

Reverse Redistribution in Resting Thallium-201 Myocardial Scintigraphy in Patients with Coronary Artery Disease: Relation to Coronary Anatomy and Ventricular Function

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We studied 25 male patients, with coronary artery disease, mean age 56 ± 8 yr. All underwent ^{201}Tl rest-redistribution and resting $^{99\text{m}}\text{Tc}$ methoxyisobutyl isonitrile (MIBI) cardiac imaging. Regional ^{201}Tl and MIBI uptake were quantitatively analyzed. Regional left ventricular wall motion (WM) was visually assessed on MIBI gated images using a three-point scale (0 = normal, 1 = hypokinetic, 2 = a/dyskinetic). Two patterns of reverse redistribution (RR) were identified: RR-A when ^{201}Tl uptake was normal on rest images and abnormal on redistribution images, and RR-B when ^{201}Tl uptake was abnormal on rest images and a significant decrease in uptake was observed on redistribution images. Of the total 375 myocardial segments analyzed, 229 were classified as normal (NI), 40 as reversible defect (RD), 74 as irreversible defect (ID); 26 showed RR-A while 6 myocardial segments had RR-B. Myocardial segments with RR-A differed from NI in the degree of coronary artery stenosis ($81\% \pm 33\%$ versus $57\% \pm 39\%$, respectively, $p < 0.05$), in WM score (1.1 ± 0.7 versus 0.5 ± 0.6 , respectively, $p < 0.01$), and in MIBI uptake ($81\% \pm 10\%$ versus $92\% \pm 9\%$, respectively, $p < 0.0001$). Moreover, the percent of myocardial segments supplied by a totally occluded coronary artery was significantly higher ($p < 0.05$) in myocardial segments with RR-A (46%) than in NI (22%). Segments with RR-B did not show any significant difference either from RD and ID. These results suggest that myocardial segments with RR-A on resting ^{201}Tl images have impaired function and are supplied by severely stenosed coronary arteries and should not be considered normal.

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Thallium-201 (^{201}Tl) myocardial scintigraphy has been widely used in identifying viable myocardium in patients with coronary artery disease (CAD). In particular, exercise-redistribution ^{201}Tl myocardial scintigraphy with rest reinjection of the tracer (1-4), and rest-redistribution ^{201}Tl

cardiac imaging (5-7) have been proposed to differentiate fibrotic tissue from severely ischemic, but still viable, myocardium in patients with chronic CAD. Using rest-redistribution protocol, myocardial segments showing severe reduction in ^{201}Tl uptake on both rest and 4-hr redistribution images are defined as necrotic, while myocardial segments with reversible defects are identified as viable (6). However, it has also been shown that a pattern of reverse redistribution (RR), with ^{201}Tl defect present or more prominent only on redistribution images, could be found using the rest-redistribution approach (8). While the RR phenomenon on exercise-redistribution ^{201}Tl images has been extensively investigated (9-15), this finding in rest-redistribution cardiac imaging has not yet been completely explained. In a previous study in patients with acute myocardial infarction, Weiss et al. (8) showed (1) that the RR pattern was associated with patency of the infarct-related coronary artery and (2) that an improvement in myocardial perfusion and left ventricular (LV) function was observed after streptokinase therapy in myocardial segments with the RR phenomenon on ^{201}Tl rest-redistribution images. However, the occurrence and clinical significance of RR on resting ^{201}Tl cardiac images in patients with chronic CAD have not been investigated.

The present study was designed to assess the frequency of RR pattern in rest-redistribution ^{201}Tl myocardial scintigraphy in patients with chronic CAD and impaired left ventricular function, and to evaluate the clinical significance of this phenomenon.

MATERIALS AND METHODS

Patient Population

We studied 25 male patients (mean age 56 ± 8 yr, range 43-70 yr) with chronic CAD and LV dysfunction. The mean LV ejection fraction by resting radionuclide angiography was $33\% \pm 11\%$. All patients had previous myocardial infarction; however, no patient had an acute myocardial infarction or unstable angina within 6 mo of the study. In all patients, resting ^{201}Tl and $^{99\text{m}}\text{Tc}$ methoxyisobutyl isonitrile (MIBI) cardiac imaging were performed after

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withdrawal of all antianginal medications. Patients were fully informed of the protocol and study goals and gave informed consent.

