

ORIGINAL ARTICLE

A Post-marketing Clinical Study to Confirm the Efficacy of ^{18}F -fluorodeoxyglucose for the Diagnosis of Myocardial Viability: A Prospective Multicenter Study in Patients with Ischemic Heart Disease

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Abstract

Background: A number of previous studies have shown that myocardial viability can be assessed by positron emission tomography (PET) using ^{18}F -fluorodeoxyglucose (^{18}F -FDG). However, there has been no multicenter study that verified the ability of this modality for diagnosing myocardial viability in Japan. We therefore conducted a prospective one arm's unrandomized multicenter clinical trial in order to confirm the diagnostic ability of ^{18}F -FDG for myocardial viability.

Methods: This study included patients with heart failure and impaired left ventricular function where conventional myocardial perfusion scintigraphy was not contributive for the diagnosis of myocardial viability, and assessed the diagnostic ability of ^{18}F -FDG for myocardial viability in these patients. The diagnostic ability was determined on the basis of post-coronary vascularization improvement in myocardial wall motion in a myocardial segment with ^{18}F -FDG uptake (i.e., positive predictive value). We also assessed the safety of ^{18}F -FDG.

Results: Out of 49 patients who received ^{18}F -FDG administration, 30 were included in the efficacy analysis set (mean age 64.4 ± 14.6 years; 27 men and 3 women; mean follow-up period 228.6 ± 74.5 days). The positive predictive value of ^{18}F -FDG (95% two-sided confidence interval) in the 30 patients of the efficacy-analysis set was 63.9% (54.6–72.5%). Moreover, the proportion of patients with improved wall motion, on a per-patient basis, was 86.7% (26 of 30 cases). As for the safety, no serious adverse events occurred and the agent was well-tolerated.

Conclusions: The identification of myocardial viability by ^{18}F -FDG will be widely beneficial in predicting improvement in myocardial wall motion after coronary revascularization. No serious safety concerns associated with the use of ^{18}F -FDG were observed.

Keywords: ^{18}F -fluorodeoxyglucose, Clinical trial, Ischemic left ventricular dysfunction, Myocardial perfusion, Myocardial viability, Positron emission tomography

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Contractile and expanding dysfunction of the myocardium as a result of ischemic heart disease or other cardiovascular diseases causes abnormal left ventricular (LV) systolic function, leading to heart failure. However, despite the myocardial ischemia, some myocardia escape necrosis even though their contractile function is chronically depressed. In these ischemic regions, myocardial wall motion could be expected to recover after reperfusion by coronary revascularization. The myocardial viability is thus defined as the potential for recovery of myocardial wall motion after coronary revascularization (1,2).

The main energy sources of the myocardium are free fatty acids and glucose, and normal myocardium in a fasting state derive $\geq 60\%$ of the energy requirement from β -oxidation of fatty acids. However, in ischemic myocardium fatty acid metabolism is decreased and glycolysis system becomes the dominant energy source. As an ischemia worsens, anaerobic glycolysis system becomes dominant, ultimately resulting in myocardial necrosis (infarction) with no metabolic activity. Because glucose metabolism persists in the ischemic regions of the myocardium, it is possible to differentiate ischemic and infarcted myocardium on the basis of the presence of glucose metabolism (1).

Specifically, a region of myocardium with reduced perfusion that shows preserved or decreased uptake of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) can thus be diagnosed as ischemic and infarcted, respectively. This diagnosis will predict the recovery of myocardial wall motion (i.e. the presence or absence of myocardial viability) prior to coronary revascularization (1). Thus, the Guidelines for Treatment of Chronic Heart Failure by the Japanese Circulation Society highlights the importance of the diagnosis of myocardial viability prior to coronary revascularization in patients with chronic LV dysfunction due to ischemic heart disease (3).

Positron emission tomography (PET) with ¹⁸F-FDG, myocardial perfusion single photon emission computed tomography (SPECT) with thallium chloride (²⁰¹Tl) or ^{99m}Tc-labeled imaging agent, and low-dose dobutamine stress echocardiography have been used to diagnose myocardial viability (4). It has been demonstrated that 10 to 20% of the myocardial regions classified as fibrotic (infarcted) by myocardial perfusion SPECT are identified as ischemic myocardium by ¹⁸F-FDG PET (5). Moreover, the acquisition and interpretation of low-dose dobutamine stress echocardiography images require expertise (4).

Myocardial PET using ¹⁸F-FDG is a recognized modality for the assessment of myocardial viability (6), however, prospective studies using ¹⁸F-FDG PET have in fact been quite limited and only the University of Ottawa Heart Institute group has

conducted prospective trials to date (7,8). Also, while ¹⁸F-FDG PET has been approved for the diagnosis of myocardial viability in Japan (9,10), there has been no report of a multicenter clinical study in Japan that evaluated the diagnostic ability of this modality. We therefore conducted a prospective multicenter clinical trial in Japan to confirm the diagnostic efficacy of ¹⁸F-FDG PET for myocardial viability.

