Assessment of Myocardial Viability after Thallium-201 Reinjection or Rest–Redistribution Imaging: A Multicenter Study

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To establish the real nature of ^{201}Tl defects in the assessment of myocardial viability (e.g., fixed versus reversible), ^{201}Tl reinjection was evaluated in a multicenter trial involving 402 consecutive patients with ischemic heart disease and exercise ^{201}Tl defects. **Methods:** Twelve hospitals, using the same type of gamma camera and computer software, adopted one of the two most widely used reinjection protocols. In 230 patients (Group A), reinjection was performed immediately after stress-redistribution planar imaging; in 172 patients (Group B), reinjection was performed on a separate day and followed by rest-redistribution imaging. The images were interpreted by three blinded observers in a core laboratory on a five-point qualitative scale; the reproducibility in visual scoring was excellent. **Results:** Groups A and B had a similar prevalence of myocardial segments with abnormal uptake at stress (39%, 40%), as well as with reversible (16%, 17%), partially reversible (21%, 19%) and irreversible (63%, 64%) defects at redistribution. After reinjection, ^{201}Tl uptake improved in 27% and 36% of both partially reversible and irreversible defects in Groups A and B. No differences were found when comparing early and delayed reinjection imaging in Group B. **Conclusion:** This study confirms the validity of ^{201}Tl reinjection in a large, unselected population, but the discordance with stress/redistribution is less than has been previously reported for both ^{201}Tl reinjection protocols, the prevalence of improved segments after reinjection was higher with the separate day approach.

Key Words: thallium-201; rest-redistribution imaging; myocardial viability; multicenter trial; planar myocardial imaging

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Over the past 15 yr, ^{201}Tl imaging has proved to be a powerful tool in the diagnostic and prognostic assessment of coronary artery disease (CAD). The single injection stress 4-hr redistribution protocol, first proposed by Pohost et al. (*1*), is still the most popular and widely used technique for characterizing uptake defects as fixed or reversible. Early studies were mainly designed to test the accuracy of ^{201}Tl imaging in diagnosing CAD, and so some discrepancies between a single injection stress 4-hr redistribution study and a separate rest injection study did not give rise to the problem of scar overestimation (*2–4*). Recently, the ability of noninvasive imaging techniques to differentiate scarred and viable myocardium has attracted considerable attention. A number of studies (*5,6*) have clearly shown a functional improvement in some fixed perfusion defects at redistribution imaging after myocardial revascularization. With the reinjection of an additional dose of ^{201}Tl after the completion of the 4-hr redistribution study, up to 50% of apparently fixed uptake defects have shown evidence of reversibility (*7–11*). This method is now widely used, despite the lack of conclusive data concerning its clinical impact and the fact that there is no evidence of any substantial advantages over the stress-rest ^{201}Tl approach, formerly proposed as the method of choice for the assessment of defect reversibility.

Subsequent studies (*12–14*) have proposed some modifications in order to optimize the protocol. This SIRT (Italian Study on Thallium Reinjection) multicenter trial was undertaken to test the prevalence of discordant results between 4-hr redistribution, single-day reinjection and separate day rest-redistribution imaging in a large patient population obtained under everyday clinical conditions.

METHODS

Study Design

Twelve Italian sites (six university and six general hospitals) experienced in nuclear cardiology participated in the study. The interinstitutional nature of the study, the enrollment of consecutive patients and the involvement of both university and general hospitals were all designed to ensure a large, unselected patient population. This gave us the opportunity of assessing the preva-

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TABLE 1
Comparison of Clinical, Electrocardiographic and Echocardiographic Variables in Groups A and B

	Group A (n = 230)	Group B (n = 172)	p value
Age (yr)*	56 ± 9.2	59 ± 9.1	0.0013
Sex (% of males)*	87	91	0.37 ns
History of infarction (%)*	81	71	0.06 ns
Q-wave infarction (%)	72	79	0.17 ns
>85% MPHR (%)*	52	64	0.02 ns
RPP (a.u.)	24,926 ± 5770	25,879 ± 5394	0.08 ns
Exercise duration (sec)*	519 ± 162	607 ± 231	5×10^{-6}
ST changes during exercise (%)*	49	49	ns
Angina during exercise (%)*	40	27	0.009
Positive EST (%)	59	52	0.18 ns
WMSI*	1.39 ± 0.37	1.48 ± 0.38	0.04 ns

*Variables submitted for Bonferroni correction for multiple comparisons.

Continuous data are expressed as mean ± s.d.; RPP = rate-pressure product; a.u. = arbitrary unit; MPHR = maximum predicted heart rate; EST = exercise stress test; WMSI = wall motion score index; and ns = not significant.

lence of discordant results between conventional stress/redistribution studies and reinjection imaging performed following the two most widely used protocols: reinjection of ^{201}Tl shortly after completion of a stress/redistribution study and a rest/redistribution study performed on a separate day. All participating sites used the same type of gamma camera, acquisition protocol and computer software. Moreover, a core laboratory was used for blinded rereading of the entire set of ^{201}Tl images and the computer process of data, as well as ensure quality control. The strictly controlled method of image acquisition, processing, display and data analysis was adopted to eliminate external sources of variability, minimize operator intervention and to obtain the greatest reproducibility for visual analysis.

Patient Population

Participation was predicated on the demonstration of at least one ^{201}Tl defect on planar poststress images in consecutive patients referred for an exercise ^{201}Tl study between January 1991 and May 1992. Patients scheduled for a dipyridamole stress test, SPECT study or planar acquisitions with gamma cameras and computers different from the protocol requirements were not included in this study. Other exclusion criteria were: patients less than 18 or more than 76 yr, recent acute myocardial infarction or unstable angina, valvular heart disease, nonischemic cardiomiopathies, left bundle branch block or the presence of a pacemaker.

