

Relationship Between Resting ^{201}Tl Reverse Redistribution, Microvascular Perfusion, and Functional Recovery in Acute Myocardial Infarction

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^{201}Tl reverse redistribution is a common finding early after reperfusion therapy for myocardial infarction. Its mechanism and clinical implications remain unclear. The aim of this study was to clarify the relationships between reverse redistribution, microvascular perfusion, and myocardial viability. **Methods:** Resting, 10-min-postinjection, and redistribution ^{201}Tl data obtained for 33 patients 8 and 42 d after the onset of acute myocardial infarction were compared with echocardiographic wall motion measured acutely and on day 42. Microvascular perfusion was assessed by myocardial contrast echocardiography performed 10 min after restoration of complete patency of the infarct artery. **Results:** Marked significant reverse redistribution was found on day 8 (absolute change, $7.5\% \pm 7.9\%$ of the 10-min-postinjection defect size; $P < 5 \times 0.000001$) and significantly decreased on day 42 ($2.7\% \pm 6.8\%$; $P = 0.004$ between days 8 and 42). The 10-min-postinjection defect size best predicted the final infarct size on day 42 and was closely related to microvascular perfusion. Patients with adequate reperfusion had a smaller postinjection defect on day 8 ($21.1\% \pm 14.6\%$) and a larger reverse redistribution ($10.2\% \pm 6.1\%$) than did patients with no reflow ($35.3\% \pm 13\%$ and $3.2\% \pm 9.2\%$, respectively; $P < 0.04$ for both). **Conclusion:** Reverse redistribution was marked early after myocardial infarction in patients with complete patency of the infarct artery and decreased in subsequent weeks. Reverse redistribution was associated with restoration of adequate microvascular reperfusion and with myocardial salvage and viability. The early postinjection scans on day 8 were the relevant images for assessing myocardial salvage and predicting wall motion recovery.

Key Words: reverse redistribution; microvascular perfusion; myocardial contrast echocardiography; TIMI-3

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During the last decade, management of patients with acute myocardial infarction was based on the open-artery theory and, therefore, on restoration with reperfusion therapy

of complete patency (i.e., Thrombolysis in Myocardial Infarction [TIMI] trial grade 3 coronary flow) of the infarct-related artery (1). Beyond the open-artery theory, the importance of microvasculature status was emphasized by myocardial contrast echocardiography (MCE), defining a subgroup of patients with inadequate reperfusion (no reflow) despite patency of the infarct-related artery (2–4). Restoration of adequate microvascular perfusion may be more important for myocardial salvage than is patency of the epicardial infarct-related coronary artery (5–11). Therefore, microvascular perfusion appears to be the missing link between epicardial coronary artery status and cell viability. Patients treated with reperfusion for acute myocardial infarction often undergo early assessment of myocardial viability using ^{201}Tl SPECT (12,13). Because myocardial ^{201}Tl uptake depends on coronary artery patency, microvascular perfusion, and myocardial viability, interpretation of ^{201}Tl imaging before discharge may be difficult. Reverse redistribution, i.e., the worsening of a perfusion defect during the redistribution phase of ^{201}Tl , has been reported to be frequent in this setting and to be associated with patency of the infarct-related artery, residual viability of the myocardium, and preservation of regional contractility (12–23). However, the mechanisms of reverse redistribution remain unclear. In addition, myocardial metabolic and functional involvement persisting beyond the acute phase (i.e., myocardial stunning) may impair the interpretation of ^{201}Tl redistribution images and lead to underestimation of myocardial viability. Therefore, whether the postinjection or the redistribution images should be used as indicators of myocardial viability is uncertain.

To elucidate the relationship between reverse redistribution early after acute myocardial infarction, microvascular perfusion, and myocardial viability, we selected a patient population with complete (i.e., TIMI coronary flow grade 3) patency of the infarct-related artery, thereby controlling for artery patency, but with a wide range of infarct sizes and various degrees of microvasculature impairment leading either to adequate microvascular reperfusion or, conversely,

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to a no-reflow phenomenon. We aimed to compare early resting ^{201}Tl imaging (postinjection images and redistribution images obtained on day 8), microvascular perfusion, and functional recovery. Our hypothesis was that early postinjection images on day 8 closely depend on microvascular reperfusion in the acute phase. Because adequate reperfusion is required for myocardial salvage and functional recovery, postinjection images should be related to late regional function and late myocardial ^{201}Tl uptake. In this study, microvascular perfusion was assessed acutely by intracoronary MCE performed after recanalization of the infarct-related artery.