Materials and Methods

This one arm's unrandomized multicenter clinical trial was conducted at 10 medical institutions (Hokkaido University Hospital, Kanazawa Cardiovascular Hospital, National Cerebral and Cardiovascular Center, National Center for Global Health and Medicine, Mitsubishi Kyoto Hospital, Shizuoka Cancer Center, Takinomiya General Hospital, Tokyo Women's Medical University Hospital, University of Miyazaki Hospital, and Nippon Medical School Hospital) from February, 2007 to March, 2011. The study protocol was approved by the Institutional Review Board of each of the 10 participating institutions prior to the study. The study was conducted in accordance with the ethical principles outlined in the Helsinki Declaration, the Good Clinical Practice (GCP) and the Good Post-Marketing Surveillance Practice (GPSP). Written informed consent for participation in the study was obtained from all patients prior to the study.

Patients

The patients enrolled in this study were ≥ 20 years old when informed consent was obtained and they also met the following inclusion criteria: 1) impaired LV function with left ventricular ejection fraction (LVEF) $\leq 50\%$; 2) heart failure; 3) significant stenotic lesions in the coronary arteries; 4) patients who were scheduled for coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) and required diagnosis of myocardial viability; 5) patients where routine myocardial perfusion SPECT was not contributive for the diagnosis of myocardial viability; 6) patients evaluable for LV wall motion at 3–12 months post-revascularization using an identical method of pre-revascularization assessment; 7) patients evaluable for recanalization of the occluded artery after revascularization; and 8) patients evaluable for restenosis of the culprit vessel before post-revascularization assessment of LV wall motion.

The exclusion criteria were: 1) within 4 weeks after the onset of acute myocardial infarction; 2) unstable angina; 3) patients who are pregnant, of childbearing potential, or breastfeeding; 4) enrollment in other clinical trial; and 5) patients who were deemed ineligible for participation in the trial by the investigators.

Investigational drug

¹⁸F-FDG was manufactured by Nihon Medi-Physics Co., Ltd. (Tokyo, Japan) or the Medical and Pharmacological Research Center Foundation (Ishikawa, Japan), and provided in vials containing 185 MBq/2 mL (radioactivity at calibration time), and an excipients was added to ensure high stability during commercial transportation.

Selection of patients

Myocardial viability was assessed by myocardial perfusion SPECT at screening using ^{99m}Tc-tetrofosmin, ²⁰¹Tl, or ^{99m}Tc-sestambi (MIBI). Myocardial perfusion stress-rest SPECT was conducted with some of the patients using either pharmacological (adenosine or dipyridamole) or exercise stress. Wall motion was assessed at screening by gated SPECT, echocardiography, or left ventriculography.

¹⁸F-FDG PET imaging

The patients were fasted for at least 4 h prior to ¹⁸F-FDG administration and their blood glucose levels were controlled using methods specified by each medical institution, to ensure adequate uptake of ¹⁸F-FDG in normal myocardium. Glucose challenge with insulin injection was performed in the majority of patients as summarized in Table 1. 2 mL of ¹⁸F-FDG (radioactivity at calibration time: 185 MBq) was administered intravenously. PET imaging was started ≥30 min after ¹⁸F-FDG administration using Eminence-B (Shimadzu, Kyoto, Japan), Advance NXi (GE Healthcare Japan, Tokyo, Japan), ECAT EXACT 47, ECAT EXACT HR+, ECAT ACCEL, Biograph Sensation 16 (Siemens Healthcare K.K., Tokyo, Japan), or Gemini GXL 16 (Philips Electronics Japan, Tokyo, Japan) PET cameras.

Emission scans were collected for 6-25 min. Transmission scans were acquired after ¹⁸F-FDG administration or simultaneously with emission scans.

Coronary revascularization

Scheduled coronary revascularization (PCI or CABG) was conducted following post-¹⁸F-FDG PET assessment of safety.

Assessment of recanalization

Recanalization of the culprit vessel was assessed after revascularization by coronary angiography, coronary artery computed tomography (CT), post-operative graft flow measurement, doppler echocardiography, or intraoperative assessment.

Assessment of restenosis of the culprit vessel

Restenosis of the culprit vessel was assessed by coronary angiography or CT within 1 week prior to the assessment of wall motion at 3-12 months post-revascularization. Stenosis of

≥75% (AHA classification) in the target region was considered restenosis.

Post-revascularization assessment of myocardial wall motion

Myocardial wall motion was assessed by gated SPECT, echocardiography, or left ventriculography at 3-12 months post-revascularization using the identical method used for the pre-revascularization assessment.

Safety assessment

Subjective symptoms, objective findings, pulse rate, and blood pressure were examined and laboratory examinations (hematology, blood chemistry, qualitative urinalysis) were carried out before and at 2-7 days after ¹⁸F-FDG administration. Pre- and post-administration results were compared to assess the safety of ¹⁸F-FDG. Adverse events were collected and coded using MedDRA/J 14.0.

The study protocol is outlined in Fig. 1.

