Rest-Injected Thallium-201 Imaging for Assessing Viability of Severe Asynergic Regions

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To evaluate the utility of rest-injected ^{201}Tl initial and delayed images for assessing the viability of severe asynergic regions, we studied 17 patients with apparently prior infarcted myocardium in combination with ^{99m}Tc ventriculography before and after revascularization. In 51 regions with severe asynergy, the percent ^{201}Tl uptake was calculated as the ratio of counts on the segment with asynergy to the maximum counts on the normal segment. Eleven of 14 regions with resting ^{201}Tl redistribution (Group 1) had improved wall motion after revascularization. However, 14 of 37 regions without redistribution also improved (Group 2). Twenty-three regions without redistribution or improved wall motion after revascularization (Group 3) had lower regional ^{201}Tl uptake on their delayed images than those in Groups 1 and 2. Moreover, the initial regional uptake of Group 2 was higher than that of Group 3. These results suggest that redistribution on rest-injected ^{201}Tl scans indicates reversibility of severely asynergic myocardium and that high ^{201}Tl uptake in regions without redistribution may predict improvement in wall motion after revascularization. We conclude that ^{201}Tl uptake may be useful as a marker of viability of severe asynergic regions before revascularization.

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In patients with apparently infarcted myocardium, differentiating viable but functionally impaired myocardium from irreversibly infarcted myocardium is important if revascularization for myocardial salvage is contemplated. Stress ^{201}Tl myocardial imaging has been widely used for assessing myocardial viability (*1–3*). Recent studies have reported, however, that some persistent defects without redistribution may improve in regional perfusion and function after revascularization (*3–5*). To obviate possible underestimation of viability on exercise ^{201}Tl 4-hr delayed images, some investigators have espoused the utility of 24-hr delayed images (*5–7*), ^{201}Tl reinjection images after a 4-hr delayed image (*8*), and resting ^{201}Tl images separated by 1–2 wk from the exercise ^{201}Tl image (*9, 10*). However, previous investigators reported that ^{201}Tl redistribution was observed in the resting state in regions with severe coronary artery stenosis (*11, 12*), suggesting that ^{201}Tl imaging would be useful for assessing viability. It is important to define regions with severe asynergy that will have improved function after revascularization (*13–16*). Regional wall motion abnormality at rest may be due to persistently depressed blood flow or to prolonged myocardial cellular dysfunction following transient ischemia or myocardial scarring (*17–20*). The different causes of severe asynergy may be differentiated by examining myocardial perfusion with rest-injected ^{201}Tl images.

In this study, we attempted to clarify the utility of the rest-injected ^{201}Tl delayed image for distinguishing reversible asynergic regions from irreversible infarcted ones by comparing regional wall motion before and after revascularization.

SUBJECTS AND METHODS

Subjects. The subjects were 17 (14 male, 3 female, median age 62 ± 9 yr) patients with anterior myocardial infarction and severe stenosis of 90% or more in left anterior discending (LAD) artery. Patients were selected by identification of severe hypokinesis, akinesis or dyskinesis in anterior, septal and apical regions, and no asynergy in other regions on ^{99m}Tc radionuclide ventriculography. No patient had suffered from acute myocardial infarction for the last 3 mo nor congestive heart failure. Two patients, however, complained of chest pain for a few minutes during exercise. Coronary angiograms showed one lesion in ten patients, two lesions in three and three lesions in four. No patients had 99% or more stenosis in other coronary arteries. Nine patients were treated with percutaneous transluminal coronary angioplasty (PTCA), the result of which was successful in all lesions. In all patients, restenosis of the LAD artery was not observed on coronary angiography 5 mo after PTCA. Five patients underwent coronary artery bypass graft (CABG) surgery. One patient had a single graft, one patient had two grafts, and three patients had three grafts. Patency was confirmed in all grafts for LAD arteries on coronary angiography 1 mo after CABG surgery.