Four hundred and two patients with ischemic heart disease, as revealed by history and physical examination, were studied (356 males and 46 females); the mean age was 57 yr (range 25–72). A Q-wave myocardial infarction (*15*) was present in 75% of enrolled patients (Table 1). All cardiac medications were withdrawn in 46% of the patients; in the rest, cardiac medications included either one or a combination of nitrates, calcium antagonists and beta-blockers. Ischemia was detected in 55% of patients by exercise electrocardiography versus 58% by conventional, poststress redistribution ^{201}Tl imaging. All patients underwent two-dimensional echocardiography performed within 15 days of the scintigraphic study. Wall motion impairment was detected in 84% of the whole study group; 34% had a wall motion score index higher than 1.5. Coronary angiography within 60 days was performed for clinical reasons in 92 and 89 patients of Groups A and B, respectively. Twenty-two and 33 of these patients underwent previous percutaneous transluminal coronary angioplasty or coronary artery bypass grafting.

Stress images of poor quality, echocardiography not performed within 15 days and patients unavaliable for repeat imaging on a separate day (Group B) were the main reasons for drop-outs.

Thallium Imaging

A symptom-limited exercise test was performed in an upright position and in a fasting state on either a treadmill or a calibrated bicycle ergometer using step-wise increases in work load (*16,17*); criteria for exercise termination were: maximal age-predicted heart rate, angina, dyspnea, severe arrhythmias, exhaustion, dizziness, abnormal systolic blood pressure or a fall superior to 20 mmHG with respect to the resting value, asymptomatic ST segment depression of 2 mm or more. At peak exercise, 74 MBq (2 mCi) of ^{201}Tl were injected, and the patient continued to exercise for at least one more minute. Immediately after exercise, sequential 8-min or 750 kcts in the total field of view were recorded in the best septal left anterior oblique, anterior and left lateral views. The images were acquired using a general-purpose, parallel-hole collimator with a 25% window on the 80 keV peak and a 20% window on the 167 keV peak in a 128 × 128 byte matrix, and a standardized zoom factor. A second set of redistribution images was acquired in the same views and for the same time as the stress images 3–4 hr later. All of the patients were also evaluated by reinjection of ^{201}Tl under baseline conditions. Seven centers followed a same-day approach in which 230 patients (Group A) received a second injection of 1 mCi of ^{201}Tl immediately after the redistribution study. Five centers followed a different day approach in which 172 patients (Group B) received a reinjection of 2 mCi of ^{201}Tl at rest 48–72 hr after the stress-redistribution study. In both groups, acquisition started no earlier than 30 min after reinjection in the same views and following the same criteria as for the stress-redistribution study. Only in Group B was a fourth set of images acquired 4 hr after the reinjection of ^{201}Tl (Fig. 1).

Visual Thallium Analysis

The analytic details have been previously reported (*18*). Briefly, three experienced observers independently and blindly reread the studies on a black and white video terminal. The images were displayed before and after background subtraction

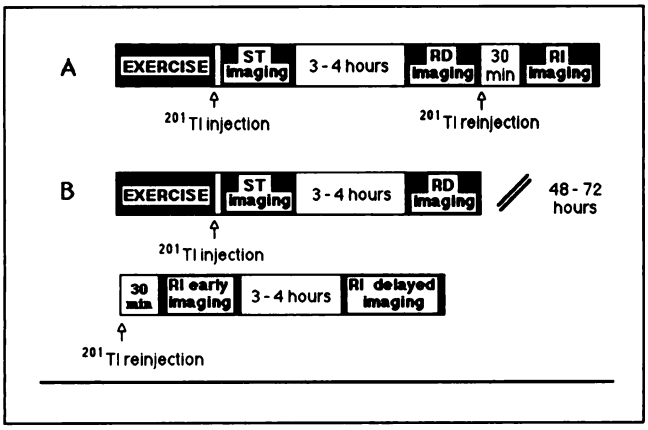

FIGURE 1. Protocol A. Thallium-201 stress/redistribution and reinjection imaging on the same day. Protocol B. Thallium-201 stress/redistribution and rest-redistribution imaging on a different day. ST = stress; RD = redistribution; RI = reinjection.

(*19*), and the video display was programmed to minimize operator interventions. In each view, the left ventricle was divided into five segments, each segment being visually graded according to a five-point scale (0 = normal, 1 = equivocal, 2 = mild, 3 = severe, 4 = no uptake). The median score was calculated for each segment, and the scores corresponding to the apical region were then grouped in a single value by obtaining their median value. Thus, a total of 5226 segments (13 per patient) were available for evaluation.

Abnormal segments were defined as segments having a score ≥1 at stress imaging. Reversible segments were any segment abnormal during stress imaging that normalized on the delayed scans; the segments which improved by one grade but did not normalize were considered as partially reversible. Myocardial segments with either irreversible or partially reversible defects were considered as having improved ^{201}Tl uptake after reinjection if the score decreased in comparison to the redistribution study; if the ^{201}Tl uptake score after reinjection remained the same or worsened, the segments were considered unchanged.

Thallium-201 diagnostic conclusions of the conventional stress/redistribution studies were first classified for each patient in the following manner: ischemia (ISCH) if all abnormal segments at stress improved or normalized at redistribution imaging; ischemia mixed with scar (ISCH and SCAR) if there was a variable proportion of abnormal segments at stress that improved or remained fixed during redistribution imaging; scar (SCAR) if all abnormal segments at stress were found unchanged during redistribution imaging. The same classification was used after paired analysis of stress and reinjection images.

