Imaging of Inflamed and Vulnerable Plaque in Coronary Arteries with ^{18}F-FDG PET/CT in Patients with Suppression of Myocardial Uptake Using a Low-Carbohydrate, High-Fat Preparation

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PET/CT imaging with ^{18}F-FDG has been used to detect inflammation in carotid and aortic plaque; its use in detecting coronary plaque has been limited by avid ^{18}F-FDG uptake by the myocardium. We investigated whether ^{18}F-FDG PET/CT could be used to image inflammation in coronary arteries as a potential noninvasive method to detect vulnerable plaque. **Methods:** We retrospectively studied 32 patients treated for malignancy who underwent ^{18}F-FDG PET/CT and concomitant cardiac catheterization. As part of the recently described protocol, all patients were instructed to eat a low-carbohydrate, high-fat meal the night before and drink a vegetable oil drink the morning of the study. We reviewed the patients' baseline characteristics and their ^{18}F-FDG PET/CT scans for adequacy of myocardial uptake suppression and correlated the presence of angiographically apparent plaque with ^{18}F-FDG uptake in the major coronary arteries. Two independent observers assessed the angiographic images and ^{18}F-FDG PET scans. **Results:** A total of 95% of patients had 2 or more coronary disease risk factors, and 25% had unstable symptoms; 30% of index catheterizations resulted in intervention. In 20 of 32 patients (63%), myocardial suppression was good (12) or adequate (8). Inadequate suppression was due to self-reported dietary nonadherence. Patients with good, adequate, and poor suppression had maximal myocardial standardized uptake values of 2.8 ± 0.7, 5.0 ± 1.3, and 17.0 ± 9.7, respectively. We identified ^{18}F-FDG uptake in 15 patients in 1 or more coronary segments. A trend to significance in correlation between presence of angiographic disease and signal in the vessel was observed ($P = 0.07$; 80 vessels examined). A total of 7 patients with significant coronary artery disease had aortic ^{18}F-FDG uptake. **Conclusion:** In this retrospective study, we demonstrated the potential use of ^{18}F-FDG PET in imaging of inflammation in coronary arteries. The potential of ^{18}F-FDG PET is also being investigated in a prospective study.

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The pathogenesis of atherosclerosis involves a component of chronic inflammation (*1–3*). Atherosclerotic specimens obtained from autopsy cases or patients undergoing carotid atherectomies have been shown to be rich in inflammatory cells such as macrophages. ^{18}F-FDG is a tracer that is taken up not only by metabolically active tumor cells but also by cells such as macrophages (*4*). Both retrospective and prospective studies have shown that ^{18}F-FDG accumulation can be detected in the aortic and carotid arteries of patients undergoing ^{18}F-FDG PET/CT and that the uptake in carotid arteries correlates with the presence of macrophages. In addition, statins, which have both lipid-lowering and antiinflammatory properties, have been shown to attenuate ^{18}F-FDG uptake by plaque (*5*). Patients with hypercholesterolemia and insulin resistance and other features of metabolic syndrome have higher ^{18}F-FDG uptake in the aortic and carotid arteries (*6*). The interobserver variability of the scans obtained from the same patient appears to be low, making this technique a reliable method to assess the degree of inflammation and plaque vulnerability (*7*).

Acute myocardial infarction is commonly caused by coronary lesions with a thin fibrous cap, large necrotic core, and high number of inflammatory cells and occluding the vessel by 40%−50%. Imaging techniques to assess the plaque morphology and assess its instability usually require invasive cardiac catheterization and placement of angios-

copy, intravascular ultrasound, or optical coherence tomography catheters (*8*). Noninvasive methods such as MRI and computer tomography have been investigated with some success. MRI enhanced with ultra-small particles of iron oxide that are avidly taken up by macrophages is particularly promising, as are some other activatable fluorescent probes, including myeloperoxidase- and cathepsin-targeting probes (*9–12*). Dual-source CT also appears promising in discerning plaque composition but is a technology under development and requires validation (*13*). ^{18}F-FDG PET/CT for coronary plaque imaging has been limited by the avid ^{18}F-FDG uptake by the myocardium. We have previously described a dietary preparation consisting of a low-carbohydrate, high-fat meal and a vegetable oil drink, ClearScan (E-Z-Em Inc.), which suppresses myocardial uptake of ^{18}F-FDG (*14–18*). We present herein the results of a retrospective examination of scans from 32 patients who underwent both ^{18}F-FDG PET/CT for malignancy and invasive coronary angiography within 3 mo of their PET/CT scan.

MATERIALS AND METHODS

Patient Population

A total of 32 consecutive patients with malignancies comprised this retrospective observational study. These patients had undergone clinically indicated ^{18}F-FDG PET/CT at our institution and concomitantly undergone invasive coronary angiograms within 3 mo of the ^{18}F-FDG PET/CT scan, from 2005 to 2007 (the time when the novel dietary preparation protocol was instituted). Most of the angiograms were indicated as part of the preoperative risk assessment to determine whether tumor resection was safe to perform on those patients who presented with unstable symptoms (including ST segment elevation myocardial infarction in 2 cases). The study protocol was approved by the local Institutional Review Board. Patient baseline coronary risk factors such as age, sex, hypercholesterolemia, diabetes, renal insufficiency, smoking history, family history, prior myocardial infarction, prior bypass grafting or percutaneous intervention, cerebrovascular or peripheral vascular disease history, presence of unstable symptoms, treatment with statins, and positive stress test were assessed. Patients with insulin-dependent diabetes were excluded.

