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NUCLEAR CARDIOLOGY

Thallium-201 Reverse Redistribution at Reinjection Imaging Correlated with Coronary Lesion, Wall Motion Abnormality and Tissue Viability

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Previous studies based on standard stress-redistribution ^{201}Tl scintigraphy provided conflicting results about the clinical significance of ^{201}Tl reverse redistribution. Recent observations indicate that the majority of these defects normalize following reinjection reflecting viable myocardium. **Methods:** In this study, the meaning of reverse redistribution occurring at reinjection imaging, its relation to standard 4-hr redistribution, coronary lesion, abnormal wall motion and tissue viability were assessed. A region with normal activity in the stress image was considered as having reverse redistribution if ^{201}Tl activity at reinjection imaging was definitely abnormal with a decrease in relative tracer uptake >15% of the peak. From a series of 270 patients, 29 showed reverse redistribution. Of these 29 patients, 27 had evidence of previous myocardial infarction. Coronary lesions were detected in all but 1 patient. Average ejection fraction was 0.38 ± 0.11. **Results:** On a segmental basis, 50/377 regions showed the pattern of reverse redistribution. A significant coronary lesion (≥50%) was found in 78% of these regions; occlusion rate was 50%, and collateral circulation was found in 35% of occluded vessels. Hypokinesis or akinesis was present in 72% of segments. Tissue viability, defined as an uptake >55% of the peak, was found in 44% of these segments. The 50 segments showing reverse redistribution were divided into two groups according to an abnormal uptake also at 4-hr redistribution (group 1, 25 segments) or appearing only following reinjection (group 2, 25 segments). Despite segments of group 1 showing a higher degree of coronary stenosis (80 ± 32 versus 59 ± 43%, $p < 0.01$), a similar rate of coronary occlusion, ventricular dysfunction and maintained viability was found in the two groups. **Conclusion:** Reverse redistribution in chronic coronary artery disease is frequently associated with significant coronary lesion, collateral-dependent dysfunctioning myocardium and preserved tissue viability. The occurrence of reverse redistribution following reinjection expands the indication for viability imaging to all patients with known coronary artery disease and regional wall motion abnormalities who undergo diagnostic and prognostic ^{201}Tl scintigraphy.

Key Words: thallium-201 scintigraphy; regional ventricular function; coronary artery disease

J Nucl Med 1996; 37:735–741

Clinical studies have demonstrated that the dynamic change in defect extension and severity detected by sequential stress-redistribution ^{201}Tl imaging has a high diagnostic and prognostic accuracy (*1,2*). Furthermore, a series of experimental observations have confirmed these findings in normal, ischemic and hyperemic conditions (*3,4*). The recent introduction of reinjection imaging shifted a great proportion of scintigraphic defects from the fixed to the reversible category, with a reclassification of ^{201}Tl abnormalities (*5,6*).

On the other hand, the observation where initially normal areas of ^{201}Tl uptake subsequently show defects on postexercise images (reverse redistribution) has still neither clinical correlate nor experimental models. Thallium-201 studies performed before the introduction of reinjection imaging provided conflicting results. Some authors showed a good correlation to vessel patency and nontransmural myocardial infarction (*7,8*) that was not observed by others (*9,10*). Technical explanations, such as background oversubtraction or slow redistribution occurring in

Received Mar. 29, 1995; revision accepted Aug. 17, 1995.
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contralateral myocardial walls, have also been proposed to explain this scintigraphic pattern (*11*). Following the introduction of reinjection imaging, Marin-Neto et al. (*12*) have demonstrated that most segments show reverse 4-hr redistribution fill-in following reinjection and appear viable at positron emission tomography. The occurrence of reverse redistribution persisting or occurring at reinjection imaging has no univocal clinical correlate since it may also occur in patients with normal coronary anatomy and ventricular function and no previous myocardial infarction (*12*). This study aims to investigate reverse redistribution at reinjection imaging, its relation to standard 4-hr redistribution, coronary lesions, abnormal wall motion, previous myocardial infarction and tissue viability.

MATERIALS AND METHODS

Patients

From a series of 270 patients with stable angina referred for an exercise ^{201}Tl study from 1992 to 1994, 29 were selected on the basis of the appearance of a new scintigraphic defect (reverse redistribution) observed following reinjection.

