for a busy nuclear medicine department. Accordingly, the aim of our study was to investigate the feasibility of an immediate ^{201}Tl reinjection protocol that potentially offers an effective and time-saving approach for both the patient and the nuclear medicine department. For that purpose, the immediate reinjection images were compared with 3-hr redistribution images, and it was determined whether elimination of 3-hr redistribution images would have a major impact on detection of myocardial viability and subsequent patient diagnosis.

METHODS

Patient Selection

The study population consisted of 120 consecutive patients who were referred to the division of nuclear medicine between January and April 1992 for detection and evaluation of myocardial ischemia. All patients received ^{201}Tl reinjection immediately following postexercise image acquisition. The age of the patients was 59 ± 10 yr (mean ± s.d., range 30–79 yr). There were 84 males and 36 females. Documented coronary artery disease (CAD), as evidenced by coronary arteriography or a sustained myocardial infarction, was present in 84 (70%) patients. Thirty-five (29%) patients underwent diagnostic coronary arteriography and CAD was determined based on significant narrowing (50% or more narrowing in luminal diameter) at coronary arteriography. Forty-nine (41%) patients had sustained a myocardial infarction, of whom 37 (31%) patients had transmural myocardial infarction in accordance with Q-wave criteria of

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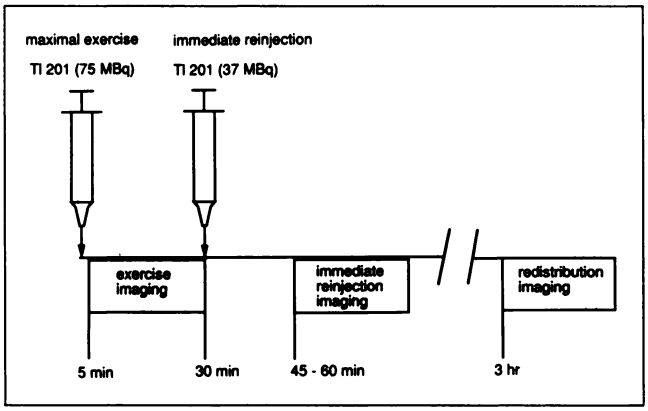

FIGURE 1. Protocol for ^{201}Tl immediate reinjection. Thallium-201 is reinjected immediately following postexercise imaging. Images are acquired at 45–60 min and reacquired 3 hr after reinjection.

the New York Heart Association (*14*). Fourteen patients with Q-wave myocardial infarction had previous percutaneous transluminal coronary angioplasty or coronary artery bypass surgery. No patient had suffered from acute myocardial infarction or unstable angina for the last 6 mo.

Thallium-201 Cardiac Imaging Protocol

All patients underwent ^{201}Tl myocardial exercise scintigraphy as previously described (*15*) (Fig. 1). Briefly, exercise was performed in an upright position on a calibrated bicycle ergometer using a symptom-limited test with stepwise increased work. Beta-blocking agents and calcium-antagonists were stopped 3 days before the test and digitalis derivatives were withheld 1 wk before the test.

At maximal exercise, a dose of 75 MBq (2 mCi) of ^{201}Tl was injected through an indwelling intravenous cannula and exercise was continued for 1 min thereafter. After termination of the exercise protocol, three-view myocardial scintigrams were obtained starting at 5 min postinjection of ^{201}Tl. Imaging was performed in the anterior and left anterior oblique views (35° and 70°) for a maximum of 8 min/view in order to obtain 500,000 counts per image. Immediately following poststress imaging, a dose of 37 MBq (1 mCi) of ^{201}Tl was administered and 45–60 min later an additional set of images was acquired for 8 min/view (immediate reinjection images). Three hours later, redistribution images were obtained in the same predetermined projections for 8 min/view. The patients' physical activities and food consumption were restricted between the three recordings.

