Myocardial ^{18}F-FDG Uptake After Exercise-Induced Myocardial Ischemia in Patients with Coronary Artery Disease

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We have recently demonstrated the potential of ^{18}F-FDG as an imaging marker of myocardial ischemia if injected at peak exercise. However, how long increased ^{18}F-FDG uptake can be observed after an episode of exercise-induced myocardial ischemia is not known. We performed the current study to determine whether increased regional myocardial ^{18}F-FDG uptake at exercise in patients with coronary artery disease (CAD) persists on rest imaging (24 h later), after an episode of exercise-induced myocardial ischemia. **Methods:** Twenty-four patients with suspected CAD underwent exercise ^{99m}Tc-sestamibi and ^{18}F-FDG imaging. Repeated ^{18}F-FDG imaging was performed 24 h after exercise imaging, after an injection of a second dose of ^{18}F-FDG at rest in 20 patients. Perfusion imaging with ^{99m}Tc-sestamibi was simultaneously performed with ^{18}F-FDG imaging. All patients underwent coronary angiography. **Results:** Eighteen patients had greater than or equal to 70% luminal narrowing of 1 or more coronary vessels. Fifteen patients (83%) showed increased regional ^{18}F-FDG uptake on exercise imaging, but only 11 patients (61%) had perfusion abnormalities. Of these 15 patients with increased regional ^{18}F-FDG uptake on exercise imaging, 8 (53%) had no discernible ^{18}F-FDG uptake, 5 (33%) had decreased ^{18}F-FDG uptake, and only 2 (13%) had persistent ^{18}F-FDG uptake on rest ^{18}F-FDG images. The summed ^{18}F-FDG uptake score significantly decreased, from 14.4 ± 10.3 at exercise to 6.7 ± 9.2 at rest ($P = 0.01$). Patients with persistent ^{18}F-FDG uptake at rest had more ^{18}F-FDG uptake and lower peak rate–pressure product at exercise, compared with patients with no residual ^{18}F-FDG uptake at rest. **Conclusion:** Exercise-induced regional myocardial ^{18}F-FDG uptake is highly specific and sensitive for exercise-induced myocardial ischemia. Regional myocardial ^{18}F-FDG uptake may persist 24 h after an episode of exercise-induced myocardial ischemia in some patients.

Key Words: myocardium; ischemia; coronary artery disease; exercise; rest; ^{18}F-FDG

J Nucl Med 2008; 49:1986–1991
DOI: 10.2967/jnumed.108.052936

Scintigraphic myocardial perfusion imaging is a widely used noninvasive modality for the detection and risk stratification of coronary artery disease (CAD) (*1*). Despite its extensive use, this technique suffers from several limitations. Artifacts during image acquisition and reconstruction degrade the image quality. Rest–stress imaging sequences take several hours to complete. Despite a high sensitivity of exercise–rest perfusion imaging for the detection of CAD, its sensitivity for the detection of individual vessels with significant disease is not high (*2*). A technique for direct imaging of myocardial ischemia can potentially overcome some of these limitations. Myocardial ischemia results in a dramatic and sustained switch to glucose uptake (*3–7*). A differential uptake of glucose between normal and ischemic myocardium can be used for hot-spot imaging of myocardial ischemia. Several studies have recently documented the potential of ^{18}F-FDG as an ischemic marker (*8–12*), and a successful demonstration of ^{18}F-FDG as an ischemia imaging agent also raises several important questions (*13*). A series of carefully planned studies is needed to address these issues before stress ^{18}F-FDG imaging can be considered for routine clinical use. An important issue is how long after an episode of exercise-induced myocardial ischemia increased myocardial ^{18}F-FDG uptake can be observed. This information is critical for designing an optimal clinical imaging protocol for imaging exercise-induced myocardial ischemia with ^{18}F-FDG and for understanding the pathophysiology and molecular biology of myocardial ischemia.

