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Viable myocardium identified by reinjection thallium-201 imaging: Comparison with regional wall motion and metabolic activity on FDG-PET

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Summary

Reinjection thallium-201 scans were performed in 68 patients with coronary artery disease after the routine stress-delayed scans for more accurate identification of new fill-in. Following the stress and 3 hour delayed thallium-201 SPECT scans, 40 MBq (1.1 mCi) was injected at rest, and 10 min later, the reinjection SPECT scan was obtained. To determine whether the reinjection method can aid in identifying ischemic but viable myocardium, the thallium-201 findings were compared with regional wall motion on radionuclide ventriculography in 61 patients and with metabolic activity on positron emission tomography (PET) using F-18 fluorodeoxyglucose (FDG) in 18 patients. The reinjection scan identified new fill-in which had not been shown on the stress-delayed scans in 6 of the 22 patients (27%) or in 29 of the 105 segments (28%). Regional wall motion was preserved more in the segments that exhibited new fill-in after reinjection (wall motion score=1.64 ± 1.29) than in those without new fill-in (score=2.72 ± 1.04) ($p<0.01$). In the comparative study with FDG-PET, persistent FDG uptake

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was observed in all segments with new fill-in (20/20 segments: 100%); whereas, it was seen in only 7 of the 28 segments (25%) without new fill-in after reinjection ($p<0.05$). We concluded that the segments having new fill-in after reinjection may represent ischemic but viable myocardium. Thus, the reinjection thallium-201 scan should be performed to identify ischemic myocardium which occasionally cannot be detected by the routine stress-delayed thallium-201 scans.

Key words
Emission computed tomography | Thallium-201 | Ischemic heart disease | F-18 deoxyglucose

Introduction

Although stress thallium-201 myocardial imaging is valuable for differentiating reversible ischemic myocardium[1], it has limited value when the initially hypoperfused areas do not show the definite redistribution on the delayed scan[2,3]. Positron emission tomography (PET) using F-18 fluorodeoxyglucose (FDG) has also been used to identify metabolic viable myocardium[4-6]. Recent studies have suggested the continual presence of metabolic activity in some hypoperfused segments though redistribution is not shown on the routine stress and 2–4 hour delayed thallium-201 scan[7,8]. In an attempt to improve detection of reversible ischemia using the thallium-201 scan, the 24 hour delayed scan[9,10] or reinjection thallium-201 scan[11-14] has recently been employed. However, whether the segments showing new fill-in after reinjection represent ischemic but viable myocardium remains unknown. This study describes the usefulness of the reinjection thallium-201 scan compared with the evaluation of regional wall motion and metabolic activity using FDG-PET.

Methods

The reinjection thallium-201 scan was performed in 68 patients with initial perfusion abnormalities on the stress thallium-201 scan, of whom 18 patients were randomly selected for the FDG-PET study. There were 56 men and 12 women ranging in age from 40 to 75 years (mean=60.8). Forty-eight patients had prior myocardial infarction.

Each patient underwent graded bicycle exercise starting with 25 watts with increasing increments of 25 watts every 3 min. At peak exercise, 100 MBq (2.7 mCi) thallium-201 was injected and the exercise was continued for one more min. The stress thallium-201 scan was performed within 10 min after the tracer injection. Three hours later, the delayed thallium-201 scan was obtained. Immediately after the delayed scan, 40 MBq (1.1 mCi) thallium-201 was reinjected at rest (**Fig. 1**), and the reinjection thallium-201 scan was obtained 10 min later. For each thallium-201 scan, single-photon emission computed tomography (SPECT) was obtained, collecting 32 projection images, each of 30 sec, through 180 degrees[15-17]. A series of transaxial slices was reconstructed with a filtered back-projection without using attenuation correction. Oblique tomograms parallel to the long- and short-axes of the left ventricle were also reconstructed[15-17].

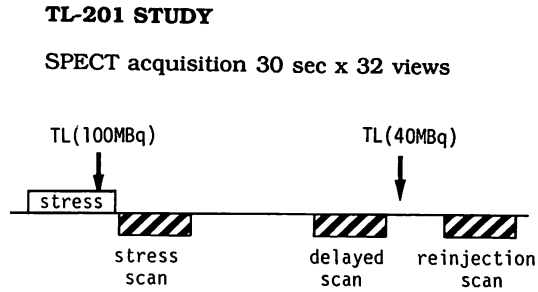

Fig. 1. Schematic time schedule of stress, delayed and reinjection scans.