A Toshiba GCA 40A large-field-of-view camera (35 cm) with a low-energy, high-sensitivity collimator with a 20% energy window centered on the 80 keV photon peak of ^{201}Tl was used. All images were stored on the computer by magnetic disk in a 128 × 128 matrix (MDS-A^2).

Data Analysis

The scintigraphic images were visually assessed by two independent observers blinded to patient identity with a previously described semiquantitative method (*15*). Disagreement in interpretation was resolved by a third independent observer. Eight myocardial regions were defined from the three views: anterior, anteroseptal, anterolateral, apical, inferior, inferoseptal, posterolateral and posterior region (Fig. 2). The ^{201}Tl scintigrams were inspected on a computer grey scale without smoothing or background subtraction. Matching views from initial uptake, immediate reinjection images and redistribution images were displayed side by side for comparison. Thallium-201 uptake in each region was visually scored using a four-point grading system (0 = no uptake, 1 = clearly diminished uptake, 2 = slightly diminished uptake, 3 = normal uptake). Each segment was classified as normal, reversible defect or persistent defect. Reversibility was defined as either a shift towards normal of one grade or more or as complete normalization on the delayed image compared to the initial image. A defect was considered to be persistent if the assigned grade was abnormal and the defect showed no change in ^{201}Tl uptake on subsequent images.

Reverse redistribution was defined as diminished activity of one grade or more in segments observed on the second and third imaging series compared to the previous image series.

Statistical Analysis

Agreement of the two scintigraphic procedures (exercise-immediate reinjection imaging and exercise-immediate reinjection-3-hr redistribution imaging) was quantified with Cohen's kappa.

RESULTS

Segmental Analysis

In the three series of images, a total of 2880 segments (120 patients × 8 segments × 3 imaging series) were available for evaluation (Fig. 3). The image quality of the immediate reinjection images was consistently better than the 3-hr redistribution images (Fig. 4).

Stress Images. On the immediate postexercise images, 320 (33%) of 960 segments showed perfusion defects.

Immediate Reinjection Images. On these images, the 320 segments with perfusion defects showed reversibility in 220 (69%) segments, while no change was observed in 97 (30%) segments. Reverse redistribution was seen in three (1%) segments.

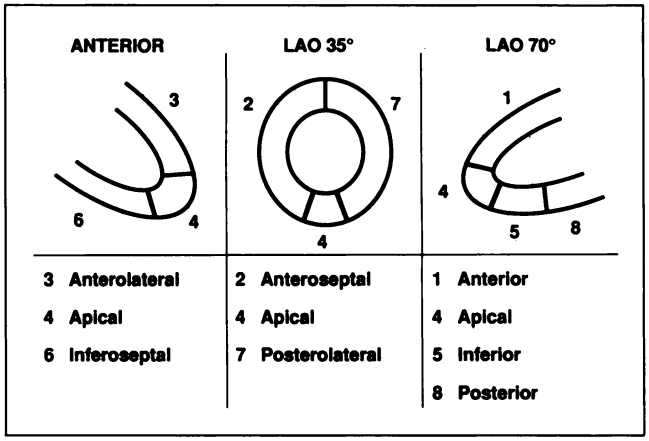

FIGURE 2. Diagram of the standard segmentation scheme used for scoring ^{201}Tl images. The anterior view contains the anterolateral, apical and inferoseptal segments. The 35° left anterior oblique view (LAO 35°) includes anteroseptal, apical, and posterolateral segments. The LAO 70° view contains anterior, apical, inferior and posterior segments.

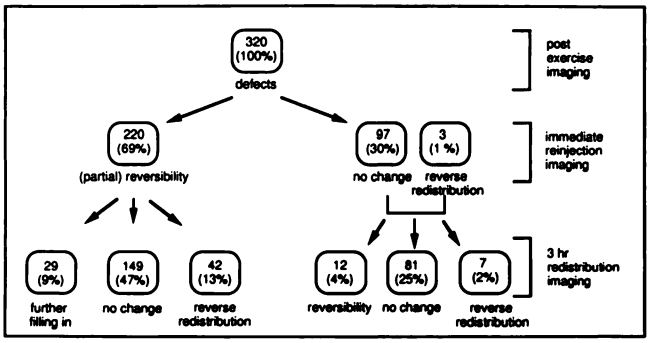

FIGURE 3. Nomogram of 320 perfusion defects immediately after exercise.

