Positron Emission Tomography

— Usefulness in assessing myocardial viability —

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Positron emission tomography (PET) using N-13 ammonia and F-18 fluorodeoxyglucose (FDG) has been used to evaluate myocardial viability in comparison with thallium-201 single photon emission computed tomography (SPECT), and left ventricular wall motion in comparison with contrast ventriculography. Forty patients with anterior myocardial infarction underwent stress and delayed resting perfusion imaging using Tl-201 SPECT and ammonia PET, a glucose metabolism study using FDG PET, and wall motion assessment with left ventriculography. Out of a total of 600 segments of left ventricular imaging, SPECT demonstrated 197 fixed perfusion defects, 99 with redistribution on delayed imaging and 304 normal segments. Of 197 segments with fixed defects, 24 (12%) were normal and 71 (36%) ischemic according to PET criteria. Nineteen of 28 with infarction and all of 12 with non-Q wave infarction showed a viable myocardium. Left ventricular wall motion was significantly better in patients with normal PET findings compared with those with ischemia or scar on PET. Post-PTCA PET revealed improved ammonia PET in 6 of 11 patients but reduced FDG uptake was noted only in 3. These data suggests that Tl-201 SPECT significantly underestimates myocardial viability and that PET imaging is a promising tool for assessing the presence of salvaged myocardium.

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MYOCARDIAL infarction has been diagnosed clinically by electrocardiographic changes and enzymatic changes. Thallium-201 myocardial perfusion imaging has been used, and is valuable in the assessment of myocardial infarction^{1,2}. Exercise loading with delayed imaging is often undertaken to differentiate reversible ischemic myocardium from infarction. However, because of inherent limitations of poor resolution and relatively inadequate counts, this

technique may not be suitable for assessing subtle changes in myocardial perfusion³.

Positron emission tomography (PET), on the other hand, enables precise evaluation of regional myocardial blood flow and metabolism in vivo^{4–11}. Our previous studies^{3,12} using high resolution PET with N-13 ammonia demonstrated high diagnostic accuracy for detecting coronary artery disease. Previous results^{10,11,13,14} have also shown an increased uptake in F-18 labeled fluorodeoxyglucose (FDG), a glucose analogue, relative to blood flow in the ischemic but viable myocardium in patients with myocardial infarction. The purpose of this study is to demonstrate sig-

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TABLE I CORRELATION OF SEGMENTAL FINDINGS OF SPECT WITH THOSE OF PET

SPECT	PET			
	Normal	Ischemic	Scar	Total
Normal	280 (92.1)	14 (4.6)	10 (3.3)	304 (100)
Redistributed	16 (16.2)	77 (77.8)	6 (6.1)	99 (100)
Fixed	24 (12.2)	71 (36.0)	102 (51.8)	197 (100)
Total	320 (53.3)	162 (27.0)	118 (19.7)	600 segments

nificance of PET in assessing myocardial viability in comparison with Tl-201 single photon emission computed tomography (SPECT) and regional wall motion studies.

METHODS

Study patients

Forty patients (36 men and 4 women) with anterior myocardial infarction determined by electrocardiographic and enzymatic criteria were studied. Eight patients also had inferior myocardial infarction. Twenty-eight patients had Q wave infarction, and 12 non-Q wave infarction.

Tl-201 SPECT

Each patient underwent bicycle exercise in sitting position starting from 25 watt with a 25-watt increment every 3 min. At peak exercise 100 MBq Tl-201 was injected and the exercise continued for 1 more min. Stress Tl-201 SPECT was begun within 10 min after the tracer injection. Three hours later, delayed imaging was performed. In each Tl-201 scan, SPECT was acquired by collecting 32 projection images with 30 sec each over 180 degrees. A series of transverse slices were reconstructed with a filtered back-projection without using attenuation correction.