Methods. Resting ^{201}Tl initial and delayed scans were performed about 1 wk before revascularization. The resting ^{201}Tl initial image was taken 10 min after intravenous injection of 111 MBq ^{201}Tl and the delayed image was taken 4 hr after injection. Thallium-201 imaging was performed in the anterior, 45°–60° left anterior oblique (LAO) views, which were the same views as

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in ^{99m}Tc radionuclide ventriculography, and the left lateral view using a single crystal gamma scintillation camera (GCA-401, Toshiba) equipped with a middle-energy parallel-hole collimator. A 20% energy window centered at 80 keV was selected. Images were exposed in a 64 × 64 matrix format for 6 min for each view. Each view was divided into five segments for a total of 15 segments (Fig. 1). Small-size (4 × 4 pixels) regions of interest (ROIs) were placed within these 15 segments by operators (Fig. 2) and %^{201}Tl uptake was calculated from the formula:

$$\%\ \text{Tl uptake} = \frac{\text{Tl counts in segments with asynergy}}{\text{maximal Tl counts in normal segments}} \times 100.$$

In Figure 1, asynergic regions consisted of the anterior region of segments 2 and 9, the septal region of 6a and 6b, and the apical region of 3 and 10. The ROI size was appropriate for assessing ^{201}Tl uptake within the left ventricular myocardium as shown in Figure 2. The mean counts per pixel in ROIs ranged from 218 to 1028 in the normal segments and from 147 to 645 in segments with asynergy. Regional ^{201}Tl uptake in the anterior region was determined by the average of % uptake in segments 2 and 9. Septal ^{201}Tl uptake was an average of those in segments 6a and 6b and apical uptake was an average of those in segments 3 and 10. Redistribution was present when the regional ^{201}Tl uptake increased on the delayed image compared with the initial image more than 1 s.d. of regional ^{201}Tl uptake calculated from 12 normal subjects (Table 1).

Technetium-99m radionuclide ventriculography was performed 1 wk before and 1.5 mo after revascularization. Red blood cells were labeled in vivo after intravenous injection of about 740 MBq of ^{99m}Tc. Multiple-gated blood-pool scintigraphy was performed using the same gamma camera-collimator system as described for ^{201}Tl scintigraphy and a standard digital computer system (Shimadzu Scintipac 700). Data acquisition was made in an anterior view and a 45°–60° LAO view to provide optimal separation of left and right ventricles. A 20% window was used around the 140 keV gamma peak and a total of 5 to 8 million counts was exposed in a 64 × 64 matrix format with a 1.4× zoom. A commercially available automated variable edge detection program was used for the determination of left ventricular ejection fraction (LVEF). Segmental wall motion was interpreted by two experienced observers without knowledge of the clinical and angiographic findings by one display analysis. The anterior view was divided into the same five segments as those of the ^{201}Tl

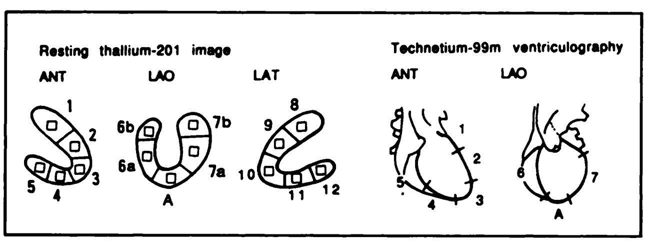

FIGURE 1. Schematic representation of left ventricular segments of ^{201}Tl image and ^{99m}Tc radionuclide ventriculography. ANT= anterior view, LAO = left anterior oblique, LAT = lateral view. Segments: 1 = basal anterior, 2 = anterior, 3 = apex, 4 = inferior, 5 = posterior, 6b = basal septum, 6a = apical septum, A = apical inferior, 7a = apical lateral, 7b = basal lateral, 8 = basal anterior, 9 = anterior, 10 = apex, 11 = inferior, 12 = posterior.

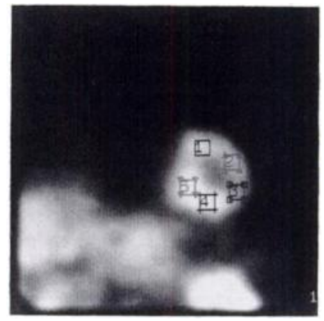

FIGURE 2. Placement of ROIs within left ventricular myocardium on ^{201}Tl image. ROIs (4 × 4 pixels) were placed within each segment.

image, and the LAO view was divided into segments 6, A, and 7 as shown in Figure 1. Segments 2, 3, and 6 correspond to anterior, apical, and septal regions, respectively. Left ventricular wall motion before revascularization was evaluated into five grades: normokinesis, hypokinesis, severe hypokinesis, akinesis, and dyskinesis. Change in regional wall motion was assessed by simultaneously viewing radionuclide ventriculography images before and after revascularization without knowing which study was post-revascularization. After assessing change in wall motion, regional wall motion after revascularization was classified into five grades.