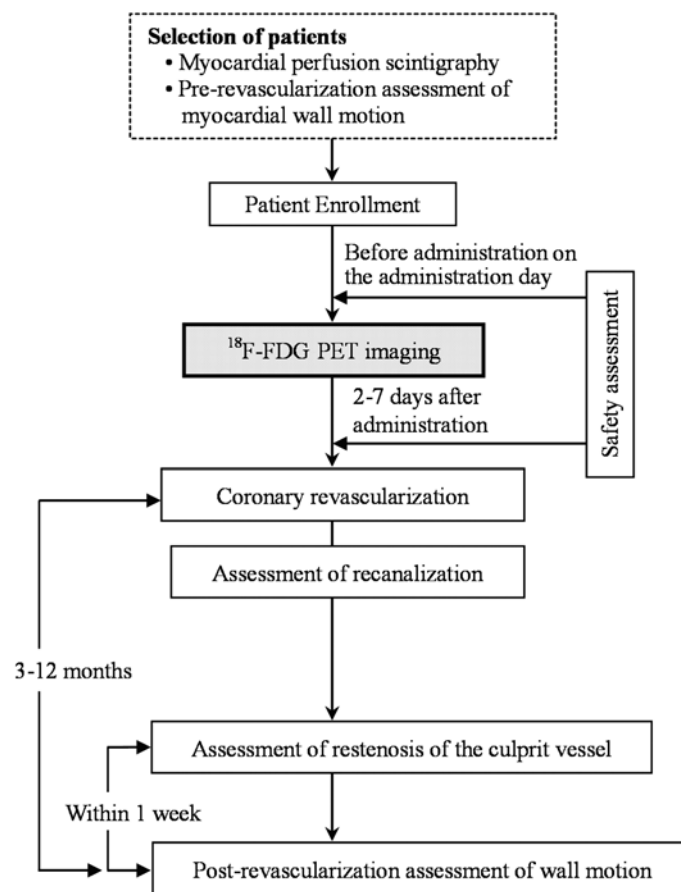
Data analysis

Wall-motion images pre- and post-revascularization were assessed in consensus by two members of the Image Evaluation Committee who were independent of the participating institutions and were blinded to the patient backgrounds, with the images of pre- and post-revascularization displayed side-by-side. The myocardium in the images was divided into 17 segments as shown in Fig. 2 (11) and each segment was scored using a 6-point model: 1=normal; 2=mildly hypokinetic; 3=severely hypokinetic; 4=akinetic; 5=dyskinetic; and 6=unevaluable.

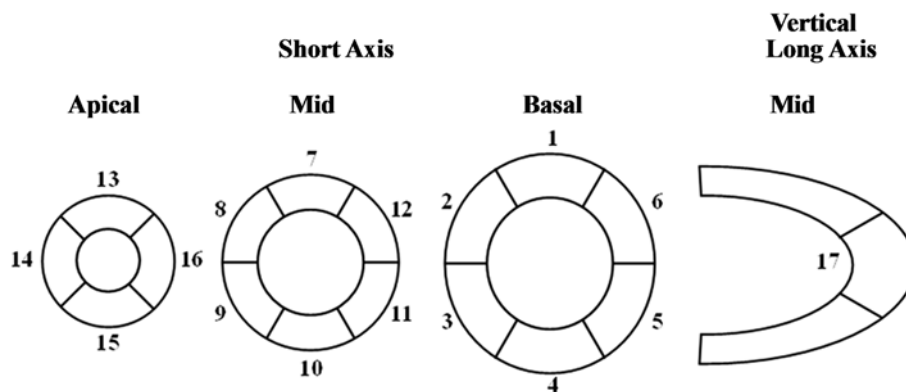
¹⁸F-FDG PET and myocardial perfusion SPECT images were independently assessed by three members of the Image Evaluation Committee who were independent of the participating institutions and were blinded to the patient backgrounds, with the images of PET and SPECT displayed side-by-side. The myocardium was divided into 17 segments (Fig. 2) and each segment was scored using a 5-point scale: 0=normal uptake; 1=slight reduction of uptake; 2=moderate reduction of uptake; 3=severe reduction of uptake; and 4=absence of uptake.

Analysis of diagnostic ability of ¹⁸F-FDG for myocardial viability

The diagnostic ability of ¹⁸F-FDG for myocardial viability was assessed on the basis of the presence or absence of post-revascularization improvement in wall motion in the segments that showed: 1) abnormal LV motion; 2) severe reduction or absence of, or incomplete redistribution of the imaging agent on myocardium perfusion SPECT, i. e., “the diagnosis of myocardial viability is difficult”; and 3) ¹⁸F-FDG uptake. The

**Fig. 1** Study design

The scheduled study period was defined as the time from enrollment to post-revascularization assessment of wall motion.

**Fig. 2** Segmental models for image evaluation

Images of wall motion, ¹⁸F-FDG PET, and myocardial perfusion SPECT were divided into 17 segments and each segment was scored visually.

segments analyzed for the efficacy analysis were chosen by the following procedure, based on the results of the image analysis by the Image Evaluation Committee.

1) Assessment of pre-revascularization myocardial wall motion: segments with scores of 2 (mildly hypokinetic), 3 (severely hypokinetic), 4 (akinetic), and 5 (dyskinetic) were subjected to further analysis.

