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Thallium-201 for Assessment of Myocardial Viability: Quantitative Comparison of 24-Hour Redistribution Imaging With Imaging After Reinjection at Rest

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Redistribution thallium-201 imaging 2 to 4 h after exercise may be incomplete and therefore may be inadequate to fully assess myocardial variability. Late redistribution imaging 24 h after exercise has been proposed to overcome this limitation of thallium stress imaging. However, because of poor count density the image quality on these studies is often suboptimal. In the present study the diagnostic information on 24-h planar thallium redistribution images was compared with that on images obtained after a reinjection of thallium at rest.

Eighty-four patients with a stress thallium-201 defect had delayed redistribution imaging after 2 to 4 h and 24 h later, and again after an injection of thallium at rest. Defect reversibility on 24-h redistribution images was compared quantitatively with that on images after injection of thallium at rest. The quality of thallium images at rest was consistently better than that of 24-h redistribution images. Poor quality studies occurred in 13% of 24-h redistribution images compared with 0.4% of the studies at rest. Significantly more defect reversibility was detected on images after the reinjection at rest.

Of 41 patients who appeared to have a fixed defect at 2- to 4-h redistribution imaging, 11 (27%) had a reversible defect by 24-h redistribution imaging compared with 29 (71%) after thallium-201 reinjection. No clinical variables at the time of stress testing were predictive of late defect reversibility. It is concluded that in patients with fixed a thallium defect at 2 to 4 h after exercise, reimaging after a reinjection at rest provides better diagnostic information than does 24-h late redistribution imaging.

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Thallium-201 is widely used to detect exercise-induced myocardial ischemia and to differentiate viable from nonviable myocardium (1). With use of traditional imaging protocols, images are obtained immediately after stress and again after a delay of 2 to 4 h, which allows evaluation of redistribution of thallium (2).

Classically, a reversible defect has been considered an indicator of transiently ischemic and viable myocardium, whereas a fixed defect has been thought to indicate nonviable and scarred myocardium. Recently several studies (3–5) have shown that defects that appear fixed at 2- to 4-h redistribution imaging may occasionally be reversible when late 24-h redistribution imaging is performed. However, these late redistribution images are frequently of suboptimal quality because of low heart to background ratio and low cardiac count density, thereby rendering interpretation of images difficult.

In the present study we prospectively evaluated an alternative approach to assure optimal delayed image quality by performing imaging after reinjection of thallium-201 at rest. Furthermore, most previous reports involving late thallium imaging, whether by planar or single-photon emission computed tomographic (SPECT) imaging, have been based on only subjective visual interpretation. In the present study *quantitative* analysis was used to provide a more reproducible and accurate assessment of the presence and extent of defect reversibility.

Methods

Study patients. The study group comprised 84 consecutive patients with a stress thallium-201 myocardial perfusion defect. These patients were referred to our institutions between March and August 1989 for either treadmill exercise (67 patients) or dipyridamole (17 patients) planar thallium imaging. There were 70 men and 14 women whose age ranged from 40 to 89 years (mean 62).

Imaging protocol. The patients either exercised on a motor-driven treadmill in accordance with a Bruce protocol or received a dipyridamole infusion (0.56 mg/kg body weight

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intravenously over 4 min) for pharmacologic vasodilation. At either peak exercise or 4 min after completion of dipyridamole infusion, 2.5 mCi of thallium-201 was administered. The gamma camera was peaked on the 80 keV X-ray peak (25% window) and on the 167 keV gamma peak (20% window). The camera was equipped with a general all-purpose parallel hole collimator. Imaging was performed in the left anterior oblique, left lateral and anterior projections, each for 8 min, accumulating ≥600,000 counts/view. The angulation of the gamma camera detector head was recorded by the technologist to assure accurate repositioning on subsequent imaging.

Imaging was started within 5 min after injection of thallium-201. Redistribution imaging was performed 2 to 2.5 h after exercise and 3 to 4 h after dipyridamole administration, in identical projections with use of the same acquisition time. All patients with a myocardial perfusion defect on 2- to 4-h delayed imaging were asked to return the next day for repeat imaging.

