Direct Imaging of Exercise-Induced Myocardial Ischemia With Fluorine-18–Labeled Deoxyglucose and Tc-99m-Sestamibi in Coronary Artery Disease

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Background—Scintigraphic myocardial perfusion imaging is the most widely used noninvasive modality for the detection of coronary artery disease (CAD). A technique for direct imaging of exercise-induced myocardial ischemia is highly desirable and preferable over perfusion imaging but is presently unavailable. We evaluated the feasibility and diagnostic accuracy of direct imaging of exercise-induced myocardial ischemia with fluorine-18-2-deoxyglucose (18FDG).

Methods and Results—Twenty-six patients with known or suspected CAD and no prior myocardial infarction underwent simultaneous myocardial perfusion and ischemia imaging after the intravenous injection of Tc-99m-sestamibi (99mTc-sestamibi) and 18FDG at peak exercise. Rest perfusion imaging was carried out separately. All patients underwent coronary angiography. Exercise 18FDG myocardial images were compared with exercise-rest 99mTc-sestamibi images and coronary angiography. Of 22 patients with ≥50% narrowing of ≥1 coronary arteries, 18 had perfusion abnormalities (sensitivity 82%) whereas 20 had abnormal myocardial 18FDG uptake (sensitivity 91%, P=NS). Perfusion abnormalities were seen in myocardial segments corresponding to 25 vascular territories of a total of 51 vessels with ≥50% luminal narrowing in 22 patients (sensitivity 49%), whereas increased 18FDG uptake was seen in 34 vascular territories (sensitivity 67%, P=0.008). 18FDG images were of high quality and easy to interpret but required simultaneous perfusion images for localizing abnormal myocardial 18FDG uptake.

Conclusions—Exercise-induced myocardial ischemia can be imaged directly with 18FDG. Combined exercise 18FDG-99mTc-sestamibi imaging provides a better assessment of exercise-induced myocardial ischemia compared with exercise-rest perfusion imaging. Direct ischemia imaging eliminates some of the limitations of presently used myocardial perfusion imaging. Large-scale clinical studies are warranted. (Circulation. 2003;108:1208-1213.)

Key Words: myocardium ■ ischemia ■ coronary artery disease ■ exercise ■ imaging

Coronary artery disease (CAD) is the single most important cause of morbidity and mortality on a global scale. Early detection and risk stratification are critical for reducing the morbidity and mortality associated with CAD. Radionuclide myocardial perfusion imaging during exercise or pharmacological stress and at rest is widely used for diagnosis and risk stratification of CAD.1,2 This technique relies on the demonstration of perfusion abnormalities on stress images, which normalize on rest images in the presence of myocardial ischemia but persist in the presence of scar attributable to prior myocardial infarction. However, despite being in extensive clinical use, this technique suffers from limitations inherent to cold spot imaging, such as suboptimal sensitivity and specificity attributable to limited resolution, partial volume effect, scatter, and soft tissue attenuation.3,4 Availability of a radiotracer with selective uptake in the ischemic myocardium (hot spot imaging) can potentially eliminate these limitations. However, presently no ischemia-imaging agent is available for routine clinical use. There is a need for the development of radiotracers targeted for ischemic myocardium.

Myocardial ischemia results in a dramatic and sustained switch to glucose uptake.5–15 The differential uptake of glucose in ischemic myocardium can help develop a hot spot imaging agent for myocardial ischemia. Fluorine-18 (18F)-labeled 2-deoxyglucose (18FDG), a glucose analog, tracks the initial steps of glucose transport and uptake across the cell membrane and is used extensively in oncology and neurology for imaging tumors and brain lesions.16,17 In cardiovascular medicine, 18FDG use has remained confined to the detection

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Drs He and Jain have a patent pending for the technique of myocardial ischemia imaging with FDG.

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of myocardial viability in segments with previous myocardial infarction and resting wall motion abnormalities. For viability, resting 18F-FDG imaging after glucose loading and resting perfusion imaging are performed. Recent technical modifications allow the use of conventional gamma cameras for 18F imaging instead of the PET imaging system.

In this study, we evaluated the feasibility and accuracy of exercise 18F-FDG imaging for direct imaging of exercise-induced myocardial ischemia. The results of exercise 18F-FDG imaging were compared with those of standard exercise-rest perfusion imaging and coronary angiography.

