Nitrates Improve Detection of Ischemic but Viable Myocardium by Thallium-201 Reinjection SPECT

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Thallium-201 reinjection imaging improves myocardial viability detection when compared to standard 3–4-hr redistribution imaging, however, the extent of ischemic but viable myocardium is still underestimated. We tested whether the sensitivity of reinjection imaging could be increased by giving nitrates postexercise to improve blood flow during the redistribution period. Twenty patients with coronary artery disease were included, 11 of them with a recent myocardial infarction. All patients underwent two exercise/4-hr redistribution ^{201}Tl SPECT protocols: one with reinjection alone and the other with nitrates and reinjection. In the latter case, 20 mg of Isosorbide Dinitrate were given to patients immediately after postexercise imaging. Fifteen patients had reversible defects with reinjection alone, three additional patients were defined as ischemic with nitrates/reinjection protocol. Reinjection alone identified 41 reversible segmental defects, all except one were also evaluated as reversible with nitrates/reinjection. However, among the 54 segments showing fixed defects after reinjection only, 14 (26%) presented as reversible with the nitrates/reinjection protocol. The redistribution extent (segments/patient) was 2.05 ± 0.41 segments with reinjection alone and 2.75 ± 0.38 ($p < 0.01$) with nitrates/reinjection. In 15 patients showing reversible defects with both protocols, the redistribution extent was 2.73 ± 0.41 segments with reinjection alone and 3.20 ± 0.40 ($p < 0.05$) with nitrates/reinjection. Thallium-201 SPECT with nitrates and reinjection improves the detection of ischemic but viable myocardium in comparison to SPECT with reinjection alone.

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In patients with coronary artery disease who are being considered for coronary revascularization, the differentiation between irreversible and reversible myocardial dysfunction is of utmost clinical importance. Myocardial dysfunction is expected to be irreversible in regions with myocardial necrosis, but can be improved in regions that are viable but hibernating (*1–3*).

Thallium-201 (^{201}Tl) myocardial scintigraphy has been commonly used for assessment of ischemic yet viable myocardium (*4,5*). However, standard stress/3–4-hr redistribution ^{201}Tl myocardial scintigraphy significantly underestimates the extent of ischemic but viable myocardium on the assumption that nonreversible defects correspond to necrotic tissue and reversible defects to ischemic and viable myocardium (*6–8*).

It has been shown that ^{201}Tl delayed redistribution imaging (18–24 hr) may improve the detection of ischemic but viable myocardial segments (*9–11*), but this imaging technique is of limited clinical application (*12*). Thallium-201 myocardial imaging with reinjection at rest has been recently proposed for identification of viable myocardium (*13*). Several studies demonstrated that ^{201}Tl stress-reinjection imaging significantly improves the detection of reversible hypoperfusion when compared to standard ^{201}Tl stress 3–4-hr redistribution imaging (*13–17*). This technique also accurately predicts the functional outcome after coronary revascularization (*16–18*). However, further reports (*19–21*) have shown that ^{201}Tl stress/reinjection imaging still underestimates the extent of ischemic/viable myocardium when compared to metabolic imaging with positron emission tomography (PET), which has been the most reliable method for evaluation of myocardial viability.

Thallium redistribution in ischemic but viable myocardial regions depends upon the residual coronary blood flow and the serum thallium concentration (*22*). Reinjection of ^{201}Tl before delayed imaging increases the tracer blood level. Nitrates have been shown to increase the regional coronary blood flow to ischemic myocardial regions (*23–27*). We hypothesized that a protocol that combined the physiologic effect of oral nitrates and ^{201}Tl reinjection might improve the detection of ischemic but viable myocardium. This study was undertaken to compare the results of ^{201}Tl myocardial single-photon emission computed tomography (SPECT) using nitrates and reinjection to reinjection alone for detecting myocardial viability.

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MATERIALS AND METHODS

Study Group

Twenty patients (19 males, 1 female, mean age of 62 yr (29–73)), with documented coronary artery disease were included in the present study. Eleven patients had had an acute myocardial infarction and a thrombolytic treatment 2 wk before the radionuclide studies; six patients had a previously documented myocardial infarction and two had severe coronary artery disease without myocardial infarction. Nineteen patients underwent coronary angiography; five had triple-vessel disease; six had two-vessel disease and eight had one-vessel disease.