Quantitative Thallium Analysis

After background subtraction, circumferential maximal count profiles (*20*) of the myocardial ^{201}Tl distribution were obtained. Each point in these profiles represents the average of the two hottest pixels along a radius traversing the myocardium and emanating from the center of the left ventricle cavity, as visually assessed by the operator. The operator also identified the location of the scintigraphic apex on the circumferential profile by visually inspecting the stress images. The profile was computer-generated from the values of 50 radii, plotted clockwise at 6° intervals, excluding the 60° of the basal portion of the left ventricle. The curves were then normalized to the maximum pixel value found in each profile. Roughly speaking, each segment corresponds to 10 points on the circumferential profile of the corresponding view. The minimum value for each segment was calculated in order to assess the correlation of visual scores to the quantitative results of the corresponding territories on the stress circumferential profiles.

Echocardiography

Two-dimensional echocardiograms were obtained following the recommendations of the American Society of Echocardiography (*21*). The left venticular wall was divided into 16 segments and scored using a four-point scale (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = diskinetic). The wall motion score index was calculated as the sum of the scores in the visualized segments plus 16 and divided by the number of segments visualized.

Statistical Analysis

Data are presented as mean ± s.d. or as experimental percentages. The differences between the patients in Groups A and B with respect to clinical, ECG, echocardiographic and scintigraphic variables were analyzed by either a two-tailed unpaired t-test or chi square analysis. Correlation of visual to quantitative analysis was represented by box-plots and quantitated using the Spearman rank correlation coefficient and corrected for ties. The agreement between the segmental scoring of early and delayed imaging after reinjection in Group B was evaluated with the weighted K-statistic method (*22*). Statistical significance was set at $p < 0.01$. Since individual comparisons between Groups A and B were made for each variable in Tables 1 and 2, we corrected the data for multiple comparisons by applying the Bonferroni method: we divided the nominal level of statistical significance by the number of tests performed on the 10 variables labeled with an asterisk in Tables 1 and 2, thus obtaining a new level of statistical significance at $p = 0.001$. The remaining unlabeled variables were considered for Bonferroni correction since they are not independent.

RESULTS

Two hundred and twenty-seven patients exercised to 85% or more of their expected maximal heart rate, corrected for age; 348 patients reached an adequate exercise end point, defined as the development of typical angina, ischemic ST segment depression (≥2 mm downsloping) or the achievement of 85% or more of the maximal predicted heart rate (Table 1).

Segmental Analysis

Details of inter- and intraobserver reproducibility of the visual scoring of ^{201}Tl images have been previously reported (*18*). Briefly, interobserver reproducibility of the averaged visual scores of the three core observers was 0.91, 0.90 and 0.89 for stress, redistribution and reinjection images. The reproducibility for the score change of the stress-redistribution, stress-reinjection, redistribution-reinjection sequences was 0.74, 0.76 and 0.58. The precision of the change assessment is within one point at the 95% confidence level.

Figure 2 shows the score frequency distribution of myocardial segments after stress imaging. The correspondence between visual scores and the quantitation of ^{201}Tl uptake in myocardial segments at stress imaging is shown in Fig-

TABLE 2
Comparison of Scintigraphic Variables between Patients in Groups A and B

	Group A (n = 230)	Group B (n = 172)	p value
Number of stress defects*	5.1 ± 2.0	5.2 ± 2.0	0.62
Number of irreversible* defects at redistribution	3.2 ± 2.2	3.3 ± 2.2	0.65
Stress severity score	13.6 ± 6.9	14.6 ± 7.2	0.16
Redistribution severity score	11.3 ± 6.9	12.2 ± 7.9	0.23

*Variables submitted for Bonferroni correction for multiple comparisons.
Data are expressed as mean ± s.d.; the severity score is the sum of the scores of the 13 segments.

ure 3. Spearman rank correlation coefficient corrected for ties was $\rho = -0.64$ ($p < 0.001$).

Figure 4 shows the visual classification of the 5195 evaluable segments after stress, redistribution and reinjection imaging obtained at 30 min in both Groups A and B. After stress, 40% of segments showed uptake defects. After redistribution, 16% of the defects were considered completely reversible, 20% partially reversible and 64% irreversible. After reinjection, ^{201}Tl uptake increased in 26% of the abnormal regions: in 30% of the partially reversible and in 31% of the irreversible defects. Of the 415 segments with fixed and severe (scores 3 and 4) defects after stress/redistribution, 105 (25%) improved after reinjection. Apparent ^{201}Tl washout between the redistribution and the reinjection studies occurred in only 112 of all abnormal segments (5%); this percentage increased to 10% (73/745) in segments that were either completely or partially reversible at redistribution imaging. The change in segmental uptake between redistribution and reinjection was of only one grade in 94% of all cases.

In 181 patients submitted for coronary angiography, the reassignment after reinjection of fixed defects to reversible or partially reversible defects occurred in 36% of segments (207/573) versus 26% of segments (196/740) in the remaining patients who did not undergo cardiac catheterization ($p < 0.01$).

Group Analysis

Significant differences between patients in Groups A and B were observed in terms of age, development of typical angina during exercise and exercise duration. No significant differences were found in the clinical, ECG or echographic variables (Table 1). Moreover, no differences were found in the number of defects at stress, number of fixed defects at redistribution or in the stress and redistribution severity score (Table 2). When the Bonferroni correction for multiple comparison was applied, the differences in age and typical angina were no longer statistically significant.

Figures 5 and 6 show the segmental classification of ^{201}Tl defects for Groups A and B because they had a similar prevalence of myocardial segments with abnormal uptake on stress images (39% versus 40%), as well as reversible (16% versus 17%), partially reversible (21% versus 19%) and irreversible (63% versus 64%) defects on redistribution images. Among the clinically relevant group of fixed defects from conventional stress/redistribution studies, the prevalence of improved segments after reinjection was higher in Group B than in Group A (36% versus 27%, $p < 0.01$).