Coronary Angiography

Coronary angiography was performed by percutaneous transfemoral approach using Seldinger's technique within 3 wk of radionuclide studies in all patients. Each artery was filmed in 4–6 projections, including angulated views in the sagittal plane. All images were recorded on 35-mm film at 50 frames/sec, reviewed on a Tagarno projector and interpreted by a consensus of three independent observers unaware of patients' clinical condition. Stenoses of coronary vessels were coded according to criteria of the American Heart Association (16). Significant stenoses were defined as reduction $\geq 50\%$ in the luminal diameter of at least one of the three major epicardial coronary vessels.

Thallium-201 Myocardial Scintigraphy

All patients underwent rest-redistribution ^{201}Tl myocardial scintigraphy. After an overnight fast, ^{201}Tl images were acquired 15 min postintravenous injection of 2 mCi of ^{201}Tl (rest images); 4 hr postinjection, ^{201}Tl images were again obtained (redistribution images). A small field-of-view gamma camera (Starcam 300 A/M General Electric), equipped with a low-energy general purpose collimator and connected with a dedicated computer system (General Electric), was used for study acquisition. Both rest and redistribution ^{201}Tl images were acquired for 10 min/image in the anterior, 45° and 70° left anterior oblique views (LAO) using a 128 \times 128 word matrix. During the time between rest and redistribution ^{201}Tl images, patients were ambulatory and remained in the fasting state.

Technetium-99m MIBI Myocardial Scintigraphy

Resting MIBI myocardial scintigraphy was performed in all patients within 3 days of the ^{201}Tl study. Images were acquired 1 hr postinjection of 20 mCi of MIBI for 5 min/image, in the same three views used for ^{201}Tl imaging. The same gamma camera, matrix and computer system were used. Dynamic gated MIBI images were also acquired in the same three standard views dividing the cardiac cycle in 16 frames, using a 64 \times 64 pixel matrix, and acquiring at least 200,000 counts for each frame, as previously described (17).

Data Analysis

In each patient, corresponding ^{201}Tl , resting MIBI and dynamic gated MIBI images were evaluated for direct comparison. Analysis of the regional ^{201}Tl and MIBI myocardial uptake and of regional LV wall motion was performed by dividing each image into five segments for a total of 15 myocardial segments in each patient, as shown in Figure 1. Each myocardial segment was assigned to one of the three major coronary artery territories (Fig. 1). Regional ^{201}Tl and MIBI uptake were quantitatively analyzed using an 8 \times 8 pixel region of interest (ROI) for each myocardial segment on images without background subtraction. In each view, the myocardial region with the maximum counts, either for ^{201}Tl or for MIBI images, was used as the normal reference region for that view. The ^{201}Tl and MIBI uptakes in all other myocardial segments were then expressed as a percentage of the activity measured in the reference region. Regional LV wall motion was visually evaluated on MIBI-gated images in each myocardial segment using a three-point scale (0 = normal, 1 = hypokinetic, 2 = a/dyskinetic) by consensus of two experienced nuclear physicians without knowledge of clinical, electrocardiographic or angio-

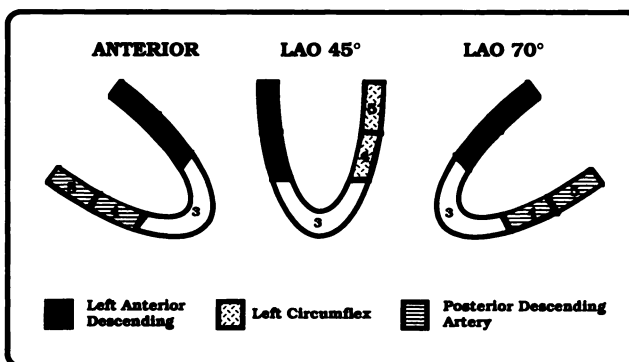


FIGURE 1. Diagram of the standard segmentation scheme used for regional thallium and $^{99\text{m}}\text{Tc}$ -MIBI uptake and assignment of coronary vascular territories. Assignment of the left ventricular apex was variable and based on the presence of adjacent perfusion defects. LAO = Left anterior oblique view.

graphic findings. A third investigator reviewed the studies blindly when the first two investigators were not in agreement.