Methods

Patients

Patients with documented or suspected CAD based on the symptoms of angina pectoris or presence of multiple risk factors for CAD who were referred for exercise myocardial perfusion imaging were included. Patients with evidence of prior myocardial infarction or unstable angina and those unable to exercise were excluded. All antianginal and other cardiac medications were withheld on the morning of the exercise test and were resumed after completion of the exercise test. Only patients who subsequently underwent coronary angiography and had no interval change in their symptoms or clinical condition were included in this study. Patients with significant valvular heart disease and cardiomyopathy were excluded. Written informed consent was obtained from the patients before enrollment, and this protocol was approved by the institutional review board.

Imaging Studies

All patients underwent a symptom-limited exercise test with ergometer bicycle using standard protocol after an overnight fast. Twelve-lead ECG was monitored continuously during exercise, and blood pressure was checked every 3 minutes. Patients were encouraged to exercise until they developed angina, shortness of breath, or ≥2-mm ST-segment depression or attained age-predicted maximum heart rate or were unable to exercise any further. 99mTc-sestamibi (25 mCi) and 18F-FDG (8 to 10 mCi) were injected intravenously at peak exercise. After 40 to 60 minutes of radiotracer injection, the patients underwent imaging using a dual-head large-field-of-view single-crystal SPECT camera (Varicam, GE) equipped with ultra-high-energy parallel-hole collimators. This camera was equipped with 7/8-inch-thick sodium iodide crystal instead of the traditional 3/8- to 5/8-inch-thick crystal to optimize the detection of high-energy (511-KeV) 18F photons. Use of separate energy windows of 99mTc (140±20%) and 18F (51±30%) allowed simultaneous imaging of 99mTc-sestamibi and 18F-FDG. Sixty projection images were acquired over a 180-degree arc (45-degree left posterior oblique to 45-degree right anterior oblique position) at 3-degree intervals. Resting 99mTc-sestamibi perfusion imaging was performed on a separate day within 2 to 7 days (average delay, 2.5 days; ≥2 days in only 5 patients) of the stress imaging.

Myocardial images were reconstructed using a standard filtered backprojection and displayed as series of short-axis, horizontal, and vertical long-axis slices. Two separate sets of tomographic slices for exercise 99mTc-sestamibi and 18F-FDG were simultaneously obtained, with exact correspondence in spatial orientation. Rest 99mTc-sestamibi images were processed in the same manner and aligned with exercise 99mTc-sestamibi images.

Image Interpretation

Exercise-rest 99mTc-sestamibi and exercise 99mTc-sestamibi-18F-FDG images were interpreted in 2 separate pairs in a blinded manner by 3 expert nuclear cardiologists without knowledge of the coronary angiography or clinical data. 18F-FDG uptake was intense but focal or regional in a large proportion of patients with abnormal images and required corresponding 99mTc-sestamibi perfusion images for a pre-

cise segmental localization within the myocardium. Qualitative analysis was performed using a 13-segment model, with an apical segment and anterior, lateral, inferior, and septal segments at the apical, mid, and basal parts of the left ventricle. Uptake of 99mTc-sestamibi in each myocardial segment was scored on a 0 to 4 scale (0, normal uptake; 1, mild; 2, moderate; 3, severe reduction in uptake; and 4, no uptake) on stress and rest images. A score of ≥1 involving ≥2 segments on exercise perfusion images was considered abnormal. Abnormal exercise perfusion segments with complete normalization on resting images were classified as ischemia, with partial normalization as scar and ischemia and no change as scar. 18F-FDG uptake was scored on a 0 to 2 scale, with 0 representing no discernible 18F-FDG uptake above the background, 1 representing mild uptake, and 2 representing intense uptake. Exercise-rest 99mTc-sestamibi and 18F-FDG images were compared for the presence and concordance of abnormalities. The myocardial segments were assigned to different vascular territories: anterior and septal segments to the left anterior descending and inferior wall segments to the right and lateral wall segments to the left circumflex coronary arteries, respectively, for angiographic comparison.

Coronary Angiography

Coronary angiography was performed in multiple views and interpreted by an expert coronary angiographer for the presence, localization, and severity of CAD. Luminal diameter narrowing of ≥50% in any of the major epicardial coronary arteries was considered significant. Angiographic interpretation was performed without knowledge of the exercise test or scintigraphic studies.

Statistical Analysis

All parameters were recorded as mean and standard deviation (SD) of the mean. χ2 test and McNemar’s analysis were used to test the significance of differences between the sensitivities of the 2 imaging modalities. P<0.05 was considered significant.