There were 23 men and 6 women (mean age of 56 ± 9 yr). Of the 29 patients, 27 had a history of previous myocardial infarction documented by prolonged chest pain and significant electrocardiographic and serum enzyme changes. All patients underwent stress ^{201}Tl scintigraphy, basal echocardiography and coronary angiography. The selection of patients for the reinjection imaging was performed without knowledge of the patients' coronary anatomy or left ventricular function. Medical therapy was discontinued at least 48 hr before all studies and no patient was receiving beta-blockers. Exclusion criteria were recent myocardial infarction (<3 mo), unstable angina, left ventricular hypertrophy, valvular heart disease and idiopathic cardiomyopathy. All patients gave their informed consent as part of a protocol approved by the local Ethical Committee on Human Studies.

Thallium-201 Imaging Protocol

All patients, after an overnight fast, exercised using a standard Bruce protocol. At peak exercise, 2–2.5 mCi (74–92 MBq) of ^{201}Tl were injected intravenously, after which the patients continued exercise for an additional 90 sec. Thallium images were acquired with a small field of view mobile camera starting at 6 min after exercise had been terminated. A high-resolution, parallel-hole collimator and a 20% window centered on the 80 keV x-ray peak of ^{201}Tl were used. Imaging commenced in preset time in the anterior projection, followed sequentially by 45° and 70° left anterior oblique projection (T1). After the completion of the imaging, the patients remaining in the fasting state, and 4-hr redistribution images (T2) were acquired for the same time as T1. Because of the persistence of evident defects at T2, all patients received an additional 1 mCi (37 MBq) of ^{201}Tl at rest immediately after T2, and a third set of imaging was acquired 30 min later (T3). The acquisition time was kept constant for all three sets of images (480 sec).

Scintigraphic Analysis

Thallium-201 uptake was initially qualitatively assessed. Images were divided into 13 segments generally used for planar scintigraphic analysis. Each segment was then assigned to 1 of the 3 coronary vascular territories (*13*). Assignment of the apex to a specific coronary territory was variable and based on the presence of adjacent defects. Qualitative assessment of tracer uptake was performed by two investigators. All myocardial segments were scored on a 4-point scale as: 0 = absent activity; 1 = severely reduced; 2 = moderately reduced; 3 = normal uptake. For the 29 patients, a total of 377 segments were evaluated as T1, T2 and T3. A region with normal activity at T1 imaging was considered as having reverse redistribution if ^{201}Tl activity at T3 was qualitatively abnormal (score 0/1), and the assigned score was decreased by at least one point. Following the identification of reverse redistribution based on T1 and T3, the same observers scored T2 as previously described.

Quantitation of ^{201}Tl studies was performed following background subtraction as described by Goris et al. (*14*). The count activities within the 13 myocardial sectors were expressed as a percentage of the peak activity in each view. A region with normal activity at T1 (≥75% of the peak) was considered as having reverse redistribution if the decrease in normalized ^{201}Tl activity at reinjection imaging was at least 15%. All segments showing reverse redistribution at qualitative analysis were also scored as "paradox" by quantitative criteria.

The remaining segments were assigned to the group of normals if they did not show any change from a score of 1 at T1, T2 and T3 or any significant uptake reduction (≥15% of the peak) among the three images. Reversible segments were identified as having an increase ≥1 grade from T1 to T3 associated with a significant increase at reinjection imaging in ^{201}Tl percent uptake (≥15%). Segments with a score of 0/1 at T1 persisting through T3 and associated with minimal changes in ^{201}Tl uptake (<15% of the peak) were defined as representing fixed defects. Based on a previous study from our laboratory (*15*), the quantitative criterion for ^{201}Tl viability at T3 was defined according to the cut-off of 55% of the peak. This value, representing 2.5 s.d. below the uptake of normal segments at rest, is similar to that reported by other investigators using tomographic or planar ^{201}Tl imaging (*5,16*) and provided optimal diagnostic accuracy in predicting functional outcome following revascularization. Although all segments showing an abnormal ^{201}Tl uptake at T3 also showed a qualitative score of 0/1, only quantitative data were used to define residual viability as present or not.

For the washout analysis, absolute counts in the stress and 4-hr redistribution images were considered, and washout was defined as (1-redistribution counts/stress counts) × 100. Washout rates in regions with reverse redistribution were measured and compared with those regions showing normal, reversible and fixed scintigraphic patterns in all patients. Transient cavity dilation was evaluated quantitatively in stress and redistribution images as previously described (*17*). Finally, the lung-to-myocardial count ratio in the stress study was obtained by measuring the activity in the myocardial and lung areas showing the maximal counts. Only a ratio ≥0.6 was considered as increased ^{201}Tl uptake during the stress test (*18*).