The normal range of resting ^{201}Tl uptake was assessed in 10 normal subjects (sex and age matched). In this group, the mean value of ^{201}Tl uptake at rest was $94\% \pm 7\%$. A value equal to the mean minus 2 s.d. (i.e., 80%) was chosen as the lower normal limit. In the 25 patients with chronic CAD, myocardial segments were classified on the basis of results of rest-redistribution thallium imaging. When relative ^{201}Tl uptake measured 80% or more of the normal reference region on both rest and redistribution images, myocardial segments were considered normal (NI). Myocardial segments with relative ^{201}Tl uptake measuring less than 80% of the reference region on rest image, were considered as ^{201}Tl defects. A ^{201}Tl defect was defined as reversible (RD) when relative tracer uptake increased more than 7% (i.e., 1 s.d. in the normal group) on the corresponding redistribution image. A thallium defect was defined as irreversible (ID) when relative tracer uptake was unchanged or increased less than 7% on the corresponding redistribution image. Two patterns of RR were identified: pattern A when relative ^{201}Tl uptake was normal ($\geq 80\%$) on rest image and reduced ($< 80\%$) on redistribution image, and pattern B when relative ^{201}Tl uptake was reduced ($< 80\%$) on rest image and decreased at least 7% on redistribution image.

Statistical Analysis

Data are expressed as mean \pm 1 s.d. In all groups of myocardial segments, differences in ^{201}Tl and MIBI uptake, in wall-motion score and in the degree of coronary artery stenosis were analyzed using the Student's t-test for unpaired data with Bonferroni's correction when appropriate. Chi square analysis was used to assess differences between proportions. Probability values ($p < 0.05$) were considered significant.

RESULTS

In seven patients, significant stenosis of all three major coronary vessels was present; ten patients had significant stenosis of two major coronary vessels; and in the remaining eight, only one major coronary vessel was significantly stenosed. Of the total number of significantly stenosed coronary arteries, 25 (51%) had proximal stenosis and 24 (49%) had distal stenosis. Of the same 49 vessels, 21 (43%) showed total occlusion and eight of these (38%, 8/21) had proximal occlusion. Good collateral circulation was ob-

TABLE 1
Comparison Between Normal Myocardial Segments (NI) and Those with Reverse Redistribution (RR) Pattern A

| | NI | RR pattern A |
|---|---------------|-----------------|
| Number of segments | 229 | 26 |
| Rest ^{201}Tl uptake (%) | 94 ± 7 | $85 \pm 5^*$ |
| Redistribution ^{201}Tl uptake (%) | 94 ± 6 | $74 \pm 4^*$ |
| Rest MIBI uptake (%) | 92 ± 9 | $81 \pm 10^*$ |
| Wall motion score | 0.5 ± 0.6 | $1.1 \pm 0.7^*$ |
| Coronary stenosis (%) | 57 ± 39 | $81 \pm 33^†$ |

$^*p < 0.0001$.
 $^†p < 0.01$.

served in 43% (9/21) of the totally occluded coronary arteries. Of the total 375 myocardial segments analyzed, 108 (29%) were supplied by totally occluded coronary vessels, 154 (41%) by coronary vessels with significant stenosis and 113 (30%) by normal or nonsignificantly stenosed coronary vessels.