In experimental animal studies, upregulation of glucose uptake by the ischemic myocardium can persist for hours to days, even after a brief episode of ischemia (*6,7*). It is quite likely, but not necessarily definitive, that in humans increased regional ^{18}F-FDG uptake may also persist for several hours after an episode of exercise-induced myocardial ischemia. Moreover, whether this persistence of increased regional ^{18}F-FDG uptake would allow diagnostic-quality images to be obtained if ^{18}F-FDG were injected hours after an episode of exercise-induced myocardial ischemia and whether the persistence of ^{18}F-FDG uptake correlates with the severity of

Received Mar. 31, 2008; revision accepted May 28, 2008.
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ischemia or with the severity of luminal obstruction of coronary arteries are both unclear. This information is important for the evaluation of ^{18}F-FDG as a memory marker of myocardial ischemia.

In the present study, we repeated ^{18}F-FDG imaging 24 h after exercise by injecting a second dose of ^{18}F-FDG at rest in patients with CAD who showed increased ^{18}F-FDG uptake at exercise. The primary aim of this study was to determine whether increased myocardial ^{18}F-FDG uptake at exercise persists at rest after (24 h) an episode of exercise-induced myocardial ischemia. The secondary aims were to determine the frequency of the occurrence of persistent ^{18}F-FDG uptake after an episode of exercise-induced myocardial ischemia and to determine its relationship with the clinical, angiographic, and scintigraphic variables.

MATERIALS AND METHODS

Patients

Patients with strong clinical suggestion of CAD, based on the symptoms of exertional angina and risk factors for CAD, or patients with angiographic CAD were enrolled. Patients were excluded if they had 1 of the following conditions: prior myocardial infarction (history of previous documented myocardial infarction or Q waves on electrocardiogram consistent with prior myocardial infarction), diabetes mellitus, unstable angina, prior coronary revascularization, or inability to exercise. Patients with diabetes were excluded because of the logistic difficulties in controlling variables such as the degree of control, pharmacotherapy, and fasting for at least 12 h for imaging sessions. Written informed consent was obtained from the patients before they enrolled, and the protocol was approved by the institutional review board.

Study Protocol

All patients underwent exercise myocardial ^{99m}Tc-sestamibi and ^{18}F-FDG imaging. Patients with increased myocardial ^{18}F-FDG uptake on exercise ^{18}F-FDG images underwent a repeated ^{99m}Tc-sestamibi and ^{18}F-FDG scan using a second injection of ^{99m}Tc-sestamibi and ^{18}F-FDG 24 h later. The exercise testing and imaging protocol have been described previously (*11*). In brief, after overnight fasting (>12 h), a symptom-limited exercise test using a bicycle ergometer was performed with continuous electrocardiography and blood pressure monitoring. Antianginal medications (β-blockers, calcium channel blockers, and nitrates) were withheld for at least 12 h before exercise testing. ^{99m}Tc-sestamibi (740–925 MBq) and ^{18}F-FDG (185–296 MBq) were injected intravenously at peak exercise. Simultaneous tomographic images of ^{99m}Tc-sestamibi and ^{18}F-FDG were acquired 1–2.5 h (mean, 92 min; range, 60–136 min) after tracer injection. Rest imaging was performed on the next day (the interval between exercise and rest imaging was 23.5 h; range, 23.1–23.9 h). The patients also fasted overnight before rest imaging. Image acquisition was performed 1–2.5 h after tracer injection (mean, 127 min). Blood sugar levels were measured just before the exercise test and before injection of the tracers at rest imaging. Figure 1 describes the study protocol.

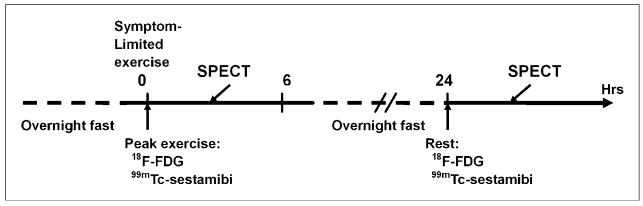

FIGURE 1. Schematic of study protocol.