Classification of Reverse Redistribution According to 4-hr Redistribution Images

Beyond the common finding of significant decrease in ^{201}Tl activity from T1 to T3 that was used as the main inclusion criterion (Fig. 1), segments that showed the same pattern also at 4-hr redistribution imaging (group 1) were separated from those segments that were still normal at T2 but showed definite loss of activity or evident defect at T3 (group 2). No segment with normal T1 and abnormal T2 activity showed complete normalization of ^{201}Tl uptake at T3; thus this hypothetical group 3 is not present in the analysis.

Echocardiographic Regional Wall Motion Analysis

Commercially available wide-angle phased-array imaging systems were used. The left ventricle was divided into 13 segments: apex and proximal distal, septal, anterior, antero-lateral, postero-lateral, posterior and inferior wall. This segmentation was adapted following the 20-segment model proposed by the American Society of Echocardiography (*19*), with the apex considered as a single segment and only two septal segments were taken into account in

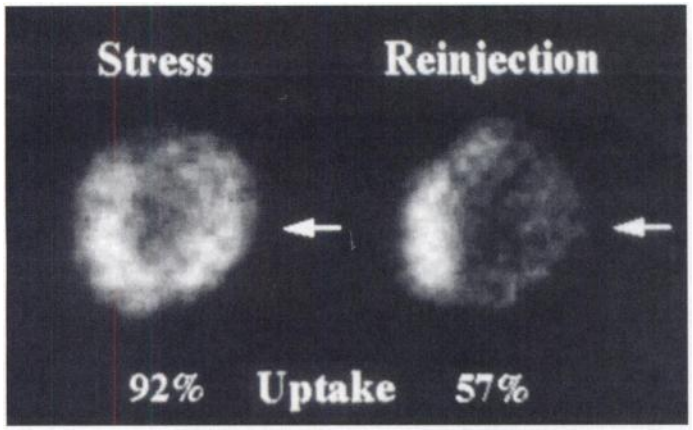

FIGURE 1. Scintigraphic criteria used for patient selection. A normal qualitative segmental uptake of ^{201}Tl at stress imaging resulting in a clear-cut defect following reinjection and associated to a reduction in percent uptake of at least 15% of the peak was considered as ^{201}Tl reverse redistribution. Opposite criteria were used for the identification of reversible defects while no significant changes from stress to reinjection identified normal and fixed defects, respectively.

order to match the nuclear segmentation. Segmental wall motion was graded on a 4-point scale: normal = 1; hypokinetic = 2; akinetic = 3; dyskinetic = 4 (*15*).

Coronary Angiography and Contrast Ventriculography

Coronary angiography and ventriculography were available in all patients. The average interval between the ^{201}Tl study and angiographic study was never longer than 2–3 wk. All angiograms were reviewed by an independent expert who had no knowledge of the scintigraphic and echocardiographic results. Digital computer-assisted calipers were used to measure stenotic arterial segments that were quantified as minimal cross-section area. Stenoses calculated as ≥50% reduction in the normal cross-section area were considered significant. Collateral circulation was graded visually on the four-grade scale described by Fujita et al. (*20*) and depending on the degree of opacification of the occluded vessel: 0/1, no opacification or filling of side branches without opacification of the epicardial vessel and 2/3, partial or complete filling of the occluded vessel via collaterals. Only those vessels with a score of 2/3 were considered as being supplied by a well-developed collateral circulation. Global ejection fraction was calculated from contrast ventriculography performed in the right anterior oblique projection using standard protocols and cut-off values as previously validated by our Institute (*15*).

Statistical Analysis

Data are presented as mean ± s.d. Sequential measurements of the relative ^{201}Tl uptake were compared by repeated measure analysis of variance (ANOVA) and significant differences in each group were sought by means of Newsman-Keuls multiple range test. Washout rates in different categories were analyzed by means of an unpaired Student's t-test. Fisher's exact test was used to compare the percent of segments in relation to clinical, electrocardiographic and angiographic findings. A p value <0.05 was considered significant.

RESULTS

Clinical Findings

Out of 29 patients, 27 had clinical evidence of previous infarction. Out of these, 8 (28%) underwent thrombolytic therapy at the time of hospital admission. Pathological Q-waves (or tall R waves) were anterior in 17 patients, inferior in 5, posterior in 1 and in more than 2 vascular territories in 4 patients. Three patients showed non-Q anterior infarcts with persistence of negative T waves. During bicycle exercise, the rate pressure product increased from 9871 ± 2866 at rest to 20919 ± 4898 at peak exercise ($p < 0.01$). Fifteen patients developed diagnostic ST segment depression (>1.5 mm) in at least two electrocardiographic leads. In the remaining 14 patients, the exercise test was stopped because of typical chest pain in 5 patients, dyspnea or fatigue in 4 patients and achievement of 85% of maximum predicted heart rate in the remaining 5 patients. No patient showed bundle branch block at rest or developed arrhythmias at peak exercise. Clinical, electrocardiographic and angiographic findings are summarized in Table 1.