The agreement between segmental scoring in Group B at 30 min and 4 hr after reinjection was Kw = 0.947. In this case, the off-diagonal segments were equally distributed above (89) and below (95) the line of agreement (Table 3).

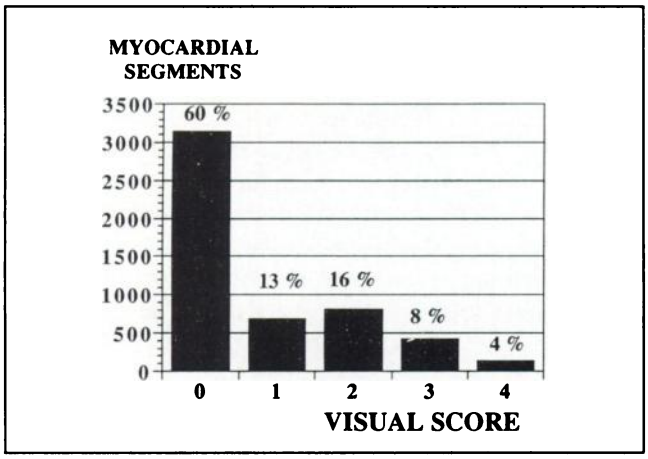

FIGURE 2. Score frequency distribution of ^{201}Tl uptake in 5195 myocardial segments during stress imaging.

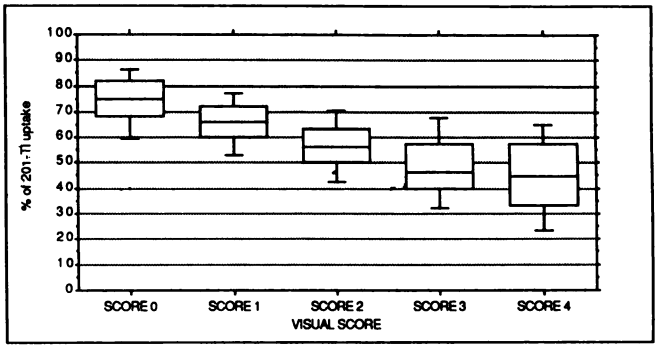

FIGURE 3. Concordance between visual scores and quantitation of ^{201}Tl uptake in myocardial segments at stress imaging.

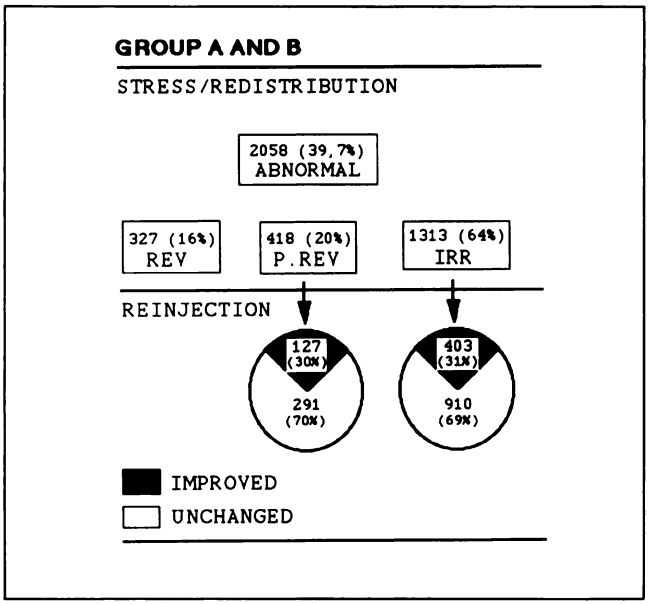

FIGURE 4. Classification of 5195 myocardial segments in 402 patients after stress, redistribution and reinjection imaging obtained 30 min p.i. in Groups A and B. REV = reversible; P.REV = partially reversible; IRR = irreversible.

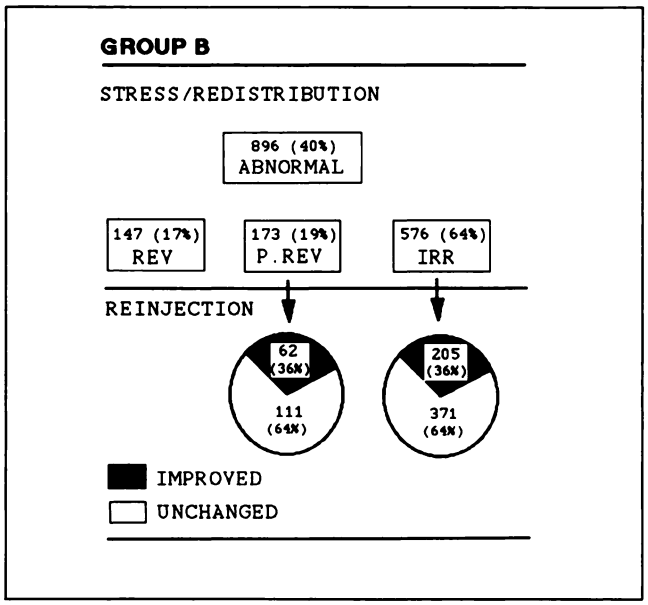

FIGURE 6. Classification of 2218 myocardial segments in 172 patients after stress, redistribution and reinjection imaging obtained 30 min p.i. in Group B. REV = reversible; P.REV = partially reversible; IRR = irreversible.