Positron emission tomography (PET)

PET was performed with a whole body, multi-slice positron camera (Positogica III, Hitachi Medical Co.). Each patient was studied after fasting for more than 5 h before the study. After accurate positioning of the patients under the PET camera using an ultrasound technique, a transmission scan was obtained for 15 min for attenuation correction. Then, 80 to 300 MBq of FDG was injected at rest. Approximately 60 min later,

FDG scanning was undertaken for 8–10 min. Immediately after the first scan, the second scanning was carried out in a position 8 mm caudal to the first scan. These 2 scans provide a total of 14 contiguous transverse slices of the myocardium with an 8 mm interval.

The N-13 ammonia perfusion study was performed separately within 2 weeks of the FDG study. Approximately 400–600 MBq of N-13 ammonia was injected, and 2 emission scans were obtained for 5 and 8 min, successively. Two hours after the resting study, a repeat study was carried out with exercise loading. Symptom-limited submaximal multi-stage exercise testing was performed using a supine ergometer attached to a bed of the PET camera with a 25-watt increment every 3 min, with an initial 25 watt work load. Thirty seconds before termination of exercise, N-13 ammonia was injected intravenously, and tomographic scanning was performed in the same way as in the resting state.

Regional wall motion

Regional wall motion at rest was assessed by contrast left ventriculography performed within 3 weeks of the PET study. The left ventricle was divided into 3 segments (the septum, apex and lateral wall). Two experienced observers scored regional wall motion using a 4-point grading system (2=normal, 1=hypokinesis, 0=dyskinesis) without knowledge of clinical or scintigraphic data.

Image analysis

The left ventricular myocardium was divided into 5 segments to assess Tl-201 SPECT and PET. Two experienced observers scored the Tl-201 uptake using a 5-point grading system (0=normal, 1=equivocal, 2=mild, 3=moderate, and 4=severe reduc-

TABLE II CORRELATION OF Q AND NON-Q WAVE INFARCTION WITH PET FINDINGS (NUMBER OF CASES)

PET	QMI (28)	Non-QMI (12)
Normal	0	1
Ischemia	19*	11**
Scar	9	0

Defect at rest *: 19, **: 5 cases

TABLE III CORRELATION BETWEEN PET FINDINGS AND WALL MOTION SCORES

PET	No of Seg	Wall Motion Score (at rest)
Normal	70	1.53 ± 0.70
Ischemia	33	$0.62 \pm 0.79^*$
Scar	17	$0.31 \pm 0.65^*$

3 Segs/pt; Nor: 2, Hypo: 1, Akin: 0, Dys: -1,
* $p < 0.01$

tion) without knowledge of clinical or angiographic data. When a myocardial segment showed a post-exercise score of 2 or more, the initial perfusion abnormality was considered present. When the score decreased one or more on the delayed scan, the segment was considered to be redistributed.

N-13 ammonia and FDG uptakes in the myocardium were quantitatively measured and displayed as percentage dose per 100 g tissue. Ammonia uptake for myocardial perfusion and FDG uptake for glucose utilization were compared at the corresponding areas. The segments with normal perfusion were defined as PET normal. The hypoperfused segments with increased FDG uptake above the lower limits of the normal values in individual segments were defined as PET ischemia. On the other hand, the hypoperfused segments with no FDG uptake or slight uptake below the normal limits were defined as PET scar.

Statistical analysis

Values were shown as mean $\pm$ standard deviation. Differences in wall motion score

TABLE IV EFFECTS OF PTCA ON PET IMAGING

	Improved FDG	Unimproved FDG	Total
Improved NH_3	3	3	6
Unimproved NH_3	0	5	5
Total	3	8	11
MI to PTCA	av 3.0 mo	av 12.9 mo	

were compared with Student's t-test or analysis of variance. Comparison of proportions were performed by way of Chi-square analysis or Fisher's exact test. Probability values < 0.05 were considered significant.