Thallium-201 Findings

According to the ^{201}Tl analysis, 4/29 patients only showed reverse redistribution; in the remaining 25 patients, reverse redistribution was associated to reversible, fixed and reversible + fixed defects in 4, 9 and 12 patients, respectively. Transient cavity dilation, pathological lung uptake or both were observed in 4, 3 and 3 patients, respectively; 8 of these patients showed multivessel coronary disease. On a segmental basis, a total of 377 myocardial regions were analyzed. On the basis of T1 and T3 images, 248 regions were considered normal, 50 showed reverse redistribution, 30 showed reversible and 49 fixed defects. Normal regions showed similar uptake of ^{201}Tl in the three sets of images (87% ± 13% at T1, 88% ± 12% at T2 and 88% ± 13% at T3, p = ns). Segments with reverse redistribution showed a significant decrease in activity from T1 to T3 (81% ± 8% versus 56% ± 10%, respectively; $p < 0.01$), with T2 having an intermediate uptake of 66% ± 16% of the peak ($p < 0.01$ versus T1 and T3). In regions with fixed defects, the mean uptake of ^{201}Tl remained unchanged from T1 (36% ± 12%) to T2 (41% ± 11%) and T3 (40% ± 19%, p = ns for all values). In the 30 segments with reversibility, the mean regional uptake increased from 50% ± 14% at T1 to 67% ± 19% at T2 ($p < 0.01$) and maintained similar value at T3 (70% ± 12%, p = ns versus T2 and $p < 0.01$ versus T1). The washout rate was higher in reverse redistribution than in normal segments (40% ± 20% versus 31% ± 18%, $p < 0.05$), while it was significantly lower in reversible and fixed defects (6% ± 35% and 19% ± 35%, respectively, $p < 0.01$). Results for quantitative analysis of ^{201}Tl relative uptake, in all groups, are represented in Figure 2.

Coronary Anatomy, Ventricular Function and Electrocardiographic Q-waves. Normal, single and multivessel disease were found in 1, 7 and 21 patients, respectively (Table 1). The only patient with normal coronary arteries had evidence of previous myocardial infarction associated with regional wall motion abnormalities at rest. In the whole study population, the minimal cross sectional area was 81% ± 18%. Coronary occlusion was found in 20 of the 56 diseased vessels. Of the 50 segments showing reverse redistribution, 78% were related to a significant stenosis of the corresponding coronary artery that averaged 70% ± 39%. In these segments, occlusion rate was 50%, with efficient collaterals in 35% of vessels. In segments with reversible defects, 83% of regions were related to an average stenosis of 79% ± 35% (p = ns versus reverse redistribution), with the same 50% rate of occlusion. Collaterals were less represented (20% of occluded vessels, $p < 0.05$ versus reverse redistribution).

Almost all segments (98%) with fixed defects were related to a coronary lesion that averaged 86% ± 23% ($p < 0.05$ versus reverse redistribution and reversible segments). Rate of occlusion was 59% and was similar to that observed in the other groups; however, collaterals were present only in a minority of occluded vessels (7%). Vessel patency, considered as nonoc-

TABLE 1
Clinical, Electrocardiographic and Angiographic Findings in 29 Patients

Patient no.	Sex	Age (yr)	Type and site of MI	Vessels with CAD	EF (%)	Exercise stress test	
						ST segment	Pain
1	F	59	Q, Inf-lat	0	47	=	+
2	M	76	Q, Ant	1	26	↓	+
3	M	58	Q, Ant	1	18	=	+
4	M	44	Q, Ant	1	38	=	−
5	M	53	Non-Q, Ant	1	30	↓	+
6	F	58	Non-Q, Ant	1	38	↓	−
7	M	69	Non-Q, Ant	1	50	↓	−
8	M	42	Q, Ant	1	39	=	−
9	M	67	Q, Ant	2	33	↓	−
10	M	54	No MI	2	60	=	+
11	M	52	Q, Post	2	46	=	−
12	M	40	Q, Inf-post	2	41	=	−
13	M	51	Q, Inf	2	42	=	−
14	F	70	Q, Inf	2	38	↓	−
15	F	61	No MI	2	42	=	−
16	F	63	Q, Ant	2	40	↓	+
17	M	51	Q, Ant	2	47	↓	+
18	M	50	Q, Ant	2	45	=	−
19	M	53	Q, Inf	2	30	↓	+
20	M	54	Q, Ant	2	27	↓	+
21	M	53	Q, Ant	2	54	=	+
22	M	41	Q, Ant	2	42	=	−
23	M	58	Q, Ant-inf	3	45	↓	−
24	M	70	Q, Ant	3	23	↓	−
25	M	66	Q, Ant	3	15	=	+
26	F	57	Q, Inf-lat	3	48	↓	−
27	M	52	Q, Inf	3	43	↓	−
28	M	44	Q, Ant	3	32	=	−
29	M	68	Q, Inf-post	3	34	↓	+