Coronary arteriography was performed by the Judkins technique. The severity of a coronary artery stenosis was expressed as a percentage based on the American Heart Association classification (*21*).

Classification of Subjects

Only six patients had more than 5% improvement in global LVEF 1.5 mo after revascularization. Twenty-five regions, however, had improved wall motion. On the basis of resting ^{201}Tl scintigraphy and the change in asynergy, regions were divided into three groups. Group 1 consisted of 14 regions that exhibited resting ^{201}Tl redistribution. Thirty-seven regions without redistribution constituted Groups 2 and 3. Group 2 consisted of 14 regions in which wall motion abnormalities improved after revascularization. On the other hand, Group 3 consisted of 23 regions that had no improvement in wall motion abnormality in spite of revascularization.

Statistical Analysis

All data were expressed as the mean ± standard deviation. The non-paired Student's t-test and F-test were used to compare data among the groups. The paired t-test was performed to determine the statistical significance from the paired data. The chi-square test was used to determine the significance of the difference in the rate of occurrence. A probability (p) value of less than 0.05 was considered to be significant. Interobserver variability of re-

TABLE 1
Mean and Standard Deviation of Regional ^{201}Tl Uptake in Twelve Normal Subjects

	Mean ± s.d.
Anterior region	93.7 ± 5.5
Septal region	90.2 ± 4.4
Apical region	90.1 ± 6.0

gional ^{201}Tl uptake was calculated for 24 regions. The reproducibility of ^{201}Tl uptake was determined by re-scoring the thallium scans for 18 regions in three patients.

RESULTS

Observer Variability and Reproducibility of Regional ^{201}Tl Uptake

The interobserver variability of regional ^{201}Tl uptake for analysis of 24 regions from four patients was excellent (interobserver variability $r = 0.874$, $y = 0.97\times + 0.98$, Fig. 3). Studies of the reproducibility of regional ^{201}Tl uptake was performed in three patients within a 3-mo interval. Figure 4 demonstrated that determination of regional ^{201}Tl uptake in the same patient was reproducible ($r = 0.834$, $y = 0.99\times - 0.31$).

Change in LVEF and Hemodynamics

Six patients had improved global LVEF after revascularization (before: 41.3% ± 6.3% versus after: 53.8% ± 6.4%; $p < 0.01$). Four of the six patients had the regions with resting ^{201}Tl redistribution (Fig. 5). The LVEF of the other eleven patients did not improve significantly after revascularization (before: 34.6% ± 6.9% versus after: 34.1% ± 8.6%: n.s.). Three of these eleven patients had regions with resting ^{201}Tl redistribution and improved wall motion after revascularization. Systemic blood pressure and heart rate did not change in patients with and without improved ejection fraction (Table 2).

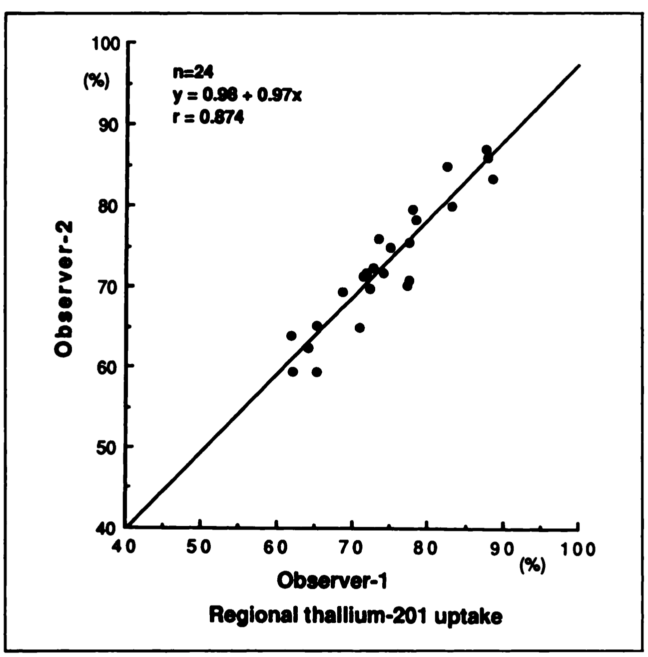

FIGURE 3. Interobsever variability in regional ^{201}Tl uptake from four patients. These data represent the result of analysis of 24 regions.