2) Assessment of myocardial viability on myocardial

perfusion SPECT images: (i) if myocardial perfusion SPECT was conducted only at rest, segments with scores of 3 (severe reduction of uptake) or 4 (absence of uptake) were considered as “the diagnosis of myocardial viability is difficult” and were subjected to further analysis, or (ii) if myocardial perfusion SPECT was conducted both at rest and at stress, segments with scores of 3 (severe reduction of uptake) or 4 (absence of uptake) at rest, or 2 (moderate reduction of uptake) at rest and

3 (severe reduction of uptake) at stress, were considered as “the diagnosis of myocardial viability is difficult” and were subjected to further analysis.

3) Assessment of myocardial viability on ¹⁸F-FDG PET images: of the segments selected in the procedure 1), those considered as “the diagnosis of myocardial viability is difficult” in the procedure 2) were further analyzed on ¹⁸F-FDG PET images. The segments on ¹⁸F-FDG PET images that were scored 0 (normal uptake), 1 (slight reduction of uptake), and 2 (moderate reduction of uptake) by the Image Evaluation Committee were considered as “segment with myocardial viability (mismatch segment)”. And those scored 3 (severe reduction of uptake) and 4 (absence of uptake) were considered “segment without myocardial viability (match segment)”. A segment was scored in consensus by at least two of the three members of the Image Evaluation Committee.

4) Assessment of post-revascularization myocardial wall motion: of the segments selected in the procedure 1) and 2), a segment with “improved myocardial wall motion” was defined as one with the following pre- and post-revascularization scores: i) pre-revascularization score of 4 or 5, and post-revascularization score of 1 to 3; ii) pre-revascularization score of 3 and post-revascularization score of 1 or 2; and iii) pre-revascularization score of 2, and post-revascularization score of 1. Those segments that did not fall under the definitions i) to iii) were considered “with unimproved wall motion”.

There are other studies that have assessed the diagnostic ability of ¹⁸F-FDG (12-20). While there are differences between the previous studies and this one in segmental models used to divide the myocardium, methods for assessing ¹⁸F-FDG PET images (visual/quantitative assessments), and assessment criteria of myocardial wall motion, the diagnostic ability of ¹⁸F-FDG PET was assessed consistently through the same procedure, i. e., first analyzing each segment for a difference between the uptake of ¹⁸F-FDG and cardiac perfusion and subsequent analysis of myocardial wall motion of the corresponding segment after revascularization.

Statistical analysis

1) ¹⁸F-FDG for diagnosis of myocardial viability

With the results from the image analysis by the Image Evaluation Committee, positive predictive value (PPV) and negative predictive value (NPV) of ¹⁸F-FDG were calculated using the following equation. The 95% two-sided confidence interval (CI) of the PPV and NPV were calculated as well.

PPV (%) = (Number of segments with “improved wall motion” from the post-revascularization assessment of myocardial wall motion)/(Total number of mismatch segments analyzed) x100.

NPV (%) = (Number of segments with “unimproved wall

motion” from the post-revascularization assessment of myocardial wall motion)/(Total number of match segments analyzed) x100.

2) Number of patients with improved wall motion

The number and proportion of patients with one or more segments with “improved wall motion” were calculated to assess the diagnostic efficacy of ¹⁸F-FDG for myocardial viability on a per-patient basis. The proportion was calculated using the total number of patients in the analysis set as the denominator.

3) PPV of ¹⁸F-FDG for diagnosis of myocardial viability with the findings from myocardial perfusion SPECT at rest alone

As a routine practice, the diagnosis of myocardial viability by myocardial perfusion SPECT is often made by determining the uptake of a radioactive agent by myocardium at rest alone. We therefore assessed the diagnostic efficacy (PPV) of ¹⁸F-FDG in patients where myocardial perfusion SPECT at rest is performed, based on the results from myocardial perfusion SPECT at rest alone, excluding the results of SPECT at stress. The 95% two-sided confidence interval of the PPV was calculated as well.

4) Subgroup analysis with LVEF on PPV of ¹⁸F-FDG for diagnosis of myocardial viability

The PPVs of ¹⁸F-FDG were calculated for each of the subgroups of LVEFs (<30%, ≥30% and <40%, and ≥40%) at screening.

Data managements and statistical analyses were implemented by contract research organizations.

All statistical analyses were performed using SAS Version 9.1 (SAS Institute Japan, Tokyo, Japan).

