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Prognostic Value of an Increase in Fluorine-18 Deoxyglucose Uptake in Patients With Myocardial Infarction: Comparison With Stress Thallium Imaging

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Objectives. **This study was undertaken to evaluate the prognostic value of an increase in fluorine (F)-18 deoxyglucose uptake compared with clinical, angiographic and stress thallium findings in patients with myocardial infarction.**

Background. **Positron emission tomography (PET) imaging using F-18 deoxyglucose has been applied to assess tissue viability in patients with coronary artery disease. We hypothesized that patients with a myocardial segment with augmented F-18 deoxyglucose uptake are at high risk for a future cardiac event.**

Methods. **One hundred fifty-eight consecutive patients with myocardial infarction referred for F-18 deoxyglucose PET and stress thallium scans were studied. Follow-up was obtained in 84 patients at a mean interval of 23 months to investigate prognostic implications of radionuclide studies.**

Results. **Seventeen patients had a cardiac event during the follow-up interval. Univariate analysis showed that an increase in F-18 deoxyglucose uptake was the best predictor of a future cardiac event ($p = 0.0006$), followed by the number of stenosed vessels ($p = 0.008$). In the multivariate analysis, when an increase in F-18 deoxyglucose uptake was entered into the model, only angiographic variables had an independent prognostic value, whereas no other radionuclide variables showed significant prognostic value. Among patients who did not show redistribution, a future cardiac event was observed more often in patients with than in those without an increase in F-18 deoxyglucose uptake ($p < 0.05$).**

Conclusions. **Thus, an increase in F-18 deoxyglucose uptake seemed to be the best predictor of a future cardiac event among all clinical, angiographic and radionuclide variables in this study of stable patients with myocardial infarction. Even when a stress thallium-201 scan does not show redistribution, those patients who have an increase in F-18 deoxyglucose uptake in a PET study may be at risk for a future cardiac event, and these patients may need aggressive treatment to prevent a future cardiac event.**

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A major goal in the management of patients with coronary artery disease is to identify patients at high risk for a future cardiac event so that active treatment may be considered to prevent such events. Patients with left ventricular dysfunction have a distinctly worse prognosis during medical therapy than do those with preserved ventricular function (1,2). Although patients in stable condition after myocardial infarction have a relatively good clinical course, some patients have residual ischemia, which has the potential to cause future cardiac events. Thus, the development of methods to detect viable but jeopardized myocardium in such patients is of clinical importance, particularly for determining the most appropriate management of such patients.

Radionuclide imaging has been widely used for the detection and management of patients with coronary artery disease. Stress thallium-201 imaging and stress radionuclide ventriculography have been considered to play important prognostic roles in identifying patients at high risk (3–9). In particular, the presence of redistribution on a stress thallium-201 scan has been shown to predict future cardiac events in follow-up studies of patients with coronary artery disease (5,6,9,10).

Recently, positron emission tomography (PET) imaging has emerged as a promising tool for demonstrating myocardial viability in patients with coronary artery disease (11–15). Fluorine (F)-18 deoxyglucose has been used as a marker of exogenous glucose utilization. Thus, a pattern of increased F-18 deoxyglucose uptake in hypoperfused areas (termed the perfusion-metabolism mismatch) is considered to represent ischemic but viable myocardium, whereas a concordant

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decrease in metabolism and blood flow may represent myocardial necrosis (11). Segments showing an increase in F-18 deoxyglucose uptake in hypoperfused areas may indicate jeopardized myocardium as well. Thus, we hypothesized that PET imaging may have prognostic value in patients with myocardial infarction. Preliminary studies indicated that this technique seems to be valuable for predicting future cardiac events (16,17); however, its relation to other routinely performed techniques as a prognostic tool remains unknown. The purpose of this study was to assess the ability of PET imaging to predict cardiac events compared with clinical, angiographic and radionuclide findings in patients with myocardial infarction.