MATERIALS AND METHODS

Population

The patient population consisted of consecutive patients with acute myocardial infarction of less than 6-h duration and with successful reperfusion therapy, defined as complete patency (i.e., TIMI grade 3 flow) and <50% residual stenosis of the infarct-related artery seen on angiograms obtained in the acute phase. Myocardial infarction was defined as prolonged (>30 min) chest pain associated with an ST-segment elevation of more than 1 mV in at least 2 contiguous leads and was confirmed by a creatine kinase elevation above twice the normal value. We excluded patients who were more than 80 y old or who had cardiogenic shock or hemodynamic instability, a history of previous myocardial infarction or coronary bypass surgery, or >50% stenosis of the left main coronary artery. We also excluded patients who were unwilling to participate in the study. For all patients, the persistence of vessel patency was verified by repeated coronary angiography at the end of the first week. All patients gave informed consent to the study, and the protocol was approved by the institutional ethics committee on human research.

Coronary Angiography and Coronary Angioplasty

All patients underwent coronary angiography on admission as well as on day 8, using a femoral artery approach with 6-French catheters. All patients received aspirin (250 mg orally or intravenously), a bolus of 5000 IU of heparin intravenously on admission, and a second bolus of 5000 IU if angioplasty was performed. Coronary angioplasty was performed using standard methods as required to achieve an optimal angiographic result. Successful angioplasty was defined as a residual stenosis of <50% in diameter, with TIMI-3 coronary flow in the infarct-related artery.

Baseline 2-Dimensional Echocardiography

Baseline 2-dimensional echocardiography was performed on admission and on day 42, with the patients lying supine, using a 2.5-MHz transducer fitted on a dedicated echocardiographic system (Sonos 1500; Hewlett-Packard Co., Andover, MA). Images were recorded on videotape and analyzed off-line by 2 experienced observers who were unaware of clinical, hemodynamic, and scintigraphic data. Discrepancies were resolved by consensus reading. Four views were used: parasternal long- and short-axis views (at the level of the papillary muscles) and apical 2- and 4-chamber views. The left ventricle was divided into 16 segments according to the American Society of Echocardiography method of segmentation (24). In each segment, wall motion was scored as follows: 1 for normal motion, 2 for hypokinesia, and 3 for akinesia or dyskinesia. The wall motion score per patient was calculated as

the sum of the wall motion scores of each segment divided by the total number of segments visualized. The number of akinetic segments was also considered. Follow-up on day 42 was not available for 4 patients.

MCE

MCE was performed 10 min after the angiographic demonstration of stable TIMI-3 patency, using the same echocardiographic system. For each echocardiographic view, 3 mL sonicated ioxaglate (Hexabrix 320; Guerbet, Paris, France) were separately injected into each coronary artery. Recording started 10 s before injection of contrast material and continued until myocardial contrast enhancement disappeared. Echocardiographic views, myocardial segmentation, and image analysis were similar to those used for 2-dimensional echocardiography. For each segment, perfusion was scored as follows: 0 for absence of contrast; 0.5 for incomplete, heterogeneous contrast; and 1 for complete, homogeneous contrast. For each segment, the highest perfusion score measured after injection into either coronary artery was used. A mean perfusion score was calculated as the sum of the contrast scores in the hypokinetic and akinetic segments divided by the number of segments in the same area, as previously described (3,8). Inadequate reperfusion was defined as a perfusion score ≤ 0.5 , and effective reperfusion was defined as a perfusion score > 0.5 (8). Because of technical problems, echocardiographic data were not available for 6 patients. The κ value for interobserver reproducibility of echocardiographic data analysis was 0.71.

Resting and Redistribution ^{201}Tl SPECT

The first resting ^{201}Tl acquisition was on day 8 and started 10 min after intravenous administration of 111–148 MBq (3–4 mCi) ^{201}Tl according to each patient's body weight, using a rotating γ camera (model 409; Elscint Ltd., Haifa, Israel) fitted with a high-resolution collimator. The acquisition was repeated 4 h later for redistribution imaging. The same protocol was applied on day 42, again yielding 10-min-postinjection and redistribution images.