Patient Analysis

Figure 7 shows the patient classification of stress/redistribution and stress/reinjection studies. After blinded rereading in the central laboratory, only equivocal defects (Grade 1) were found in 50 patients at stress imaging; they were thus considered negative for the presence of significant scar and/or transient ischemia. During redistribution, 69, 165 and 118 patients were classified as ISCH, ISCH and SCAR and SCAR, respectively. For the entire patient population, ^{201}Tl reinjection improved reversibility detection in 83 of 402 patients (20%) compared to the conventional stress/redistribution study. In the clinically relevant subset of patients showing only fixed defects (median number = 4 segments/patient) during redistribution, ^{201}Tl reinjection revealed reversible or partially reversible defects in 58 of 118 patients (49%). This change involved only one segment in 31 patients (Fig. 8). On the other hand, ^{201}Tl was less effective in reversibility detection in 13 of 402 patients (3%).

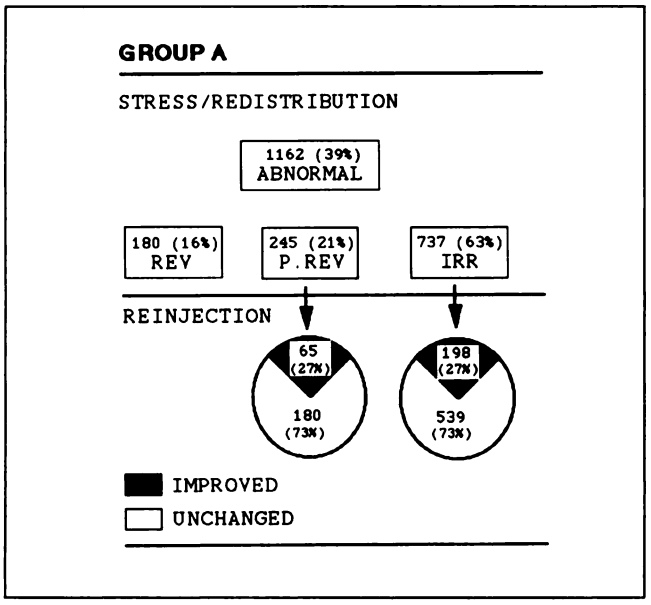

FIGURE 5. Classification of 2977 myocardial segments in 230 patients after stress, redistribution and reinjection imaging obtained 30 min p.i. in Group A. REV = reversible; P.REV = partially reversible; IRR = irreversible.

DISCUSSION

The visual scale used in this study to score ^{201}Tl images proved to be highly reproducible, particularly when the scores of the three observers were averaged; in this case

TABLE 3
Agreement in Segmental Scoring of ^{201}Tl Uptake Defects in Group B between the Two Imaging Procedures after Reinjection in 172 Patients

		REINJ 30 min					
	Visual Score	0	1	2	3	4	Total
R	0	1507	44	8	—	—	1559
E	1	41	212	19	—	—	272
I	2	1	25	166	13	—	205
N	3	1	1	17	103	5	127
J	4	—	—	2	7	46	55
4 hr	Total	1550	282	212	123	51	2218

Statistical results: Kw = 0.947.

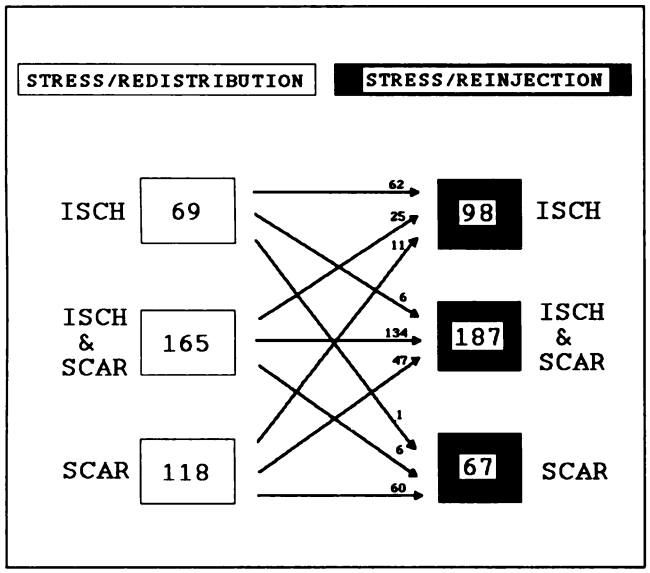

FIGURE 7. Patient analysis of ^{201}Tl images after stress/redistribution and stress/reinjection imaging. Fifty patients were excluded from this analysis because of transient ischemia or presence of significant scar.

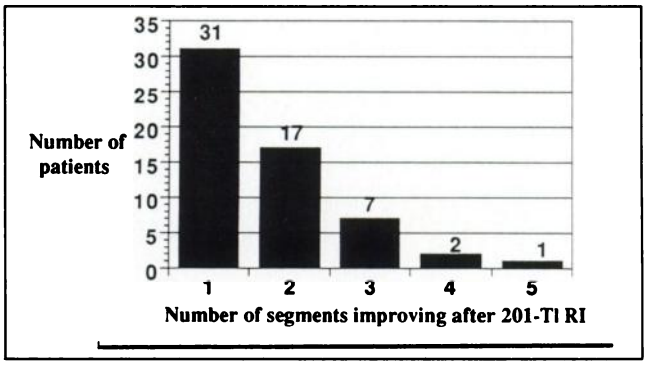

FIGURE 8. Frequency distribution of improving segments after ^{201}Tl reinjection in the 58 patients with only fixed defects at redistribution and reversibility during reinjection imaging.

the reproducibility values (*18*) were similar to those reported using quantitative techniques (*23*). Furthermore, the precision of change assessment was within one point at the 95% confidence level, and thus change scores can be used to assess the reversibility of defects.