Twenty-four hour redistribution imaging was performed in identical projections for 10 min acquisitions with the same gamma camera. After completion of this third set of images, an additional 2.5 mCi of thallium-201 was injected at rest. After an interval of 30 to 45 min, 8 min acquisitions were obtained in identical projections with the same gamma camera.

Quantitative analysis. For each patient, four three-view image sets were available: 1) initial (stress) images, 2) 2- to 4-h redistribution images, 3) 24-h redistribution images, and 4) reinjection thallium-201 images. Thus, a total of 756 stress-delayed imaging pairs (9 pairs/patient) were available for quantitative analysis. Thallium-201 myocardial distribution on the stress images was compared with that on the corresponding 2- to 4-h redistribution images, 24-h redistribution images and reinjection images at rest. To minimize interobserver variability, a single operator performed quantitative analysis of images obtained in the same patient.

Our quantitative analysis technique for planar thallium-201 images has been described, standardized and validated previously (6–8). In brief, after modified interpolative background subtraction (9) circumferential count profiles were generated. The left ventricular region of interest was determined for each view from the initial stress image and was used in the processing of all image pairs from the same patient. By using the same region of interest for each image, a potentially important source of processing variability was minimized.

The left ventricle was divided into 36 segments, each subtending a 10° arc. The mean count density in each of the 36 segments was determined and the segment with maximal mean count density was designated as 100%. The value for the remaining segments was defined in relation to this maximal value and expressed as a percent.

Myocardial defect size was quantified by integrating the hypoperfused area under the lower limit of normal curve (mean − 2 SD). The same lower limit of normal was employed for physical exercise and pharmacologic stress thallium-201 studies. The area under the curve was expressed as a proportion (×100) of the total potentially visualized normal myocardium (Fig. 1). This value defines the defect integral, which is without unit and reflects both the extent and the severity of the perfusion defect (7).

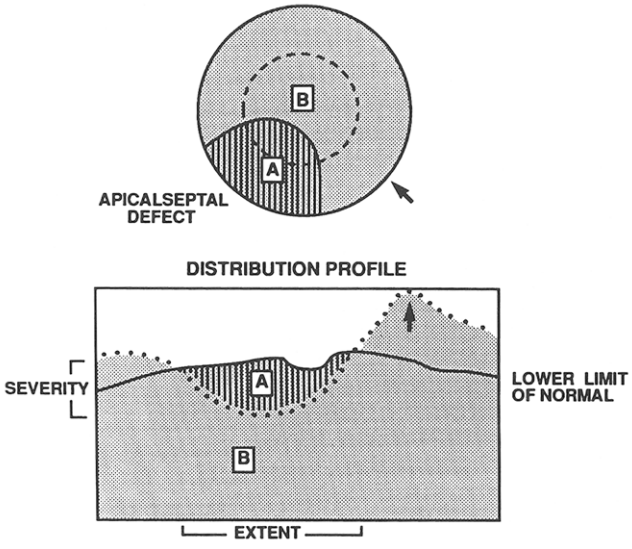

Figure 1. Quantification of perfusion defect. The schematic diagram (**top**) shows an apical septal defect (**A**) on a left anterior oblique image. The left ventricle (A + B) is divided into 36 10° segments. A circumferential distribution profile (**black dots, bottom**) is generated by plotting the mean count density of each segment. The segment with the highest mean count density is assigned 100% (**arrow**) and the other segments are plotted as a percent of this maximal value. This profile is superimposed on a curve (**solid black line**) indicating the lower limit of normal (mean − 2 SD) distribution of the radiopharmaceutical. The defect integral is calculated by expressing the defect (A) as a proportion (×100) of the total potentially visualized normal myocardium: A/(A + B) × 100. (Reproduced with permission from Koster et al. [9].)

The intraobserver variability of the quantitation of thallium-201 defects has been reported previously (8). For small defects (defect size 1 to 5), the mean absolute intraobserver variability was 1.1 ± 1.2; for medium defects (defect size 6 to 15), it was 1.8 ± 1.7; and for large defects (defects size >15) it was 2.9 ± 3.1. For defect reversibility, the difference in defect size from one study to another had to exceed the mean value + 1 SD of variability based on the initial defect size.