The acquisition parameters were a 180° circular orbit, starting with the right anterior oblique 30° view with the patient supine; a 64 × 64 matrix; and 30 projections in a step-and-shoot mode (30 s per projection for resting images and 40 s per projection for redistribution images). Slices were obtained by filtered backprojection (Hamming-Hann filter) and were reoriented along the 3 axes with a dedicated computer device (Sophy; SMVi Sopha Medical Systems, Buc, France). Background subtraction and attenuation correction were not used. A 2-dimensional map of SPECT data was automatically drawn using 3-dimensional radial sampling. A polar map (bull's-eye) of the maximal value of the myocardial pixels (counting rate density) was displayed to compare resting and redistribution slices (25). First, for each polar map, the isocontour delineating the area visually estimated as having normal uptake was generated. This isocontour level divided the bull's-eye polar map into 2 regions of interest, as previously described (26): the area of normal ^{201}Tl uptake and the ^{201}Tl defect (expressed as a percentage of the total area of the polar map). The choice of the isocontour value was validated in previous studies (25,26). Interobserver agreement in validating the contour of the perfusion defect was 100%. Because processing was fully automatic, maximal reproducibility in the computed values was ensured. Reverse redistribution was defined as a relative increase in the initial defect size of >10% (twice the variability of the complete determination of the defect area, including SPECT reconstruction and oblique reorientation). The severity of the ^{201}Tl defect was evaluated by the

ratio of the average ^{201}Tl counts in the defect area divided by the average ^{201}Tl counts in the normal area.

Study Design and Statistical Management

MCE was used to assess acute microvascular reperfusion. Coronary angiography was used to evaluate coronary artery patency and TIMI grade flow in the acute phase and on day 8. Myocardial viability was defined as improvement in regional wall motion and was evaluated with echocardiographic wall motion studies on day 42. To assess the accuracy of ^{201}Tl images on day 8 in predicting myocardial salvage, the sizes of the early (10-min-postinjection) and redistribution ^{201}Tl defect on day 8 were compared with the final infarct size, estimated by wall motion studies on day 42, using linear regression ($n = 29$). ^{201}Tl data on days 8 and 42 were also compared by paired t testing and linear regression ($n = 33$). For the 27 patients who had MCE, the ^{201}Tl results of those who had adequate reperfusion were compared, using unpaired t testing, with the ^{201}Tl results of those who had a no-reflow phenomenon. All values were expressed as mean \pm SD. Student's paired or unpaired t testing and linear regression analysis were performed on Statistica software (International Business Machines, White Plains, NY) for personal computers. $P < 0.05$ was considered significant.

RESULTS

Population

Thirty-three consecutive patients (3 women, 30 men; mean age, 53.0 ± 11.9 y) entered the study. Coronary patency was obtained by primary percutaneous transluminal coronary angioplasty ($n = 25$), rescue angioplasty after unsuccessful thrombolysis ($n = 2$), or recombinant tissue plasminogen activator alone ($n = 6$). The patients' characteristics are summarized in Table 1.

No deaths or major adverse cardiac events occurred during the 6 weeks of the study. All patients had normal renal function as determined by the creatinine serum level. All patients received β blockers and aspirin during the hospital phase. Three patients received nitrates after the acute phase, and 21 patients received angiotension-converting enzyme inhibitors. Treatment remained unchanged during the follow-up period.

Coronary Flow and Microvascular Perfusion

All patients had complete (i.e., TIMI grade 3) and persistent patency, with $<50\%$ residual stenosis of the infarct-related coronary artery both acutely and on day 8. The average MCE perfusion score was 0.7 ± 0.2 . Six of 27 patients (22%) had a perfusion score ≤ 0.5 and were therefore considered as exhibiting no reflow despite complete angiographic patency of the infarct-related artery. The time to reperfusion was similar in patients with adequate reperfusion (246 ± 75 min) and in patients with no reflow (218 ± 60 min; not statistically significant [NS]).

