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Thallium-201 reinjection images can identify the viable and necrotic myocardium similarly to metabolic imaging with glucose loading ^{18}F-fluorodeoxyglucose (^{18}FDG)-PET

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We compared the usefulness of ^{18}F-fluorodeoxyglucose (^{18}FDG)-PET with glucose loading and thallium-201 (^{201}Tl) reinjection imaging for determining the viability of the myocardium in 21 patients with an old anterior myocardial infarction. We obtained transaxial views during ^{201}Tl reinjection imaging performed 10 minutes after post-exercise injection of 37 MBq ^{201}Tl. PET imaging with 75 g oral glucose loading was performed 60 min after injection of 148 MBq of ^{18}FDG. Wall motion was evaluated by echocardiography. Excellent ^{18}FDG-PET images were obtained in 19 of 21 subjects in whom plasma glucose levels were below 251 mg/d*l*. The results of ^{201}Tl reinjection imaging and ^{18}FDG-PET imaging were in agreement in 20 of the 21 subjects. Echocardiography demonstrated hypokinesis or akinesis in segments identified as abnormal in imaging studies. Our results showed that ^{201}Tl reinjection imaging identified the viable and necrotic myocardium similarly to metabolic imaging obtained by ^{18}FDG-PET with glucose loading.

Key words: myocardial infarction, myocardial viability, ^{201}Tl reinjection, positron emission tomography, ^{18}FDG

INTRODUCTION

IDENTIFICATION of the viable and necrotic myocardium is important for clinical and therapeutic decisions. The viability of the myocardium has been assessed in terms of coronary artery patency and preserved regional contractile function, but when certain conditions are present, such as hibernating myocardium or stunned myocardium, the prolonged regional left ventricular dysfunction may be completely reversible.[1,2]

Myocardial imaging with thallium-201 chloride (^{201}Tl) can be used to evaluate myocardial viability on the basis of myocardial perfusion, and cell membrane integrity. However, 4-hour ^{201}Tl redistribution images have been found to underestimate myocardial viability in patients with coronary artery disease (CAD).[3] Previous studies found that 31 to 52% of persistent defects identified by ^{201}Tl redistribution images exhibited normal perfusion after revascularization on reinjection images.[4–7] Recently, positron emission tomography with glucose analog ^{18}F-deoxyglucose (^{18}FDG-PET) during fasting has been used in evaluating the metabolic tissue activity in patients who have an indication for revascularization. Previous studies comparing the results of ^{18}FDG-PET with ^{201}Tl imaging found that ^{18}FDG-PET during fasting identified myocardial viability in 25 to 50% of myocardial segments that showed fixed early defects on ^{201}Tl images.[8–10] However, it has been pointed out that ^{18}FDG-PET during fasting might overestimate the myocardial viability.[11,12]

We compared the usefulness of ^{18}FDG-PET with glucose loading and ^{201}Tl reinjection imaging in determining the viability of the myocardium in 21 patients with an old anterior myocardial infarction.

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MATERIALS AND METHODS

Subjects

We studied 21 subjects (19 men and 2 women, average age: 61.6 ± 9.0 years) with coronary artery disease diagnosed by coronary angiography (Table 1). All subjects had been treated for myocardial infarction. Angina pectoris was identified in 19 subjects. Fourteen subjects had Q