Thallium-201 Stress/Redistribution SPECT Protocol

Ergometric Test. All patients underwent two ergometer bicycle exercises with continuous monitoring of symptoms, heart rate, ECG and blood pressure until 2 min after the end of exercise. The test was stopped in case of maximal predicted heart rate achievement or angina pectoris, leg fatigue or dyspnea. Thallium-201 (111 MBq was injected intravenously at peak exercise and stress was continued for an additional 60 sec. All patients underwent two stress/4-hr redistribution ^{201}Tl SPECT protocols: protocol A with reinjection only and protocol B with nitrates and reinjection (Fig. 1). The two studies were performed within 1 wk in a randomized order. The second exercise stress was stopped when the previous load was reached.

Exercise/Reinjection Imaging: Protocol A. An immediate postexercise SPECT acquisition was started approximately 5–10 min following the completion of the exercise test. Four hours later, a second dose of ^{201}Tl (37 MBq) was administered intravenously and a second set of SPECT images (reinjection) were again acquired 15 min later (Fig. 1A).

Exercise/Nitrates/Reinjection Imaging: Protocol B. Immediate postexercise imaging was performed the same way. In addition, the patients were given 20 mg of Isosorbide Dinitrate orally immediately after completion of the postexercise SPECT acquisition. Delayed imaging with reinjection was identical to protocol A (Fig. 1B).

Acquisition and Processing of Thallium-201 SPECT

SPECT studies were acquired using a rotating gamma camera (General Electric 400T, Milwaukee, WI) equipped with a low-energy, high-resolution collimator. Thirty-two projections were acquired over a 180° arc, from left posterior oblique to right anterior oblique (32 sec per step). Oblique angle myocardial tomograms were reconstructed using a filtered backprojection algorithm and a Hamming/Hann filter. The reconstructed tomographic data were displayed in three planes (horizontal long-axis, vertical long-axis and short-axis) on a Sophy Computer (Sopha Medical, Buc, France).

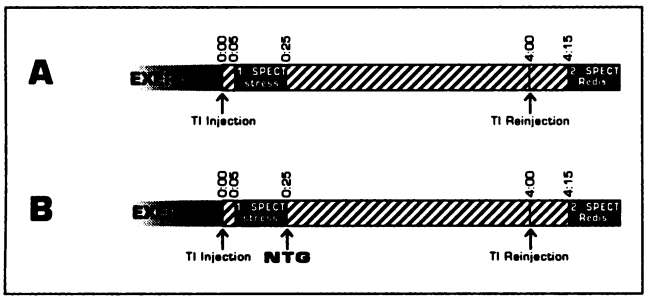

FIGURE 1. Protocol A: exercise/reinjection alone with thallium-201 SPECT. Protocol B: exercise/nitrates/reinjection with thallium-201 SPECT (NTG = Isosorbide Dinitrate).

TABLE 1
Exercise Responses for the Two Protocols

	A Reinjection	B Nitrates/reinjection
%MPHR	74.8 ± 3.2	75.6 ± 2.8
MRPP/1000	18.1 ± 1.3	19.2 ± 1.6
Chest pain	5+/15−	5+/15−
ECG response	5+/15−	4+/16−

MPHR = maximal predicted heart rate for age (220-age); MRPP = maximal rate-pressure product.

Image Interpretation

The left ventricular myocardium of each patient was divided into ten segments: three for the horizontal long-axis (septal, apex, lateral); three for the vertical long-axis (anterior, apex, inferior); and four for the short-axis (anterior, lateral, inferior, septal).

Segmental ^{201}Tl uptake was scored semiquantitatively by blinded visual analysis using a 6-point system (0 = normal; 1 = equivocal; 2 = mild defect; 3 = moderate defect; 4 = severe defect; and 5 = absence of activity). A segmental score higher or equal to 2 was considered as abnormal. The extent of perfusion abnormalities was expressed as the number of abnormal segments. The severity of perfusion defect was expressed by the defect score. Redistribution was considered present when the segmental score on delayed imaging improved by one or more points compared to stress imaging. A redistribution index was calculated as the difference of defect scores between exercise and redistribution images.

Statistical Analysis

All parameters are presented as the mean ± standard error of the mean (s.e.m.). A paired Student's t-test was used to test the difference between the paired data. A chi square was used to compare the percentages of fixed and reversible defects obtained with the two protocols. A p value of less than 0.05 was considered statistically significant.