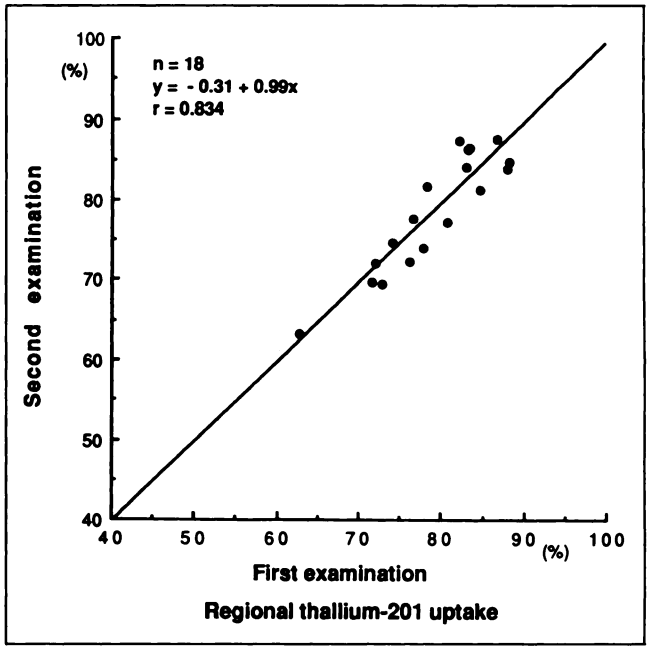

FIGURE 4. Reproducibility in regional ^{201}Tl uptake from three patients. Each was restudied twice within 3 mo. These data represent the result of analysis of 18 regions.

Change in Regional Wall Motion

Figure 6 shows changes in regional wall motion of the three groups. Eleven patients (78.6%) of Group 1 had improved wall motion after revascularization. As defined in classification of the groups, regional wall motion of Group 2 improved after revascularization, and that of Group 3 did not improve. The grade of wall motion abnormality before revascularization is shown in Table 3. The occurrence of dyskinesis or akinesis was more frequent in Group 3 than in the other two groups ($p < 0.05$). Most regions of Group 1 exhibited severe hypokinesis.

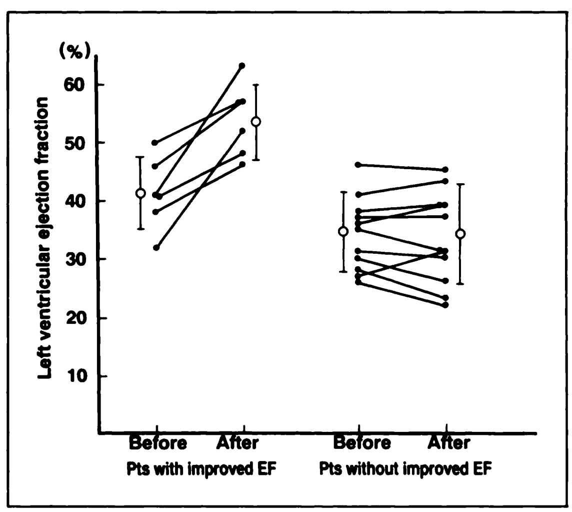

FIGURE 5. LVEF before and after revascularization. Six patients revealed improved ejection fraction more than 5% as shown in left side.

TABLE 2
Hemodynamics Before and After Revascularization

	Number		Systolic pressure	Diastolic pressure	Heart rate
Patients with improved EF	6	Before	132 ± 15	85 ± 5	76 ± 7
		After	134 ± 21	70 ± 9	79 ± 11
Patients without improved EF	11	Before	128 ± 14	77 ± 10	75 ± 7
		After	125 ± 16	80 ± 10	78 ± 8

Severity of Coronary Artery Stenosis and Collateral Flow

Table 4 shows the severity of coronary artery stenosis of the involved vessel and occurrence of collateral flow in each region. The severity of coronary artery stenosis was not different between the three groups. In addition, the occurrence of collateral flow did not differ between the three groups.