Table 1 Clinical characteristics

Case	Age	Sex	ECG	MI lesion	AP	DM	CHF	CAG	LVEF	WM	Tl reinjection	Fill in	FDG PET	BS 1 hr
1	59	M	Q	ant	(+)	(−)	(−)	LAD	51	akinesis	reduced	(+)	reduced	143
2	42	M	Q	ant, inf	(−)	(−)	(+)	LAD, LCX, RCA	22	akinesis	defect	(−)	defect	172
3	59	M	non-Q	ant	(+)	(−)	(−)	LAD, LCX, RCA	71	normal	normal	(+)	normal	132
4	62	M	non-Q	ant	(+)	(+)	(+)	LAD, LCX, RCA	34	hypokinesis	defect	(−)	defect	444
5	68	F	Q	ant, lat	(+)	(+)	(−)	LAD, RCA	47	akinesis	defect	(−)	defect	149
6	56	M	Q	ant, inf	(+)	(−)	(−)	LAD, LCX, RCA	42	akinesis	defect	(−)	defect	119
7	62	M	Q	ant	(+)	(−)	(−)	LAD, LCX	70	hypokinesis	reduced	(+)	reduced	187
8	50	M	Q	ant,inf	(+)	(−)	(−)	LAD, LCX	37	akinesis	defect	(−)	defect	139
9	75	M	non-Q	ant	(+)	(−)	(−)	LAD, LCX, RCA	58	hypokinesis	reduced	(+)	reduced	198
10	63	M	Q	ant, lat	(+)	(−)	(−)	LAD, LCX	(−)	akinesis	reduced	(+)	reduced	114
11	64	M	Q	ant	(+)	(−)	(−)	LAD	69	hypokinesis	reduced	(+)	reduced	144
12	71	M	Q	ant	(+)	(−)	(−)	LAD, RCA	55	akinesis	defect	(−)	defect	129
13	65	M	non-Q	ant	(+)	(+)	(+)	LAD, LCX	35	hypokinesis	defect	(−)	reduced	325
14	76	F	non-Q	ant	(+)	(−)	(−)	LAD	71	akinesis	reduced	(+)	reduced	179
15	68	M	Q	ant	(+)	(+)	(−)	LAD, LCX	38	akinesis	defect	(−)	defect	197
16	47	M	Q	ant	(+)	(−)	(+)	LAD, RCA	48	akinesis	defect	(−)	defect	125
17	58	M	Q	ant	(+)	(−)	(−)	LAD, LCX	26	akinesis	defect	(−)	defect	140
18	61	M	Q	ant	(+)	(−)	(−)	LAD	60	akinesis	defect	(−)	defect	174
19	73	M	non-Q	ant	(+)	(−)	(−)	LAD	79	normal	normal	(+)	normal	182
20	64	M	Q	ant	(−)	(+)	(−)	LAD, LCX	31	akinesis	defect	(−)	defect	251
21	51	M	non-Q	ant	(+)	(+)	(−)	LAD, LCX, RCA	46	hypokinesis	reduced	(+)	reduced	144

M: male, F: female, Q: Q wave, non-Q: non-Q wave, ant: anterior, inf: inferior, lat: lateral, AP: angina pectoris, DM: diabetes mellitus, CHF: congestive heart failure, CAG: coronary angiography, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, LVEF: left ventricular ejection fraction, WM: anterior wall motion on echocardiography, fill in: redistribution on Tl reinjection image at anterior wall, (+): positive, (−): negative, BS 1 hr: blood sugar 1 hour after glucose loading (mg/d*l*)

waves and poor R progression in one or more precordial leads on a standard ECG. None had had an acute myocardial infarction within the 2 weeks before the study. Coronary angiography was performed by Judkins' method.[13,14] Significant lesions were identified by the presence of stenosis greater than 75%.

Study protocol

We assessed myocardial viability in transaxial views obtained by ^{201}Tl reinjection images and ^{18}FDG-PET with glucose loading. Wall motion was assessed by echocardiography.

Exercise ^{201}Tl reinjection imaging

A multistage exercise test with a bicycle ergometer was initiated at 25 watts with an increase of 25 watts every 3 min. Standard 12-lead electrocardiograms and blood pressure levels were monitored at 1-minute intervals during the exercise test. Exercise endpoints were defined as the appearance of chest pain, ST depression exceeding 0.2 mV, or achievement of the target heart rate (THR = 85% of maximum HR). When subjects reached an endpoint, 74 MBq ^{201}Tl was injected and an additional 1 minute of exercise was performed. Exercise ^{201}Tl imaging was performed 10 minutes after the tracer injection. Reinjection images were obtained 10 minutes after the injection of 37 MBq ^{201}Tl, 4 hours after the completion of the exercise.

Single photon emission computed tomography (SPECT) images were obtained over a 180° arc with a gamma camera (Hitachi Gamma View-D [RC-135T]) and an on-line mini-computer (Harp) equipped with an all-purpose, low-energy, general-purpose collimator. Data aquisition times were 40 seconds per step for a total of 32 steps. Images on the short axis, vertical, horizontal, and transaxial planes were reconstructed with a Wiener filter.

^{18}FDG positron emission tomography (PET)

PET was performed with a whole-body, multi-slice positron camera (Headtome IV, Shimadzu SET-1400W, Kyoto, Japan). ^{18}FDG was synthesized from $^{18}F_2$ by an automated synthesis system (FDG-CBB, Shimadzu, Kyoto, Japan) *via* the acetylhypofluorite method. Transmission scanning was performed with ^{68}Ge/^{68}Ga standard line source for correction of photon attenuation for 12 minutes. After transmission scanning for accurate collection of photon attenuation, 148 MBq (4 mCi) of ^{18}FDG was injected. Images were recorded 60 minutes later for 10 minutes. We obtained 7 contiguous transverse myocardial slices at 13 mm intervals. Patients ingested a meal containing carbohydrate (approximately 2-hour before the PET study) and were given a 75 g glucose load 1 hour before tracer administration. Plasma glucose levels were measured before and 1 hour after ^{18}FDG administration with a SPOTCHEM SP-4410 (Kyoto Daiichi Kagaku, Kyoto, Japan).