Ant = anterior; CAD = coronary artery disease; EF = ejection fraction; Inf = inferior; MI = previous myocardial infarction; Non-Q = non-Q-wave myocardial infarction; Post = posterior; Q = Q-wave myocardial infarction; ↓ = significant ST-segment depression.

cluded native vessel or efficient collaterals, was similar in paradox and reversible defects (67% and 60%, respectively) and was higher than that observed in fixed defects (45%, $p < 0.01$ for both values).

In the whole study population, left ventricular ejection fraction averaged 0.38 ± 0.11. Among the 377 regions that were analyzed at rest by echocardiography, 175 showed normal wall motion, 109 hypokinesis and 93 were akinetic or diskinetic. The incidence of regional ventricular dysfunction was higher in fixed than in reverse redistribution or reversible defects (98% versus 72% and 76%, $p < 0.05$). In particular, of the 36 out of 50 regions showing ^{201}Tl reverse redistribution, 17 were hypokinetic and 19 akinetic. Electrocardiographic Q-waves were found in 60% of segments showing reverse redistribution. This value was significantly lower than that observed in segments showing fixed defects in whom the correlation with electrocardiographic Q-waves was 94% ($p < 0.01$).

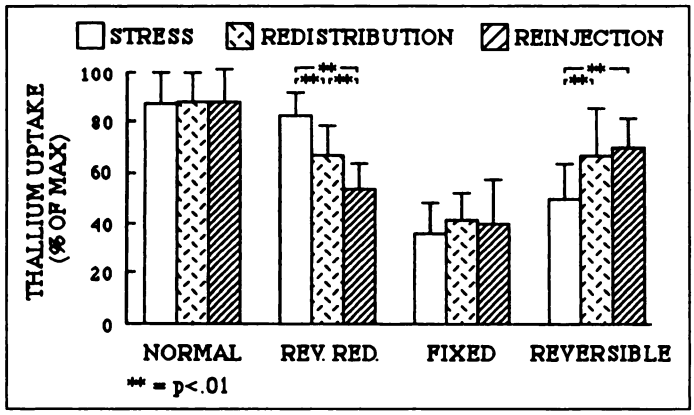

FIGURE 2. Quantitative analysis of percent ^{201}Tl uptake in segments with normal, reverse redistribution, fixed and reversible defects. Normal and fixed defects do not show changes in any condition. Asterisk indicates only significant differences.

Tissue Viability in Different Types of Defects. According to the cut-off value of 55% of the peak, 22 out of 50 segments showing reverse redistribution, or 44%, were defined as viable by quantitative analysis. All segments scored as having reversible defects had a percent activity that was above the cut-off value and thus were all viable. On the contrary, only 2 out of 49 segments showing fixed defect, or 4%, showed a maintained tissue viability. According to these data, the percentage of tissue viability within different types of defects decreased from segments showing reversible defects, all viable at quantitative analysis, to nearly absence of viability in segments with abnormal activity that persisted through T2 and T3, with segments with reverse redistribution showing an intermediate behavior.

Results in Segments Showing Different Patterns of Reverse Redistribution. The 50 segments showing reverse redistribution were divided into 2 groups according to a definitely abnormal T2 persisting at T3 (group 1, 25 segments) or appearing only at T3 (group 2, 25 segments), associated in both cases with a normal T1. As described above, no segment showed an abnormal T2 that normalized at T3. Percent uptake of ^{201}Tl at T1 and