RESULTS

Exercise Responses

The exercise loads, peak heart rates, percentages of the predicted maximal heart rate reached, peak rate/pressure products and ECG responses were similar during both exercises (Table 1). There was no significant difference with respect to the average defect severity on stress images between protocols (4.09 ± 0.10 for Protocol A; 4.12 ± 0.09 for Protocol B).

Comparison Between SPECT with Reinjection Only and with Nitrates and Reinjection

All patients had at least one perfusion defect with both stress tests. Protocol A identified 15 (75%) patients with reversible defects, 4 (20%) with fixed ^{201}Tl defects and 1 (5%) with reverse redistribution. Protocol B identified 18 (90%) patients with reversible defects, only 2 patients (10%) with fixed defects and 1 (5%) with reverse redistri-

TABLE 2
Comparison of the Results of ^{201}Tl SPECT with Reinjection Alone and with Nitrates/Reinjection with Respect to Different Types of Myocardial Defects

		Protocol B: Nitrates/reinjection			
		Reversible	Fixed	Reverse	Total
Protocol A: Reinjection alone	Reversible	40	0	1	41
	Fixed	14	40	0	54
	Reverse	0	1	0	1
Total		54	41	1	96

Evolution of exercise defects on delayed imaging with both protocols: reversible, fixed or reverse redistribution.

Chi square analysis calculated on the 94 segments defined as reversible or fixed shows a significant difference between both protocols ($p < 0.0001$).

bution (reverse redistributions were observed on two different patients with the two protocols).

A total of 96 abnormal segments were detected on both stress studies. Their evolution on delayed imaging of both protocols are presented in Table 2 and Figure 2. Eighty (83%) of them had identical redistribution patterns for both protocols: 40 reversible, 40 fixed defects.

With Protocol A (reinjection alone), 41 (43%) segmental defects were reversible, 54 (56%) were fixed and 1 (1%) presented with a reverse redistribution. With Protocol B (nitrates and reinjection), 54 (56%) segmental defects were reversible, 41 (43%) were fixed and 1 (1%) presented with a reverse redistribution by SPECT.

All 41 reversible myocardial segments with Protocol A were also reversible with Protocol B except one which exhibited reverse redistribution. In contrast, among the 54 fixed defects with Protocol A, 14 (26%) were reversible with Protocol B ($p < 0.0001$). An example of such a fixed defect with reinjection which redistributes with nitrates is shown in Figure 3.

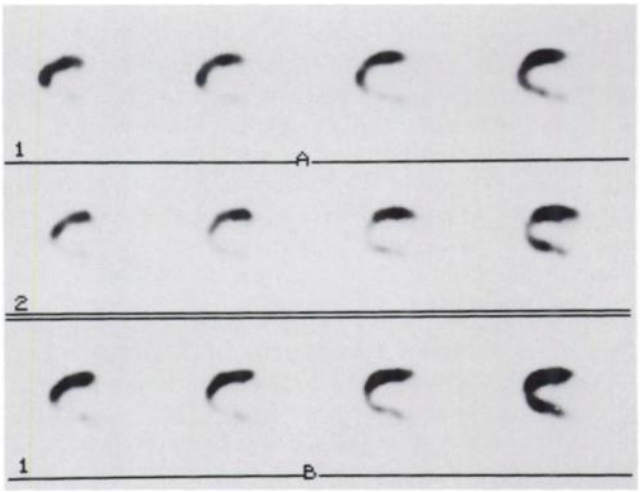

FIGURE 3. Example of a 73-yr-old male patient with coronary artery disease but without myocardial infarction (50% LAD, 50% LCx and 80% RCA stenoses). Protocol A: exercise SPECT images (A1) showed an inferior defect which was fixed on delayed imaging with reinjection alone (A2). Protocol B: exercise SPECT images (B1) also showed an inferior defect which completely normalized on delayed imaging with nitrates and reinjection (B2).