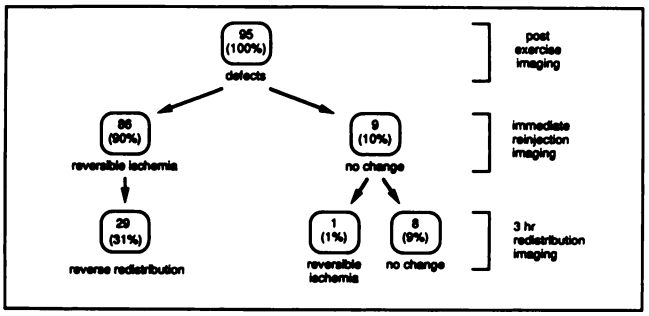

FIGURE 5. Nomogram of 95 patients with perfusion defects immediately after exercise shows the diagnostic capability of immediate reinjection imaging.

Redistribution Images. With 3-hr redistribution imaging, 220 (69%) reversible defects showed further fill-in in 29 (9%) segments and remained unchanged in 149 (47%) segments. Reverse redistribution was observed in 42 (13%) segments. The 100 (31%) persistent defects showed fill-in ^{201}Tl in 12 (4%) segments. In 81 (25%) segments, no change in ^{201}Tl uptake was observed and 7 segments (2%) showed reverse redistribution.

Redistribution Versus Immediate Reinjection Imaging. In comparing redistribution imaging with immediate reinjection imaging, ^{201}Tl uptake was seen in only 12 (4%) segments. Reverse redistribution was observed in 49 (15%) segments with 3-hr redistribution imaging, whereas this was seen in only 3 (1%) segments with immediate reinjection imaging. Table 1 shows the agreement between the two procedures (kappa = 0.97).

Q-wave Related Segments. A comparison of exercise/immediate reinjection imaging and exercise/3-hr redistribution imaging shows that 34 (54%) of the 63 Q-wave related exercise defects showed enhanced ^{201}Tl uptake with immediate reinjection imaging and that 29 (46%) segments showed improvement with 3-hr redistribution imaging (kappa = 0.76).

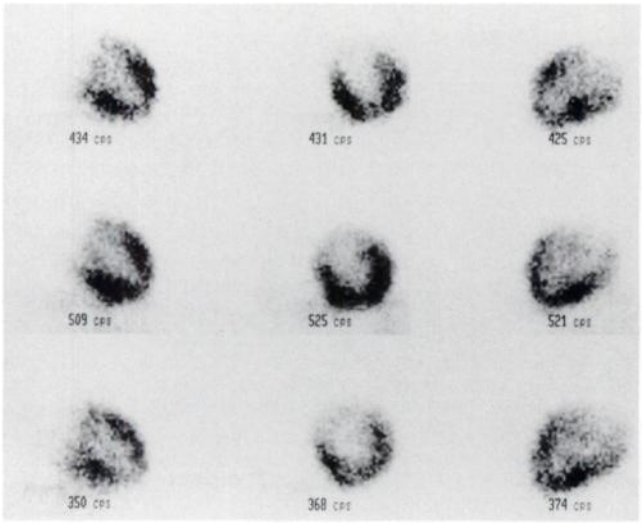

FIGURE 4. Representative sample of postexercise (upper row), immediate reinjection (middle row) and 3-hr redistribution imaging (bottom row) in the three standard views. From left to right, anterior, LAO 35° and LAO 70° views. The immediate reinjection images show improved image quality due to a higher count rate per second (cps).