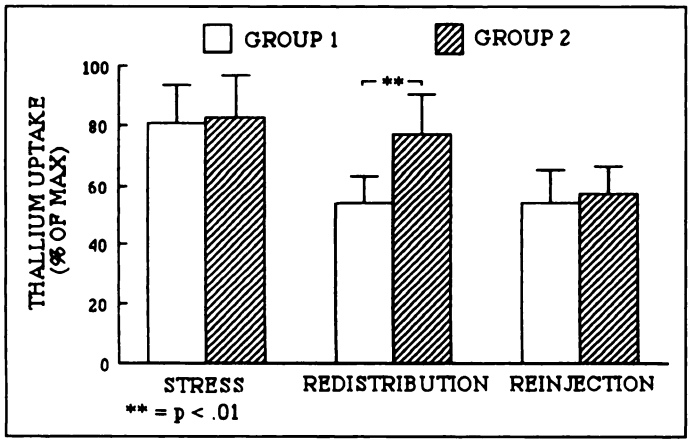

FIGURE 3. Quantitative analysis of ^{201}Tl distribution in segments showing different patterns of reverse redistribution. Despite significant differences at 4-hr imaging, tracer uptake following exercise and reinjection is almost superimposable in the 2 groups. Occurrence of reverse redistribution after reinjection expands the indication for this technique to those patients with previous infarction that now show absence of significant defect on 4-hr redistribution imaging.

T3 was not different in the two groups (group 1: 80 ± 7 and 54 ± 10; group 2: 82 ± 9 and 58 ± 9 at T1 and T3, p = ns for all values). Segments of group 1 showed an abnormal uptake at T2 (54% ± 9% of the peak) that was not distinguishable from that detected at T3 in the same segments (p = ns). On the contrary, segments of group 2 had a ^{201}Tl activity at T2 that was superimposable to that observed at T1 (78% ± 11% of the peak, p = ns) and significantly felt at T3 as described above (Fig. 3). A fast washout was found only in segments of group 1 (48% ± 20%, $p < 0.05$ versus normal segments) while segments of group 2 did not show any difference when compared to normal segments (33 ± 18 versus 32% ± 18%, p = ns). Coronary anatomy was significantly different between the 2 groups. A coronary lesion was detected in 88% of segments of group 1 and in 68% of those of group 2 ($p < 0.01$); similarly, coronary stenosis averaged 80% ± 32% and 59% ± 43% in the 2 groups, respectively ($p < 0.01$). Despite these differences, rate of occlusion was similar and not statistically different (44% versus 36%) as well as the occurrence of ventricular dysfunction (80% versus 74%). The evaluation of contiguous segments showed the same distribution with respect to areas showing fixed and reversible defects. In fact, most segments of group 1 and 2 were contiguous to normal segments (57% and 54% in the 2 groups, respectively) and a similar percentage of them was related to reversible (12% and 14%) or fixed (31% and 32%) defects (p = ns for all values). Finally, tissue viability was present in 42% of segments of group 1 and in 46% of group 2 (p = ns). Clinical, radioisotopic, angiographic and echocardiographic findings in segments of group 1 and 2 are summarized in Table 2.

TABLE 2
Clinical, Radioisotopic, Angiographic and Echocardiographic Findings Group 1 and 2 Segments

Finding	Group 1	Group 2
Presence of Q-waves (%)	68	52
Tissue viability by ^{201}Tl (%)	42	46
Washout rate (%)	48 ± 20*	33 ± 18*
Contiguity to (%):		
Normal segment	57	54
Reversible defect	12	14
Fixed defect	31	32
Coronary stenosis (% cross-sectional area)	80 ± 32*	59 ± 43*
Significant coronary lesion (%)	88*	68*
Rate of occlusion (%)	44	36
Regional ventricular dysfunction (%)	80	74

* = $p < 0.01$.

DISCUSSION

In this article, we associated under the term "reverse redistribution" the standard aspect of a ^{201}Tl defect appearing after 4-hr redistribution to that occurring only after reinjection. Although reverse redistribution should classically indicate only the first condition, we extended the concept to those segments that showed after reinjection the same pattern of a normal initial uptake becoming abnormal. The results of this investigation demonstrated that ^{201}Tl regions with reverse redistribution were associated with significant coronary stenosis, abnormal wall motion, maintained antegrade or collateral blood flow and tissue viability in 44% of cases. In addition, our results identified another ^{201}Tl pattern, reverse redistribution appearing only at reinjection imaging, that has clinical correlates similar to those observed in segments showing reverse redistribution after 4-hr imaging and that increase the indication for ^{201}Tl reinjection to patients with known coronary artery disease and wall motion abnormalities in whom standard 4-hr redistribution appears still normal.