Results

Twenty-six patients (21 men and 5 women, age 58±7 years) with known or suspected CAD underwent imaging studies and coronary angiography. Three patients had diabetes mellitus, 5 had a history of coronary angioplasty, and 1 had a history of prior coronary artery bypass surgery (>6 months ago). As per inclusion criteria, none had documented prior myocardial infarction. The exercise time was 8.0±2.9 minutes, and the peak heart rate was 121±22 bpm. Sixteen patients (62%) developed angina on exercise and 14 (54%) developed ≥1 mm ST-segment depression.

Coronary Angiography

Coronary angiography demonstrated ≥50% narrowing of 1 coronary vessel in 3 patients, 2 vessels in 9 patients, and 3 vessels in 10 patients. Four patients had normal coronary arteries.

Exercise-Rest 99mTc-Sestamibi Images

Exercise-rest 99mTc-sestamibi images were abnormal in 18 (69%) and normal in 8 patients. Of 22 patients with significant angiographic CAD, 18 had perfusion abnormalities (sensitivity 82%). Of 18 patients with perfusion abnormalities, 12 had reversible perfusion abnormalities (ischemia), 4 had partially reversible perfusion abnormalities (scar and ischemia), and 2 had persistent perfusion abnormalities (scar). All 4 patients with no CAD had normal perfusion (Table 1).
Exercise 18FDG Images

Exercise 18FDG images were of good quality in all cases, with only minimal background or extracardiac activity in the field of view (Figures 1 through 4). Radiotracer uptake in the liver and other organs was minimal. Abnormal myocardial 18FDG uptake was seen in 20 of 22 patients with significant CAD (sensitivity 91%, \( P < 0.001 \)). Unlike 99mTc-sestamibi, the entire contour of the myocardium was not visualized with exercise 18FDG images in all cases. However, simultaneously acquired 99mTc-sestamibi images allowed precise processing, myocardial localization, and interpretation of the 18FDG images. Of the 4 patients with no significant CAD, 18FDG uptake was either not discernible at all (grade 0) (n = 2) or showed a very faint uniform uptake, barely above the background (grade 1) (n = 2) in the entire left ventricular myocardium.

Exercise 99mTc-MIBI and 18FDG Images

All 18 patients with abnormal myocardial perfusion on exercise-rest 99mTc-sestamibi SPECT had abnormal myocardial 18FDG uptake (Figures 1 and 2). Two additional patients with significant CAD but normal exercise 99mTc-sestamibi images had abnormal 18FDG images (Figure 3) (3-vessel disease in 1 and 2-vessel disease in 1). On comparing the nature of abnormalities with 2 imaging modalities in 22 CAD patients, 18 had perfusion abnormalities (reversible in 12, partially reversible in 4, and fixed in 2) whereas 20 had abnormal 18FDG images (Table 1). 18FDG detected more extensive ischemia compared with 99mTc-sestamibi. Of 51 coronary vessels with \( \geq 50\% \) luminal narrowing in 22 patients, 25 corresponding myocardial regions showed perfusion abnormalities (sensitivity 49%), whereas 34 showed abnormal 18FDG uptake (sensitivity 67%, \( P = 0.008 \)). Furthermore, of 25 myocardial regions with perfusion abnormalities, only 16 were reversible, 6 were partially reversible, and 3 were fixed. However, all of these regions showed intense 18FDG uptake, indicating the presence of ischemic and viable myocardium. Of 10 patients with disease involving all 3 coronary vessels, global intense 18FDG uptake was seen in 4.

Use of \( \geq 70\% \) luminal narrowing as a criterion for significant CAD resulted in no difference in the results. Twenty-one of 26 patients had \( \geq 70\% \) narrowing of \( \geq 1 \) coronary vessels, 18 (86%) had abnormal exercise-rest 99mTc-sestamibi images, and 20 (95%) had increased myocardial 18FDG uptake (\( P = 0.008 \)). Forty coronary vessels had \( \geq 70\% \) luminal narrowing in 21 patients and 24 (60%) vascular territories had perfusion abnormalities, whereas 32 (80%) had increased 18FDG uptake (\( P < 0.01 \)).

18FDG Imaging and Diabetes

Only 3 patients had overt diabetes (controlled with insulin in 2 and with an oral hypoglycemic agent in 1). Euglycemic hyperinsulinemic clamp was not used. Of these, 2 had significant angiographic CAD. Abnormal 18FDG uptake was seen in 1 of the 2 patients with CAD. The remaining 2 patients had no myocardial 18FDG uptake.