On the basis of both quantitative and visual analysis, each set of images was categorized as *normal* or as showing a *reversible* or *fixed* myocardial perfusion defect. The circumferential thallium-201 distribution profiles and the companion analog thallium images were interpreted by two experienced observers (F.J.Th.W., R.S.), using quantitative criteria for defect reversibility. This combined (visual and quantitative) information is routinely used in our daily practice of interpreting thallium stress images. In small defects (size 1 to 5) noise may interfere with quantification. There-

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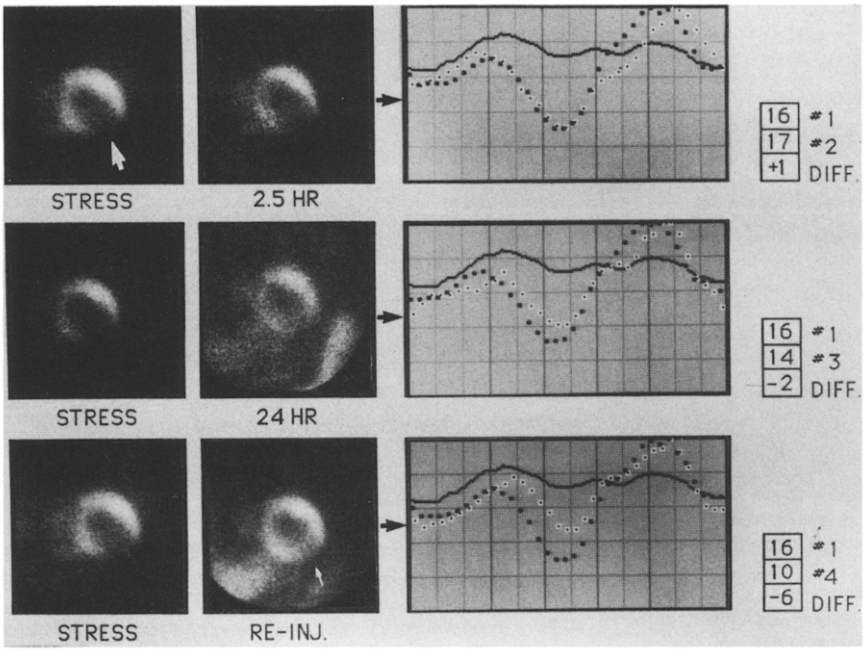

Figure 2. Representative example of repeat imaging (**anterior view**) and quantification of defect size. The analog images are shown on the **left**. The image after exercise stress is shown three times for comparison with those obtained 2.5 h and 24 h after stress and with the image obtained after reinjection (RE-INJ.) of thallium-201 at rest. Quantitative comparison by circumferential profiles is shown on the **right**. The **black dots** indicate the count distribution profile of the stress image. The **white dots with black center** indicate the count distribution of the repeat images. The **solid black curve** is the lower limit of normal thallium distribution. Defect integrals after stress (#1), at 2.5-h (#2) and 24-h (#3) delayed imaging and after reinjection at rest (#4) are shown in the **boxes at right**; the quantified difference (DIFF.) between defects at repeat imaging is also shown. At 2- to 4-h delayed imaging, the apical-septal perfusion defect (**large arrow**) is *fixed* by visual and quantitative profile analysis. At 24-h redistribution imaging some reversibility can be noted. After a reinjection of thallium at rest, substantially more thallium has accumulated in the defect (**small arrow**).

fore, in the latter situation apparent discordance between quantification and visual impression defect was resolved by consensus of the readers.

Image quality. The 24-h redistribution images and the images after reinjection at rest were *subjectively* graded for quality as good, average or poor. The main subjective determinant was the perceived count density in the heart and heart to background ratio.

Statistical analysis. Changes in the frequency of categorization of studies as fixed or reversible at each imaging time point were compared by using chi-square analysis. The frequency of clinical variables in patients with late reversible and late fixed images were also compared with chi-square analysis. A p value <0.05 was considered statistically significant.

Results

Image quality. The images after reinjection of thallium-201 were judged overall to be of considerably better quality than those after 24-h redistribution. Of 252 late redistribution images, 34 images (13%) in 17 patients were graded as poor. In contrast, of 252 images obtained after reinjection at rest only 1 (0.4%) was considered of poor quality ($p < 0.001$).