Myocardial Salvage

Between the acute phase and day 42, the number of hypokinetic or akinetic segments was significantly reduced (Table 1; $P = 0.01$) and the wall motion score was significantly improved (Table 1; $P = 0.001$). Patients with adequate reperfusion (MCE perfusion score > 0.5) had a

TABLE 1
Patient Characteristics

Parameter	Value
Time to emergency coronary angiography (mean \pm SD)	186 ± 72 min
Time to restoration of TIMI grade 3 flow (mean \pm SD)	233 ± 73 min
Peak of serum creatine kinase	
Mean \pm SD	$3,683 \pm 2,261$ IU
Range	352–10,020 IU
Infarction location	
Anterior	20 patients
Inferior	12 patients
Lateral	1 patient
Multivessel disease	
1-vessel disease	20 patients
2-vessel disease	10 patients
3-vessel disease	3 patients
X-ray left ventricular ejection fraction	$50.5\% \pm 13.4\%$
Acute data (Day 0) (mean \pm SD)	
MCE perfusion score	0.7 ± 0.2
No. of hypokinetic or akinetic segments	6.9 ± 2.4
Wall motion score	1.8 ± 0.29
Day 8 (mean \pm SD)	
Postinjection defect size	$22.5\% \pm 15.0\%$
Redistribution defect size	$30.1\% \pm 14.3\%$, $P = 0.0000051^*$
Day 42 (mean \pm SD)	
Postinjection defect size	$21.5\% \pm 15.5\%$
Redistribution defect size	$24.2\% \pm 14.8\%$, $P = 0.035^*$
No. of hypokinetic or akinetic segments	5.7 ± 2.7 , $P = 0.01$ vs. day 0
Wall motion score	1.6 ± 0.3 , $P = 0.001$ vs. day 0

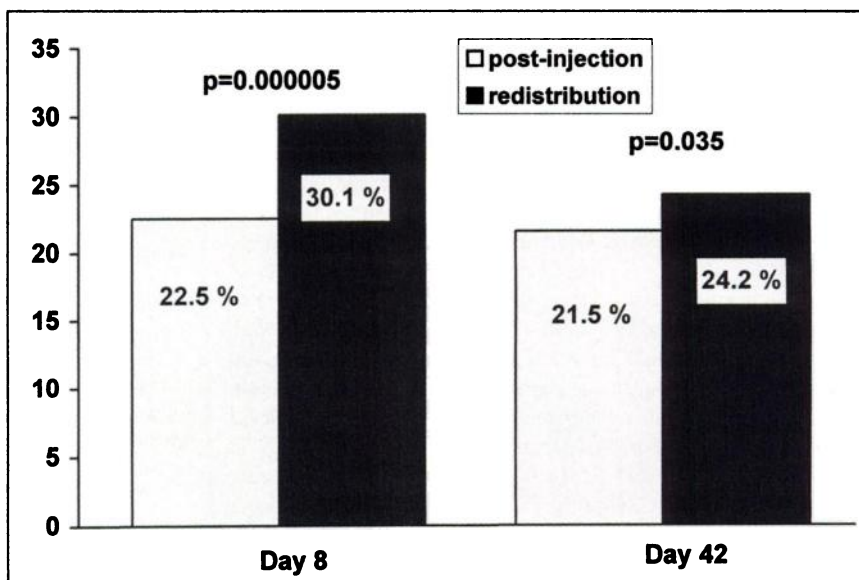
*Between postinjection and redistribution images.

larger reduction in the number of hypo- or akinetic segments than did patients with no reflow (respective absolute reduction of 5.1 ± 0.5 versus 2.1 ± 2.7 segments; $P = 0.002$). On day 42, the redistribution defect size correlated closely with wall motion score ($r = 0.79$; $P < 0.001$) and with the number of hypokinetic or akinetic segments ($r = 0.74$; $P < 0.001$).

Resting ^{201}Tl Reverse Redistribution

On day 8, postinjection ^{201}Tl images showed a smaller defect than did redistribution images (Table 1; $\Delta = 7.5\% \pm 7.9\%$ of the polar map area; $P < 0.00001$), indicating marked reverse redistribution (Fig. 1). Of 33 patients, 1 had normal ^{201}Tl findings and only 5 (15%) had no significant reverse redistribution. An example of an obvious ^{201}Tl reverse redistribution and the corresponding MCE is shown in Figures 2 and 3. Conversely, mild reverse redistribution was found on day 42 (Table 1; $\Delta = 2.7\% \pm 6.8\%$ of the polar map area; $P = 0.035$). Therefore, the large reverse redistribution observed 8 d after acute myocardial infarction markedly decreased at 6 weeks ($P = 0.004$ between days 8