Methods

Patients. The study group comprised 158 consecutive patients with myocardial infarction who underwent PET imaging with F-18 deoxyglucose and stress thallium-201 imaging during the years 1985 to 1991. Patients who had experienced acute myocardial infarction <1 month previously or within 2 weeks after revascularization or who were in an unstable condition, and thus could not perform a stress thallium study, were excluded. Follow-up data for at least 6 months in 107 patients (65%) were obtained. Fifty-six patients (35%) were lost to follow-up. There were no differences observed in baseline clinical variables between patients with or without follow-up. All patients had evidence of myocardial infarction occurring at least 1 month previously on the basis of a prolonged (>30 min) episode of chest pain and electrocardiographic changes with elevated serial cardiac enzymes. In addition, they were in stable condition at the time of the study, with no signs of unstable angina or congestive heart failure.

Twenty-two patients underwent coronary bypass surgery or percutaneous transluminal coronary angioplasty after the radionuclide study. Eighteen of the 22 who underwent early revascularization (≤3 months after the radionuclide study) were excluded from study because the decision to perform this procedure may be subjective and related to the test findings and, by itself, does not represent an adverse outcome (8). However, late revascularization in the remaining four patients was include . .n this study as an adverse outcome.

Each subject gave written informed consent approved by the Kyoto University Clinical Study Committee.

Coronary angiography. Standard cardiac catheterization and coronary angiography were performed in each patient at the time of admission. Significant coronary stenosis was defined as >50% lumen stenosis.

Positron emission tomographic study. Positron emission tomography was performed with a whole-body, multislice positron camera (Positologica III, Hitachi Medical Co.). It provided seven transverse slices at 16-mm intervals. The effective resolution was approximately 10 mm, and the axial resolution was 9.8 mm at full-width, half-maximum (18). Each patient was studied in the fasting state for at least 5 h to maintain steady state during the study (14,19,20). After accurate positioning of the patient under the positron camera using the ultrasound technique, a transmission scan was performed for 15 min for accurate correction of photon attenuation. Then, 100 to 300 MBq (2.7 to 8.1 mCi) of F-18 deoxyglucose was injected at rest. Approximately 60 min later, glucose metabolic imaging was performed for 8 to 10 min. Immediately after the first scan, the patient was moved 8 mm in the axial direction, and the second scan was performed. These two scans provided a total of 14 contiguous transverse slices (8-mm spacing) covering a 104-mm field of view in the axial direction (14,19,20).

The nitrogen (N)-13 ammonia perfusion study was performed separately within 1 week after the F-18 deoxyglucose study. Approximately 400 to 800 MBq (10.8 to 21.6 mCi) of N-13 ammonia was injected at rest, and the rest perfusion scan was started 3 min later. Two emission scans were obtained, each for 5 to 8 min. From a series of transverse slices of the metabolic and perfusion images, oblique tomograms perpendicular to the long and short axes of the left ventricular myocardium were also reconstructed to compare the segments obtained by thallium-201 imaging (21).

Stress thallium-201 study. Each patient performed graded bicycle exercise starting at 25 W, with an increment of 25 W every 3 min. At peak exercise, 110 MBq (3 mCi) of thallium-201 was injected, and the exercise was continued for another 1 min. The stress thallium-201 scan began within 10 min after the tracer injection. Three hours later, a delayed thallium-201 scan was performed. In each thallium-201 scan, single-photon emission computed tomographic images were acquired, collecting 32 projection images of 30 s each over 180° (22,23). A series of transaxial slices were reconstructed with a filtered backprojection without using attenuation correction. Oblique tomograms parallel to the long and short axes of the left ventricle were also reconstructed (22,23).

Image analysis. The left ventricular myocardium was divided into five segments (i.e., anterior, septal, apical, inferior and lateral segments) to assess the positron tracers and thallium uptake in each segment. Both N-13 ammonia and F-18 deoxyglucose uptake in the myocardium (cpm/100 ml) were divided by injected dose (cpm) for display as percent dose/100 ml of tissue for comparison with each other at the corresponding areas (20). The segments with normal perfusion were defined as PET-normal. The hypoperfused segments with increased F-18 deoxyglucose uptake above the lower limits of the normal values in individual segments, based on the normal data base, were defined as *ischemia*. The hypoperfused segments with no F-18 deoxyglucose uptake or slight uptake below the lower limits were defined as *scar* (19,20).