Analysis of images. An example of repeat imaging in an individual patient is shown in Figure 2. Of 252 views in 84 patients, 30 (12%) were normal by quantitative analysis, 63 (25%) showed a reversible defect and 159 (63%) showed a fixed perfusion defect (Table 1). At 24-h redistribution imaging, 12% of the views were normal, 35% showed a reversible defect and 54% showed a fixed defect. After reinjection of thallium-201 at rest, only 33% of the views demonstrated a fixed defect, 52% showed a reversible defect and 15% were normal. The distribution of defects was statistically significantly different at each of the imaging times ($p < 0.001$).

The outcome of an initially fixed defect when reimaged 24 h later is shown in Figure 3. Of the 159 views with a fixed defect at 2- to 4-h redistribution imaging, 126 (79%) were still fixed at 24-h redistribution imaging. After reinjection of thallium-201, only 76 (48%) of these were still fixed by quantitative analysis. Conversely, whereas only 33 views (21%) were identified as showing a reversible defect at 24-h redistribution, 83 (52%) showed a reversible defect after reinjection of thallium. The mean quantitative defect size of each category at each imaging time is shown in Table 2. Thus, reinjection demonstrated an additional 50 views (31% of 159 initially fixed defects) with significant reversibility ($p < 0.001$).

Table 1. Distribution of Defects in 252 Views in 84 Patients at 2- to 4-Hour and 24-Hour Delayed Redistribution Imaging and After Reinjection of Thallium-201

Thallium-201 Distribution Pattern	Time of Imaging		
	2- to 4-Hour Delayed	24-Hour Delayed	Reinjection at Rest
Fixed	159 (63%)	135 (54%)	82 (33%)
Reversible	63 (25%)	87 (35%)	130 (52%)
Normal	33 (12%)	30 (12%)	42 (15%)

Data indicate number and percent of defects.

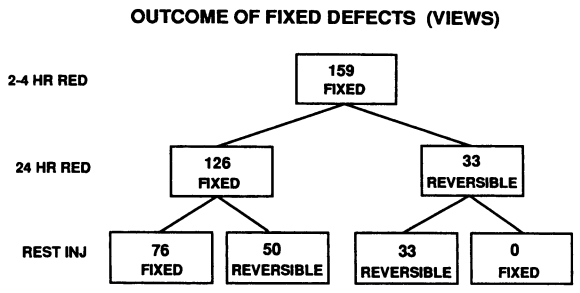

Figure 3. Outcome of repeat imaging of 159 views with a fixed thallium-201 defect at 2- to 4-h delayed imaging. INJ = imaging after injection of thallium-201; RED = redistribution imaging.

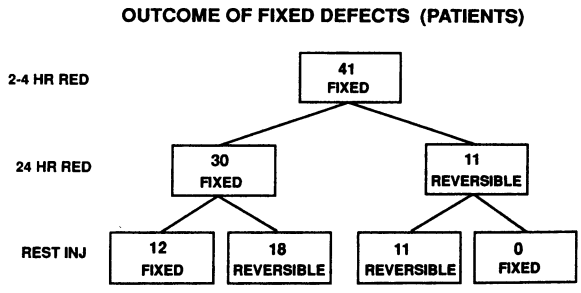

Figure 4. Outcome of repeat imaging in 41 patients with a fixed thallium-201 defect at 2- to 4-h delayed imaging. Abbreviations as in Figure 3.

Analysis by patient. The diagnostic implications of these results are demonstrated when this same analysis is performed by patient rather than by image view (Fig. 4). Forty-one patients had a fixed defect at 2- to 4-h redistribution. At 24-h imaging before reinjection of thallium-201, 30 of the 41 patients had a fixed defect and 11 (27%) had a reversible defect. After reinjection of thallium, only 12 of the 30 patients with a fixed defect still had a fixed defect; 18 of these patients now had a reversible defect. The 11 patients with a reversible defect at 24-h redistribution imaging still had a reversible defect after reinjection of thallium. Thus, a total of 29 (or 71%) of the initial 41 patients were identified as having a reversible defect after reinjection of thallium. Eighteen patients (44%) were not recognized with 24-h redistribution imaging alone.