Extent of Thallium-201 Redistribution

The overall extent (segments/patient) of redistribution was 2.05 ± 0.41 segments with Protocol A and 2.75 ± 0.38 ($p < 0.01$) with Protocol B. In 15 patients with redistribution identified by both imaging protocols, the redistribution extent was 2.73 ± 0.41 segments by SPECT with reinjec-

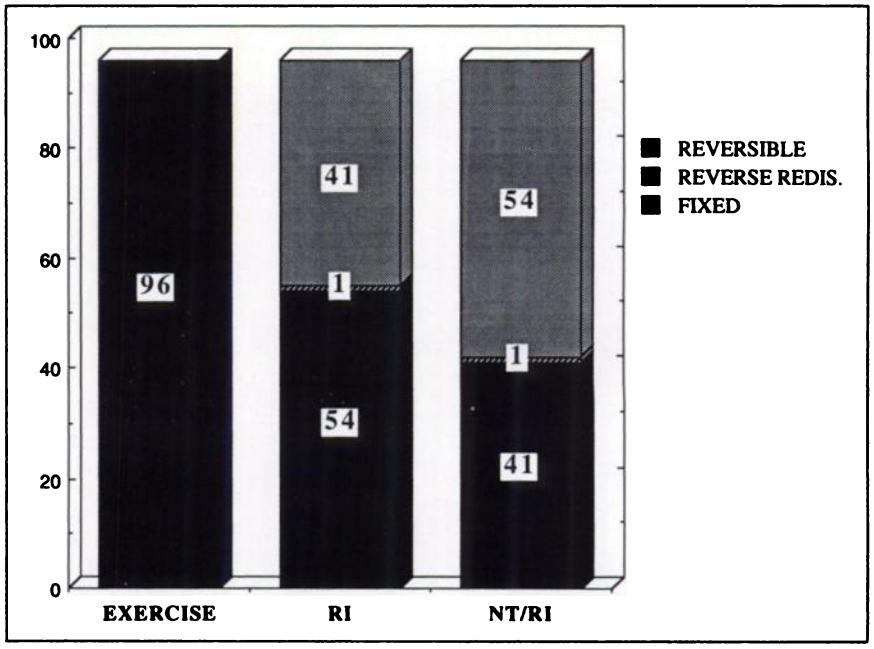

FIGURE 2. Delayed imaging evolution of the 96 abnormal segments at exercise. Comparison of Protocol A with reinjection alone (RI) and Protocol B with nitrates and reinjection (NT/RI).

tion alone and 3.20 ± 0.40 ($p < 0.05$) segments by SPECT with nitrates and reinjection. In the three patients in whom viable myocardium was found with Protocol B but not with Protocol A, the redistribution extent was two, two and three segments.

Degree of Thallium-201 Redistribution

The overall redistribution index of all defects was 1.37 ± 0.28 and 1.52 ± 0.23 (p = ns) by SPECT with reinjection only and with nitrates and reinjection, respectively. In the 14 segments that were fixed with Protocol A and reversible with Protocol B, the redistribution index was 1.64 ± 0.25, which was not significantly different from the overall redistribution index with both protocols.

DISCUSSION

Myocardial dysfunction in patients with coronary artery disease can be caused either by myocardial necrosis or ischemic but viable (hibernating) myocardium (*1–3*). While ischemic yet viable myocardial segments may improve after coronary revascularization, no functional benefit is expected in dysfunctional segments with myocardial necrosis. Therefore, it is of utmost importance to provide a method capable of making this differential diagnosis.

Myocardial viability is predicted by PET on the basis of preserved metabolic activity despite hypoperfusion in regions with abnormal wall motion at rest. The "mismatch" pattern between perfusion and ^{18}F-fluorodeoxyglucose (FDG) images indicates ischemic or hibernating myocardium (*28–31*) with a high probability of recovery of left ventricular contractile function after revascularization (*32–34*).

The present study shows that the use of nitrates can improve the sensitivity of ^{201}Tl SPECT reinjection technique for this diagnosis since 14 (26%) of the 54 fixed defects by reinjection alone showed significant redistribution with nitrates/reinjection. Among our 20 patients, three (15%) presented with ischemia after nitrates/reinjection, whereas they were not considered ischemic with conventional protocol (one of them showed reverse redistribution). Furthermore, in the myocardial segments which were reversible by both protocols, the extent of redistribution was larger when nitrates were used.

Each patient underwent both protocols at a 1-wk interval in a randomized order with similar performances for the two exercises, allowing for a precise comparison between redistribution/reinjection phenomena occurring with and without nitrates. Therefore, our study demonstrates that oral nitrates improve the detection of viable myocardium when compared to standard ^{201}Tl reinjection technique.