Comparison of Regional ^{201}Tl Uptake

Table 5 shows regional ^{201}Tl uptake on resting ^{201}Tl initial and delayed images in the three groups. Only in Group 1 did regional ^{201}Tl uptake increase from the initial to the delayed image ($p < 0.001$). The regional ^{201}Tl uptake on the delayed image was higher not only in Group 1 but also in Group 2 than in Group 3 ($p < 0.001$). Moreover, it is noteworthy that even on the initial image the regional ^{201}Tl uptake of both Group 1 and Group 2 was higher than that of Group 3 ($p < 0.05$). Interestingly, the initial regional ^{201}Tl uptake was highest in Group 2.

Case Presentation

A 70-yr-old man who suffered from acute myocardial infarction on April 4, 1989 came to our hospital for cardiac examination in November 1989. He did not complain of chest pain after his acute infarction. Electrocardiogram revealed poor R-wave progression on leads V1, V2 and V3. The treadmill test provoked significant ST depression on leads V4, V5 and V6, although he did not complain of chest pain. A rest-injected ^{201}Tl scan on February 3, 1990 revealed a perfusion defect on anteroseptal segments with incomplete redistribution (Fig. 7). On radionuclide ventriculography, segments 2, 3, and 6 exhibited severe hypokinesis and LVEF was 41%. Coronary arteriography on February 13, 1990 revealed complete obstruction of the LAD with collateral flow from the right coronary artery, which was treated successfully to 0% with PTCA. The radionuclide ventriculography 1.5 mo after PTCA showed improved wall motion and ejection fraction was 48% (Fig. 8).

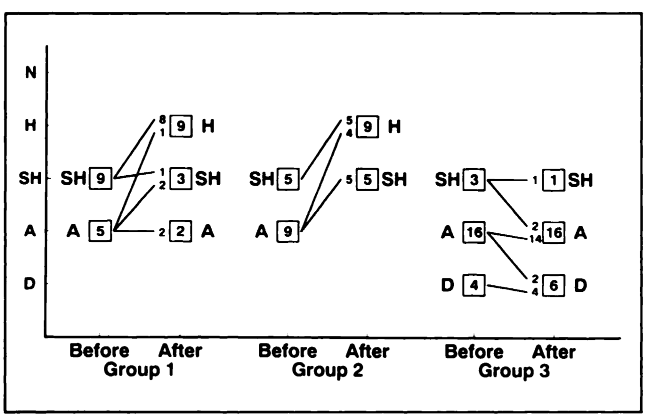

FIGURE 6. Comparison of segmental wall motion abnormality before and after revascularization between the three groups. N = normal wall motion, H = hypokinesis, SH = severe hypokinesis, A = akinesis, and D = dyskinesis.

DISCUSSION

Initial myocardial uptake of ^{201}Tl is known to depend on blood flow and myocardial extraction fraction, which was defined under physiologic conditions (*22–24*). Therefore, the initial uptake of ^{201}Tl is proportional to myocardial blood flow. In this study, patients with 99% or more stenosis of other coronary arteries were excluded. The intracellular accumulation of ^{201}Tl is caused by a passive transport mechanism by the transmembrane electropotential gradient (*25*). Consequently, myocardial uptake of ^{201}Tl is considered to mean the presence of viable muscle.

Beller et al. explained that ^{201}Tl redistribution in fixed coronary artery stenosis is the result of the slower intrinsic washout rate at a reduced perfusion level (*26, 27*). Berger et al. reported that resting ^{201}Tl redistribution was observed in regions with decreased blood flow at rest (*12*). In partially infarcted regions, however, ^{201}Tl redistribution may be related not only to the severity of coronary artery

TABLE 3
Wall Motion Grade Abnormality Before Revascularization in Each Patient Group

	Total	Severe hypokinesis	Akinesis	Dyskinesis
Group 1	14	9 (64.3%)	5 (35.7%)	0 (0%)
Group 2	14	5 (35.7%)	9 (64.3%)	0 (0%)
Group 3	23	3 (11.5%)	16 (69.6%)	4 (17.4%)
				$p < 0.05$

TABLE 4
Severity of Coronary Artery Stenosis and Occurrence of Collateral Flow in Each Patient Group

		Coronary artery stenosis				Collateral
	Total	100%	99%D	99%	90%	flow (+)
Group 1	14	7	6	1	0	7
Group 2	14	4	7	1	2	11
Group 3	23	7	11	4	1	19
						n.s.

stenosis but also to the presence of viable myocardium with depressed contractile function. "Hibernating myocardium," as described by Rahimtoola, refers to ischemic myocardium in which myocardial contraction is "down-regulated" in response to a long-standing, low-perfusion state which supplies sufficient nutrients for the myocardium to remain viable, but does not support myocardial contraction (*13,19,20*). Therefore, ^{201}Tl uptake in a rest-injected image, especially in the delayed image, might be useful for differentiating hibernating myocardium from scar.