Clinical characteristics. Selected clinical characteristics of the 41 patients with a fixed defect at initial 2- to 4-h redistribution imaging are shown in Table 3. There was no difference between patients who demonstrated a reversible defect after reinjection of thallium-201 and the patients whose defect remained fixed, with respect to history of myocardial infarction, electrocardiographic (ECG) evidence for Q wave infarction, angina or ECG ST segment changes during exercise. Therefore, clinical characteristics before imaging could not be utilized to develop a priori imaging strategy.

Initially reversible defects. The outcome of defects that were initially reversible at 24-h redistribution imaging is shown in Figure 5. Of the 63 views with a reversible defect at 2- to 4-h imaging, 54 (86%) continued to demonstrate a reversible defect, whereas 9 defects (14%) were fixed at 24-h imaging. After reinjection of thallium-201, 57 views (90%) again showed a reversible defect and 6 (10%) a fixed defect. Mean quantitative defect size of each category at each imaging time is shown in Table 4. Thus, 10% to 14% of defects that were initially reversible at 2- to 4-h imaging were fixed at either 24-h redistribution imaging or at imaging after reinjection of thallium.

Table 2. Quantitative Defect Size (mean ± SD) at Repeat Imaging of 159 Views With a Fixed Defect (see Fig. 3)

Imaging			
	n = 159 fixed		
Exer	7.8 ± 6.9 } *		
2- to 4-hour	7.8 ± 6.6 }		
	n = 126 fixed	n = 33 reversible	
Exer	8.2 ± 7.1 } †	6.2 ± 5.7 } †	
24-hour	10.9 ± 7.8 }	2.7 ± 4.1 }	
	n = 76 fixed	n = 50 reversible	n = 33 reversible
Exer	8.9 ± 7.5 } ‡	6.7 ± 6 } §	6.2 ± 5.7 } †
Reinjection	10 ± 8.2 }	3.9 ± 4.1 }	1.6 ± 2.3* }
at rest			

*p = NS; †p < 0.001; ‡p < 0.02; §p < 0.01. Exer = exercise imaging; 2- to 4-hour and 24-hour = delayed imaging at 2 to 4 hours or 24 hours; Reinjection at rest = imaging after reinjection of thallium-201 at rest.

Discussion

Thallium-201 reinjection at rest versus 24-h redistribution imaging. This study clearly indicates that for evaluation of myocardial viability thallium imaging after a repeat injection at rest is preferred to 24-h redistribution imaging. The *quality* of thallium images after reinjection was consistently better than that of the 24-h redistribution thallium images. Poor quality studies, making interpretation difficult, occurred in 13% of 24-h redistribution studies. With *quantitative* image analysis, imaging after reinjection of thallium at rest revealed significantly more defect reversibility. From this observation one could reasonably infer a greater presence of viable

Figure 5. Outcome of repeat imaging of 63 views with a reversible thallium-201 defect at 2- to 4-h delayed imaging. Abbreviations as in Figure 3.

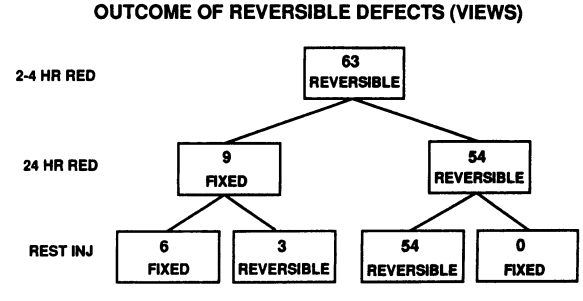

Table 3. Selected Clinical Characteristics of 41 Patients With a Fixed Defect at 2- to 4-Hour Delayed Redistribution Imaging

	Defect Reversible With Reinjection (n = 29)	Defect Fixed With Reinjection (n = 12)
History of infarction	24	10
Q wave infarction	16	5
Angina during exercise	4	2
ST changes during exercise	6	3

None of the variables differed significantly between the groups with and without a reversible defect after reinjection of thallium.

myocardium with this technique than after 24-h redistribution imaging.

Of 41 patients who appeared to have a fixed defect at 2- to 4-h redistribution imaging, 27% had a reversible defect at 24-h redistribution imaging. In contrast, after reinjection of thallium-201 at rest, 71% of these patients had a reversible defect. These proportions may differ, depending on patient selection. However, the present series of patients is representative of patients with abnormal thallium studies in our laboratory.