RESULTS

SPECT vs PET

Three contiguous slices of Tl-201 SPECT and PET in the middle of the heart were selected from each patient, and each slice was divided into 5 segments. SPECT illustrated 304 normal segments (50.6%), 99 segments with redistribution (16.5%), and 197 with fixed defects (32.8%), as shown in Table I. Out of 304 normal segments by SPECT, 280 (92%) were normal, 14 (5%) ischemic and 10 (3%) scarred by PET. Of 99 segments with redistribution by SPECT, 77 (78%) were ischemic, 16 (16%) normal and 6 (6%) scarred by PET. Of 197 segments with fixed defects on SPECT, 102 (52%) were scarred, 24 (12%) normal and 71 (36%) ischemic. Thus, 459 out of 600 segments (77%) were identified as concordant between SPECT and PET, but 30 segments (5%) were underestimated and 111 segments (19%) were overestimated by SPECT. In fact, 48% of 197 segments judged as fixed perfusion defects by SPECT were observed normal or ischemic on PET.

Q wave and non-Q wave infarction

Of 40 patients, 8 had Q wave infarction and 12 had non-Q wave infarction on electrocardiograms (Table II). All patients with Q wave infarction had a perfusion abnormality on PET, which showed as scar in only 9 patients and ischemia in 19. PET imaging in patients with non-Q wave infarction demonstrated perfusion abnormality at rest in 5 pa-

tients, and ischemia on exercise in 11 including the above 5. One patient was normal in both resting and exercise PET. Therefore, all patients with non-Q wave infarction were revealed to have viable myocardium, and at least half of the patients with Q wave infarction were also found to have residual myocardium in infarcted areas.

PET findings and left ventricular wall motion

Visual assessment of wall motion by left ventriculography, which was undertaken within 3 weeks of PET study, demonstrated significantly better regional wall motion in normal segments on PET imaging (1.53 ± 0.70 vs 0.62 ± 0.79 and 0.31 ± 0.65 in regions with PET-ischemic and PET-scar, respectively; $p < 0.01$ in both) (Table III). Thus, PET imaging demonstrates a good correlation with resting regional wall motion.

Effects of percutaneous transluminal coronary angioplasty (PTCA) on PET imaging

Eleven patients with Q wave infarction underwent PTCA (Table IV). All PTCA was successful, but perfusion PET with N-13 ammonia demonstrated improvement in 6 patients, of which 3 improved in FDG imaging with disappearance of focal uptake; 3 did not. All patients who failed to show an improvement in perfusion PET did not improve in FDG PET. The interval between acute myocardial infarction and PTCA procedure was shorter in patients with improved FDG finding (average 3.0 months) than those without (average 12.9 months). Other parameters such as location or size of infarction, degree of coronary stenosis before and after PTCA did not appear to play a significant role, and none of the patients had diabetes mellitus.

DISCUSSION

The present PET study demonstrated that metabolic activity in the myocardium was observed in 48% of the segments with fixed perfusion defect on Tl-201 SPECT. Therefore, it is quite important to differentiate between the ischemic but viable myocardial tissue and the irreversible infarcted myocardium.

Thallium-201 vs PET

Analysis of Tl-201 redistribution has been considered to be useful for detection of ischemic but viable myocardium.¹⁵ The initial Tl-201 defect that persists with time is considered to represent the nonviable infarcted myocardium, whereas reduced initial Tl-201 uptake that redistributes in delayed images represents the viable myocardium. However, recent reports describe significant improvements in perfusion and cardiac function after coronary bypass surgery or angioplasty in some regions with a fixed perfusion defect on a preoperative Tl-201 scan.^{16,17} Brunken et al¹⁸ using the planar Tl-201 scintigraphy, and our recent data¹² using Tl-201 SPECT, showed similar findings in the comparative study of Tl-201 with FDG PET imaging. These data suggest that the routinely performed 3 to 4h delayed scan may not be late enough in interval to show equilibrium of the tracer in the potassium pool and thus, it may not show redistribution. In this respect, the reinjection of Tl-201¹⁹⁻²¹ or a 24h delayed scan^{22,23} may help the equilibrium state to be reached identifying new fill-in of the tracer in the severely ischemic myocardium.