Image Acquisition and Reconstruction

Images were acquired using a dual-head, large-field-of-view SPECT camera (Varicam; GE Healthcare), equipped with a 1.6-cm (5/8-in)-thick crystal and ultra-high-energy parallel-hole collimators. Thirty projection images were acquired over a 180° arc at 6° intervals. The acquisition time was 50 s at each projection. Both exercise and rest myocardial images were reconstructed using standard filtered backprojection and displayed as a series of short-axis and horizontal and vertical long-axis slices. Two separate sets of tomographic slices for exercise ^{99m}Tc-sestamibi and ^{18}F-FDG were simultaneously obtained, with exact correspondence in spatial orientation.

Image Interpretation

Perfusion and ^{18}F-FDG ischemia images were visually interpreted by 2 experienced nuclear cardiologists, in a masked manner. The differences were resolved by consensus. Perfusion images on both exercise and rest ^{99m}Tc-sestamibi imaging were scored using a 17-segment model and 5-score scale (0, normal uptake; 1, mild reduction in uptake; 2, moderate reduction in uptake; 3, severe reduction in uptake; and 4, no uptake). Myocardial segments were scored as normal, ischemic, ischemic and scarred, or scarred on the basis of abnormalities on stress and rest images. ^{18}F-FDG images were scored using the same 17-segment model on a 0–2 scale (0, no discernible ^{18}F-FDG uptake above the background level; 1, mild uptake but above the background level; and 2, intense uptake). Myocardial segments with uptake scores of 1 and 2 were defined as showing ischemia. Stress and rest ^{18}F-FDG images were compared for changes in ^{18}F-FDG uptake observed on stress images. Changes were classified as no uptake on rest images with a change in scores to 0 from 1 or 2 on exercise images. Decreased ^{18}F-FDG uptake was defined as a decrease in ^{18}F-FDG uptake score from 2 to 1, and persistent ^{18}F-FDG uptake was defined as no change or an increase from 1 to 2. The summed ^{18}F-FDG uptake score was obtained by summing the score of each segment. Myocardial segments were assigned to vascular territories for angiographic comparison as follows: anterior and septal segments to the left anterior descending coronary artery, lateral segments to the left circumflex coronary artery, and inferior segments to the right coronary artery.

Coronary Angiography and Left Ventriculography

Coronary angiography was performed within 1 wk of scintigraphy and interpreted by 2 expert interventional cardiologists. The presence, localization, and severity of coronary arteries were analyzed using quantitative coronary angiographic analysis. Luminal diameter narrowing of 70% or more in any of the major epicardial coronary arteries was considered significant disease, luminal narrowing in the range of 50%−69% was considered mild disease, and luminal narrowing of less than 50% was considered insignificant disease. Left ventriculography was performed in the 30° right anterior oblique projection, left ventricular ejection fraction was calculated using the area–length method, and wall motion was visually assessed.

TABLE 1
Angiographic (Percentage Luminal Narrowing) and Scintigraphic Data

Patient no.	Left main artery	Left ascending artery	Left circumflex artery	Right coronary artery	Perfusion abnormalities	Exercise ^{18}F-FDG uptake
1	—	80	80	80	Ant	Ant
2	—	99	—	80	Ant, Sep	Ant, Sep, Lat
3	—	—	—	85	Inf	Inf
4	—	90	—	—	Ant, Sep	Ant, Sep
5	—	90	50	80	Ant, Sep	Ant, Sep
6	—	95	95	—	Ant, Sep	Ant, Sep
7	—	90	80	80	Ant, Sep	Ant, Sep
8	60	60	90	—	—	Ant, Sep, Lat, Inf
9	—	100	70	70	Ant, Sep	Ant, Sep, Lat
10	—	70	—	60	—	Ant, Sep, Lat, Inf
11	—	90	60	90	Ant, Sep, Inf	Ant, Sep, Lat, Inf
12	—	95	—	50	Ant	Ant, Lat
13	—	100	—	—	Ant	Ant, Sep, Lat, Inf
14	—	80	80	90	—	Ant, Sep, Lat, Inf
15	—	80	80	—	—	Apex
16	—	—	70	—	—	—
17	—	—	—	50	—	—
18	—	60	—	—	—	—
19	—	75	60	—	—	—
20	—	70	—	—	—	—
21	—	—	—	—	—	—
22	—	—	—	—	—	—
23	—	—	—	—	—	—
24	—	—	—	—	—	—

— = no abnormality; Ant = anterior wall; Sep = interventricular septum; Lat = lateral wall; Inf = inferior wall.
Apex is mentioned only if this was the only site of abnormality.