In the thallium-201 imaging study, two experienced observers scored uptake using a 5-point grading system (0 = normal, 1 = equivocal, 2 = mild, 3 = moderate, 4 = severe reduction) without knowledge of the clinical or angiographic

Table 1. F-18 Deoxyglucose-Positron Emission Tomographic and Thallium-201 Findings in Relation to Cardiac Events in 84 Study Patients*

Thallium Findings	FDG-PET Findings		
	FDG Increase	No FDG Increase	Total
Redistribution	41 (14)	10 (0)	51 (14)
No redistribution	7 (2)	26 (1)	33 (3)
Total	48 (16)	36 (1)	84 (17)

*Parentheses denote the number of patients experiencing cardiac events. FDG = F-18 deoxyglucose; PET = positron emission tomography.

data. When a myocardial segment showed a postexercise score ≥2, an initial perfusion abnormality was considered to be present. When the score decreased by ≥1 on the delayed scan, the segment was considered to show redistribution (19). The number of segments showing redistribution was also calculated as a prognostic variable.

Prognostic analysis. Each patient was followed up by chart review or telephone interview with regard to the development of cardiac events, including cardiac death, nonfatal myocardial infarction, unstable angina and late revascularization. The mean follow-up interval was 23.0 ± 12.7 months (range 6 to 48).

Values are presented as mean value ± SD. Mean values were compared with an unpaired *t* test. Frequency comparisons were made by chi-square analysis to compare proportions. Actual event-free rates were analyzed using Kaplan-Meier survival curves with regard to the presence of F-18 deoxyglucose uptake and redistribution on the thallium scan. In addition, stepwise logistic regression analysis was used to compare the predictive value of the radionuclide variables with that of the clinical and angiographic variables. Variables were entered from the regression equation on the basis of a computed significance probability to allow the identification of the most powerful variable compared with all other significant variables. When the most powerful variable was removed from the model, additional power of discrimination was sought until the two most powerful variables were obtained.

Results

Radionuclide findings. An increase in F-18 deoxyglucose uptake in at least one myocardial segment was observed in 48 patients. Redistribution on the stress thallium-201 images was observed in 51 patients. Forty-one patients had positive findings, on both scans, and 26 patients had negative findings, on both scans. Thus, concordance between the two tests was observed in 80% of the patients. There were 10 patients who showed positive redistribution but no increase in F-18 deoxyglucose uptake, whereas 7 patients showed no redistribution but increased F-18 deoxyglucose uptake (Table 1).

Table 2. Clinical, Angiographic and Radionuclide Variables as a Function of Cardiac Events in 84 Study Patients

	No Events (n = 67)	Events (n = 17)	p Value
Age (yr)	58 ± 9	62 ± 8	NS
M/F	62/5	16/1	NS
Anterior/inferior MI	38/29	10/7	NS
Recurrent MI	6/67	5/17	0.026
Interval from MI (wk)	23/27	29/35	NS
Diseased vessels (no.)	1.85 ± 0.93	2.53 ± 0.70	0.007
LVEF (%)	50 ± 12	42 ± 14	0.028
Thallium redistribution	37/67	14/17	0.041
No. of redistribution segments	1.1 ± 1.2	2.0 ± 1.2	0.009
Increase in lung thallium uptake	15/67	8/17	0.042
Increase in FDG uptake	32/67	16/17	0.009

Values presented are mean value ± SD or number. F = female; FDG = F-18 deoxyglucose; LVEF = left ventricular ejection fraction; M = male; MI = myocardial infarction.

Cardiac events. During the follow-up period, a total of 17 cardiac events were observed, including 3 cardiac-related deaths, 3 nonfatal infarctions, 7 cases of unstable angina and four cases of late (>3 months) revascularization. Unstable angina was considered present when the patient had progressive chest pain or chest pain at rest.