FIGURE 1. Bar graph shows magnitude of reverse redistribution on days 8 and 42. Defect size on postinjection and redistribution images at days 8 and 42 is expressed as percentage of polar map area. Magnitude of reverse redistribution is significantly greater on day 8 than on day 42 ($P = 0.004$).



and 42; Figure 3). Patients with significant reverse redistribution on day 8 had fewer hypokinetic or akinetic segments on day 42 than did patients without reverse redistribution (5.2 ± 2.1 and 7.7 ± 3.7 segments, respectively; $P = 0.04$), despite a similar initial area at risk (6.6 ± 2.5 segments and 8.3 ± 1.9 segments, respectively; $P = 0.12$, NS).

Evaluation of the Final Infarct Size on Day 8

On day 8, the defect obtained on redistribution images markedly overestimated the final infarct size as evaluated on redistribution images on day 42 (Table 1; $\Delta = 5.9\% \pm 8.0\%$; $P = 0.0007$). Conversely, the defect obtained on postinjection images on day 8 was similar (Table 1) and closely correlated (Fig. 4) with the one obtained on redistribution images on day 42 ($\Delta = 1.1\% \pm 8.6\%$; NS; $r = 0.84$; $P < 0.001$). Furthermore, the postinjection defect on day 8 also correlated with the echocardiographic wall motion score on day 42 ($r = 0.77$; $P < 0.001$). Therefore, postinjection

images on day 8 appeared to best reflect the final infarct size on day 42.

Relationship between ^{201}Tl Data on Day 8 and Acute Microvascular Perfusion

A mild but significant correlation was found between the postinjection defect size on day 8 and the acute MCE perfusion score ($r = -0.49$; $P = 0.01$). The area at risk was similar in patients with adequate reperfusion and in patients with no reflow as acutely assessed by the number of hypokinetic or akinetic segments on echocardiography (6.6 ± 2.7 segments and 8.3 ± 1.0 segments, respectively; NS) and the wall motion score (1.8 ± 0.3 and 2.0 ± 0.08 , respectively; NS). In contrast, patients with adequate reperfusion had smaller postinjection defects on day 8 ($21.1\% \pm 14.6\%$) and a larger reverse redistribution ($10.2\% \pm 6.1\%$) than did patients with no reflow ($35.3\% \pm 13\%$ and $3.2\% \pm 9.2\%$,

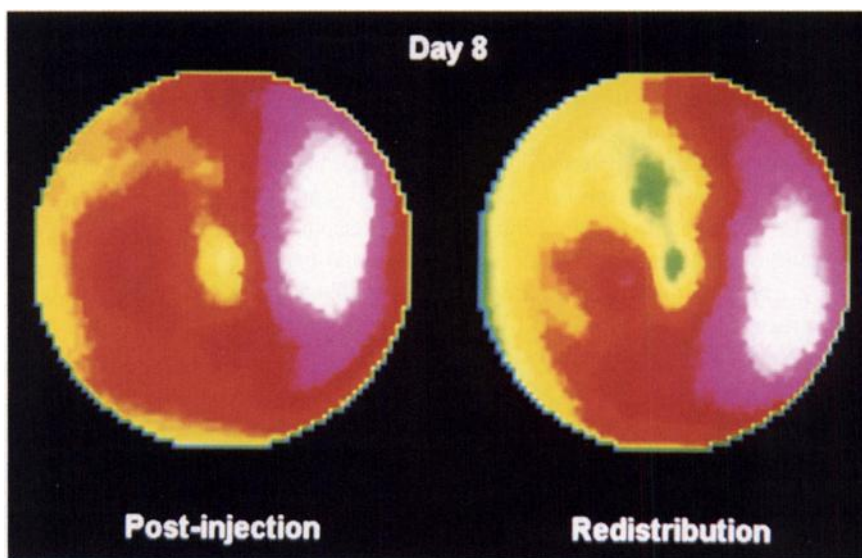


FIGURE 2. Bull's-eye display of SPECT data on day 8 for patient with reperfused anterior myocardial infarction. Reverse redistribution occurs between postinjection images and redistribution images in reperfused anterior and septal areas.