Statistical Analysis

Continuous variables are described as mean and SD of the means, and categoric variables are described as frequencies. The paired *t* test was used to compare the difference in continuous variables between exercise and rest values. To determine the variables related to persistent ^{18}F-FDG uptake, the Mann–Whitney *U* test was used to compare the difference in continuous variables, and the χ^2 test was used to compare the difference in categoric variables. A *P* value of less than 0.05 was considered significant.

RESULTS

Twenty-six patients were initially recruited. Two patients were excluded because one patient did not undergo angiography, and the other, who showed increased ^{18}F-FDG uptake on exercise imaging, declined rest imaging. The remaining 24 patients (21 men; age, 60 ± 10 y) constitute our patient population.

Exercise Testing

The mean exercise time was 442 ± 135 s (range, 208–683 s). Heart rate increased from 64 ± 13 beats per minute at baseline to 119 ± 18 beats per minute at peak exercise ($P < 0.0001$); systolic blood pressure increased from 133 ± 24 mm Hg to 171 ± 23 mm Hg ($P < 0.0001$). During exercise testing, chest pain developed in 14 patients and ischemic electrocardiography changes in 13.

Coronary Angiography

Eighteen patients showed greater than or equal to 70% luminal narrowing of 1 or more coronary vessels or their major branches. Two patients showed only mild disease (50%−69% luminal narrowing range), and 4 had no luminal narrowing (Table 1). Left ventricular wall motion and ejection fraction were normal in all patients.

^{99m}Tc-Sestamibi Images

Eleven of 18 patients (61%) with significant CAD had perfusion abnormalities. Of these, 7 patients had reversible perfusion abnormalities, 4 had partially reversible perfusion abnormalities, and none had persistent defects. None of the

TABLE 2
Rest ^{18}F-FDG Uptake in Patients with Increased ^{18}F-FDG Uptake on Exercise Study

Parameter	Rest ^{18}F-FDG uptake		
	No uptake	Decreased	Persistent
Patients (n = 15)	8	5	2
Vascular territories (n = 28)	12	12	4
Myocardial segments (n = 123)	73	16	34

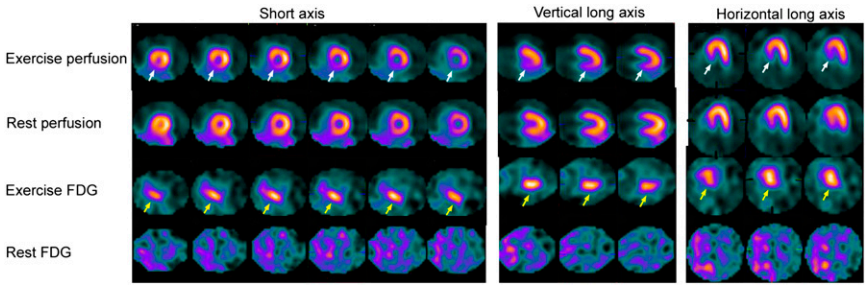

FIGURE 2. Exercise and rest ^{99m}Tc-sestamibi perfusion and ^{18}F-FDG images of 49-y-old man (patient 3) with exertional angina, in short-axis and vertical and horizontal long-axis slices. Exercise-induced perfusion abnormality in septum and inferior wall (white arrows) is demonstrated, which is reversible on rest images. Intense ^{18}F-FDG uptake on exercise images (yellow arrows) is shown in corresponding segments, which is not present in rest images. This patient had 85% right coronary artery stenosis.

2 patients with mild CAD or the 4 patients with no CAD had perfusion abnormalities. Of 39 vascular territories supplied by arteries with luminal narrowing of at least 50%, 12 (31%) had perfusion abnormalities on exercise images; of 31 vascular territories with luminal narrowing of at least 70%, 12 (39%) had perfusion abnormalities.