Patient Analysis

Stress Images. Twenty-five (21%) patients showed completely normal postexercise ^{201}Tl images and 95 (79%) patients showed perfusion defects (Fig. 5).

Immediate Reinjection Images. On the immediate reinjection images, reversible defects were seen in 86 of 95 (90%) patients, of whom 44 (46%) showed reversible defects only and 42 (44%) patients had both persistent and reversible defects. Nine (10%) patients had persistent defects only. Reverse redistribution was seen in three (3%) patients.

Redistribution Images. For 3-hr redistribution imaging of the 86 (90%) patients with reversible defects, 20 (20%) had additional fill-in and no change was seen in 37 (39%). Reverse redistribution was seen in 29 (31%) patients. Of the nine (10%) patients with persistent defects, one patient showed further fill-in of defects.

Redistribution Versus Immediate Reinjection Imaging. A comparison of redistribution imaging with immediate reinjection imaging showed that in only 1% of the patients (n = 1) was the diagnosis changed from myocardial necrosis to myocardial ischemia after analysis of the 3-hr redistribution images. In all other patients (n = 94), the diagnosis of myocardial ischemia could already be inferred from the immediate reinjection images. Reverse redistribution was observed in 3% of the patients (n = 3) on immediate reinjection images, whereas this was present in 31% of the patients (n = 29) on 3-hr redistribution images. Table 2 shows the agreement between the two procedures (kappa = 0.98).

DISCUSSION

The ^{201}Tl reinjection technique has become a standard procedure in many nuclear medicine laboratories that use ^{201}Tl exercise scintigraphy. The procedure improves the detection of myocardial viability in about 50% of segments with irreversible defects on redistribution imaging (*8,15*) and these results are similar to data from PET

TABLE 1
Segmental Agreement Between Exercise/Immediate Reinjection Imaging and Exercise/Immediate Reinjection/Redistribution Imaging

Segmental agreement (kappa = 0.97)	Exercise/Immediate reinjection/Redistribution			
Exercise/Immediate reinjection	Normal	Reversible defects	Persistent defects	Total
Normal	640			640
Reversible defects		220		220
Persistent defects		12	88	100
Total	640	232	88	960

(*16,17*). The protocol requires one additional series of images after conventional 3–4-hr redistribution imaging, which is disadvantageous in terms of patient convenience and laboratory logistics. It prolongs the investigation time by approximately 1 hr and requires a second venipuncture. To overcome these problems, several other protocols have been suggested, including immediate reinjection followed by 4-hr redistribution imaging (*18*) and isolated 4-hr reinjection imaging without the intervening 3–4-hr redistribution study (*19*). However, both protocols yielded unsatisfactory results despite their theoretical physiological and practical advantages. Immediate reinjection followed by 4-hr redistribution imaging resulted in a high frequency of defect reversibility observed on late imaging (18–72 hr post-stress). As a result, Kiat et al. (*18*) suggested that reinjection of ^{201}Tl should not be given immediately following completion of stress acquisition.

Dilsizian et al. (*19*) demonstrated that elimination of 3–4-hr redistribution images and sole reliance on 4-hr ^{201}Tl reinjection images also led to a large number of persistent defects (25% of regions) that showed reversibility on 24-hr imaging. The authors concluded that either stress-redistribution-reinjection or stress-reinjection-24-hr imaging should be used for assessment of myocardial ischemia and viability (*19*).