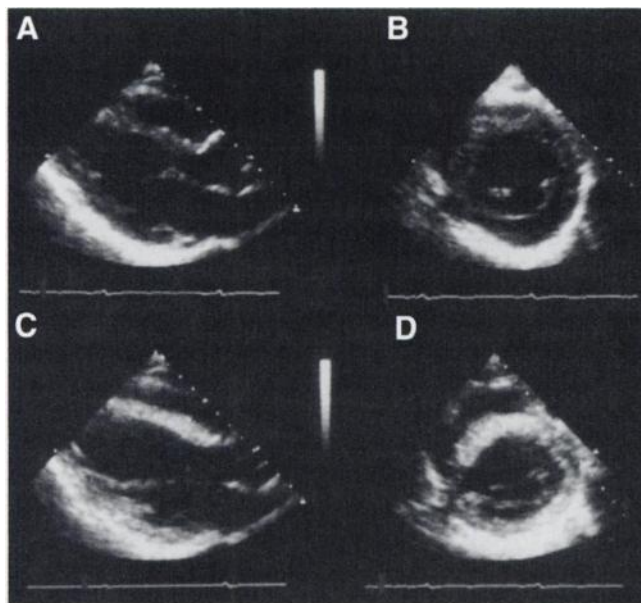


FIGURE 3. MCE images of same patient as for Figure 1. Parasternal long-axis (A and C) and short-axis (B and D) images before (A and B) and during (C and D) injection of contrast material. Anterior wall and basal septum show contrast enhancement, confirming effective microvascular reperfusion immediately after primary angioplasty.

respectively; $P < 0.04$ for both; Fig. 5). No such relationship was found with redistribution defect size on day 8.

DISCUSSION

Because of the clear clinical benefit of re-establishing complete patency of the infarct-related artery in acute myocardial infarction (1), efforts are made to increase the number of patients receiving effective reperfusion therapy (intravenous thrombolysis or primary or rescue percutaneous transluminal coronary angioplasty). Consequently, a growing number of patients with complete recanalization of the infarct-related vessel are being referred for evaluation of myocardial viability using ^{201}Tl scanning early after myocardial infarction. Usually, assessment of myocardial viability

is based mostly on redistribution images. In patients undergoing early coronary reperfusion, reverse redistribution has been reported and appears related to vessel patency and to wall motion improvement (18–21,23): a 75% prevalence of reverse redistribution has been reported (13), and reverse redistribution occurred only in the patients with a patent infarct-related artery. Recently, the same pattern has been reported for $^{99\text{m}}\text{Tc}$ -sestamibi after direct coronary angioplasty in acute myocardial infarction (27). However, after myocardial infarction, adequate microvascular perfusion appears to be a strong prognostic factor for functional recovery (5–11), and the relationship between reverse redistribution and microvascular perfusion has not yet been evaluated. Furthermore, whether postinjection images or redistribution images should be used to evaluate myocardial viability remains unclear.

Our findings indicate that reverse redistribution is associated with myocardial salvage and viability in patients in whom early and complete recanalization of the infarct-related vessel is obtained. Furthermore, reverse redistribution clearly depends on microvascular perfusion, because patients with adequate reperfusion had a smaller postinjection defect on day 8 but a larger magnitude of reverse redistribution. This difference was not explained by the time to reperfusion because TIMI grade 3 flow was obtained slightly earlier in patients with no reflow than in patients with adequate reperfusion (NS). Different pathophysiologic conditions can lead to reverse redistribution. Reverse redistribution may be related to delayed functional recovery caused by preserved microvasculature in the area of injured but viable myocardium (28). We hypothesize, as previously suggested, that some jeopardized myocardial cells may be capable of transient ^{201}Tl uptake but not prolonged uptake over several hours (13,29–31). Such transient uptake is related to the normal blood flow delivered in the reperfused zone and may be evidenced by postinjection ^{201}Tl uptake. This early postinjection uptake may occur in areas of stunned myocardium. Myocardial stunning may be respon-