The fair correlation of quantitative and qualitative analysis of stress images deserves some explanation. The operators were only asked to identify the left ventricle and the apex on 1208 stress images. Afterward, the subdivision in five 60° sectors for each view, corresponding to 6030 visual segments, was automatically performed by dedicated software. The median value of the visual scores assigned by the three observers was compared to the minimum value of the 10 corresponding points on the circumferential profile (1 point = 6° interval). This minimum value criterion was preferred to the average value or to the integral method, in an attempt to improve differentiation between mild-moderate and severe perfusion defects. Possible anatomical misalignment between segments and sectors could account for the overall weak correlation. Despite this drawback, this correlative study is useful to demonstrate that the vast majority of mild-to-moderate defects (scores 1 and 2) are visually assigned to segments with thallium uptake superior to 50% of the maximum.

In our study, ^{201}Tl reinjection improved detection of reversibility in 30% of partially reversible defects and in 31% of irreversible defects during redistribution imaging. Among the latter, postreinjection improvement was slightly lower in severe defects (scores 3 and 4) than in equivocal/mild (scores 1 and 2) defects (25% versus 33%). It was also shown that ^{201}Tl reinjection was less effective in detecting reversibility in 5% of abnormal segments in the stress/redistribution study. These findings have a number of theoretical and experimental consequences.

First, the reversibility of apparently fixed defects during stress/redistribution imaging is real and not merely attributable to statistical oddities or imaging artifacts. In particular, our results exclude the possibility that regression toward the mean (*24*) accounts for a significant amount of information conveyed by the reinjection study. If this hypothesis were true, we could expect the percentage of mild/severe defects during stress/redistribution imaging (scores 2-3-4) after reinjection regressing toward a mean score of 1 to be the same order of magnitude as the percentage of normal segments (score 0) worsening toward the same value. This is not the case (Fig. 9).

Second, the prevalence of this phenomenon is lower than that published by other authors who have reported up to 50% improvement in segments with fixed defects during redistribution. The discrepancy between our study and Kuijper's study (*25*) may partially be due to differences in the criteria adopted to establish reversibility (a shift towards normal of ≥1 grade in our study versus a shift of ≥2 grades in Kuijper's study). This high threshold leads to 77% of defects being classified as irreversible after stress/redistribution compared with only 64% in our study. This higher number of fixed defects is obtained at the expense of partially reversible segments (only 6% in Kuijper's study against our 20%), and this might overestimate the percentage of fixed defects improving after reinjection by adding an extra contribution from segments that are really partially reversible after stress/redistribution and which improve after reinjection.

Furthermore, in Kuijper's study, there is an unusual bimodal distribution of poststress segmental scores that points towards problems in the scoring scale (*14,25*). The discrepancies between our results and those of other investigations (*7,9–10*) are more likely attributable to differences in the study populations: 24 patients referred for coronary artery bypass grafting (*9*); 16 patients with angiographically proven multivessel CAD and left ventricular dysfunction (*10*); 100 patients with angiographically proven CAD, 12 of whom had previously undergone coronary artery bypass grafting (*7*). The prevalence of abnormal segments at stress imaging was, respectively, 80%, 62% and 52%, and the

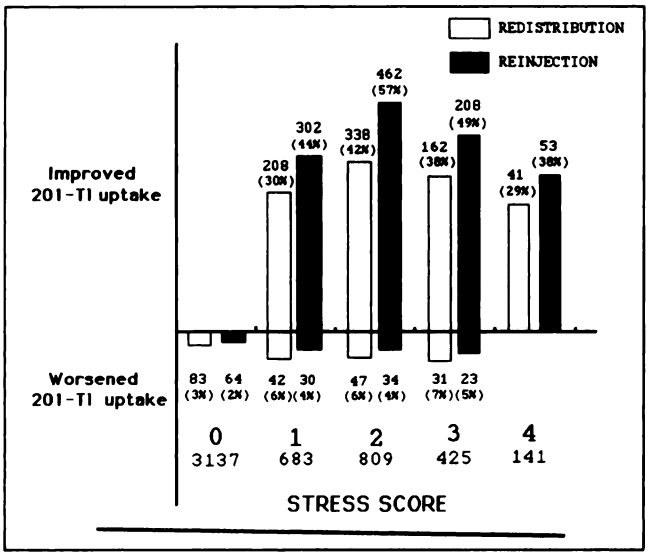

FIGURE 9. Frequency distribution of myocardial segments with improving and worsening of ^{201}Tl uptake after redistribution and reinjection.

percentage of fixed defects at redistribution was 50%, 42% and 33%, compared to our 40% and 64%. The higher frequency of new filling-in after reinjection in the above mentioned studies probably reflects a selected patient population and is related to the severity of the underlying CAD that prompted invasive study. Indirect confirmation of this hypothesis is provided by the 181 patients in our study who underwent coronary angiography: in this subset, the frequency of new filling-in increased to 36%. This circumstance has been previously reported (*8*). In 41 patients, enrolled only on the basis of the demonstration of a persistent defect during conventional stress/redistribution study, the overall percentage of new filling-in after reinjection was 31%, but this increased to 44% in the subgroup of 21 catheterized patients.

Apparent ^{201}Tl washout (defect worsening) between the redistribution and reinjection studies in regions that were either completely or partially reversible at redistribution, occurred in a percentage similar to that reported by Dilsizian et al. when using visual analysis (*26*), but noticeably lower than the percentage (25%) reported in the same study when using quantitative analysis. This discrepancy between qualitative and quantitative analyses in Dilsizian's investigation may be related to the broad confidence intervals in the estimate of such percentages due to the small sample size. Further studies are needed to establish the prevalence of apparent ^{201}Tl washout between redistribution and reinjection and to evaluate the risk of misclassifying reversible segments when substituting redistribution with reinjection images.