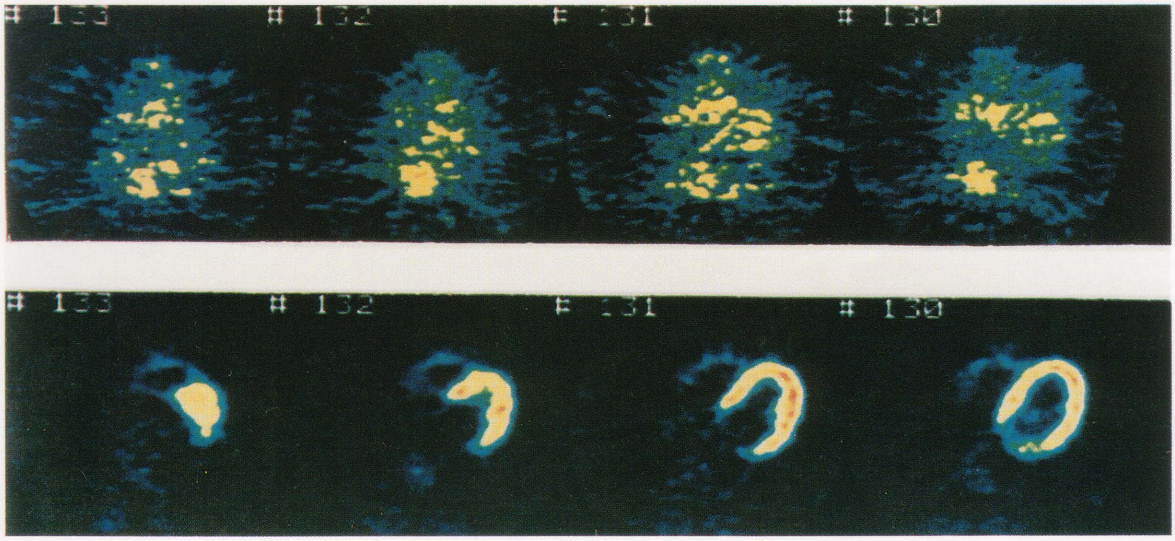

Fig. 1 Representative ^{18}FDG-PET images obtained during fasting and glucose loading in a normal volunteer. This subject had a fasting plasma glucose level of 94 mg/d*l*, and a plasma glucose level of 140 mg/d*l* after glucose loading.

Fig. 2 A case with anterior myocardial infarction with effort angina. Left panel: ^{201}Tl stress image; middle panel: ^{201}Tl reinjection image; right panel: ^{18}FDG-PET image.

Analysis of ^{201}Tl reinjection images and ^{18}FDG-PET images

Three experienced nuclear cardiologists visually assessed ^{201}Tl myocardial images in five segments: anteroseptum, anterior, apical, lateral, and posterolateral. In both the stress and reinjection studies, segmental activity was graded as normal, reduced, or defective. ^{18}FDG-PET images were assessed in the same fashion as ^{201}Tl images, and the ^{201}Tl images were compared with those of ^{18}FDG-PET.

Echocardiography

Echocardiography was performed with an Aloka SSD-9000 system (Tokyo, Japan). The left ventricular ejection fraction (EF) was measured in the M-mode or 2-chamber view, and LV wall motion was assessed in the 4-chamber view. Wall motion was classified as normal, hypokinetic, akinetic, or dyskinetic.

RESULTS

Coronary angiography showed coronary stenosis greater than 75% in all 21 cases. Single-vessel disease was identified in 5 subjects, double-vessel disease in 10 and triple-vessel disease in 6.

Perfusion abnormalities of anterior wall were present in all subjects on the ^{201}Tl stress images. Reinjection imaging showed that 12 of these abnormalities were fixed, 7 were partially reversible, and 2 were completely reversible. All 14 cases of Q wave myocardial infarction (MI) demonstrated abnormal ^{201}Tl uptake on ^{201}Tl reinjection images; 71% (10 of 14) of the subjects showed ^{201}Tl defects on reinjection images. Of 7 non-Q wave MI, 2 had a fixed ^{201}Tl defect, and the other subjects showed normal or reduced ^{201}Tl uptake (Table 1).