Exercise ^{18}F-FDG Imaging

Fifteen of 18 patients (83%) with significant CAD had increased myocardial ^{18}F-FDG uptake. Of the 15, 3 had 1-vessel disease, 6 had 2-vessel disease, and 6 had 3-vessel disease. None of the 2 patients with mild CAD or 4 patients with no CAD had increased ^{18}F-FDG uptake.

Of 39 vascular territories with luminal narrowing of 50% or more, 22 (56%) had increased ^{18}F-FDG uptake; of 31 vascular territories with luminal narrowing of 70% or more, 19 (61%) had increased ^{18}F-FDG uptake. Six vascular territories with no significant luminal obstruction had abnormal ^{18}F-FDG uptake. However, this uptake was seen in myocardial segments adjoining the vascular territories with significant luminal obstruction and intense ^{18}F-FDG uptake.

Change in Myocardial ^{18}F-FDG Uptake from Exercise to Rest Imaging

Fifteen patients with increased ^{18}F-FDG uptake on exercise imaging underwent rest imaging. Table 2 shows the change in myocardial ^{18}F-FDG uptake from exercise to rest imaging. Eight of these 15 patients (53%) with increased ^{18}F-FDG uptake on exercise imaging had no discernible ^{18}F-FDG uptake, 5 patients (33%) had decreased ^{18}F-FDG uptake, and only 2 patients (13%) had persistent ^{18}F-FDG uptake at rest (Figs. 2–4). The summed ^{18}F-FDG uptake score significantly decreased from 14.4 ± 10.3 (range, 2–34) at exercise to 6.7 ± 9.2 (range, 0–28) at rest ($P < 0.01$).

^{18}F-FDG uptake was observed in 28 vascular territories on exercise images (22 with ≥50% narrowing of coronary arteries and 6 with normal coronaries). By vascular territory analysis, 12 (43%) of the 28 vascular territories with increased ^{18}F-FDG uptake at exercise showed no ^{18}F-FDG uptake, 12 (43%) showed decreased ^{18}F-FDG uptake, and 4 (14%) showed persistent ^{18}F-FDG uptake at rest. The average ^{18}F-FDG uptake score of those vascular territories decreased from 7.7 ± 3.5 at exercise to 3.1 ± 4.1 at rest ($P < 0.0001$).

By segmental analysis, 123 segments showed ^{18}F-FDG uptake at exercise. Of these, 73 (59%) showed no ^{18}F-FDG uptake, 16 (13%) showed decreased uptake at rest, and only 34 (28%) showed persistent ^{18}F-FDG uptake. The average ^{18}F-FDG uptake score of those segments decreased from 1.7 ± 0.4 at exercise to 0.7 ± 0.9 at rest ($P < 0.0001$).

Five of 9 patients who had no ^{18}F-FDG uptake on exercise imaging underwent rest imaging (3 had angiographic CAD and 2 had normal coronary arteries). None of these patients showed any ^{18}F-FDG uptake on rest images.

Variables Related to Persistent ^{18}F-FDG Uptake

Those patients with residual (persistent or decreased) ^{18}F-FDG uptake had more ^{18}F-FDG uptake and a lower rate–pressure product at peak exercise than did patients with no residual ^{18}F-FDG uptake at rest (Table 3). The vascular territories with residual ^{18}F-FDG uptake had more