Variables in patients with a cardiac event. Table 2 shows the clinical, angiographic and radionuclide variables in patients with and without a cardiac event. Cardiac events were more often seen in patients who had recurrent infarction than in those with a first infarction (5 [29%] of 17 vs. 6 [9%] of 67), but no other clinical variables showed significant correlation with the cardiac event. However, all angiographic and radionuclide variables showed a significant correlation with the cardiac event, including the number of stenosed vessels on coronary angiography ($p = 0.007$), left ventricular ejection fraction on contrast ventriculography ($p = 0.028$), redistribution ($p = 0.041$), the number of redistribution segments ($p = 0.009$) and an increase in lung uptake ($p = 0.042$) on the stress thallium-201 images and an increase in F-18 deoxyglucose uptake on the positron scan ($p = 0.004$) (Table 2). In particular, all but one patient who had a cardiac event showed an increase in F-18 deoxyglucose uptake. Thus, patients who show increased F-18 deoxyglucose uptake in at least one segment may be more likely to have a future cardiac event than are those without increased F-18 deoxyglucose uptake (Fig. 1). Similarly, those who show redistribution on the stress thallium scan may be more likely to have a future cardiac event than are those without redistribution (Fig. 2).

On stepwise multivariate logistic regression analysis (Table 3), an increase in F-18 deoxyglucose uptake was the most significant predictor of a cardiac event (chi-square = 13.53), followed by the number of stenosed vessels (chi-square = 7.67).

When an increase in F-18 deoxyglucose uptake was

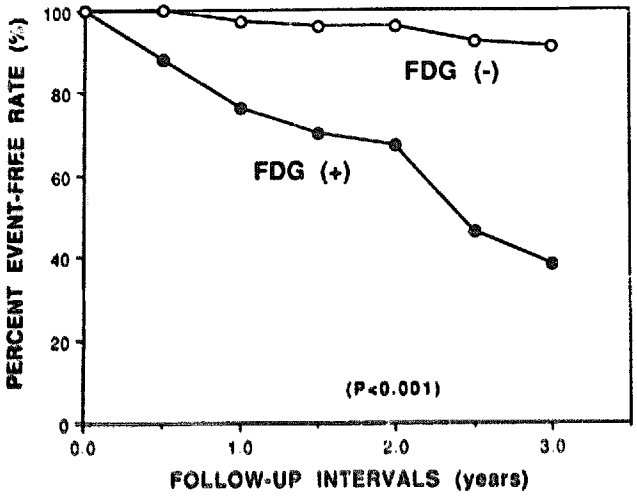

Figure 1. Kaplan-Meier event-free rates for patients with stable myocardial infarction who had an increase in F-18 deoxyglucose (FDG) uptake (**solid circles**) in at least one myocardial segment and those without increased F-18 deoxyglucose uptake (**open circles**). The incidence of cardiac events was significantly greater in patients with (+) than in those without (−) an increase in F-18 deoxyglucose uptake ($p < 0.001$).

removed from this model, only the angiographic variables, including the number of stenosed vessels (chi-square = 6.35) showed additional value for predicting a cardiac event. Thus, F-18 deoxyglucose uptake and the angiographic findings provided independent prognostic information.

Patients who did not show redistribution. When the 33 patients who did not show redistribution in any segment were selected for prognostic study, 7 (21%) showed an increase in F-18 deoxyglucose uptake. Two of the 7 patients had a cardiac event compared with only 1 of 26 patients who did not show an increase in F-18 deoxyglucose uptake ($p < 0.05$).

Figure 2. Kaplan-Meier event-free rates for patients with stable myocardial infarction who showed redistribution (RD) on stress thallium-201 scan (**solid squares**) and those without redistribution (**open squares**). The incidence of cardiac events was significantly greater in patients with (+) than in those without (−) redistribution on stress thallium-201 scan ($p < 0.01$).