In this study, immediate reinjection of ^{201}Tl after stress acquisition followed by imaging 60 min later yielded results almost similar to 3-hr redistribution imaging. The overall agreement between exercise/immediate reinjection imaging and exercise/immediate reinjection/3-hr redistribution imaging was excellent (kappa = 0.97). Only a limited number of irreversible defects (4%, n = 12) at immediate reinjection proved to be reversible on redistribution images, and in only one patient was the diagnosis of myocardial ischemia inferred from the 3-hr images. Although further fill-in was seen in 29 segments (9%) on the 3-hr redistribution images, it did not impact on the detection of myocardial ischemia. Also, in Q-wave related segments, 3-hr redistribution imaging showed no additional value. These findings indicate that elimination of redistribution imaging has no major impact on detection of myocardial viability and subsequent patient diagnosis. However, direct comparisons to conventional redistribution imaging and to initial ^{201}Tl reinjection protocols are difficult to infer from our data. Definite advantages of this procedure are improved image quality due to higher count rates shortly after reinjection and the low incidence of reverse redistribution (differential washout) on immediate reinjection images.

The current protocol streamlines the reinjection approach by obviating the need for an additional set of images following 3–4-hr redistribution imaging. In practical terms, the approach reduces total study time, is convenient for the patient and increases patient throughput.

Rationale

The rationale for our protocol warrants clarification of the uptake and washout kinetics of ^{201}Tl in normal, ischemic and scarred myocardium (*20*). Uptake and washout of ^{201}Tl by the myocardium are governed by myocardial flow, membrane potential and intracellular and extracellular ^{201}Tl gradients (*21–26*). When ^{201}Tl is reinjected 30

TABLE 2
Patient Agreement Between Exercise/Immediate Reinjection Imaging and Exercise/Immediate Reinjection/Redistribution Imaging

Patient agreement (kappa = 0.98)	Exercise/Immediate reinjection/Redistribution			
Exercise/Immediate reinjection	Normal	Ischemia	Scar	Total
Normal	25			25
Ischemia		86		86
Scar		1	8	9
Total	25	87	8	120