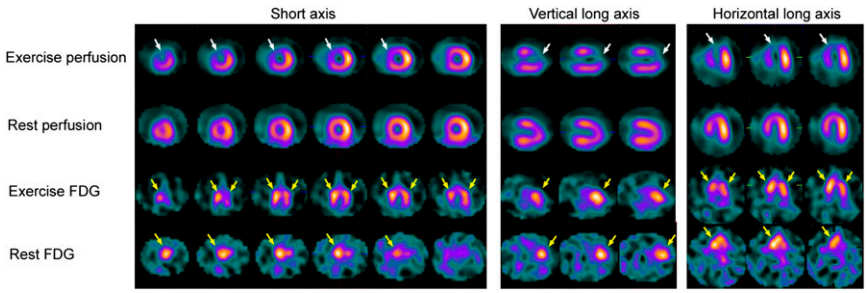

FIGURE 3. Exercise and rest ^{99m}Tc-sestamibi perfusion and ^{18}F-FDG images of 51-y-old man (patient 2) with exertional angina, in short-axis and vertical and horizontal long-axis slices. Reversible perfusion abnormality involving anterior and septal walls (white arrows) is demonstrated. Intense ^{18}F-FDG uptake in anterior, septal, and lateral walls on exercise images is shown. ^{18}F-FDG uptake persists on rest images but is significantly less intense (yellow arrows). This patient had 99% stenosis of left anterior descending and 80% stenosis of right coronary artery.

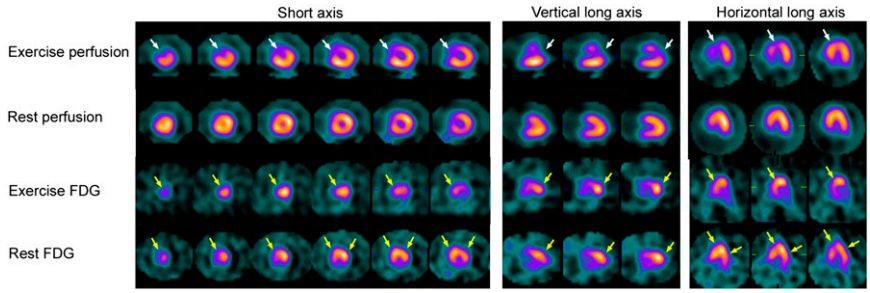

FIGURE 4. Exercise and rest ^{99m}Tc-sestamibi perfusion and ^{18}F-FDG images of 71-y-old man (patient 7) with exertional angina, in short-axis and vertical and horizontal long-axis slices. Reversible perfusion abnormality involving anterior and septal walls (white arrows) is shown. Intense ^{18}F-FDG uptake in anterior and septal walls on exercise images is demonstrated. ^{18}F-FDG uptake persists on rest images in anterior and septal walls, and lateral wall also showed intense ^{18}F-FDG uptake (yellow arrows). This patient had 90% stenosis of left anterior descending and 80% stenosis of circumflex and right coronary artery.

^{18}F-FDG uptake at exercise than did vascular territories with no residual ^{18}F-FDG uptake (Table 4).

DISCUSSION

These data show that a majority (87%) of patients with exercise-induced myocardial ^{18}F-FDG uptake had no discernible uptake or decreased ^{18}F-FDG uptake at 24 h after exercise. This finding indicates that in this patient population, exercise-induced increased regional myocardial ^{18}F-FDG uptake is specific for exercise-induced myocardial ischemia. Nevertheless, ischemic ^{18}F-FDG uptake may persist 24 h after exercise in some patients.

Duration of ^{18}F-FDG Uptake After Myocardial Ischemia

It is well known that myocardial ischemia is accompanied by increased exogenous glucose use in experimental animal models (*3–7*). ^{18}F-FDG, an analog of glucose, is a suitable agent for imaging myocardial ischemia (*13–15*).

In experimental animal studies, a postischemic increase of myocardial glucose uptake can persist for 24 h or longer. McNulty et al. (*6*) demonstrated that reperfused myocardial regions exhibited an increase in absolute ^{18}F-FDG activity relative to the control region, ranging from 40% in the endocardium to 15% in the epicardium. In the present study, the exercise-induced myocardial ^{18}F-FDG uptake substantially decreased but may persist in some patients when ^{18}F-FDG was reinjected 24 h later.