Images obtained by ^{18}FDG-PET with glucose loading were more homogeneous than those obtained during fasting in a normal volunteer (Fig. 1).

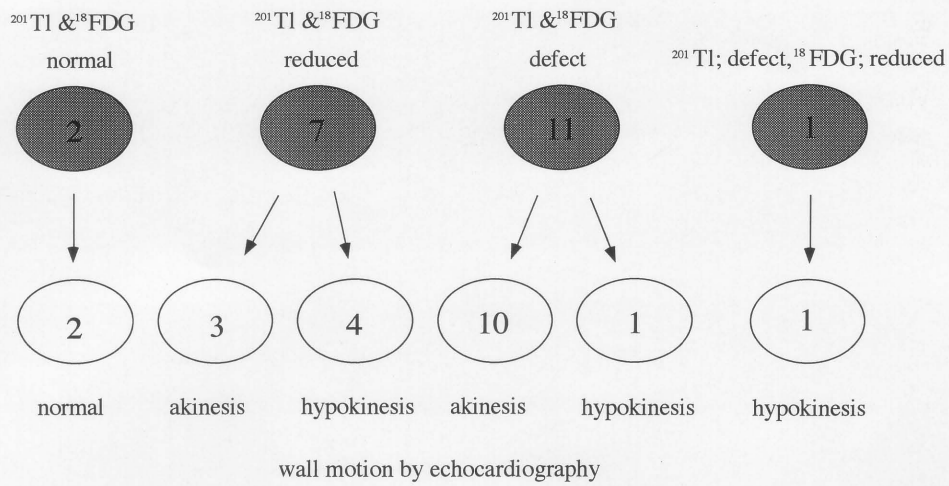

Fig. 3 Numbers in the shaded ellipses indicate the cases displaying normal, reduced, or defect on images obtained by ^{201}Tl reinjection images and ^{18}FDG-PET images, while those in the open ellipses indicate the cases displaying normal, akinesis, or hypokinesis by wall motion (echocardiography). One case, in which there was an area of defect on the ^{201}Tl reinjection images, as well as reduced ^{18}FDG uptake in the same area, was identified as hypokinesis on echocardiography.

Plasma glucose levels were below 251 mg/d*l* in 19 subjects (average plasma glucose: 161 mg/d*l*); excellent ^{18}FDG-PET images were obtained in these subjects. Plasma glucose levels were above 300 mg/d*l* (444 and 325 mg/d*l*) in the 2 subjects in whom inadequate ^{18}FDG-PET images were obtained (Table 1).

^{18}FDG-PET images demonstrated complete defect in 71% (10 of 14) of Q wave MI and reduced or normal uptake in 86% (6 of 7) of non-Q wave MI.

Relationship between ^{201}Tl reinjection imaging and ^{18}FDG-PET with glucose loading

The results of the imaging studies were in agreement in 20 of the 21 subjects. Representative images in the patient (No. 11) with anterior MI and effort angina are shown in Figure 2.

Relationship between imaging studies and echocardiography

The relationship between imaging studies and echocardiography in assessing myocardial viability is shown in Figure 3. Echocardiography showed normal wall motion in 2 segments that showed a normal uptake on ^{201}Tl reinjection imaging and ^{18}FDG imaging. Of the 7 segments that showed a reduced uptake on both imaging studies, echocardiography showed akinesis in 3 segments and hypokinesis in 4 segments. Both techniques showed defects in 11 segments. Echocardiography showed akinesis in 10 of those segments and hypokinesis in 1 segment. Echocardiography identified hypokinesis in 1 segment in which the results of imaging studies were inconsistent, as shown in Figure 3.

DISCUSSION

The results of ^{18}FDG-PET with glucose loading and ^{201}Tl reinjection imaging were consistent in 20 of the 21 cases of old anterior myocardial infarction. Echocardiography demonstrated hypokinetic or akinetic wall motion in the regions identified by both imaging techniques as abnormal. Our results showed that ^{201}Tl reinjection images can be used to identify viable and necrotic myocardium with similar identification to metabolic imaging obtained by ^{18}FDG-PET with glucose loading.