The images of left ventricular myocardium were divided into 5 segments to assess the thallium-201 uptake for each SPECT. Two experienced observers scored the uptake using a 5-point grading system (0=normal, 1=equivocal, 2=mild, 3=moderate, and 4=severe re-

ductions) without the knowledge of the clinical or angiographic data. The segments with post-exercise scores of 2 or more were considered to have initial perfusion abnormalities. The segments with scores decreased by one or more on the delayed scan were considered to have redistribution. The segments with unchanged score on the delayed scan, but decreased on the reinjection scan, were considered to have new fill-in.

Regional wall motion was assessed by radionuclide ventriculography in 61 patients. Multigated blood pool scans were obtained in the anterior and left anterior oblique projections after the intravenous injection of 740 MBq (20 mCi) technetium-99m red blood cells. Two experienced observers reviewed the regional wall motion using a cine-mode display and scored it using a 5 point grading system (0= normokinesis to 4=dyskinesis).

PET was performed in 18 patients using a whole body, multislice positron camera (Positologica III, Hitachi Medical Co)[18]. Each patient was studied after fasting for at least 5 hours to maintain a steady state during the study. After proper positioning of a patient under the PET camera using ultrasound technique, a transmission scan was performed for 15 min for accurate correction of photon attenuation. Then, 80 to 300 MBq (2.2 to 8.1 mCi) FDG was injected at rest. Approximately 60 min later, a glucose metabolic scan was performed for 8–10 min, and the second scan was performed without delay in a position 8 mm caudad of the first scan. These 2 scans provided images of a total of 14 contiguous transverse slices of the myocardium at 8 mm intervals[19].

The N-13 ammonia perfusion study was performed separately within one week after the FDG study in 12 patients. Approximately 400 to 600 MBq (10.8 to 16.2 mCi) N-13 ammonia was injected at rest, and a resting perfusion scan was begun 3 min later. Two emission scans were obtained for 5 to 8 min each. From a series of transverse slices, oblique tomograms perpendicular to the long- and short-axes of the left ventricular myocardium were aslo reconstructed and compared with the thallium-201 imaging[19]. In the remaining 6 patients, thallium-201 images were used as references for perfusion images in relation to the FDG images.

Both N-13 ammonia and FDG uptakes in the myocardium were quantitatively measured and expressed as percent dose per 100 gram tissue. Perfusion and FDG uptakes were compared for the corresponding areas. The segments with normal perfusion were defined as PET normal. The hypoperfused segments with the FDG uptakes increased to above the lower normal limits were defined as PET ischemia. However, the hypoperfused segments with no FDG uptake or slight uptake below the lower limits were defined as PET scar[4-6].

Values were expressed as means±SD. Deviations in the wall motion scores were compared using the Student's t-test or analysis of variance (ANOVA). Comparisons of proportions were made using chi-square analysis or Fisher's exact test. Probability values less than 0.05 were considered significant.

Results

1. Reinjection thallium-201 findings

Among 68 patients, 44 had redistribution in at least one myocardial segment, while none of the remaining 22 patients had segments with redistribution. The reinjection thallium-201 scans demonstrated new fill-in in 6 of these 22 patients (27%).

Table 1. Thallium-201 SPECT findings in the 68 patients

Thallium findings			No. of segments
Stress	Delayed	Reinjection	
Normal	Normal	Normal	143
Reduced	RD	Fill-in	92
Reduced	No RD	New fiill-in	29
Reduced	No RD	No fill-in	76
Total			340

RD=redistribution.

Table 2. Thallium-201 SPECT findings in relation to regional wall motion in 61 patients who underwent radionuclide ventriculography

Thallium findings			n	Wall motion score					Mean±SD	
Stress	Delayed	Reinjection		0	1	2	3	4		
Normal	Normal	Normal	134	96	26	5	6	1	0.43±0.82	*
Reduced	RD	Fill-in	85	38	27	5	14	1	0.98±1.13	#
Reduced	No RD	New fill-in	25	5	9	4	4	3	1.64±1.29	*
Reduced	No RD	No fill-in	61	3	7	5	35	11	2.72±1.04	

* $p<0.01$; # $p<0.05$.
Wall motion score: 0=normokinesis; 1=hypokinesis; 2=severe hypokinesis; 3=akinesis; 4=dyskinesis.