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**TABLE 1. Comparison of Abnormalities Observed in Patients With \( \geq 50\% \) Narrowing of \( \geq 1 \) Coronary Vessel**

<table>
<thead>
<tr>
<th></th>
<th>Ischemia (%)</th>
<th>Ischemia and Scar (%)</th>
<th>Scar (%)</th>
<th>No Abnormality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients* (n = 22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99mTc-sestamibi</td>
<td>12 (55)</td>
<td>4 (18)†</td>
<td>2 (9)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>18FDG</td>
<td>20 (91)</td>
<td>0†</td>
<td>0</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

**Vascular territories with \( \geq 50\% \) narrowing† (n = 51)**

<table>
<thead>
<tr>
<th></th>
<th>Ischemia (%)</th>
<th>Ischemia and Scar (%)</th>
<th>Scar (%)</th>
<th>No Abnormality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99mTc-sestamibi</td>
<td>16 (31)</td>
<td>6 (12)§</td>
<td>3 (6)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>18FDG</td>
<td>34 (67)</td>
<td>0§</td>
<td>0</td>
<td>17 (33)</td>
</tr>
</tbody>
</table>

*\( P < 0.04 \), †\( P = \text{NS} \) if ischemia and ischemia and scar categories are combined; §\( P < 0.001 \), §\( P = 0.02 \) if ischemia and ischemia and scar categories are combined.

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**Figure 1.** Exercise (Ex) and rest (R) 99mTc-sestamibi and exercise 18FDG (FDG) images of a 67-year-old man with angina and no prior myocardial infarction. There is a large area of partially reversible perfusion abnormality involving the septum, anterior wall, and apex (small arrows). Intense 18FDG uptake is present in these areas (solid arrowheads). Coronary angiography showed 90% stenosis of the left anterior descending coronary artery and a 60% stenosis of the left circumflex artery.
Discussion

Our results show the potential of $^{18}$FDG as an effective, sensitive, and easy-to-use radiotracer for direct imaging of exercise-induced myocardial ischemia. Availability of direct ischemia imaging for routine clinical use adds a new and interesting dimension to the evaluation and management of CAD by eliminating some of the drawbacks of conventional cold spot myocardial perfusion imaging.\textsuperscript{1-4} Whereas the overall sensitivity of exercise-rest myocardial perfusion imaging for the detection of CAD is high, its sensitivity for the detection of individual coronary arteries with significant disease is relatively low. Furthermore, one third of perfusion abnormalities on exercise and rest $^{99m}$Tc-sestamibi were either fixed or partially reversible despite no evidence of prior myocardial infarction. Standard exercise-rest perfusion imaging is known to underestimate the true extent of myocardial ischemia and viability. A significant proportion of myocardial segments with ischemia and viability show a partially reversible or even fixed perfusion abnormality on standard exercise-redistribution thallium-201 or exercise-rest $^{99m}$Tc-sestamibi imaging.\textsuperscript{28,29} This often requires additional imaging studies to evaluate the entire extent of exercise-induced myocardial ischemia and viability. Whereas the possibility of an old myocardial infarction cannot be completely excluded in vascular territories with fixed or partially reversible perfusion abnormalities, a careful exclusion of patients with any evidence of prior myocardial infarction and an intense $^{18}$FDG uptake in these segments, similar to that seen in myocardial segments with completely reversible perfusion abnormalities, favors the possibility of ischemia being underestimated by exercise-rest $^{99m}$Tc-sestamibi compared with exercise $^{18}$FDG.$^{99m}$Tc-sestamibi.

$^{18}$FDG has been in clinical use for nearly 2 decades, but this is predominantly being used in oncology for tumor imaging using PET cameras. Recent availability of SPECT cameras with capability for $^{18}$FDG imaging allows much wider and diverse use of this agent. In cardiovascular medicine, $^{18}$FDG has only been used for imaging viable myocardium using rest...
18FDG with rest perfusion imaging. Viable myocardial segments show disproportionately higher 18FDG uptake compared with perfusion.