Of the 375 myocardial segments analyzed, 229 (61%) were classified as NI; 40 (11%) as RD; 74 (19%) as ID; 26 (7%) as RR pattern A; and 6 (2%) as RR pattern B. Table 1 shows the direct comparison between NI myocardial segments and those with RR pattern A. Although myocardial segments with RR pattern A had normal ^{201}Tl uptake on rest images (as this was a selection criteria), they showed significantly lower ($p < 0.0001$) ^{201}Tl uptake on rest images than NI segments. Wall motion score was significantly higher ($p < 0.01$) in myocardial segments with RR pattern A than in NI segments. In addition, the degree of coronary artery stenosis was significantly higher ($p < 0.05$) in myocardial segments with RR pattern A than in NI segments. The percent of myocardial segments supplied by a totally occluded coronary artery was significantly higher in the RR pattern A group than in the NI group (46% versus 22%, respectively, $p < 0.05$). Good collaterals were present in 58% of the 12 myocardial segments with RR pattern A supplied by totally occluded coronary arteries. The MIBI uptake was significantly lower ($p < 0.0001$) in myocardial segments with RR pattern A than in NI segments (Table 1). Myocardial segments neighboring segments with RR pattern A were then analyzed. Forty-six percent of these were NI, 9% had RD, 40% had ID and 5% showed RR pattern B. Forty-six percent of these neighboring segments were supplied by significantly stenosed coronary arteries and 34% by totally occluded coronary arteries. Figure 2 shows an example of RR pattern A.

Only six myocardial segments showed RR pattern B. Table 2 shows the comparison between these segments and those with RD or ID. These three groups of segments differed significantly ($p < 0.05$) only in ^{201}Tl uptake on redistribution images, as was expected on the basis of the classification criteria. Of the six myocardial segments with RR pattern B, four were supplied by totally occluded coronary arteries. Fifty-six percent of the neighboring seg-

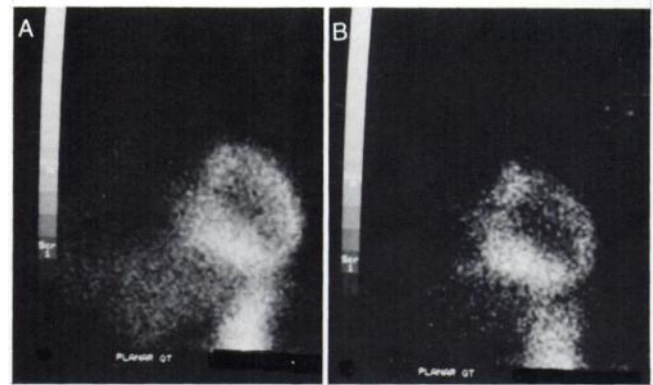


FIGURE 2. Thallium-201 myocardial scintigraphy. Rest (A) and redistribution (B) anterior projection. Normal ^{201}Tl uptake is observed in all myocardial segments on rest image, while on redistribution image the anterior segments show a lower than normal ^{201}Tl uptake (reverse redistribution pattern A).

ments were NI, 11% had RD, 11% had ID and 22% showed RR pattern A. Figure 3 shows an example of RR pattern B.

DISCUSSION

The overall incidence of myocardial segments with the RR phenomenon during rest-redistribution ^{201}Tl scintigraphy was 9% (32/375). We observed two different patterns of RR: pattern A, with normal ^{201}Tl uptake on rest images and abnormal ^{201}Tl uptake on redistribution images; pattern B, with abnormal ^{201}Tl uptake on rest images and a significant decrease of ^{201}Tl uptake on redistribution images. The rationale for considering these two patterns of RR separately is based on criteria commonly used to evaluate rest-redistribution ^{201}Tl myocardial scintigraphy. In fact, myocardial segments showing ^{201}Tl uptake $\geq 80\%$ on rest images are usually considered normal, while those having reduced ^{201}Tl uptake on rest images are then classified as segments with reversible or irreversible ^{201}Tl defects on the basis of the redistribution images. In particular, myocardial segments with a significant increase of ^{201}Tl uptake on redistribution images are considered as reversible defects. Our results show that 10% (26/255) of the myocardial segments with normal ^{201}Tl uptake on rest images showed less than 80% ^{201}Tl uptake on the 4-hr redis-