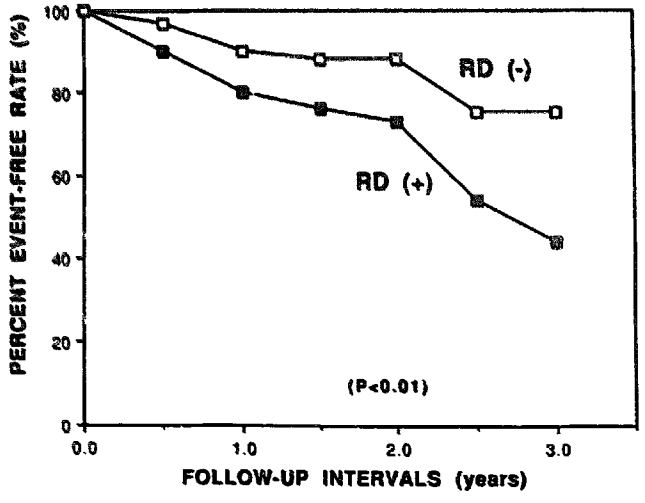

Table 3. Multivariate Predictors of Cardiac Events in 84 Study Patients

	Step 0		Step 1	
	Chi-Square Analysis	p Value	Chi-Square Analysis	p Value
Increase in FDG uptake	13.35	0.0006	—	—
No. of diseased vessels	7.67	0.008	6.35	0.02

FDG = F-18 deoxyglucose; Step 0 = before variables were entered into the model; Step 1 = after variables were entered into the model.

Discussion

The present study indicated that an increase in F-18 deoxyglucose uptake seems to be the best predictor of future cardiac events among all clinical, angiographic and radionuclide variables in the study of stable patients with myocardial infarction. Multivariate analysis indicated that when the F-18 deoxyglucose variable was entered into the model, only the angiographic variables had prognostic significance, whereas no other clinical or radionuclide variables had prognostic value. More important, even when the stress thallium-201 scan did not show any redistribution, those patients who had an increase in F-18 deoxyglucose uptake appeared to be likely to have a future cardiac event.

Significance of increase in F-18 deoxyglucose uptake. Previous experimental studies have indicated that exogenous glucose utilization is accelerated in acutely ischemic myocardium (24,25). Thus, PET imaging can identify ischemic myocardium as an area of augmented uptake of F-18 deoxyglucose, a glucose analogue (26), relative to perfusion, thereby defining a blood flow–metabolism mismatch (12).

In clinical studies, an increase in exogenous glucose utilization was observed in patients with stress-induced ischemia (27), unstable angina (28) and non-Q wave or Q wave myocardial infarction (29,30). Schwaiger et al. (31), in a study of patients with acute myocardial infarction, demonstrated that hypoperfused segments with preserved F-18 deoxyglucose uptake often showed improvement or deterioration of regional wall motion in the follow-up assessment. These areas may represent ischemic and jeopardized myocardium that may have improved regional function after spontaneous or interventional revascularization (13,14) but may also be at risk for unstable angina or infarction.

Our group (16) and Eintzmen et al. (17) first pointed out that augmented F-18 deoxyglucose uptake in hypoperfused areas was a potential prognostic indicator in patients with myocardial infarction (16,17). Patients with an increase in F-18 deoxyglucose uptake in at least one segment may be more likely to have a future cardiac event than are those

without any increase in F-18 deoxyglucose uptake. In addition, the risk for cardiac events seemed to be minimized when patients showing an increase in F-18 deoxyglucose uptake received interventional therapy (17). Our present data indicated that F-18 deoxyglucose uptake was the best predictor of future cardiac events among all clinical, angiographic and radionuclide variables in the multivariate analysis.

Relation to other prognostic variables. Assessment of ventricular function and coronary angiography may be important in the prognostic study of patients with acute myocardial infarction (32,33). In addition, prognostic study in the predischarge period might also be important in the future management of patients with myocardial infarction. The present study focused on risk stratification of patients with stable infarction, excluding those in the acute stage (<1 month) of infarction and unstable angina.

In the predischarge period after myocardial infarction, stress thallium-201 imaging has been shown to have prognostic importance (6–10). The presence of redistribution on the stress thallium-201 scan would be expected to identify patients with residual jeopardized but viable myocardium. Furthermore, an increase in lung uptake of thallium-201 on the stress scan, as a potential marker for severe coronary artery disease and left ventricular dysfunction (34–37), has been associated with a poor outcome in patients with coronary artery disease (9). The present study supported these findings.