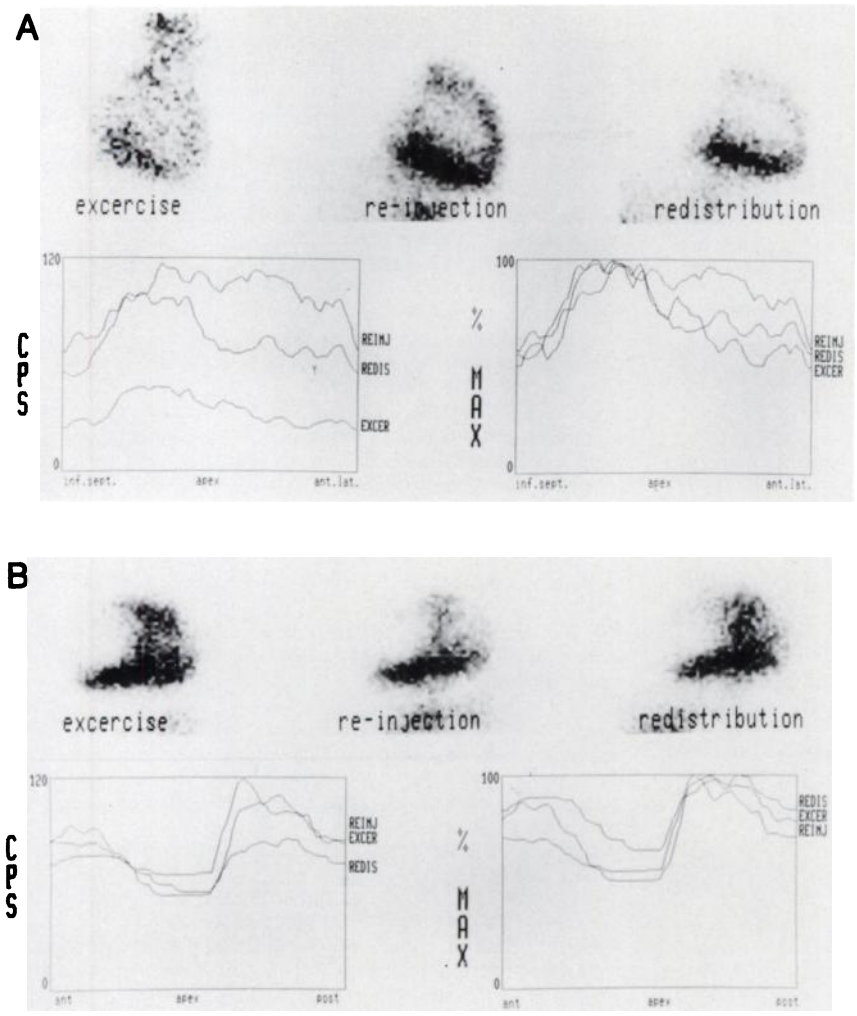

FIGURE 6. Thallium-201 images and circumferential profile analysis obtained from a patient with anterolateral ischemia and reverse redistribution (A, anterior view) and from a patient with a persistent antero-apical defect (B, LAO 70° view). The left panel shows the profiles based on absolute count rates and the right panel shows the profiles after normalization for the maximal (max) number of counts (cps, 100%) within the myocardium. In the patient with ischemia, the immediate reinjection profile shows increased activity in the anterolateral segment relative to the increase in the normal segment. This explains the fill-in seen on the immediate reinjection scintigram. The 3-hr redistribution profile parallels the postexercise profile and confirms reverse redistribution on the 3-hr delayed image. In the patient with a persistent antero-apical defect, all three profiles show a similar configuration. Excer = exercise, Reinj = immediate reinjection and Redis = 3-hr redistribution.

min following maximal exercise, the delivery of ^{201}Tl will be similar to both normal and ischemic regions due to normalization of flow (*27–29*). Since equilibrium of ^{201}Tl kinetics has not yet been reached at the time of ^{201}Tl reinjection, the net uptake of ^{201}Tl in former ischemic regions exceeds uptake in former hyperemic regions. Consequently, the difference in activity between normal and ischemic areas will further decrease following reinjection (Fig. 6). This may explain why the phenomenon of reverse redistribution was seldom observed during immediate reinjection imaging, since differential uptake is not supposed to occur so soon after reinjection (*19*). It may also explain the unsatisfactory results of immediate reinjection when followed by 4-hr redistribution imaging (*18*).

It seems logical to start the reinjection imaging procedure around 60 min after administration because maximal myocardial uptake of ^{201}Tl in resting conditions occurs at a later time (45–60 min) than under hyperemic (exercise) conditions (*28*).

At variance with our theory is the view that stress-induced perfusion imbalances might persist throughout the post-stress imaging phase and still be present to some degree during ^{201}Tl reinjection, particularly in patients with critical coronary artery stenoses (*30*). However, as stated before, myocardial perfusion has returned to baseline resting levels within 30 min after maximal exercise, independent of stenosis severity (*31*). In addition, experimental studies have shown that the presence of severe postischemic myocardial dysfunction following brief periods of coronary artery occlusion (i.e., stunning) does not affect myocardial ^{201}Tl extraction and washout kinetics (*28,29,32–34*). This finding at least suggests that ^{201}Tl reinjection at 30 min postexercise yields a true reflection of resting perfusion and viability in various myocardial regions.

Limitations

One limitation of our study is the use of planar data acquisition techniques. It can reasonably be argued that the use of single-photon emission computed tomography (SPECT) might have detected more subtle differences in perfusion (*6*). Data that assess the potential role of rest reinjection as an adjunct to conventional SPECT are clearly required (*35*). Furthermore, the data analysis in this study was based on qualitative segmental scoring. A comparison of quantitative and qualitative analyses of

^{201}Tl reinjection images must be addressed in future studies. It must, however, be realized that SPECT imaging is not yet a widely accepted routine procedure in nuclear cardiology laboratories, and that its advantages of better imaging quality and improved detectability of lesions in the right and circumflex coronary arteries are partially offset by reduced resolution, attenuated data recorded in the projection, and occasional difficulties in distinguishing between artifacts and perfusion abnormalities (*36,37*). Also, the quantitative approach is mostly used as an additional "observer" and in most cases offers no advantage to visual interpretation by expert readers (*38–40*).