Hibernating myocardium which occurred during ischemia is considered to possibly result in ventricular dysfunction that may last for months and possibly years. "Stunned myocardium," as described by Braunwald, refers to viable myocardium that has been salvaged by coronary reperfusion, yet exhibits prolonged but transient postischemic contractile dysfunction, lasting hours to weeks (*20,28*). In this study, left ventricular function after revascularization was assessed 1.5 mo after PTCA or CABG to determine whether left ventricular function reverted in the affected territory when perfusion was restored. However, some regions still might not improve 1.5 mo after revascularization because of hibernation with or without stunning.

In this study, some regions with severe asynergy exhibited improved contractile function 1.5 mo after myocardial blood flow was restored, as reported previously by many investigators (*13–16,29*). In most regions with rest-injected ^{201}Tl redistribution, myocardial function improved after revascularization. There was no difference in the severity of coronary artery stenosis and collateral flow

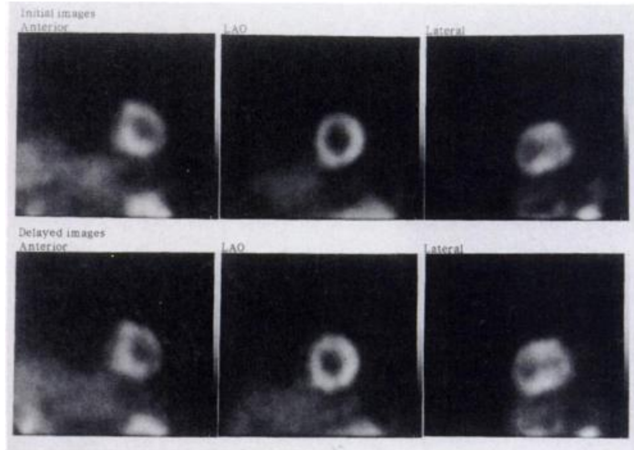

FIGURE 7. Resting ^{201}Tl scintigraphy of a case. A 70-yr-old man with prior myocardial infarction. The anterior and septal regions exhibited incomplete redistribution on delayed image.

between segments with and without rest-injected ^{201}Tl redistribution. Nevertheless, the severity of asynergy was milder in regions with rest-injected ^{201}Tl redistribution than in those without redistribution. Most regions with redistribution revealed severe hypokinesis, suggesting that rest-injected ^{201}Tl redistribution might be related to less loss of viable muscle (*30*). In these regions with redistribution, the decrease in ^{201}Tl uptake on the initial image was milder than in those of Group 3, suggesting that in regions with redistribution myocardial perfusion could be low, resulting in chronic regional dysfunction, but not low enough to cause tissue necrosis. Namely, these regions were under the condition of hibernating myocardium. The mechanism of rest-injected ^{201}Tl redistribution may be related to low myocardial perfusion associated with microvascular damage in incompletely infarcted regions.

It is particularly noteworthy that some regions without

TABLE 5
Comparison of Regional ^{201}Tl Uptake Between the Three Groups

	Initial image	Delayed image
Group 1	77.1% ± 7.2%*	85.1% ± 6.4%‡§
Group 2	83.5% ± 7.9%†‡	82.3% ± 7.1%‡
Group 3	71.8% ± 6.2%	71.2% ± 7.0%

* Versus Group 3, $p < 0.05$.
† Versus Group 3, $p < 0.001$.
‡ Versus Group 1, $p < 0.05$.
§ Versus initial image, $p < 0.01$.