^{201}Tl reinjection

Methods of ^{201}Tl reinjection have been developed for assessing myocardial viability.[3,5] When ^{201}Tl reinjection images were obtained immediately after the conventional 4-hour redistribution images, viable myocardium was detected in 34 to 49% of regions that were interpreted as having irreversible perfusion abnormalities on the conventional redistribution images.[15] In the present study, fill in on the ^{201}Tl reinjection images was found to be 43% (9 of 21) (Table 1). A possible explanation for these improved results is that the delivery of ^{201}Tl may be delayed during the 3-to-4 hour period after exercise.[16]

^{18}FDG-PET

PET, a noninvasive imaging method that uses a variety of tracers, can provide a qualitative as well as quantitative assessment of multiple physiologic and metabolic myocardial parameters. However, subsequent metabolism of these tracers can be severely affected by the metabolic milieu. The uptake of ^{18}FDG is similar to that involved in glucose uptake. However, the terminal metabolic step of ^{18}FDG uptake is phosphorylation by

hexokinase which, unlike glucose, discontinues to be metabolized. Thus, ^{18}FDG accurately traces the initial transport of glucose but not its eventual fate (i.e., Kreb's cycle, glycolysis, glycogen storage). Glucose loading and fasting alter the arterial concentrations of substrates (glucose, free-fatty acid and lactate) and hormones (insulin), altering myocardial substrate extraction and utilization. Fasting images are therefore not superior to glucose loading images.

Tamaki et al.[9] reported that uptake of ^{18}FDG was observed in about 40% of myocardial areas that demonstrated reduced ^{201}Tl uptake, indicating that these areas were viable. They also reported that cardiac contractile function improved after surgical revascularization in 78% of segments with preserved ^{18}FDG uptake, compared with 22% of segments without ^{18}FDG uptake. Because myocardial uptake of ^{18}FDG is affected by several metabolic factors,[17] studies are performed when patients are in the fasting state, after glucose loading, or postprandially, depending on the issue to be resolved.[18–20] Fasting improves the detection of increased ^{18}FDG utilization caused by ischemia. However, Gropler et al.[11] recently showed a significant heterogeneity in regional myocardial glucose utilization rates (rMGU) in fasting subjects, suggesting that the specificity of fasting ^{18}FDG studies in detecting myocardial ischemia is limited. The myocardial uptake of ^{18}FDG is more homogeneously distributed after glucose loading. This metabolic heterogeneity is unexplained to date but should be incorporated into the interpretation of clinical studies.

We obtained homogeneous images in 19 of 21 subjects. Excellent images were obtained when the average plasma glucose level was 161 mg/dl. Inhomogeneous images were obtained in 2 subjects with plasma glucose levels of 444 and 325 mg/dl. Glucose loading is inappropriate in subjects with diabetes mellitus. In such cases, glucose loading should be performed with an insulin clamp to stabilize the plasma glucose level.[21] However, the use of an insulin clamp is more complicated than glucose loading.

Comparison of ^{18}FDG-PET imaging with ^{201}Tl reinjection SPECT imaging

A recent study has compared thallium reinjection and fasting ^{18}FDG-PET imaging in differentiating the viable from the scarred myocardium.[22] There have been no comparative studies assessing myocardial viability by means of thallium reinjection and ^{18}FDG-PET after glucose loading. Fasting ^{18}FDG-PET identified 30 to 40% of ^{201}Tl defect segments. However, fasting images were not homogeneous, because of unstable glucose or insulin levels, indicating that fasting images may overestimate the extent of viable myocardium. We found that ^{18}FDG-PET images after glucose loading and perfusion ^{201}Tl images were consistent in all but one case, indicating that ^{201}Tl reinjection imaging identifies viable and necrotic myocardium similarly to ^{18}FDG-PET with glucose loading. Bonow et al.[23] also demonstrated that ^{201}Tl reinjection identified the myocardial viability the same as ^{18}FDG-PET imaging with glucose loading.

Comparison of ^{18}FDG-PET and ^{201}Tl reinjection SPECT imagings with wall motion by echocardiography

The assessment of myocardial viability was difficult in certain conditions such as hibernating myocardium or stunned myocardium. In this study, there were 3 of 7 cases identified as akinesis by echocardiography in whom ^{18}FDG-PET images after loading and ^{201}Tl reinjection imagings indicated reduced uptake. We considered that in these segments there is the possibility of the improvement in wall motion after revascularization.

CONCLUSIONS

Identification of the viable and necrotic myocardium is important in making clinical and therapeutic decisions. However the assessment of myocardial viability by regional wall motion is difficult in certain conditions such as hibernating myocardium or stunned myocardium. Our results showed that ^{201}Tl reinjection imaging identified the viable and necrotic myocardium similarly to metabolic imaging obtained by ^{18}FDG-PET with glucose loading.

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