TABLE 2
Comparison Between Myocardial Segments with Reversible Defects (RD), Irreversible Defects (ID), and Those with Reverse Redistribution (RR) Pattern B

| | RD | ID | RR pattern B |
|---|---------------|-----------------|------------------|
| Number of segments | 40 | 74 | 6 |
| Rest ^{201}Tl uptake (%) | 72 ± 7 | 69 ± 8 | 74 ± 6 |
| Redistribution ^{201}Tl uptake (%) | 84 ± 9 | $67 \pm 8^*$ | $52 \pm 23^{*†}$ |
| Rest MIBI uptake (%) | 75 ± 14 | $67 \pm 13^*$ | $62 \pm 6^*$ |
| Wall motion score | 1.1 ± 0.7 | $1.5 \pm 0.7^*$ | 1.3 ± 1.0 |
| Coronary stenosis (%) | 69 ± 38 | $85 \pm 23^*$ | 82 ± 40 |

$^*p < 0.05$ versus RD.
 $^†p < 0.05$ versus ID.

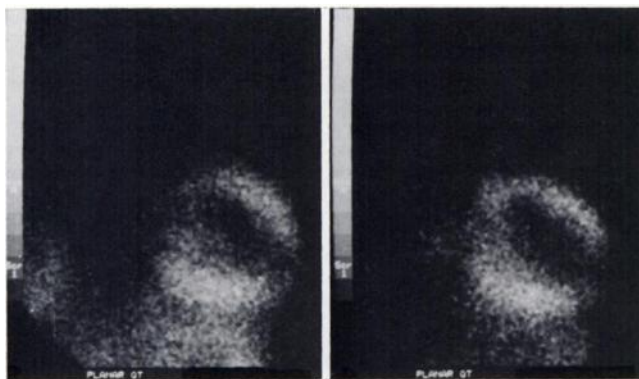


FIGURE 3. Thallium-201 myocardial scintigraphy. Rest (A) and redistribution (B) anterior projection. The apical defect is more prominent on redistribution than on rest image (reverse redistribution pattern B).

tribution images and were considered to show the RR phenomenon (pattern A). These myocardial segments differed from those with normal ^{201}Tl uptake on both rest and redistribution images in all the variables considered. In particular, myocardial segments with RR pattern A had a higher degree of coronary artery stenosis, worse LV wall motion and lower resting MIBI uptake when compared to normal segments. These results suggest that myocardial segments with this RR pattern should not be considered normal.

In six of the 120 (5%) myocardial segments with ^{201}Tl uptake < 80% on rest images, a significant decrease of tracer uptake on redistribution images was observed (pattern B). According to a previous report (6), a change in ^{201}Tl uptake of at least 1 s.d. (7%) of the normal reference group was considered significant. We did not observe any significant difference among these three groups of myocardial segments (RD segments, ID segments and segments with RR pattern B) in MIBI uptake, wall motion score and degree of CAD. However, a trend toward higher values of wall motion score and lower values of MIBI uptake in myocardial segments with RR pattern B and in ID segments was observed, but this difference did not reach statistical significance, probably because of the low number of segments.

Although the RR pattern of ^{201}Tl has been reported (8–15), its mechanism and clinical significance are still not clear. This phenomenon has been observed either with exercise (or dipyridamole)-redistribution (9–15) and with rest-redistribution cardiac imaging (8). Different results using stress-redistribution ^{201}Tl myocardial scintigraphy have been found (9–11). Tanasescu et al. (9) indicated that RR occurred in myocardial segments supplied by a normal or the least stenosed coronary artery. Hecht et al. (10) demonstrated that RR is observed more frequently in segments perfused by a stenosed coronary artery. Finally, Silberstein and DeVries (11) suggest that the RR phenomenon does not always indicate CAD. In patients with aortocoronary bypass, RR was observed in segments supplied by bypass grafting (12). Popma et al. (15), using dipyridamole

and single-photon emission computed tomography, found an RR incidence of 7% and suggest that this phenomenon does not indicate the presence of severe CAD. Higher incidence (45%) of myocardial segments with RR was found using rest-redistribution ^{201}Tl myocardial scintigraphy after early streptokinase therapy in patients with acute myocardial infarction (AMI) (8). In addition to these somewhat conflicting results, the possibility that RR can reflect an artifact of background subtraction has been advocated (13,14). It is conceivable that differences in study design and in patient selection can partially explain different results. Moreover, the majority of authors used stress-redistribution ^{201}Tl myocardial scintigraphy, and it is known that factors other than the presence of CAD influence ^{201}Tl myocardial clearance. In particular, Kaul et al. demonstrated that ^{201}Tl clearance is lower when peak exercise heart rate is lower (18).