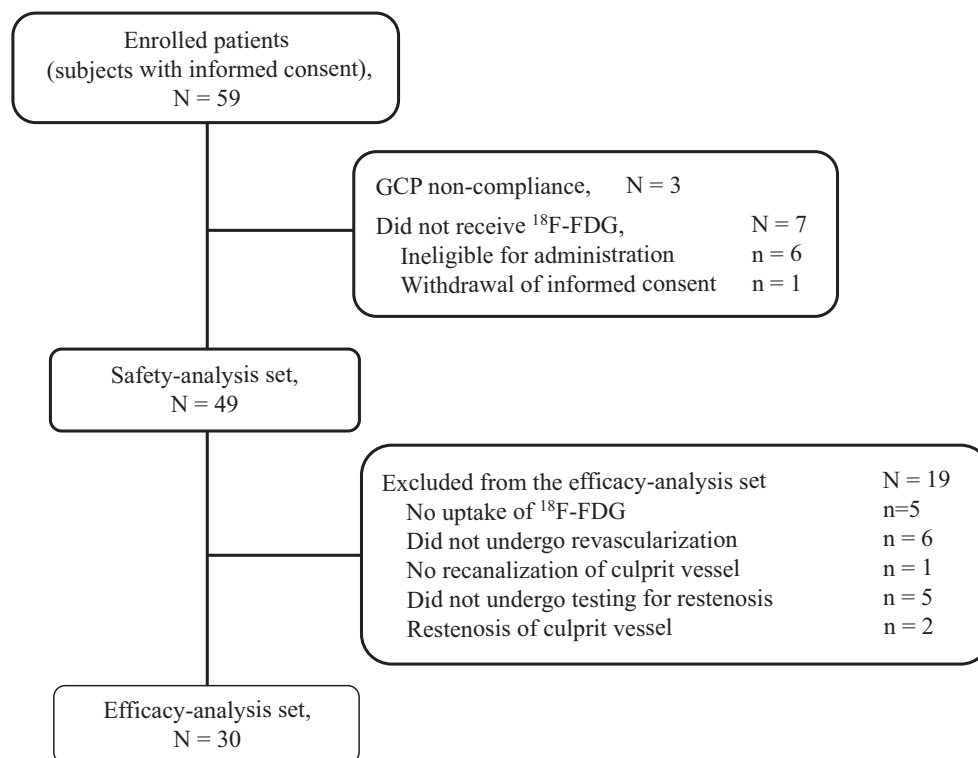
Results

Patient characteristics and disposition

The disposition of the patients analyzed in this study is shown as a flow chart in Fig. 3. A total of 59 patients were enrolled across the study sites, and 49 of them were included in the safety-analysis set. Ten patients, three due to GCP non-compliance and seven who did not receive ¹⁸F-FDG (six were deemed ineligible for administration and one withdrew consent) were excluded.

Among the 49 patients in the safety-analysis set, 30 were included in the efficacy-analysis set. Nineteen patients discontinued the study after ¹⁸F-FDG administration and were thus excluded from the efficacy-analysis set. These included five patients with the no uptake of ¹⁸F-FDG in the dysfunctional segments, six who did not undergo coronary revascularization, one without recanalization of the culprit vessel, five who did not undergo testing for restenosis, and two with restenosis of the culprit vessel.

The baseline characteristics of the 49 patients in the safety-

¹⁸F-FDG for the Diagnosis of Myocardial Viability**Fig. 3** Patient disposition

Of a total of 59 patients who were enrolled in this trial, 49 were included in the safety-analysis set: excluded three due to GCP non-compliance and seven who did not receive ¹⁸F-FDG. Of the 49 patients in the safety-analysis set, 30 were included in the efficacy-analysis set: excluded 19 who discontinued the study after ¹⁸F-FDG administration.

analysis set and the 30 patients included in the efficacy-analysis set are shown in Table 1.

In the 30 patients of the efficacy-analysis set, the mean time from ¹⁸F-FDG imaging to revascularization was 11.3 ± 15.3 days (range, 2-56 days), the mean time from coronary revascularization to assessment of myocardial wall motion was 228.6 ± 74.5 days (range: 101-358 days). The number of patients in the subgroups was 14 patients (46.7%) with 8 months or more, 11 (36.7%) with 5 months or more and less than 8 months, and five (16.7%) with 3 months or more and less than 5 months.

The results of the image analysis by the Image Evaluation Committee for the 30 patients in the efficacy-analysis set are shown in Table 2. The efficacy analysis was performed for a total of 119 segments that showed: 1) abnormal LV motion; 2) severe reduction or absence of, or incomplete redistribution of imaging agent on myocardium perfusion SPECT; and 3) ¹⁸F-FDG uptake, and were evaluable for post-revascularization wall motion. Representative images of perfusion/¹⁸F-FDG uptake mismatch are shown in Fig. 4.

Efficacy of ¹⁸F-FDG**1) ¹⁸F-FDG for diagnosis of myocardial viability**

PPV (mismatch) and NPV (match) of ¹⁸F-FDG for the diagnosis of myocardial viability are shown in Table 3.

PPV of ¹⁸F-FDG for diagnosing myocardial viability, based on the results of image analysis by the Image Evaluation Committee, was 63.9% (76/119; 95% CI: 54.6-72.5%).

NPV of ¹⁸F-FDG for diagnosing myocardial viability, based on the results of image analysis by the Image Evaluation Committee, was 63.9% (39/61; 95% CI: 50.6-75.8%).

The results were statistically significant when assessed by a Chi-square test ($p=0.0004$).

2) Number of patients with improved wall motion

The number of patients with or without improved wall motion is shown in Table 4. We assessed the improvement in wall motion on a per-patient basis by scoring a patient with at least one segment of improved wall motion as a patient with improved wall motion. Twenty-six of the 30 patients (86.7%) had improved wall motion after revascularization while four (13.3%) did not.