The potential of 18FDG for imaging exercise-induced myocardial ischemia has only been examined in a very preliminary and limited fashion using PET cameras.30–32 Camici et al30 observed 18FDG uptake in 9 of 10 patients in regions with reduced rubidium-82 uptake during exercise. Abramson et al31 observed 18FDG uptake in 8 of 9 women in myocardial segments with reversible perfusion abnormalities. These studies did not address the issue of image quality, need for a roadmap for an accurate myocardial localization of 18FDG, and an imaging protocol suitable for routine clinical use.33 Our study not only evaluates the role of 18FDG as a hot spot imaging agent for exercise-induced myocardial ischemia using SPECT imaging cameras but also addresses the issues of 18FDG image quality, need for a roadmap for an accurate myocardial localization of 18FDG, and an imaging protocol suitable for routine clinical use.

Whereas myocardial flow heterogeneity in patients with CAD is only transient during exercise, the metabolic signature of ischemia persists for a significantly longer period of time. Myocardial perfusion tracers are rapidly extracted from the blood pool after an intravenous injection. Perfusion imaging relies on capturing and freezing a snapshot of myocardial perfusion at the time of radiotracer injection, which is imaged in the postexercise period. In contrast, increased glucose uptake in the ischemic myocardium persists for several hours, even after a transient episode of ischemia.9–11,14 Myocardial glucose utilization under fasting conditions is substantially less compared with the fed state attributable to low insulin levels. Higher levels of catecholamines also suppress myocardial glucose uptake by increasing the levels of free fatty acids. Exercise under fasting condition results in a very low 18FDG uptake by the normal myocardium. In contrast, 18FDG uptake by the ischemic myocardium is less affected by the levels of insulin or free fatty acids. These factors result in a very high contrast in 18FDG uptake between the normal and ischemic myocardium.

18FDG has a relatively slow clearance from the blood pool after its intravenous injection, and a delay of 45 to 60 minutes is required before images can be acquired. For 99mTc-labeled perfusion tracers, a delay of 15 to 45 minutes between image acquisition and radiotracer injection is required to allow adequate hepatic and background clearance. Therefore, a delay of 45 to 60 minutes between the injection of 18FDG and 99mTc-sestamibi at peak exercise and image acquisition is optimum for both imaging modalities.

A slight degradation of the image quality resulting from the use of ultra-high-energy collimators instead of the standard low-energy collimators may have slightly reduced the sensitivity of 99mTc-sestamibi for the detection of CAD. However, this factor alone cannot fully explain the difference observed in this study.

Limitations
This study was primarily a feasibility study to evaluate the concept of direct imaging of exercise-induced myocardial ischemia using simultaneous exercise 99mTc-sestamibi and 18FDG imaging. Several variables for optimizing imaging protocol and technical considerations such as optimal image acquisition parameters and optimal imaging equipment characteristics, including the use of ultra-high-energy collimators, were not addressed in this study. The effect and extent of downscattering of 511-KeV photons from 18FDG into 99mTc window was not addressed in this study. These issues will require a series of carefully planned studies. Optimization of these parameters can additionally improve the results of 18FDG imaging for myocardial ischemia detection. 99mTc-sestamibi images were not gated in this study. Gating may have improved the sensitivity of 99mTc-sestamibi for the detection of CAD. Resting 18FDG imaging is often difficult in patients with diabetes. This issue was not specifically addressed in this study. Only 3 patients had diabetes in this study, of whom 2 had CAD. Of the 2 false-negative patients with 18FDG, 1 had diabetes. Feasibility of exercise 18FDG imaging in patients with diabetes needs to be examined in a separate study. The extent and pattern of myocardial 18FDG uptake on exercise studies in healthy individuals need to be
defined in a separate study. The specificity of \(^{18}\)FDG imaging for CAD could not be defined from this study, because only 4 of 26 patients had no CAD. Of these, 2 patients showed no discernible myocardial \(^{18}\)FDG uptake, whereas 2 showed a faint global myocardial uptake, barely above the background, but quite different from the global uptake pattern seen in multivessel CAD. Quantitative analysis may allow a better and more reliable differentiation between global uptake pattern, seen in patients with multivessel CAD, and the faint global uptake seen in some healthy individuals.

Conclusions

Simultaneous exercise myocardial perfusion and ischemia imaging is a highly promising technique for the detection of exercise-induced myocardial ischemia and for the diagnosis of CAD. This approach can reduce the artifacts seen on conventional myocardial perfusion imaging, reduce the time required to complete the entire imaging study, and improve the sensitivity and possibly specificity for the detection of CAD. A single simultaneous exercise \(^{18}\)FDG and perfusion study can characterize the myocardium into normal, ischemic/viable, and irreversibly scarred, obviating the need for a separate viability study needed in some patients with fixed or partially reversible perfusion defects (Table 2). Additional large-scale studies are warranted.

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