CONCLUSION

Our data indicate that immediate postexercise reinjection of ^{201}Tl followed by 1-hr image acquisition may be superior to 3-hr redistribution imaging in identifying viable myocardium in patients evaluated for myocardial ischemia. This protocol streamlines the reinjection approach by obviating the need for an additional set of 3–4-hr redistribution images and the minor inconvenience of repeat venipuncture. It offers the advantages of reduced study time, improved convenience for the patient and increased patient throughput.

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EDITORIAL

Thallium Reinjection Imaging: The Search for an Optimal Protocol

Since Pohost and associates introduced the "single injection" technique in thallium imaging, the stress/4-hr redistribution protocol has been widely used to characterize perfusion defects as fixed or reversible (*1*). This technique will remain in the archives of nuclear imaging as a novel method that has withstood the test of time, and has in no small measure, popularized the use of nuclear imaging in patient management. At the time this technique was described, the major interest in the use of exercise thallium imaging was in the diagnosis of coronary artery disease; myocardial viability was not yet an area of major concern or interest. Nevertheless, even then it was clear that 4-hr redistribution images underestimated "ischemia" and overestimated "scar" when compared to separate rest studies (*2–4*). Subsequent studies have shown that some fixed perfusion defects on 4-hr redistribution images improve after coronary revascularization and some are associated with evidence of metabolic activity by ^{18}F-fluorodeoxyglucose imaging (*2–7*). For the past few years, there has been considerable emphasis on the assessment of dysfunctional myocardium due to stunning, hibernation or scar. Based on the current understanding of myocardial metabolism and tracer kinetics, the various type of flow/function mismatches are presented in Table 1.

TABLE 1
Correlation Between Myocardial Perfusion with Wall Motion and Thallium Redistribution

	Metabolism	Wall motion	Perfusion	Redistribution
Normal	N	N	N	–
Ischemia	A*	A	A	+
Scar	A	A	A	–
Hibernating	A	A	A	+
Stunned	A	A	N	–

*Ischemia is presumed to be transient and so are the associated abnormalities.
A: abnormal; N: normal; –: no; +: yes.

There are two important modifications, which may not necessarily be exclusive, of the rest-redistribution protocol: 24-hr delayed imaging and the reinjection technique (*2,7*). There are several additional protocols that differ from each other based upon the time of reinjection, the time of reimaging, the number of sets of images to be analyzed and the thallium dose used for reinjection. The use of nitroglycerin before obtaining reinjection images and ribose infusion are thought to enhance redistribution (*8,9*). These protocols are summarized in Table 2.

There is a general consensus that a dose of 37 MBq (1 mCi) be used for thallium reinjection. In SPECT imaging, this represents approximately 30% of the initial dose used for the stress study, but in planar imaging it represents 50% of the initial dose. There are yet no conclusive data to suggest the ideal dose for reinjection.

The reinjection technique involves analysis of three sets of images; stress, 4-hr redistribution and reinjection. This method has clearly demonstrated that approximately 50% of fixed perfusion defects on 4-hr redistribution images show evidence of reversibility and that the results are at least as good as 24-hr delayed images, but image quality is better and the procedure time is shorter (*5,7*). The drawbacks, however, include the need to acquire three sets of images, which is both inconvenient to the patient and time-consuming, especially in busy nuclear laboratories. Therefore, in many institutions the procedure therefore has been modified by substituting the 4-hr delayed images with the reinjection images. This practice may result in misclassification of up to 25% of reversible defects as fixed defects (*5,7*). A further modification of the protocol was suggested using 24-hr delayed imaging in patients with fixed defects on reinjection images. When thallium imaging results are compared to metabolic markers of myocardial viability obtained with positron emission tomography, it is clear that viable myocardium can be demonstrated in some fixed defects,

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