Table 3. Thallium-201 SPECT findings in relation to FDG-PET ones in 18 patients

Thalllium findings			PET			Total
Stress	Delayed	Reinjection	Normal	Ischemia	Scar	
Normal	Normal	Normal	63	4	0	67
Reduced	RD	Fill-in	16	31	0	47
Reduced	No RD	New fill-in	1	19	0	20
Reduced	No RD	No fill-in	0	7	21	28
Total			80	61	21	162

Among a total of 340 myocardial segments studied, 197 had perfusion abnormalities on the initial thallium-201 scan, 92 of which had redistribution on the delayed scan. The reinjection thallium-201 scan showed new fill-in in 29 of the remaining 105 segments (28%), showing no redistribution (**Table 1**).

2. Relation with regional wall motion

Table 2 shows the relations of the thallium-201 findings to regional wall motion as assessed by radionuclide ventriculography in 61 patients. Regional wall motion abnormalities were observed in 171 segments. The mean wall motion score was 0.98±1.13 for the segments exhibiting redistribution on the delayed scan, 1.64±1.29 for the segments having new fill-in and 2.72±1.04 for those without new fill-in after reinjection. Thus, segments with new fill-in had more severe wall motion abnormalities than did those with redistribution ($p<0.05$), but they had less severe wall motion abnormalities than those without new fill-in ($p<0.01$). However, 7 of the 25 segments (28%) exhibiting new fill-in had akinesis or dyskinesis, indicating significant overlap of the severity of wall motion abnormalities between segments with and without new fill-in after reinjection.

3. Relation with FDG-PET

Table 3 shows the relationships of the thallium-201 findings to the FDG-PET ones. Of 95 hypoperfused segments, 47 had redistribution on the delayed scan, 20 had new fill-in, and the remaining 28 had no fill-in after reinjection. PET study identified PET normal in 80 segments, PET ischemia in 61 and PET scar in 21. All of those having redistribution on the delayed scan were either PET normal (16 segments) or PET ischemia (31 segments), indicating they were PET viable myocardium. Of the 20 segments having new fill-in after reinjection, one was PET normal, and the remaining 19 were PET ischemia. Thus, although

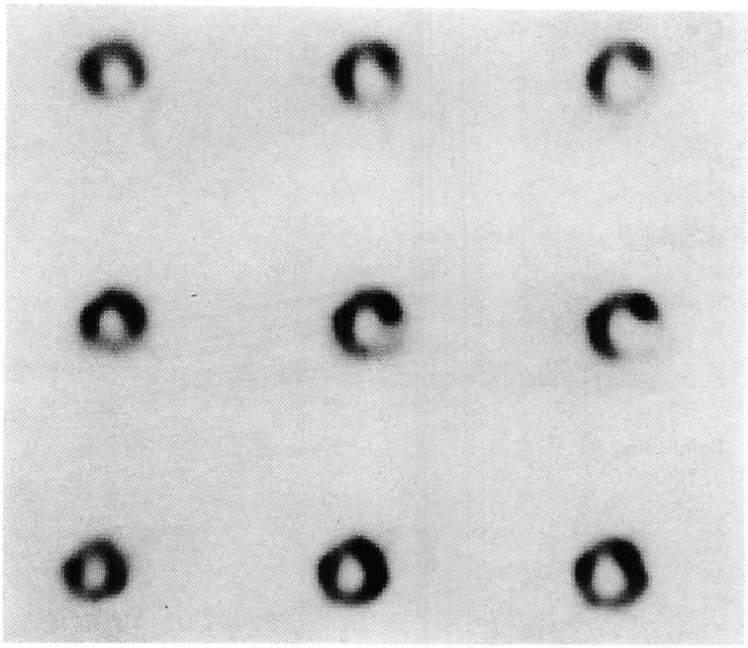

Fig. 2. Three representative short-axis slices of stress (top), **3 hour delayed** (middle) **and reinjection** (bottom) **thallium-201 SPECT images of a patient with inferior wall myocardial infarction.**

Initial perfusion defects in the inferior and posterolateral regions did not redistribute on the delayed images but filled in after reinjection.

PET ischemia was more frequently observed in the segments having new fill-in (95%) than in those having redistribution (66%) ($p<0.05$), both of which were categorized as PET viable myocardium. However, only 7 of the 28 segments (25%) having no fill-in after reinjection were PET ischemia ($p<0.01$).