3) PPV of ¹⁸F-FDG for diagnosis of myocardial viability with the findings from myocardial perfusion SPECT at rest alone

PPV of ¹⁸F-FDG for diagnosing myocardial viability with the findings from myocardial perfusion SPECT at rest alone is shown in Table 5. We calculated PPV of ¹⁸F-FDG based on the results from myocardial perfusion SPECT at rest alone, excluding the findings of SPECT at stress. PPV of ¹⁸F-FDG with the findings from myocardial perfusion SPECT at rest

Table 1 Characteristics of patients who received ¹⁸F-FDG

Parameter		No. of patients (%) / descriptive statistics	
		Safety-analysis set	Efficacy-analysis set
No. of patients analyzed		49	30
Sex	Male	43 (87.8)	27 (90.0)
	Female	6 (12.2)	3 (10.0)
Age (years)	Mean	63.6	64.4
	Standard deviation	12.7	14.6
	Min/Max	33/91	33/91
Comorbidity	Diabetes mellitus	Yes	31 (63.3)
		No	18 (36.7)
	Other comorbidities	Yes	29 (96.7)
		No	1 (3.3)
Concomitant medication	Antidiabetic drugs	Yes	24 (49.0)
		No	16 (53.3)
	Medication for primary disease	Yes	28 (93.3)
		No	2 (6.7)
LVEF at screening (%)	Mean	35.5	36.8
	Standard deviation	9.4	8.0
	Min/Max	17/50	20/49
Classification of LVEF at screening	<30%	14 (28.6)	5 (16.7)
	≥30% and <40%	17 (34.7)	14 (46.7)
	≥40%	18 (36.7)	11 (36.7)
Glycemic control prior to ¹⁸ F-FDG administration	Oral glucose loading	10 (20.4)	5 (16.7)
	Insulin clamp	23 (46.9)	15 (50.0)
	Oral glucose loading and fast-acting insulin	15 (30.6)	10 (33.3)
	Without glycemic control	1 (2.0)	0 (0.0)

FDG: fluorodeoxyglucose; LVEF: left ventricular ejection fraction.

alone was 63.0% (63/100; 95% CI: 52.8-72.4%).

4) Subgroup analysis with LVEF on PPV of ¹⁸F-FDG for diagnosis of myocardial viability

The results of the subgroup analysis with LVEF on the diagnostic efficacy of ¹⁸F-FDG are shown in Table 6. PPVs by the subgroups with LVEF at screening of <30%, ≥30% and <40% and ≥40% were 46.7%, 70.6% and 58.3%, respectively.

Safety of ¹⁸F-FDG

A total of 10 adverse events were observed in 7 (14.3%) of the 49 patients in the safety-analysis set, including two events of hypoglycemia in two patients (4.1%), and one each (2.0%) of malignant lung neoplasm, oropharyngeal pain, nausea, increased blood bilirubin, increased blood lactate dehydrogenase, increased blood potassium, decreased heart rate, and increased white blood cell count. These were non-serious.

Among the seven patients with adverse events, six events in four patients (8.2%) (nausea, increased blood bilirubin, increased blood lactate dehydrogenase, increased blood potassium, decreased heart rate, and increased white blood cell count) were considered to be adverse drug reactions of ¹⁸F-

FDG. However, these were non-serious and recovered spontaneously or became less severe without medical treatment.

Discussion

We conducted this prospective, multicenter clinical study to confirm the diagnostic ability of ¹⁸F-FDG for the identification of viable myocardium in patients with heart failure due to ischemic heart disease. In particular, we focused on patients in whom conventional myocardial perfusion SPECT did not show distinct viability in dysfunctional myocardium.

¹⁸F-FDG PET for diagnosis of myocardial viability

The results of this study demonstrated that PPV and NPV, which represented the diagnostic efficacy of ¹⁸F-FDG for myocardial viability in patients with ischemic heart disease, were 63.9% and 63.9%. The results were statistically significant when assessed by a Chi-square test (p=0.0004), suggesting that there is a significant difference in the post-revascularization improvement in wall motion between the mismatch and match segments.

Table 2 Results of image analysis by the Image Evaluation Committee

Patient No.	Sex	Age	Coronary artery with significant stenosis	Revascularization method	Evaluation by the Image Evaluation Committee	
					No. of mismatch segments	No. of segments with improved wall motion
001	M	82	RCA	PCI	4	1
002	M	58	RCA LAD	PCI	3	2
003	M	49	RCA LAD	CABG	5	3
004	M	67	RCA LAD LCX	CABG	4	4
005	M	71	RCA LAD	PCI	9	8
006	M	68	RCA	PCI	5	2
007	M	64	RCA LAD LCX	CABG	5	4
008	F	75	LAD	PCI	3	0
009	M	65	LCX	PCI	3	3
010	M	42	RCA LAD LCX	CABG	5	3
011	M	33	RCA LAD	CABG	6	2
012	M	74	RCA LMT LAD LCX	CABG	3	3
013	M	60	LAD LCX	CABG	1	1
014	M	68	LAD	PCI	4	1
015	M	56	LAD LCX	PCI	6	6
016	M	73	LAD	PCI	7	7
017	F	68	LAD LCX	PCI	5	1
018	M	87	LAD LCX	PCI	5	4
019	M	56	RCA LCX	CABG	0	0
020	M	76	LAD LCX	PCI	3	0
021	M	77	RCA LAD LCX	PCI	2	2
022	M	41	RCA LAD LCX	CABG	5	3
023	M	77	LCX	PCI	3	3
024	M	54	LAD	PCI	3	3
025	M	64	RCA LAD LCX	CABG	4	0
026	M	50	RCA LAD LCX	PCI	2	1
027	M	36	RCA LAD LCX	CABG	4	1
028	M	79	RCA LAD LCX	PCI	1	1
029	M	72	RCA	PCI	7	6
030	F	91	LAD LCX	PCI	2	1