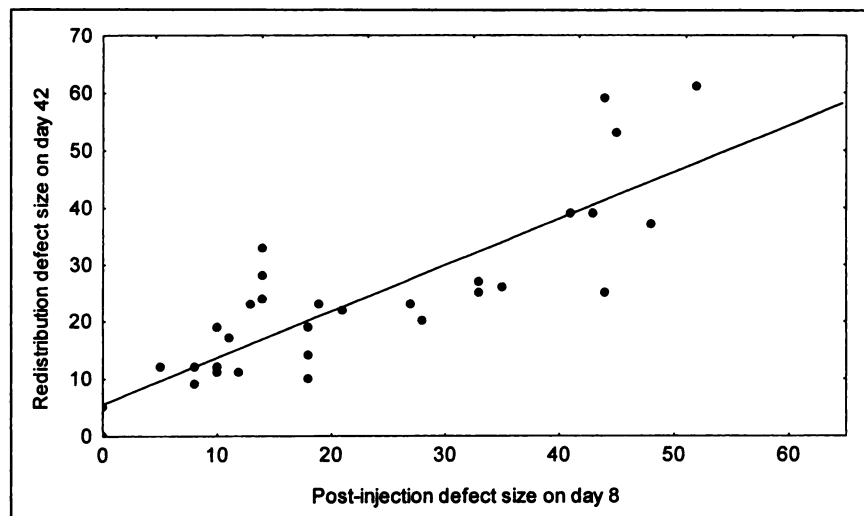


FIGURE 4. Scatter diagram shows relationship between postinjection defect size on day 8 and redistribution defect size on day 42. $r = 0.84$; $P < 0.0001$; $y = 0.8x + 5.7$.

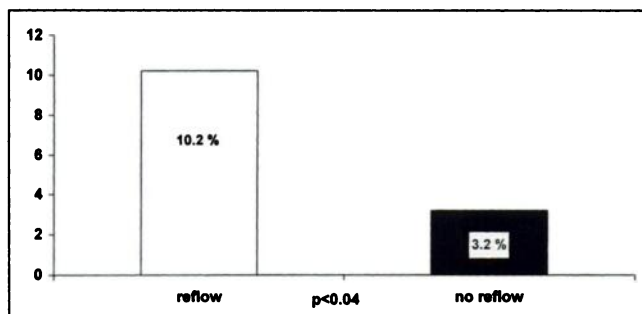


FIGURE 5. Bar graph shows magnitude of reverse redistribution on day 8 (expressed as percentage of myocardial surface) in patients with adequate reperfusion (reflow) and in patients with no reflow.

sible for increased washout of ^{201}Tl in the reperfused myocardium and may lead to a larger defect during the redistribution phase of ^{201}Tl . Therefore, the defect on postinjection images is smaller than on redistribution images, leading to reverse redistribution. Because these jeopardized cells may ultimately recover if adequate microvascular perfusion is restored and may, therefore, participate in functional recovery, postinjection findings are closely related to late regional function and ^{201}Tl uptake. Another possible mechanism is that, in these myocardial segments, interstitial edema after injury may be responsible for increased ^{201}Tl influx and early washout, resulting in reverse redistribution. These viable myocardial areas would show ultimate functional recovery. In experimental coronary occlusion and reperfusion, these 2 mechanisms probably occurred together, as shown by nuclear magnetic resonance studies. Myocytes and capillary cell membrane injury lead to alteration of water repartition within extra- and intracellular compartments. A durable decrease in the apparent diffusion coefficient of water and myocyte swelling have been reported and are associated with an alteration of membrane permeabilization to ions (32,33). This fact may explain the increase in the rate of potassium ion efflux as shown with ^{86}Rb (34), another potassium ion equivalent (like ^{201}Tl).

Semiquantitative evaluation of microvascular perfusion may limit this study, despite quantification of the extent of the reperfused area according to the American Society of Echocardiography method of segmentation. However, the goal of this evaluation was not to quantitatively assess microvascular blood flow but to discriminate segments with reflow from segments with no reflow, according to previous studies (35,36).

Finally, the clinical implications from our findings are that, in patients with TIMI grade 3 flow, the early postinjection scans are the relevant images for assessing salvage and predicting wall motion recovery.

CONCLUSION

Resting ^{201}Tl reverse redistribution is observed 8 d after acute myocardial infarction in nearly all patients with TIMI grade 3 flow. The finding appears to be closely related to

preserved microvascular function and associated with myocardial salvage and viability. Early after myocardial infarction, ^{201}Tl uptake on postinjection images is closely related to preserved myocardial perfusion. The defect size seen on these postinjection images predicts final infarct size and relates to late recovery of wall motion. Therefore, when ^{201}Tl scans are obtained early after reperfusion therapy for myocardial infarction, an increasingly frequent situation, postinjection but not redistribution images are relevant for prediction of functional recovery.

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