4. Representative cases

Fig. 2 illustrates a 73-year-old man who developed inferior wall myocardial infarction 4 months previously. His coronary angiogram showed 100% occlusion of the right coronary and left circumflex arteries and 75% stenosis of the first diagonal branch. The stress thallium-201 short-axis images showed perfusion defects in the inferior and posterolateral regions with mild hypoperfusion in the anterior region. The delayed images showed redistribution in the anterior region, but no redistribution in the remaining areas. The reinjection scan, however, demonstrated definite fill-in in the inferior and posterolateral regions. In this case, the fill-in of thallium-201 was demonstrated only after reinjection.

Fig. 3 illustrates a 59-year-old woman with a history of anterior wall myocardial infarction. Her coronary angiograms showed 90% stenosis in the right coronary artery, 99% stenosis in the proximal left anterior descending artery, and 75% stenosis in the left circumflex artery. The stress thallium-201 short-axis images showed hypoperfusion in the anterior, septal and inferior regions. The delayed images did not show definite redistribution except for slight redistribution in the septal region. The reinjection scan showed new fill-in in the anterior and inferior regions. **Fig. 4** shows N-13 ammonia and FDG short-axis images of the same patients. Diffuse uptake of FDG was observed in the anterior, septal and inferior re-

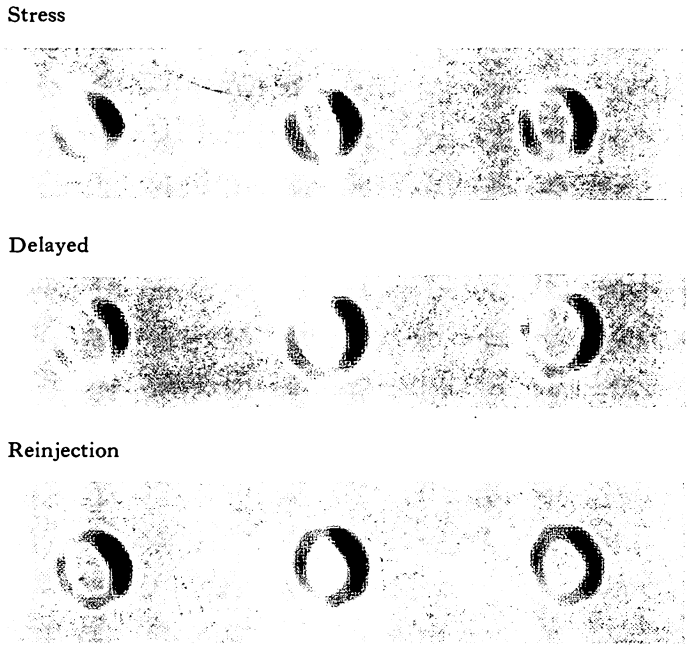

Fig. 3. Three representative short-axis slices of stress (top), **delayed** (middle) **and reinjection** (bottom) **thallium-201 SPECT images of a patient with anterior wall myocardial infarction.**

Stress scan shows hypoperfusion in the anterior, septal and inferior regions, where no definite redistribution is observed, except for slight redistribution in the septal region. The reinjection scan shows definite fill-in in these areas.

gions, indicating the presence of metabolic activity in these areas where new fill-in was observed on the reinjection thallium-201 scan.

Fig. 5 illustrates a 56-year-old man with a history of anterior wall myocardial infarction. His coronary angiograms showed 100% occlusion of his left anterior descending artery. Stress thallium-201 images showed a large perfusion defect in the anterior and septal regions. No definite fill-in was observed on either the delayed or reinjection scans. In this case, no evidence of myocardial ischemia was obtained.

Discussion

These data indicate that the reinjection thallium-201 scan may aid in identifying ischemic but viable myocardium which is often missed on routine stress and delayed scans. The segment with persistent defects without redistribution but with new fill-in after reinjection may be attributed to reversible ischemic myocardium. They are more likely to have preserved wall motion and persistent metabolic activity than those without new fill-in even after reinjection.