The present study was designed to ensure as little difference as possible between Groups A and B in terms of clinical, ECG, echographic and scintigraphic variables, as proven in Tables 1 and 2. Although statistically significant (due to the high statistical power of the test), the difference in exercise duration can hardly be interpreted as clinically significant. We can thus compare the prevalence of discordant findings between reinjection and stress/redistribution imaging in the two groups. When considering fixed defects at redistribution, the prevalence of improving segments after reinjection was higher in Group B (36%) than in Group A (27%). Once again, the higher frequency of new filling-in with Group B might be related to the severity of the underlying CAD, which prompted coronary angiography in 52% of patients in Group B against only 40% in Group A.

Our results in Group B are different from those of previous reports (*27–30*), indicating that 3–4-hr delayed imaging is required to differentiate viable from nonviable myocardium. In fact, the agreement in the segmental scoring of ^{201}Tl uptake defects following the two imaging procedures (30 min and 4 hr after rest injection) is excellent (Table 3). The differences between our results and others' results seem to be more related to random fluctuations in the scoring procedures than to systematic effects. This inconsistency may be partially due to differences in the starting time of the acquisition of the first set of images after rest injection (≥30 min in our protocol against the 10–15 min usually reported by other authors). Our later starting time was chosen to reduce the dependence of ^{201}Tl on coronary flow in order to provide images that are more representative of the real potassium pool and reduce the differences from late imaging (*31*). Another circumstance that may have contributed to lowering the amount of additional information conveyed by late imaging is the fact that, on average, our patient population was less ischemic than the populations studied in the cited papers, and thus there is a lower prior probability of temporal variation in ^{201}Tl uptake on serial imaging.

Notwithstanding the large number of papers concerning ^{201}Tl reinjection, only a few specify the number of patients in whom it changed the diagnostic outcome. Rocco et al. (*8*), who performed the stress/redistribution/reinjection protocol, detected 9 of 41 patients (22%) in whom reinjection provided the only scintigraphic evidence of ischemia; Kayden et al. (*31*), who performed stress/redistribution and late (24 hr) reinjection studies, showed that 29 of 41 patients (71%) with only fixed defects at redistribution had enhanced ^{201}Tl uptake after reinjection; Kuijper et al. (*25*), who performed the stress/redistribution/reinjection protocol, reported a change in diagnostic outcome after reinjection in 45 of 71 patients (63%) with only fixed defects during conventional stress/redistribution study.

In our patient analysis, we excluded 50 patients who showed only Grade 1 defects during stress imaging and were thus considered negative for the presence of significant scar and/or ischemia. This choice might seem arbitrary, but from a clinical point of view, a change in segmental score from 1 to 0 or vice versa on a five-point scale adds little information to a stress pattern that is already indicative of viability (*32*). Moreover, if we consider segments with a score of 1 on stress imaging that normalized

on redistribution images as being representative of inducible ischemia, we end up with 278 of 402 ischemic patients (66%) in the conventional stress/redistribution study, who increased to 333 (83%) after reinjection. This is by no means realistic with our population which mainly consisted of patients with previous uncomplicated myocardial infarction. The threshold we adopted for our patient analysis was intended to protect against an overinterpretation of scintigraphic results.

In this study, stress/redistribution imaging detected reversible defects in 58% of patients, and this figure increased to 71% after reinjection. The most important clinical result was the detection of reversible defects after reinjection in 48% of 118 patients showing only fixed defects at redistribution. In the great majority (48/58) of cases, improvement after reinjection involved only one or two myocardial segments (Fig. 8) and was limited to one grade on the five-point scoring scale.

Study Limitations

Matching views of each patient were displayed for side-by-side comparison in the same order they were acquired rather than at random. This may have led to some psychological bias in the reading of the reinjection images by the blinded observers. Even when displayed at random, stress, redistribution and reinjection images were always identifiable because of their different qualities and count statistics. Furthermore, ^{201}Tl reading without precise alignment of each sequence of views does not represent the conditions of everyday practice.

Since none of our patients underwent both ^{201}Tl reinjection protocols, no direct comparison was made in terms of agreement or accuracy (*30*), and therefore our results can only be considered indicative and not definitive as to which is the best reinjection procedure.

CONCLUSION

In this large and unselected patient population with a controlled diagnostic methodology, the segmental prevalence of postreinjection improvement in ^{201}Tl uptake of apparently irreversible defects on standard redistribution imaging is less than has been previously reported. This result applies to both reinjection protocols adopted in this study. The prevalence of improving segments after reinjection was higher in Group B (rest-redistribution) than in Group A (same-day reinjection): 37% versus 26%. No differences were found when comparing rest and redistribution imaging in Group B. Thallium-201 reinjection had a relevant impact for diagnosis in 48% of patients showing only persistent defects at redistribution, providing the only evidence of reversibility, but ^{201}Tl uptake improvement was usually limited to one or two segments per patient with an incremental value mainly restricted to one grade on the five-point scale. Therefore sufficient reproducibility in the visual scoring of reinjection images is highly recommended.