Weiss et al. (8) found a higher incidence (45%) of myocardial segments with RR. However, there are several differences between their study and ours. In our study, rest-redistribution ^{201}Tl myocardial scintigraphy was performed in male patients with chronic CAD and LV dysfunction, while Weiss et al. studied subjects with AMI after streptokinase therapy. In addition, we used a quantitative approach without background subtraction to assess ^{201}Tl uptake and thus to objectively classify myocardial segments, while Weiss et al. used qualitative analysis.

Rest-redistribution ^{201}Tl myocardial scintigraphy has been recently proposed to differentiate fibrotic from severely ischemic but still viable myocardial in patients with chronic CAD (5–7). Our results indicate that in such patients the RR phenomenon occurs with a relatively low incidence (9%). The occurrence of RR in myocardial segments with normal ^{201}Tl uptake on rest images appears to be clinically relevant, since these myocardial segments differ from those with normal ^{201}Tl uptake on both rest and redistribution images in coronary anatomy and LV wall motion. In addition, a significantly lower uptake of MIBI was found in myocardial segments with this RR pattern, suggesting a decreased myocardial blood flow. On the other hand, myocardial segments with RR pattern B (with abnormal ^{201}Tl uptake on rest cardiac images and a significant decrease on 4-hr redistribution images) did not differ significantly from segments showing reversible defect and from those with irreversible defect, probably because of the small number of segments analyzed. However, segments with RR pattern B seem to behave more closely to myocardial segments with irreversible ^{201}Tl defects in terms of both left ventricular function and MIBI uptake. Although no clear conclusions could be inferred from our data, it is reasonable to consider myocardial segments with RR pattern B as segments with irreversible defects.

Because all patients in the study were male, the possible effect due to the position of the breast, in particular attenuation on different myocardial segments on rest and redistribution images, can be excluded. All patients were studied after an overnight fast and all remained in the fasting

state through the ^{201}Tl imaging protocol. Gastrointestinal uptake was negligible (Fig. 2, 3) and did not seem to change between rest and redistribution images. In addition, the absence of background subtraction in the quantitative analysis should overcome any artifact due to oversubtraction or undersubtraction in rest or redistribution images.

In conclusion, the study results suggest that myocardial segments with normal ^{201}Tl uptake on rest images and abnormal ^{201}Tl uptake on redistribution images (RR pattern A) have impaired function and are supplied by severely stenosed coronary arteries.

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EDITORIAL

Easy Come, Easy Go: Time to Pause and Put Thallium Reverse Redistribution in Perspective

For two decades, ^{201}Tl scintigraphy has withstood the test of time as the single-photon imaging gold standard of viability. Extensive clinical experience has taught the clinician that a reversible thallium defect represents jeopardized but viable myocardium, while a persistent defect represents scar or severe hypoperfusion, and may require delayed imaging or a second dose of thallium to distinguish the two. The phenomenon of the reverse redistributing thallium defect

has continued to trouble the clinician, having evaded a clear understanding of its mechanisms and clinical significance.

Reverse redistribution has been most commonly observed following coronary thrombolysis, where it is frequently associated with patency of the infarct-related artery and relatively preserved infarct segment wall motion (1,2). It has also been described soon after angioplasty or bypass surgery (3), again in the presence of a patent graft or supplying artery. In a general referral population, reverse redistribution has been found to be associated with coronary artery disease of vary-

ing severity, using either exercise (4) or dipyridamole (5) stress. It is also observed in a variety of cardiomyopathies, including Chagas' disease and sarcoidosis (6,7).

In this issue of the *Journal*, Pace et al. further add to our knowledge on reverse redistribution in the setting of rest and delayed thallium images. They examine coronary angiography, ventricular function and rest uptake of $^{99\text{m}}\text{Tc}$ -sestamibi, in relation to rest-redistribution thallium scintigraphy in 25 patients with severe coronary disease. They report that segments with reverse redistribution are frequently subtended by occluded epicardial ves-

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