Rocco et al[11] and Dilsizian et al[12] first proposed the reinjection of thallium-201 after delayed scan for enhanced detection of new fill-in in the areas of persistent defects on the delayed scan. Our study also demonstrated that the reinjection identified new fill-in in approximately 30% of the segments without redistribution on the delayed scan. These segments had less severe wall motion abnormalities than did those without new fill-in, even after reinjection, suggesting that these areas may be less severely damaged and perhaps viable myocardium. The

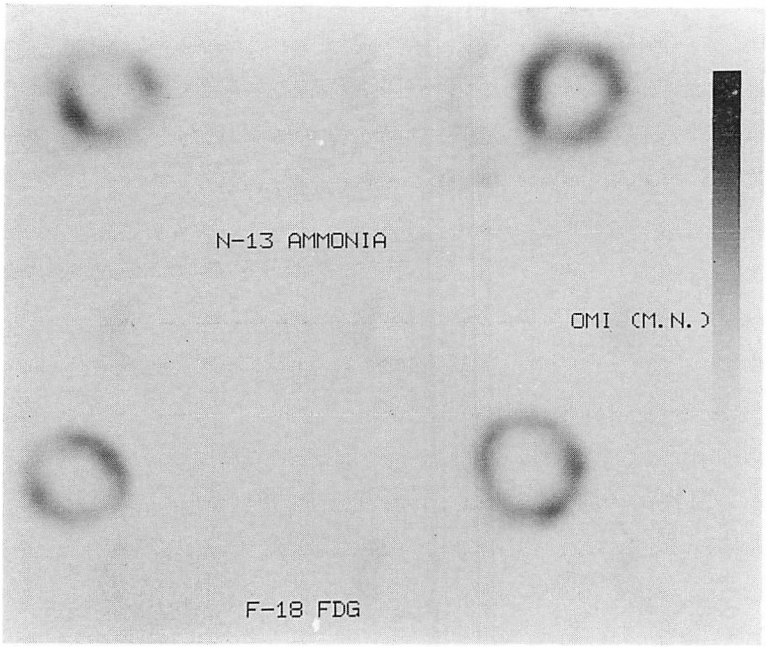

Fig. 4. Two representative short-axis slices of N-13 ammonia perfusion and FDG-PET images of the same patient as Fig. 4.

Note diffuse uptake of FDG in the anterior, septal and inferior regions.

results of the present study supported the results of our preliminary study[14] that the segments having new fill-in after reinjection had more severe wall motion abnormalities than did those with redistribution, but less severe ones than did those without new fill-in, even after reinjection. Although the severity of wall motion abnormalities may be a significant factor in identifying ischemic but viable myocardium, there may be a considerable overlap of the severity between the ischemic and infarcted myocardium, as is shown in **Table 2**.

The experimental and clinical PET studies indicated a correlation of persistent FDG uptake with the presence of viable myocardium[5,6,20,21]. Sochor et al[20] showed preservation of metabolic activity in association with the histologic presence of significant amounts of residual viable myocardium in a canine study. The clinical studies by Tillisch et al[5] and by our group[6] both indicated that myocardial segments with metabolic activity, which are likely to improve regional function after coronary bypass surgery, seem to be reversible ischemic myocardium. Therefore, it seemed important to compare the reinjection thallium-201 findings with the FDG-PET ones, and thereby determine whether the segments having new fill-in after reinjection truly represent persistent metabolic activity

In this study, the segments having new fill-in after reinjection were mainly PET ischemic myocardium with increased FDG uptake, indicating that metabolic activity was preserved in the myocardium. Bonow et al[22] in his preliminary study also indicated close correlations of reinjection thallium-201 findings with FDG accumulation.

Furthermore, Ohtani et al[13] and Dilsizian et al[12] recently reported that the segments having new fill-in after reinjection are very likely to improve in regional function after restoration of blood flow. This finding indicated that such segments are reversible ischemic myocar-