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APPENDIX

Italian Multicenter Study on Thallium Reinjection (SIRT)

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REFERENCES

1. Pohost GM, Zir LM, Moore RH, et al. Differentiation of transient ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 1977;55:294–302.
2. Strauss HW, Harrison K, Laugan J, et al. Thallium-201 for myocardial imaging: relation of thallium-201 to regional myocardial perfusion. *Circulation* 1975;51:641–645.
3. Blood DK, Mc Carthy DM, Sciacca RR, et al. Comparison of single-dose and double-dose thallium-201 myocardial perfusion scintigraphy for the detection of coronary artery disease and prior myocardial infarction. *Circulation* 1978;58:777–788.
4. Ritchie JL, Albro PC, Caldwell JH, et al. Thallium-201 myocardial imaging: a comparison of the redistribution and rest images. *J Nucl Med* 1979;20: 477–483.
5. Rozanski A, Berman DS, Gray R, et al. Use of thallium-201 redistribution scintigraphy in preoperative differentiation of reversible and nonreversible myocardial asynergy. *Circulation* 1981;64:936–944.
6. Gibson RS, Watson DD, Taylor GL, et al. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. *J Am Coll Cardiol* 1983; 3:804–815.
7. Dilsizian VD, Rocco TP, Nanette MT, et al. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. *N Engl J Med* 1990;323:141–146.
8. Rocco TP, Dilsizian V, McKusick KA, et al. Comparison of thallium redistribution with rest "reinjection" imaging for the detection of viable myocardium. *Am J Cardiol* 1990;66:158–163.
9. Othani H, Tamaki N, Yoshiharu Y, et al. Value of thallium-201 reinjection after delayed SPECT imaging for predicting reversible ischemia after coronary artery bypass grafting. *Am J Cardiol* 1990;66:394–399.
10. Bonow RO, Dilsizian VD, Cuocolo A, et al. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. *Circulation* 1991;83:26–37.
11. Tamaki N, Othani H, Yamashita K, et al. Metabolic activity in the areas of new fill-in after thallium-201 reinjection: comparison with positron emission tomography using fluorine-18-deoxyglucose. *J Nucl Med* 1991;32:673–678.
12. Kiat H, Friedman JD, Wang FP, et al. Frequency of late reversibility in stress-redistribution thallium-201 SPECT using an early reinjection protocol. *Am Heart J* 1991;122:613–619.
13. Pieri PL, Abraham S, Katayama H. Thallium-201 myocardial scintigraphy: single injection, reinjection or 24-hr delayed imaging? *J Nucl Med* 1990;31: 1390–1396.
14. van Eck Smit BLF, van der Wall EE, Kuijper AFM, et al. Immediate thallium-201 reinjection following stress imaging: a time saving approach for detection of myocardial viability. *J Nucl Med* 1993;34:737–743.
15. Criteria Committee of the New York Heart Association. *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels*, 8th ed. Little Brown, Boston; 1979.
16. Sheffield LT, Holt JH, Reeves TJ. Exercise graded by heart rate in electrocardiographic testing for angina pectoris. *Circulation* 1965;32:622–629.
17. Guideline for exercise testing. A special report of the ACC/AHA task force on assessment of cardiovascular procedures. *J Am Coll Cardiol* 1986;8:725–738.
18. Brambilla M, Inglese E, Cannizzaro G, et al. A multicenter trial on inter and intra-observer reproducibility of segmental scoring of thallium-201 planar myocardial imaging before and after reinjection. *J Nucl Med* 1994;35:601–608.
19. Watson DD, Campbell NP, Read EK, et al. Spatial and temporal quantitation of plane thallium myocardial images. *J Nucl Med* 1981;22:577–584.
20. Garcia E, Maddahi J, Berman D, Waxman A. Space/time quantitation of thallium-201 myocardial scintigraphy. *J Nucl Med* 1981;22:309–317.
21. American Society of Echocardiography Committe on Standards, Subcommittee on Quantitation of Two-dimensional Echocardiograms. Recommendations of quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echo* 1989;2:358–367.
22. Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. *Psych Bull* 1968;70:213–220.
23. Sigal SL, Soufer R, Fetterman RC, et al. Reproducibility of quantitative planar thallium-201 scintigraphy: quantitative criteria for reversibility of myocardial perfusion defects. *J Nucl Med* 1991;32:759–765.
24. Nesselroade JR, Stigler SM. Regression toward the mean and the study of change. *Psych Bull* 1980;3:622–637.
25. Kuijper AFM, Vliegen HW, van der Wall EE, et al. The clinical impact of thallium reinjection scintigraphy for detection of myocardial viability. *Eur J Nucl Med* 1992:783–789.
26. Dilsizian V, Bonow R. Differential uptake and apparent ^{201}Tl washout after thallium reinjection. Options regarding early redistribution imaging before reinjection or late redistribution imaging after reinjection. *Circulation* 1992; 82:1032–1038.
27. Berger BC, Watson DD, Burwell LR, et al. Redistribution of thallium at rest in patients stable and unstable angina and the effect of coronary artery bypass surgery. *Circulation* 1979;60:1114–1125.
28. Iskandrian AS, Hakki A, Kane SA, et al. Rest and redistribution thallium-201 myocardial scintigraphy to predict improvement in left ventricular function after coronary artery bypass grafting. *Am J Cardiol* 1983;51:1312–1316.
29. Ragosta M, Beller GA, Watson DD, et al. Quantitative planar rest-redistribution ^{201}Tl imaging in detection of myocardial viabilty and prediction of improvement in left ventricular function after coronary artery bypass surgery in patients with severely depressed left ventricular function. *Circulation* 1993;87:1630–1641.
30. Dilsizian V, Perrone Filardi P, Arrighi JA, et al. Concordance and discordance between stress-redistribution-reinjection and rest-redistribution thallium imaging for assessing viable myocardium. Comparison with metabolic activity by positron emission tomography. *Circulation* 1993;88:941–952.
31. Kayden DS, Sigal S, Soufer R, et al. Thallium-201 for assessment of myocardial viability: quantitative comparison of 24-hr redistribution imaging with imaging after reinjection at rest. *J Am Coll Cardiol* 1991;18:1480–1486.
32. Bonow RO, Dilsizian V. Assessing viable myocardium with thallium-201. *Am J Cardiol* 1992;70:10E–17E.