Methodological Considerations

Patients were selected on the basis of reinjection, thus, using the same criteria currently proposed for the best characterization of defect type in ^{201}Tl scintigraphy (*5*). Previous studies differ from the present one in that most of them did not use reinjection imaging or quantitative analysis, and thus no direct comparison can be made. The occurrence of reverse redistribution has been previously demonstrated using qualitative analysis of stress, dipyridamole and rest redistribution studies (*7–9,12*). In these studies, the occurrence of this scintigraphic pattern was found in a percentage varying from 5% to 75% of patients, with some study population showing a low incidence of coronary artery disease and others reporting a 100% occurrence of previous myocardial infarction and coronary lesions. Differences in patient selection, stress modalities and variability in qualitative analysis could explain these discrepant results. Furthermore, in these studies the absence of any type of viability imaging implies an overestimation of reverse redistribution.

Soufer et al. (*21*) used quantitative analysis of ^{201}Tl uptake and PET to assess segmental viability. They showed that 72% of segments with reverse redistribution were viable and that the presence of a wall motion abnormality did not predict whether a segment was viable or scar. Despite the absence of ^{201}Tl reinjection and the limited number of patients studied by angiography (34%) in their study and the lack of positron emission data in our study population, incidence of previous myocardial infarction, presence of coronary lesion and detection of tissue viability in segments with wall motion abnormalities were similar in both studies. The study of Marin-Neto et al. (*12*) was based on quantitative analysis of ^{201}Tl and reinjection imaging. They set a relative decrease of 10% of relative ^{201}Tl uptake as a marker of reverse redistribution on 4-hr imaging, and this criterion was used in all patients independent of the value of ^{201}Tl uptake itself or of the qualitative appearance of an evident defect. In this study, 44% of patients that showed a ^{201}Tl reverse redistribution had a regional uptake after reinjection that was over 75% of the peak, a value hardly comparable with the occurrence of any type of defect at visual analysis. Brown et al. (*11*) used an abnormally high washout rate to identify those patients with reverse redistribution and identified

background oversubtraction as a cause of false positive studies. Although correct from a methodological point of view, they did not report about qualitative analysis. In addition, other disease states such as cardiomyopathy or arrhythmia may show a rapid washout of ^{201}Tl in absence of coronary artery disease (*22,23*), thus limiting the usefulness of washout analysis alone in the evaluation of reverse redistribution. An additional methodological artefact such as a spillover from an increased lung uptake has been proposed as a possible cause of reverse redistribution (*24*). Such an event was unlikely to occur in our study since the majority of patients did not show increased lung uptake during stress.

Although additional methodological considerations may have a role in the occurrence of reverse redistribution, we believe that the method we proposed, qualitative and quantitative evidence of reverse redistribution at reinjection imaging, contributed to a more exact patient selection hence providing clinical conclusions with sufficient reliability.

Clinical Correlates of Thallium-201 Reverse Redistribution

Thrombolytic therapy and the occurrence of non-Q-wave myocardial infarction have been proposed to explain ^{201}Tl reverse redistribution (*7*). This was not the case in our study group in which the use of thrombolytic therapy in the early phase of infarction was limited to 28% of patients, with only 3 out of 29 showing electrocardiographic evidence of non-Q-wave infarction. Vessel patency in our patients, however, was high (67%), with collaterals detected in 35% of occluded vessels. From a clinical point of view and on a segmental basis, the reverse redistribution pattern allowed us to correctly identify each diseased vessel. In line with these observations, the average coronary stenosis in vessels supplying those territories showing reverse redistribution was similar to that observed in different types of defects nor was the incidence of electrocardiographic Q-waves or wall motion abnormalities reduced in this group. According to this and to previous studies that used ^{201}Tl reinjection or delayed redistribution imaging (*7,12,15*), reverse redistribution can be considered as an accurate marker of coronary lesion and abnormal wall motion associated with previous myocardial infarction in a significant percentage of patients. The present study demonstrated that tissue viability was present in 44% of segments showing reverse redistribution and in only 4% of those showing fixed defects at reinjection imaging. This striking difference could partly be ascribed to the higher degree of coronary lesion detected in fixed defects as well to the lower incidence of collaterals (7%) occurring at similar occlusion rates. These findings confirm previous observations indicating that the occurrence of collaterals and the degree of coronary stenosis modulate the dominance of the scar pattern in areas with abnormal wall motion at rest (*15,20*). According to these observations, the occurrence of reverse redistribution could be the result of a maintained blood flow through patent native or collateral circulation, with the administration of thrombolytic therapy playing a role in determining vessel patency and savaged myocardium (*25*).