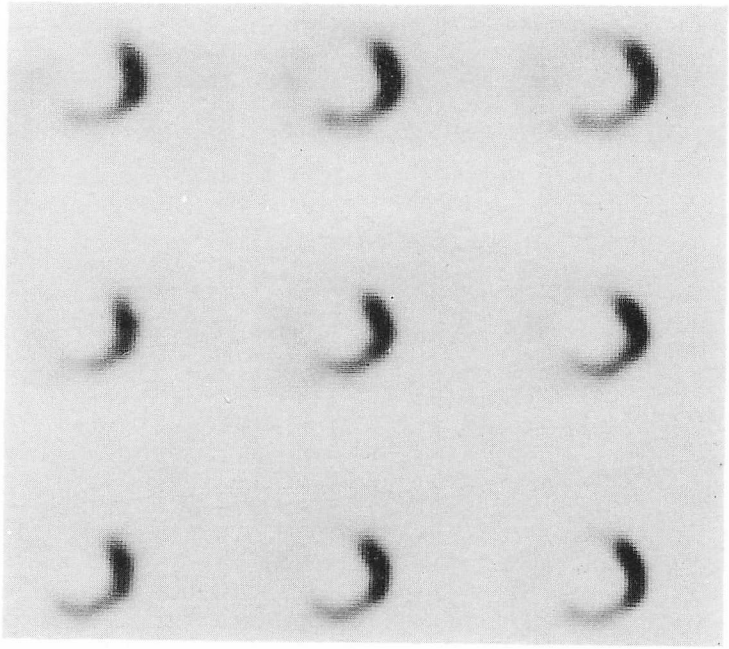

Fig. 5. Three representative short-axis slices of stress (top)**, delayed** (middle) **and reinjection** (bottom) **thallium-201 SPECT images of a patient with anterior wall myocardial infarction.**

No redistribution or fill-in is noted on the delayed or reinjection scans.

dium. However, the precise mechanism of this new fill-in remains unclear. The reinjection thallium-201 imaging provides more quality images with acceptable counts than do the delayed images, thus enhancing the detection of fill-in of thallium-201, as illustrated in **Fig. 3.** Two separate injections of perfusion tracers at rest and during exercise showed reversible ischemia more often than did the stress and delayed imagings with a single tracer injection[23-25]. Therefore, reinjection may be of help in resolving some perfusion abnormalities better than a single injection.

Redistribution also depends on the plasma concentration of the tracer. Low plasma thallium-201 concentration after injection during exercise often denotes a lack of redistribution in the ischemic myocardium[26]. Thus, reinjection of a small amount of thallium-201 after a delayed scan is considered reasonable to enhance the detection of new fill-in in the ischemic myocardium.

In the ischemic segments without redistribution, blood is supplied mostly via severely stenotic vessels[2,3]. In cases of severe coronary stenosis, the tracer delivery to the ischemic tissue may be severely prolonged due to a loss of post-stress hyperemia or resting hypoperfusion. Therefore, the routinely-performed 3 to 4 hour delayed scan may not give enough time to achieve equilibrium of the tracer in the potassium pool, and thus may not produce redistribution. In this respect, the reinjection of thallium-201 or a 24 hour delayed scan[9,10] may be of help in achieving this state of equilibrium, thereby identifying new fill-in of the tracer in the severely ischemic myocardium.

The reinjection method is easy to perform and the entire study can be completed within 4 to 5 hours, making it particularly useful for application in out-patients. Although reinjection requires a third set of images and it may be

disruptive during a busy imaging schedule, a fast computer with simultaneous data acquisition and processing may minimize these disadvantages.

We concluded that the reinjection thallium-201 scan should be performed when the routine stress and delayed scans showed persistent defects without redistribution. The segments having new fill-in after reinjection may be attributed to viable metabolic myocardium.

要　約

^{201}Tl 再静注法による虚血心筋の検出：壁運動および FDG-PET による心筋代謝との対比検討

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^{201}Tl による再分布をより明瞭にするため，虚血性心疾患68例に，通常の運動負荷 ^{201}Tl 心筋シンチグラフィーの直後に ^{201}Tl を再静注する手法を試みた．再静注は運動負荷 SPECT および3時間後の SPECT 撮像後 40 MBq (1.1 mCi) の ^{201}Tl を安静時に投与し，10分後より再静注 SPECT を行なった．再静注法がはたして蘇生可能な虚血心筋を正しく同定しているか否かをみるために，61例には心プールスキャンより求めた局所壁運動との対比を，18例には FDG を用いたポジトロン CT による局所の代謝の有無との対比を各々行なった．

通常の ^{201}Tl スキャンでは再分布のみられなかった22例中6例(27%)，105区域中29区域(28%)で，再静注により分布の改善がみられた．局所壁運動は，再静注により分布の改善した領域が，改善しない領域よりも保たれていた(壁運動スコア：1.64±1.29 vs 2.72±1.04) ($p<0.01$)．一方，ポジトロン CT による検討では，再静注により分布の改善した領域は，既に再分布のみられた領域と同様，すべて代謝の残存した蘇生可能な心筋であったのに対し，再静注でも改善しなかった領域では28区域中，蘇生可能と判定されたのはわずかに7区域(25%)のみであった ($p<0.05$)．

以上より，再分布がなくても再静注により分布の改善する領域は，蘇生可能な虚血心筋であることが示唆された．本法は通常の ^{201}Tl 心筋スキャンでは判定しきれない虚血心筋を同定する上で，試みられるべき手法と考えられる．

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