Our previous results indicated that the F-18 deoxyglucose findings were quite similar to the stress thallium-201 or N-13 ammonia findings, although the former may be slightly more sensitive for detecting ischemia (38–40). In the present study, however, there were 10 patients who showed redistribution on stress thallium-201 scan but no increase in F-18 deoxyglucose uptake on PET imaging. These areas may represent ischemic myocardium but normal perfusion at rest. None of the 10 had a cardiac event. However, seven patients had no redistribution on stress thallium-201 tomography but showed an increase in F-18 deoxyglucose uptake on PET scanning. These areas may contain ischemic and jeopardized myocardium that is at risk for future cardiac events with conservative treatment. Although the number of such patients was small in this study, two of the seven patients had a cardiac event during the follow-up interval. In this respect, PET imaging seems to be superior to conventional stress thallium-201 imaging for identifying patients at high risk. Once the F-18 deoxyglucose variable was entered into the model, no thallium-201 variables added a prognostic value to the multivariate analysis.

Potential limitations. 1) The present study is a retrospective study that focused on patients in stable condition after myocardial infarction and excluded those with acute myocardial infarction (<1 month from onset) and those with unstable angina. Thus, the rate of cardiac events seems to be rather low compared with previous results in patients with acute myocardial infarction, which may limit the present study with regard to precise statistical analysis. However, risk stratification in the predischarge period may also be important in the future management of patients with myocardial infarction.

2) Because an increase in F-18 deoxyglucose uptake was very often observed immediately after revascularization (40), patients who received thrombolytic therapy within 2 weeks were also excluded from this study. In addition, patients undergoing a revascularization procedure within 3 months after the radionuclide study were also excluded. Although such a procedure is an important cardiac event and may be related to radionuclide findings, it is not necessarily an adverse outcome. However, late revascularization was considered an adverse outcome in these patients, probably because of intolerable unstable angina, and, therefore, these events were included in this study (8).

3) F-18 deoxyglucose was injected in the fasting state. It is controversial whether the tracer should be injected in the fasting state or after a glucose load (41–44). The glucose loading study may be suitable for assessing viable tissue on the basis of the presence or absence of tracer uptake. However, a study in the fasting state may be useful for identifying ischemic and jeopardized myocardium as an area of augmented F-18 deoxyglucose uptake. Because there is heterogeneity of F-18 deoxyglucose uptake in normal myocardium, particularly in the fasting state (41), tracer uptake was assessed by comparing it with the normal range of F-18 deoxyglucose uptake in individual segments. In addition, ischemic myocardium was defined as an area of enhanced tracer uptake in a hypoperfused area (20).

4) Stress and 3- to 4-h delayed thallium-201 images were assessed with regard to the presence or absence of redistribution. Reinjection scan findings were not used in this study because the present study of risk stratification started in 1985, and the reinjection technique was not introduced until 1987 (45–48). Better correlation of thallium-201 and F-18 deoxyglucose findings may be expected (49,50).

Clinical implications. Although patients in stable condition with healed myocardial infarction may have a relatively good prognosis, risk stratification in the predischarge period might be valuable in the management of such patients. Positron emission tomography using F-18 deoxyglucose seems to be an excellent technique for identifying residual myocardial ischemia, which is often observed after myocardial infarction. The present study indicated that increase in F-18 deoxyglucose uptake is the best predictor of future cardiac events among all clinical, angiographic and radionuclide variables in the follow-up study of patients in stable condition with myocardial infarction. Although stress thallium-201 imaging has been widely used to identify residual ischemia, PET imaging seems to be a better predictor than redistribution on the stress thallium-201 scan.

Conclusions. Positron emission tomography using F-18 deoxyglucose is capable of playing an important prognostic role in the study of patients with myocardial infarction. When an increase in F-18 deoxyglucose uptake is observed,

such patients may need aggressive treatment to prevent future cardiac events.

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