Mechanisms of Reverse Redistribution in Humans

Despite the lack of experimental models of reverse redistribution, some considerations can be made from the results obtained in animal studies of occlusion and reperfusion. Irreversibly damaged myocardium may have initial ^{201}Tl uptake (*3,26–28*), mimicking normal or minimally decreased activity in the early images. Later on, the faster washout in areas of nonsalvaged, necrotic myocardium characterized by an expanded interstitial space would result in the pattern of reverse redistribution (*29,30*). This hypothesis could explain the occurrence of reverse redistribution in segments of group 1 that showed an accelerated washout when compared to normal segments. In segments of group two showing a still normal activity at redistribution, different mechanisms could induce the occurrence of a new defect appearing after reinjection. Higher than normal blood flow to previously ischemic myocardium could explain this phenomenon; however, no substantial differences were found between the two groups of segments showing early or delayed reverse redistribution, especially in terms of contiguity to reversible or fixed defects. A possible cause of reverse redistribution following reinjection could be the phenomenon of low differential uptake described by Dilsizian et al. (*31*). These authors demonstrated that regions with reversible ^{201}Tl defects on 4-hr redistribution images may demonstrate apparent washout after reinjection due to a low differential uptake in ischemic areas compared with the uptake in normal regions. Although interesting from a pathophysiological point of view, this phenomenon should not occur in segments of group 2 that showed a lower degree of coronary stenosis when compared to segments of group 1.

Furthermore, the demonstration of a normal perfusion during the exercise stress test should rule out a reduction of coronary blood flow as a cause of a low differential uptake following reinjection. Previous papers challenged the concept that a normal ^{201}Tl uptake during stress identifies viable myocardium in areas with wall motion abnormalities at rest (*7,10,12*). Our results expand these initial observations by demonstrating that "normal" regions at T2 may also show the phenomenon of reverse redistribution at T3 and indicate that similar areas of dysfunctioning myocardium do not differ too much from those showing "early" reverse redistribution. This concept expands the current indications for ^{201}Tl reinjection to patients with previous infarction and regional wall motion abnormalities in whom, even in absence of defect at T2, the detection of reverse redistribution following reinjection could indicate a specific angiographic pattern suitable for coronary revascularization.

Limitations

The data from this study were obtained applying a strict classification based on qualitative and quantitative analysis, and all schematic approximations of myocardial anatomy into segments may contain an unavoidable source of error in terms of contiguity. Furthermore the relative distribution of ^{201}Tl in different sets of images is normalized to a hot spot that changes within each study and that may induce significant artefacts, especially in patients with multivessel coronary disease. Our inclusion criteria were based on stress and reinjection imaging rather than a standard redistribution that is commonly used to decide whether tracer reinjection is needed or not. This method, however, allowed us to identify a new pattern, delayed ^{201}Tl reverse redistribution, that has never been described before in scintigraphic analysis. To minimize the possible interaction between perfusion and function, only patients with chronic coronary artery disease were studied and all those with recent myocardial infarction studied following acute reperfusion were excluded. In these patients, the complex information on residual ischemia and tissue viability may be more helpful in the clinical decision making and requires targeted studies.

In our patients no data are available on the occurrence of major adverse events in the follow-up period and thus no prognostic considerations can be obtained. Finally, the identification of tissue viability was not compared with the gold standard of post-revascularization functional recovery or with different metabolic or mechanical markers. Sufficient experience in the literature confirms that ^{201}Tl reinjection is able to

separate, with high diagnostic accuracy irreversibly damaged segments from viable ones (*5,6,12,15*).

CONCLUSION

Our data demonstrate that the majority of segments showing the scintigraphic pattern of reverse redistribution are related to stenotic coronary arteries and abnormal wall motion at rest. Viable myocardium is detected in 44% of these segments, with minor differences in the two groups of segments showing early or late reverse redistribution. These findings expand the current indications for ^{201}Tl reinjection and provide evidence that reverse redistribution at reinjection imaging has an important clinical significance that may parallel with that usually ascribed to segments showing fixed or reversible defects.

ACKNOWLEDGMENTS

We thank Nadia Sereni for her help in collecting the clinical studies, Ilaria Citti and Ginevra Quarratesi for their secretarial assistance and Andrew Mulholland for his masterful editing of the manuscript. We also thank New Elscint Technologies, Italy, for software assistance used for ^{201}Tl quantitative analysis and Italian Byk Gulden for providing part of the ^{201}Tl used in this study. Presented in part at the 6th Congress of the World Federation of Nuclear Medicine and Biology, Sydney, Australia, October 1994.

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