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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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TABLE 2
Various Protocols for Redistribution Thallium Imaging

Protocol	Reinjection time (hr)	Thallium dose (delayed) (mCi)	Reimaging time (hr)	No. of image sets	Total time (hr)
1. Stress*/rest	≥72	none	0.5	2	72–96
2. Stress/4-hr redistribution	none	none	2–4	2	4–6
3. Stress/24-hr redistribution	none	none	18–24	3	24
4. Stress/24-hr reinjection	24	1	0.5	3	24
5. Stress/4-hr redistribution/reinjection	3–4	1	0.5	3	4–6
6. Stress/4-hr reinjection	3–4	1	0.5	2	4–6
7. Stress/4-hr reinjection/24-hr redistribution	3–4	1	0.5 and 24	3	24
8. Stress/1-hr reinjection	0.5	1	1	2	2.5
9. Rest/redistribution	none	none	4	2	4–6
10. Dual-Isotope	†	†	†	†	1–2.5

*Two millicuries for planar imaging and 3 to 3.5 for SPECT imaging.
†See Table 4.

most notably those of mild or moderate degree irrespective of the presence or absence of superimposed ischemia. Thus, a clear distinction should be made between viability and reversibility (Table 3).

An alternate and more attractive protocol for the assessment of myocardial viability is the use of rest/redistribution thallium imaging (*10*). For example, this technique may be used when determining whether severe left ventricular dysfunction is due to hibernating myocardium (Fig. 1). A stress study is only necessary if the detection of ischemia is important in patient management.

TABLE 3
Comparison Between Myocardial Viability and Thallium Reversibility

Type of defect	Viable myocardium
Completely reversible	Yes
Partially reversible	Yes
Nonreversible (fixed); mild*	Yes
Nonreversible (fixed); moderate†	Yes
Nonreversible (fixed); severe‡	Maybe

*Uptake >75 of normal myocardium.
†Uptake ≥ 50% of normal myocardium.
‡Uptake < 50% normal myocardium.

At times, it is important to complete a study as quickly as possible because this maximizes patient throughput, increases patient comfort and expedites the decision making process. Therefore, attention has been directed to "fast" protocols. The protocol suggested by Kiat et al. requires reinjection of thallium immediately after the stress images are completed and reimaging 3–4 hr later (*11*). Unfortunately, this protocol underestimates the extent of reversibility in comparison to 24-hr imaging.

In this issue of the *Journal*, van Eck-Smit et al. compared 1-hr reinjection images to 3-hr delayed images (*12,13*). Their protocol involved using 75 MBq (2 mCi) of ^{201}Tl for the stress study, reinjecting 37 MBq (1 mCi) of ^{201}Tl as soon as the exercise images were completed and imaging 1 hr later. The images were compared to a third set of images obtained 3 hr after reinjection. There was good agreement between the 1-hr and 3-hr images based on segmental and patient analysis. The obvious conclusion is that 1-hr reinjection imaging is a time-saving approach for assessing viability. Before these results become routinely used, however, it should be noted that they were not compared to "standard techniques" for assessing viability, such as the 4-hr reinjection technique (reinjection of thallium at 4 hr and not immediately after stress) or 24-hr delayed imaging. Also, there was no independent validation of the accuracy of this technique (for example, wall motion analysis or metabolic imaging). It is not even clear whether the results are different from conventional 4-hr redistribution imaging. The fact that 1-hr and 3-hr images agreed with each other does not in itself prove that either is ideal or optimal. It is possible that the presence and, especially, the extent of reversibility might have been enhanced by these techniques. One observation from this study based on circumferential profile analysis in one patient (their Fig. 6) is the relatively greater increase in thallium concentration in the abnormal zone than in the apparently normal zone in the 1-hr reinjection images. This raises an important point about thallium biokinetics and suggests the importance of gradient-mediated passive uptake or persistence of postischemic coronary hyperemia. On the other hand, a decrease in resting coronary blood flow is expected to accentuate existing perfusion abnormalities.