FDG was used as a tracer of exogenous glucose utilization in the myocardium. In this study, all patients underwent tomographic imaging in a fasting condition to enhance glucose utilization in the ischemic myocardium. In the normal myocardium free fatty acids are preferentially utilized and glucose tends to be suppressed,^{10,24} resulting in low FDG uptake, while in the hypoperfused myocardium higher uptake of FDG is noted. Our method was indispensable in the current study to visualize regionally enhanced FDG uptake even in the absence of blood flow abnormalities.

Q and non-Q wave infarction

More than half of the patients with Q wave infarction and all except one with non-Q wave infarction revealed regional uptake of FDG. The patients with non-Q wave infarction and no regional FDG uptake had normal perfusion PET and good wall motion, and it is likely that a substantial amount of myocardium was salvaged in the infarcted area.

PET findings and wall motion

Although there may be a significant overlap of wall motion between the ischemic and the infarcted myocardium, segments with increased uptake of FDG in the infarcted regions exhibited less severe wall motion abnormality than those without increased FDG uptake, suggesting that the areas with increased FDG uptake may be less severely damaged and perhaps viable.

The experimental and clinical PET studies indicated the correlation of persistent FDG uptake with the presence of viable myocardium.^{11,13,26} Sochor et al²⁵ showed the preservation of metabolic activity in association with the histologic presence of significant amount of the residual viable myocardium in the canine study. Schwaiger et al²⁷ have demonstrated that segments with maintained glucose utilization in patients with acute myocardial infarction showed improved wall motion in the chronic state, although there were large variations. These data indicate that maintained glucose utilization appears to identify compromised but salvageable tissue that is difficult to recognize by conventional methods.

PTCA and PET

The perfusion images of the patients after PTCA revealed improvement in regional myocardial blood flow at rest and during exercise in the anterior region as compared with the pre-PTCA images. The clinical studies by Tillisch et al¹¹ and by our group¹³ indicated that patients with metabolic activity are likely to improve in regional function after coronary bypass surgery.

The sustained regional increase of FDG after PTCA cannot be explained simply by ischemia at rest in itself. We suggest 2 possible mechanisms of increased FDG uptake after PTCA in "infarcted" areas. First, stress perfusion studies may reveal hypoperfusion in the corresponding infarcted area. In this regard, although FDG imaging was carried out at rest, its regional uptake might reflect the presence of "stunned" myocardium²⁸ caused by repeated episodes of exercise-induced "silent" ischemia due to the patient's daily activity. Camici et al²⁹ recently found enhanced uptake of FDG after exercise in regions of a stress-induced rubidium-82 perfusion defect in patients with typical

angina. Second, we³⁰ and others²⁶ have demonstrated that there is a "time lag" phenomenon between recovery of myocardial blood flow and recovery of metabolism in the ischemic myocardium. This "time lag" phenomenon has important clinical implications; that is, it must be taken into account when evaluating the effects of myocardial revascularization on myocardial metabolism in an infarcted region. Importantly, restoration of coronary blood flow in the infarcted area does not necessarily guarantee the normalization of myocardial metabolism in the same region.

Limitations of study

SPECT, which provides cardiac short-axis and long-axis section of the heart, enables a superior 3-dimensional assessment of myocardial perfusion, while PET usually provides only transverse slices of the myocardium. Recent advances in computer software will enable reconstruction of oblique-angle tomograms perpendicular to the cardiac axes in PET as well.³¹

There is no anatomic data available in this study. This lack of pathologic data as "an absolute criterion" has made it impossible to establish positron tomographic criteria for assessment of the viable myocardium in infarcted regions.

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