In this study we did not seek to correlate improved uptake of thallium-201 after injection at rest with other variables of myocardial viability. Other investigators (4,10–12) have demonstrated convincingly that late redistribution or improved thallium uptake after reinjection at rest is indicative of myocardial viability and that regions with late reversibility show an improved contractile pattern after effective revascularization. The aim of this study was to compare prospectively the information gained from 24-h redistribution imaging with that gained from imaging after reinjection at rest.

Reinjection of thallium-201 at rest. It is conceivable that in some patients with severe coronary stenosis viable myocardium is hypoperfused at rest. Under this condition the initial thallium distribution after an injection at rest would show a perfusion defect and thus underestimate myocardial viability. Because of this concern, we started imaging after injection of thallium at rest with a delay of 30 to 40 min. Dilsizian et al. (13) reported recently that 24-h redistribution imaging after an injection at rest did not detect significant additional defect reversibility.

Table 4. Quantitative Defect Size (mean ± SD) at Repeat Imaging of 63 Views With a Reversible Defect (see Fig. 5)

Imaging			
	n = 63 reversible		
Exer	6.9 ± 6.5 } *		
2- to 4-hour	2.5 ± 4 }		
	n = 9 fixed	n = 54 reversible	
Exer	6.6 ± 7.2 } †	7.2 ± 6.1 } *	
24-hour	6.7 ± 6.3 }	2.2 ± 3.7 }	
	n = 6 fixed	n = 54 reversible	n = 3 reversible
Exer	6.5 ± 6.5 } †	6.7 ± 8.1 } *	7.2 ± 6.1 } †
Reinjection at rest	6.5 ± 6.6 }	3.1 ± 5.7 }	1.6 ± 2.2 }

*$p < 0.001$. Abbreviations as in Table 2.

Imaging protocols. The traditional protocol for thallium-201 redistribution imaging after a single injection at peak exercise was first proposed by Pohost et al. (2) in the mid 1970s and has been standard practice for >10 years. However, in the light of current concepts, it is interesting to reexamine two studies from the late 1970s. Blood et al. (14) and Ritchie et al. (15) compared dual- and single-injection thallium stress imaging in the same patients. Both groups concluded that redistribution and rest images were comparable, but observed that single-injection redistribution imaging more frequently demonstrated a fixed defect. Blood et al. (14) commented that "redistribution scintiscans were more sensitive than rest scintiscans for the detection of prior myocardial infarction (93% vs. 54%; $p < 0.01$)." Ritchie et al. (15) concluded that "defect size was often larger in the redistribution image (compared to rest image) and may overestimate the extent of prior myocardial infarction." Verani et al. (16) recommended in 1979 that "resting scintigrams may be needed in a substantial number of patients to discriminate between scar and ischemia." However, later reports (17–20) indicated that the pattern on redistribution thallium imaging reliably predicted the response of regional wall motion to coronary bypass grafting.

In the 1970s thallium-201 stress testing was primarily used for the detection of coronary artery disease. In the present era there are more options for myocardial revascularization and broader indications for interventions. Therefore, an accurate assessment of the presence of viable myocardium in patients with recent or prior myocardial infarction is of considerable clinical importance.

In recent years the traditional single-injection thallium-201 imaging protocol has been shown to be inaccurate in characterizing myocardial areas as nonviable scar in some patients. Some patients with a fixed thallium defect show improved segmental wall motion after coronary revascularization (21,22). Brunken et al. (23), using positron imaging, demonstrated metabolic activity in the majority of myocardial segments with an apparently fixed thallium defect, Tillisch et al. (24) showed that improvement of regional wall motion after revascularization could be predicted by a mismatch between decreased myocardial blood flow (assessed by N-13 ammonia) and altered metabolism (enhanced F-18-2-deoxyglucose activity). Recently Bonow et al. (25) and Tamaki et al. (26) demonstrated that enhanced glucose metabolism correlated with thallium uptake after reinjection at rest.