TABLE 3
Factors Related to Persistent ^{18}F-FDG Uptake at Patient Level

Factor	Rest ^{18}F-FDG uptake: Present (n = 7)	Rest ^{18}F-FDG uptake: Absent (n = 8)	P
BS before exercise	5.6 ± 0.4	5.5 ± 0.7	0.56
BS at rest	5.6 ± 0.5	5.8 ± 0.7	0.64
Baseline RPP (10^3)	7.7 ± 1.7	8.9 ± 2.3	0.42
Peak RPP (10^3)	16.7 ± 3.4	21.3 ± 4.2	0.04
Chest pain during exercise	7	7	1.00
Ischemic electrocardiogram change	5	7	0.57
Abnormal perfusion	4	7	0.28
Number of diseased vessels	2.3 ± 0.8	2.1 ± 0.8	0.71
Perfusion score at exercise	8.4 ± 8.3	5.5 ± 5.3	0.77
Perfusion score at rest	1.0 ± 1.3	0.3 ± 0.7	0.18
^{18}F-FDG uptake score on exercise	22.6 ± 8.7	7.3 ± 4.7	0.004

BS = blood sugar (in mmol/L); RPP = rate pressure product.

Exercise ^{18}F-FDG for Myocardial Ischemia Imaging

Human studies from our group and others have investigated the feasibility of imaging ischemia with ^{18}F-FDG in different patient subgroups and using different study protocols (*8–12*). In the present series of 18 patients with significant coronary stenosis, 83% showed regional ^{18}F-FDG uptake on exercise imaging, but only 61% had perfusion abnormalities. The results of this study confirm our previous results (*11*) and indicate the potential superiority of exercise ^{18}F-FDG and perfusion imaging over exercise and rest perfusion imaging for the detection of CAD. Simultaneous exercise ^{18}F-FDG and perfusion imaging has higher sensitivity than does exercise–rest perfusion imaging and detects more vascular territories with significant luminal narrowing.

TABLE 4
Factors Related to Persistent ^{18}F-FDG Uptake at Vascular Level

Factor	Rest ^{18}F-FDG uptake: Present (n = 16)	Rest ^{18}F-FDG uptake: Absent (n = 12)	P
Percentage luminal stenosis	66 ± 38	75 ± 26	0.75
Perfusion score at exercise	3.7 ± 6.8	4.0 ± 3.9	0.15
Perfusion score at rest	0.4 ± 1.0	0.2 ± 0.6	0.47
^{18}F-FDG uptake score at exercise	9.4 ± 2.7	5.7 ± 2.9	0.01

Interplay Between Fatty Acid and Glucose Metabolism During Myocardial Ischemia

The present study demonstrates that exercise-induced myocardial ^{18}F-FDG uptake may persist 24 h after exercise. Our findings are supported by prior data in experimental animals, in which upregulation of glucose uptake by the ischemic myocardium was shown to persist for hours to days, even after a brief episode of ischemia (*6,7*). Furthermore, Dilsizian et al. (*16*) recently demonstrated that prolonged suppression of fatty acid correlates with the magnitude of exercise-induced perfusion abnormality, and β-methyl-*p*-^{123}I-iodophenyl-pentadecanoic acid imaging can demonstrate the metabolic imprint of an exercise-induced ischemic episode within 30 h. The metabolic changes after myocardial ischemia might be imaged with SPECT and PET. It will be of great significance to correlate the glucose and fatty acid imaging on the postischemic imaging.

Study Limitations

Left ventricular wall motion was not simultaneously evaluated during the imaging period because of a technical reason: the relationship between persistence of ^{18}F-FDG uptake and the abnormalities of left ventricular wall motion cannot be determined. Second, although the ^{18}F-FDG uptake was visually scored in the present study, ^{18}F-FDG uptake on both exercise and rest images might be more reliably scored using some quantitative method. However, no such quantitative program is currently available. Finally, myocardial uptake of glucose may be influenced by substrate availability: insulin, free fatty acids, and catecholamine levels at the time of ^{18}F-FDG injection were not determined in this study. Further study of a larger sample size should be performed with quantitative analysis, and the repeatability of exercise-induced myocardial ^{18}F-FDG uptake and the effect of substrate need to be evaluated.

CONCLUSION

Exercise-induced regional myocardial ^{18}F-FDG uptake is highly specific and sensitive for exercise-induced myocardial ischemia. Regional myocardial ^{18}F-FDG uptake may persist 24 h after an episode of exercise-induced myocardial ischemia.

ACKNOWLEDGMENT

This study was supported by Specialized Research Fund for the Doctoral Program of Higher Education (20040023009) from the Ministry of Education, China.

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