The isosorbide dinitrate administered immediately at the end of the exercise SPECT, has a blood half-life of 4–5 hr, thus covering the redistribution period. A combined administration of nitrates and ^{201}Tl reinjection is advantageous as it allows both an increase of the ^{201}Tl blood level and an improvement of hemodynamic conditions for ischemic but viable myocardium.

Standard stress 3–4-hr redistribution ^{201}Tl imaging is reliable for detecting coronary artery disease (*35*) but in patients with incomplete redistribution, it significantly overestimates infarct size and therefore underestimates the amount of viable myocardium. Previous studies showed that about 50% of segments with fixed defects identified by standard 3–4-hr redistribution imaging exhibited normal myocardial uptake of ^{201}Tl and/or function after coronary revascularization (*7–9,17,33*). Furthermore, the majority of persistent ^{201}Tl defects identified by exercise/3–4-hr redistribution ^{201}Tl imaging are metabolically active as demonstrated by PET imaging using ^{18}F-FDG (*29,33,36–39*). Therefore, standard stress/3–4-hr redistribution ^{201}Tl imaging is not suitable for precise assessment of ischemic but viable myocardium.

Recently, rest ^{201}Tl reinjection after standard 3–4-hr redistribution has been proposed for evaluation of myocardial viability (*13–15*). It has been demonstrated that ^{201}Tl reinjection imaging detected myocardial viability among approximately 50% of the segments with persistent ^{201}Tl defects on standard 3–4-hr redistribution imaging (*15,17*). A recent study by Kuijper et al. (*40*) confirmed its clinical usefulness, showing that reinjection of ^{201}Tl revealed reversible defects in 63% of patients showing only persistent defects at redistribution. It has been shown that reinjection had a good predictive value for myocardial viability when compared to ^{18}F-FDG PET (*19*) or to postrevascularization ventricular function improvement (*15,17*). However, although it significantly improves detection of viable myocardium in comparison to standard 3–4-hr redistribution imaging, ^{201}Tl reinjection still underestimates (by approximately 25%–35%) the extent of myocardial viability when compared to FDG PET imaging (*20*) or systolic thickening by magnetic resonance imaging (*21*). According to our results, oral nitrates probably reduce this underestimation of viable myocardium.

A separate resting ^{201}Tl may accurately detect the ischemic but viable myocardium (*5*). But the clinical value for assessment of myocardial viability of stress/rest ^{201}Tl imaging seems to be similar to stress/reinjection ^{201}Tl imaging (*41*) and resting ^{201}Tl imaging implies a two-day protocol.

The need for three acquisitions after stress injection has been advocated by different groups; either after redistribution and before reinjection, or 18–24 hr after injection in case of fixed defects on redistribution images.

Dilsizian et al. (*15,42*) argue that a true redistribution acquisition before reinjection is necessary since a "differential uptake" phenomenon (smaller increment in thallium activity in ischemic regions as compared with normal regions after reinjection) may change the interpretation of a defect from reversible on the redistribution to irreversible when only the reinjection study is analyzed. This phenomenon, however, occurs in approximately 8% of the segments (*43*) and we believe that this number does not justify the additional logistical cost.

Thallium-201 delayed (18–24 hr) redistribution imaging was also proposed for myocardial viability evaluation.

Some studies demonstrated that delayed redistribution imaging improved its detection compared to standard 3–4-hr redistribution imaging (*10,11,17*). In a study by Kiat et al. (*10*), 37% of the segments with a fixed thallium defect on delayed redistribution imaging improved after revascularization. However, the clinical application of late redistribution is limited by the low count rates available (*12*) and this protocol was reported to add information in only 6% of the patients when compared to the reinjection technique (*44*).

Rest-redistribution is a logical protocol in patients with poor left ventricular function for whom viability is a more important issue than stress-induced ischemia. Iskandrian et al. (*5*) have shown that reversible resting perfusion defects were good predictors of postbypass grafting left ventricular function improvement.

CONCLUSION

The use of nitrates along with reinjection improves ^{201}Tl uptake in ischemic myocardium. Therefore, it increases the reliability of ^{201}Tl stress/reinjection SPECT for the evaluation of myocardial viability.

Further work is necessary to compare this approach with other protocols such as rest-redistribution imaging, but it has the merit of being readily applicable to standard one-day exercise ^{201}Tl studies. The improvement obtained by using nitrates also needs to be validated by comparison with ^{18}F-FDG PET results or preferably by postrevascularization wall motion improvement.

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