Modifications of the thallium-201 imaging protocol. At present it is generally considered appropriate that patients with a fixed thallium defect at early redistribution imaging should have repeat imaging for assessment of the full extent of viable myocardium. Several modifications of the thallium imaging protocol have been proposed for this purpose. The

first was reported by Kiat et al. (4), who performed 24-h late redistribution imaging. Our data indicate that these images not only may be of suboptimal count density (which could be a particular problem for SPECT imaging), but also may not detect all of the potentially viable myocardium. For late redistribution to occur a minimal blood level of thallium activity is required (27). If the thallium blood level is too low, redistribution may not occur, even after 24 h.

A second modification, employed by Dilsizian et al. (10) and others (11,12,28), has involved reinjection of a smaller dose (usually 1 mCi) of thallium-201 immediately after 2- to 4-h delayed imaging. The latter method may be more difficult to use in a tightly scheduled laboratory. There are also theoretical concerns about the latter imaging protocol related to thallium dosing. The second dose of thallium is smaller than the first; therefore, the images after the repeat dose are a composite of two distribution patterns: early *redistribution* and regional *myocardial blood flow* at rest. Nevertheless, practical use of this imaging protocol has shown clinical results comparable with those after 24 h redistribution or after reinjection imaging at rest.

Two other modifications have been reported (29,30) as preliminary communications. Burns et al. (29) proposed a slow intravenous infusion of 1 mCi of thallium-201 starting after postexercise imaging. This method increases the thallium blood level after imaging and enhances myocardial redistribution. A final modification (30) involves reinjection of thallium immediately after completion of initial postexercise images, and delayed imaging 4 h later. Preliminary results with the latter method seem to indicate that this variation is not optimal and may underestimate myocardial viability.

Reinjection of thallium-201 on a different day. In the present study we used yet another modification: repeat thallium injection at rest on the day after the stress test. This approach provides consistently better image quality and, as shown in our study, a greater yield in detecting viable myocardium. Another advantage involves laboratory logistics. We find it easier to schedule patients for a return visit the next day or later rather than to continue imaging on the day of the stress test.

Predictors of reversibility. It would be useful at the time of stress testing to identify clinical predictors of defect reversibility. Although angina and ST segment changes that appeared to indicate ischemia were predictive for 2- to 4-h defect reversibility, none of the clinical variables examined were predictors of reversibility after reinjection of thallium-201 at rest. By design, our study was biased toward patients with prior myocardial infarction. Surprisingly, the absence of evidence of prior infarction was not a predictor of late defect reversibility. However, our study group comprised relatively few patients without prior infarction. Nevertheless, it is clear from our results that the presence of prior myocardial infarction does not preclude the presence of reversibility on thallium images obtained at rest.

Repeat imaging of reversible defects. An intriguing observation in our study involves the reimaging in patients with a *reversible* defect at 2- to 4-h redistribution imaging. These patients also may demonstrate a change in image pattern. Although the majority of the patients with a reversible defect continue to manifest this pattern at repeat imaging, 10% to 14% showed a *fixed* rather than a reversible defect on repeat imaging. Whether this finding reflects a true pathophysiologic variation is unclear. It is also conceivable that this observation by repeat imaging represents the phenomenon of "regression to the mean" (31); when patients with a fixed defect undergo reimaging, the defect can only remain fixed or become reversible. However, when patients with a reversible defect undergo reimaging, three outcomes are statistically possible: the same reversible defect, a reversible defect of lesser degree or a fixed defect.

Our observations in reversible defects point to the possibility that chance phenomena or "regression to the mean" may play a role in serial imaging, a factor that has not been considered previously in the analysis of serial thallium-201 studies. However, published data (4,10–12) indicate that improvement of regional wall motion by revascularization can be predicted by late filling-in of an initially fixed thallium defect. Thus, it appears improbable that these observations with repeat imaging represent a statistical oddity rather than a phenomenon with pathophysiologic relevance.

Clinical implications. Traditional thallium-201 stress imaging employing redistribution imaging 2 to 4 h after a stress test may significantly underestimate the full extent of viable myocardium. Repeat imaging is necessary to overcome this limitation. Imaging after reinjection of thallium at rest appears to be the optimal approach. Of various proposed protocols, the method used in the present study, that is, a new dose of thallium administered on the day after the stress test (or later) provides, in comparison with 24-h redistribution imaging, better image quality, a higher yield for detection of viable myocardium and greater flexibility in scheduling patients in a high volume imaging laboratory.

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