Another "fast protocol" involves the use of dual-isotope imaging (Table 4). This method should not be attempted by novice users since dif-

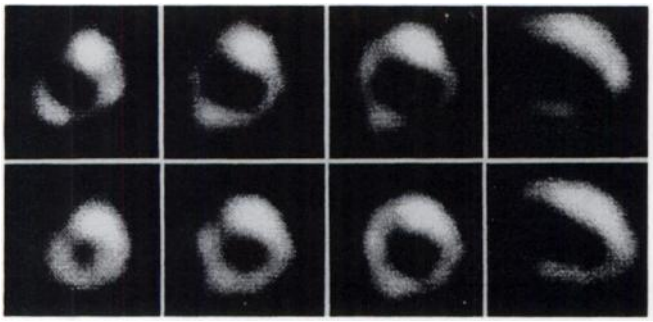

FIGURE 1. Rest redistribution SPECT thallium images in a patient with severe left ventricular dysfunction and three-vessel coronary artery disease proven by angiography. (Upper Panel) Initial rest images. (Lower Panel) Four-hour redistribution images. Three short-axis slices at the apical, mid and basal level of the left ventricle and the vertical long-axis slice at the mid-left ventricular level are shown. There are extensive perfusion abnormalities in the initial images which show partial to complete redistribution. Left ventricular ejection fraction in this patient was 23% before and 53% 7 days after coronary artery bypass grafting.

ferences in imaging properties (attenuation and scatter of perfusion agents) may result in uncertainty in precise characterization of the nature of the abnormalities, especially in patients in whom viability assessment is important. Simultaneous image acquisition, although faster and more precise, is handicapped by considerable spillover of technetium energy into the thallium energy window. Until algorithms are developed to accurately correct for spillover, this method should not be used. The use of technetium labeled perfusion imaging agents such as sestamibi or teboroxime is still not well studied for viability assessment. Imaging 3–4 hr after rest injection of sestamibi (rather than 1 hr), attention to quantitative degree of uptake, gating and simultaneous assessment of wall motion appear to be attractive features that need to be fully explored (*13–15*).

There are factors (eating, fasting, nitroglycerin and ribose infusion) that affect thallium clearance and may decrease or enhance the detection of reversibility. Eating or infusing glucose-potassium-insulin impairs detection of reversibility by increasing thallium clearance from the abnormal zones (and normal zones). This effect is probably due to a decrease in blood thallium concentration and increased thallium-potassium exchange across cellular membranes. Ribose infusion, on the other hand, appears to enhance the detection of reversibility. The exact mechanism is unknown but has been suggested to be metabolic (*9*). The role of ribose infusion in detecting viability before and after coronary revascularization has not yet been adequately studied. Finally, dynamic tomographic imaging of ^{123}I-labeled fatty acids is being studied to assess viability. Prior work with this agent was mainly in the area of detecting coronary artery disease (*16*). The renewed interest in long-chain fatty acids is based on recent studies that suggest that ^{11}C-acetate may be a better agent for viability studies (with positron emission tomography) than ^{18}F-fluorodeoxyglucose. Iodophenylpentadecanoic acid, for example, has a bioexponential clearance: the first and rapid part is due to beta oxidation, the slower one is due to incorporation into cytoplasmic triglyceride pool. In myocardial ischemia, there is a decrease in beta oxidation and an increase in retention.

After almost two decades of use, the optimal protocol for thallium imaging is still not well defined. It is clear, however, that in most patients stress/4-hr redistribution images provide the necessary information. If most perfusion defects are reversible, or the degree and extent of fixed defects are mild or limited, further testing will not be necessary. In patients who have severe and extensive fixed defects, the reinjection technique appears to be the method of choice. What is not yet clear is whether the 1-hr reinjection method provides the same results as the 4-hr reinjection technique. However, until further data are available, the 4-hr reinjection technique remains the method of choice.

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TABLE 4
Dual-Isotope Imaging Protocols

Protocol	No. of image sets	Total protocol time (hr)	Redistribution*
1. Sequential stress/thallium/rest MIBI or teboroxime*	2	≈2	Yes
2. Sequential rest thallium/stress MIBI or teboroxime	2	≈2	No
3. Simultaneous rest thallium/stress MIBI	1	≈1	No

*Teboroxime redistribution thallium imaging at 24 hr.
Stress is either exercise, dipyridamole, adenosine or dobutamine.

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