RCA: right coronary artery; LAD: left anterior descending coronary artery; LCX: left circumflex artery; LMT: left main trunk

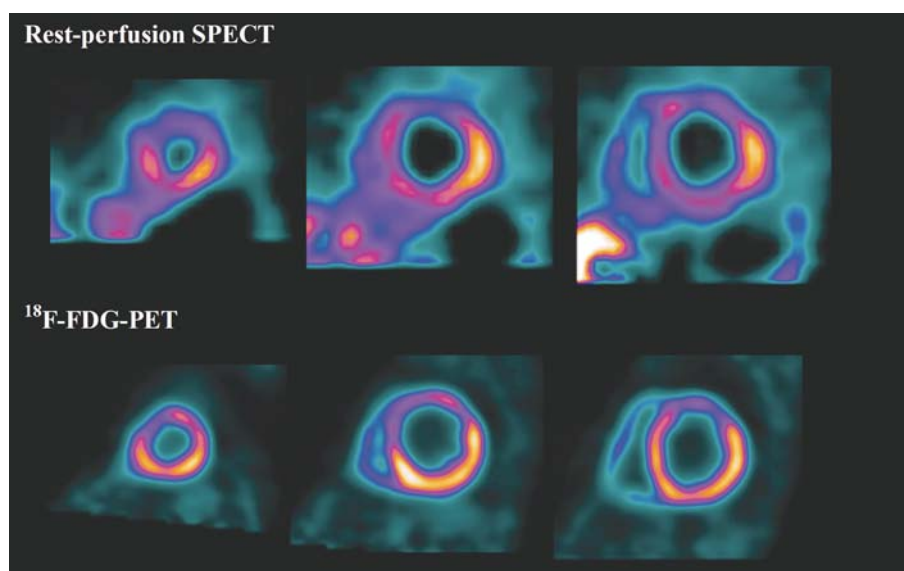


Fig. 4 Representative images of perfusion/¹⁸F-FDG uptake mismatch

Patient No. 015

Perfusion SPECT/¹⁸F-FDG uptake mismatch was present in the distal anterior, septal, and inferior myocardial segments. Improvement in wall motion was observed in all these segments after revascularization.

Table 3 ¹⁸F-FDG for diagnosis of myocardial viability

	Myocardial perfusion/ ¹⁸ F-FDG uptake* No. of segments (%)		Total number
	mismatch	match	
LV wall motion recovery (+)	76 (63.9)	22 (36.1)	98
LV wall motion recovery (−)	43 (36.1)	39 (63.9)	82
Total number	119 (100)	61 (100)	180

PPV (positive predictive value): 63.9% (95% CI: 54.6-72.5%)

NPV (negative predictive value): 63.9% (95% CI: 50.6-75.8%)

*of the segments that were assessed with “the diagnosis of myocardial viability is difficult” on myocardial perfusion SPECT

Chi-square test: $\chi^2=12.57$, df = 1, p=0.0004

It should be noted that ¹⁸F-FDG PET is performed for the assessment of myocardial viability, and when a case did not have a region that was diagnosed as “presence of myocardial viability”, the case would not be indicated for coronary revascularization. Therefore, in this study, if the uptake of ¹⁸F-FDG was absent in any of the segments that were considered as “the diagnosis of myocardial viability is difficult”, the case would be discontinued from the study, as it was not indicated for coronary revascularization.

The calculated NPV reported here was based on the limited cases where ¹⁸F-FDG uptake was observed, i.e., not including cases without ¹⁸F-FDG uptake and, therefore, it does not represent a true NPV.

On the other hand, PPV derived from previous studies (12-25) that verified that the diagnostic ability of this modality

was 72%.

The PPV obtained in this study, 63.9%, is lower than that from the previous studies, 72%. Although the previous studies as well as this study were conducted in patients with ischemic heart disease and impaired LV function, these studies did not employ a strictly standardized protocol but various study designs, for example, with differing methods and criteria of image evaluation and criteria for definite diagnosis. Furthermore, the previous results were obtained from studies that were conducted at a limited number of sites under standardized conditions. In contrast, this study was the first multicenter study in Japan with additional eligibility criteria to include patients where conventional myocardial perfusion SPECT was not contributive for the diagnosis of myocardial viability, which was one of the indications for the use of ¹⁸F-

Table 4 Number of patients with improvement in wall motion

No. of patients analyzed	Segment(s) with improvement in wall motion (No. of patients (%))	
	Yes	No
30	26 (86.7)	4 (13.3)

Table 5 PPV of ¹⁸F-FDG for diagnosis of myocardial viability with the findings from myocardial perfusion SPECT at rest alone

No. of patients analyzed	No. of segments analyzed	Improvement in wall motion (No. of segments)		PPV (%)	95% two-sided CI
		Yes	No		
30	100	63	37	63.0	52.8-72.4

CI: confidence interval; PPV: positive predictive value.