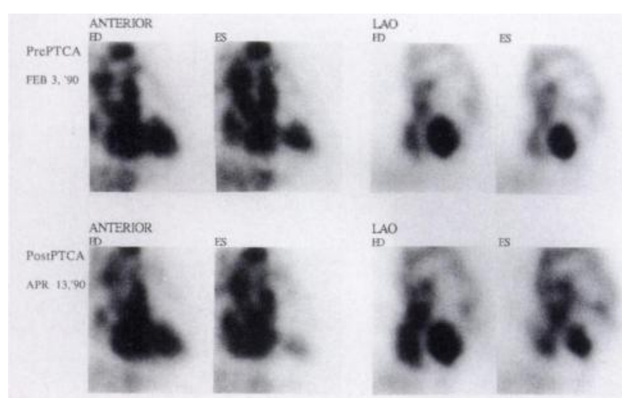

FIGURE 8. Technetium-99m radionuclide ventriculography of the patient shown in Figure 7. Segments 2, 3, and 6 with severe hypokinesis revealed improved wall motion after revascularization. The LVEF improved from 41% to 48%.

rest-injected ^{201}Tl redistribution, which had a higher ^{201}Tl uptake, exhibited improved myocardial function after revascularization. Tamaki et al. reported that in areas with a ^{201}Tl persistent defect, areas with an increase in ^{18}F-2-fluoro-deoxyglucose (FDG) uptake exhibited a milder decrease in ^{13}N-ammonia perfusion and milder wall motion abnormality than did areas without an increase in FDG uptake (*31*). The ^{13}N-ammonia distribution was proportional to myocardial perfusion (*32*). Therefore, the higher ^{201}Tl uptake in regions with improved wall motion without redistribution may indicate that their blood supply was not low enough to cause tissue necrosis. Accordingly, these regions may also represent hibernating myocardium. Failure of ^{201}Tl redistribution to occur in Group 2 may reflect the fact that perfusion defects were not as severe as those in Group 1. The prevalence of akinesis was, however, more frequent in Group 2 than in Group 1, suggesting that severe myocardial dysfunction in Group 2 might result from more viable muscle loss.

The prevalence of akinesis or dyskinesis was frequent and the regional ^{201}Tl uptake was lower in Group 3, which did not demonstrate any improvement. These findings indicate that regions in Group 3 had the most marked viable muscle loss. The standard deviation in the regional ^{201}Tl uptake was, however, large in all three groups and overlap in the distribution was great. First, it may be one of the reasons that left ventricular dysfunction due to hibernating myocardium with or without stunning may persist for a longer period than 1.5 mo when perfusion is restored. Second, it may be due in part to the resolution limits of ^{201}Tl imaging. Interobserver variability and reproducibility of regional ^{201}Tl uptake in our study was good but not perfect. However, this limitation may also reflect a general limitation of imaging that examines perfusion alone, and suggests the need for evaluating myocardial metabolism (*33,34*).

Clinical Implications

Myocardial function in regions with severe asynergy may revert in the affected territory when perfusion is restored. Our results indicate that rest-injected ^{201}Tl redistribution suggests the reversibility of severely asynergic myocardium, and that high ^{201}Tl uptake in regions without redistribution may predict improvement in myocardial dysfunction after revascularization.

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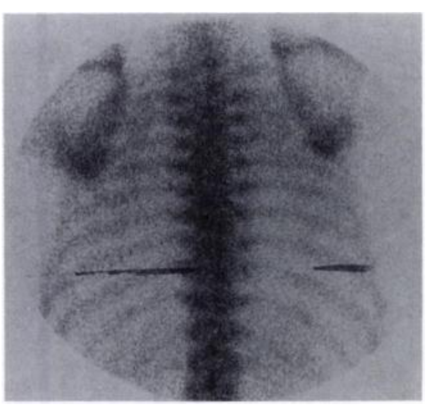
FIRST IMPRESSIONS

Anterior



Posterior

PURPOSE:
This 20-yr-old male patient was referred for bone scan evaluation of left ankle pain. Three-hour delayed images following intravenous injection of 20 mCi of ^{99m}Tc-MDP revealed serendipitous pectoralis muscle uptake of nuclide. Two days prior to imaging the patient experienced mild chest pain after bench pressing 200 lb for the first time following a long hiatus from the sport.

TRACER:
^{99m}Tc-MDP

ROUTE OF ADMINISTRATION:
Intraveneously

TIME AFTER INJECTION:
Three hours

INSTRUMENTATION:
Gamma camera

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