Table 6 Subgroup analysis with LVEF on PPV of ¹⁸F-FDG for diagnosis of myocardial viability

Parameter		No. of patients analyzed	No. of segments analyzed	Improvement in wall motion (No. of segments)		PPV (%)
				Yes	No	
LVEF at screening	<30%	5	15	7	8	46.7
	≥30% and <40%	14	68	48	20	70.6
	≥40%	11	36	21	15	58.3

LVEF: left ventricular ejection fraction; PPV: positive predictive value.

FDG. Patients in this study were thus limited to the population where the diagnosis of myocardial viability was difficult. Nonetheless, we observed that a considerable number of mismatch dysfunctional myocardium showed functional recovery after revascularization. The 95% confidence interval of the PPV obtained in this study, 54.6-72.5%, included the PPV from the previous literature (72%).

Number of patients with improved wall motion

The presence of segment (s) with post-revascularization improvement of wall motion was assessed on a per-patient basis and 86.7% of patients were considered to have segment (s) with improved wall motion. In other words, of the patients with impaired LV function where conventional myocardial perfusion SPECT was not contributive for the diagnosis of myocardial viability, more than 80% of the patients that were confirmed ¹⁸F-FDG uptake were observed with at least one segment with improved wall motion. Therefore, it is suggested that ¹⁸F-FDG is beneficial for the diagnosis of myocardial viability.

PPV of ¹⁸F-FDG for diagnosis of myocardial viability without the findings from myocardial perfusion SPECT at rest alone

PPV of ¹⁸F-FDG determined with the findings from myocardial perfusion SPECT at rest alone was 63.0%, which

was similar to that determined by including the findings of stress SPECT (63.9%). As a routine practice, diagnosis of myocardial viability by myocardial perfusion SPECT is often made by determining the uptake of a radioactive tracer by myocardium at rest alone (26). The fact that similar PPVs were obtained with or without the finding from stress SPECT further supported the benefit of ¹⁸F-FDG for the diagnosis of myocardial viability.

Subgroup analysis with LVEF on PPV of ¹⁸F-FDG for diagnosis of myocardial viability

PPVs of ¹⁸F-FDG were determined by the subgroups of LVEFs at screening. PPV in patients with an LVEF of <30% and ≥40% was relatively lower than that of ≥30% and <40% subgroup. It is suggested that the lower PPV in patients with LVEF <30% were due to the impaired LV function that prevented sufficient improvement of wall motion after revascularization, while in patients with LVEF ≥40%, LV function was relatively well-preserved and improvement on wall motion due to revascularization were not enough to produce an observable change in the wall-motion scores. The higher PPV in patients with an intermediate LVEF of ≥30% and <40% is likely to result from the relatively well-preserved LV function and observable post-vascularization improvement of wall motion.

Safety assessment

As for the safety of ¹⁸F-FDG, 10 adverse events occurred in seven of 49 patients (14.3%), and six of these events in four patients (8.2%) were adverse drug reactions of ¹⁸F-FDG. However, these events were non-serious and it suggested that ¹⁸F-FDG was well tolerated. It should be noted that two patients developed non-serious hypoglycemia, which may have been caused by pre-imaging control of blood glucose by insulin before the administration of ¹⁸F-FDG. Therefore, glycemic control should be done with caution prior to administration.

Limitations of the study

The purpose of this study was to confirm the indication for ¹⁸F-FDG and therefore when uptake of ¹⁸F-FDG was not observed in a region that showed abnormal LV motion with severe reduction or absence of, or incomplete redistribution of imaging agent on myocardium perfusion SPECT, the patient was discontinued from the study. Accordingly, true NPV was not determined. In addition, as strict eligibility criteria were specified to conform to the indication for ¹⁸F-FDG, the number of patients included in the study was limited.

Conclusions

The results of this study confirmed that the identification of myocardial viability by ¹⁸F-FDG will be widely beneficial in predicting improvement in myocardial wall motion after coronary revascularization. No serious safety concerns are expected with the clinical use of ¹⁸F-FDG.

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Conflicts of interest

At the time of this study, Ichiro Matsunari was a staff member of the Medical and Pharmacological Research Center Foundation, and has received honoraria from Nihon Medi-Physics Co., Ltd. as a medical advisor. Nagara Tamaki received honoraria for lectures and research funding from Nihon Medi-Physics. Kei Iida, Yasuyoshi Iwado and Shin-ichiro Kumita received honoraria for lectures from Nihon Medi-Physics. Shuji Sakai and Shigeki Nagamachi received research funding from Nihon Medi-Physics. Masatoshi Ikeda, Hiroaki Naito, Osamu Okazaki and Shinji Miki have no conflicts of interest. Nami Sugiura and Masako Teramachi are employees of Nihon Medi-Physics Co., Ltd.

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