PET/CT

Patients were given instructions about how to prepare for their ^{18}F-FDG PET/CT scan that included abstaining from carbohydrates the night before the scan and not eating or drinking the morning of the procedure, except for a vegetable oil drink (ClearScan). After an intravenous injection of ^{18}F-FDG (740 MBq [20 mCi]), the patients were kept in a semidarkened, quiet room for 45–60 min. The patients were then scanned using a PET/CT (4-slice) scanner (Discovery/Light Speed; GE Healthcare). An initial CT scout image (140 kVp) was obtained. The patients were then scanned from the base of the skull to the mid thighs using spiral CT at 0.8 s per rotation (150 mA, 140 kVp, with a section thickness of 5 mm and an interval of 4.25 mm). Thin oral (no intravenous) barium contrast was used in all studies. Patients were instructed to breathe normally during the acquisition. PET emission images were then obtained with 5 min per bed position and iteratively reconstructed, using CT-based attenuation correction.

Image Analysis

Two independent nuclear medicine physicians reviewed the PET/CT scans for the presence of ^{18}F-FDG uptake in the myocardium, coronary arteries, and aortic arch. Images were analyzed using PET/CT view software (*19*). The degree of background myocardial uptake (dependent on the patient's compliance with dietary preparation) was scored on a 0–2 scale (0 was poor, 1 was adequate, and 2 was good quality). Dietary compliance was determined on the basis of the patient's answers to a questionnaire and self-reporting. Myocardial ^{18}F-FDG uptake was quantified by measuring the maximum standardized uptake value (SUVmax) within a region of interest. Presence of coronary ^{18}F-FDG uptake was assessed visually in all vessel segments. In addition, the SUVmax in the vessel segments positive for ^{18}F-FDG uptake was compared with that in vessels negative for uptake. Adequate suppression was defined as an SUVmax of 5.0 or less, retrospectively.

Coronary Angiography

Within the 3-mo period, either before or after PET/CT, the patients included in the study also underwent clinically indicated coronary angiography. Standard angiographic views of the right and left coronary arteries were obtained, and 2 independent interventional cardiologists assessed the angiograms for the severity and presence of more than 50% occlusive lesions in the major coronary segments. Fifty percent lesion severity was chosen so as to capture potentially less severe, but vulnerable, soft plaques.

Fasting Versus High-Fat Dietary Preparation

In addition, patients receiving a standard fasting preparation before PET/CT over a 12-mo period were compared with patients receiving a high-fat preparation as described above over a 6-mo period (currently routinely used at Beth Israel Deaconess Medical Center). Data were collected for blood glucose level, brown fat uptake (*14,15,17,18*), and myocardial uptake.

Statistical Methods

Continuous variables were expressed as mean ± SD. The unpaired *t* test was used to check for differences between means, and the Fisher exact test was applied to nominal variables. The presence of ^{18}F-FDG signal in the coronary arteries was correlated with the likelihood of intervention at the index coronary catheterization procedure and the presence of unstable symptoms at presentation. SUVmax for diseased and nondiseased (^{18}F-FDG–negative) segments was compared by unpaired *t* test.

RESULTS

Clinical Characteristics

The baseline medical and procedural characteristics are listed in Table 1. A total of 95% of patients had 2 or more coronary disease risk factors, and 25% presented with unstable symptoms. Most of the patients were referred for cardiac catheterization as part of preoperative assessment after a positive stress test (18 patients). Percutaneous coronary intervention was performed in 30% of index catheterizations.

High-Fat Meal Preparation Protocol and Myocardial Uptake

By modifying the usual patient preparation protocol for ^{18}F-FDG PET, we have previously shown (*14,15,17,18*) a dramatic reduction in the myocardial uptake of ^{18}F-FDG.

TABLE 1. Baseline Demographics

Characteristic	Total (n = 32)
Hypertension	30
Hypercholesterolemia	27
Diabetes	9
Renal insufficiency	3
Smoking	29 (5 current)
Family history	8
Prior percutaneous intervention	9
Prior myocardial infarction	6
Prior bypass surgery	7
Prior cerebrovascular disease	2
Prior peripheral vascular disease	6
Unstable symptoms	5
Statin use	24
Positive exercise stress test	18
Intervention at index catheterization	8

Instead of the conventional fasting protocol, patients were instructed to eat a low-carbohydrate, high-fat meal before ^{18}F-FDG injection. We have also previously shown that fasting alone does not adequately suppress myocardial uptake and have hypothesized that a low-carbohydrate, high-fat meal induces the Randall cycle and preferential uptake of fatty acids by the myocardium (*14,17,18*).

^{18}F-FDG PET

The success of myocardial suppression is shown in Supplemental Table 1 (supplemental materials are available online only at http://jnm.snmjournals.org), with SUVmax given for various degrees of suppression and individual patients (because not all patients adhered strictly to the diet instructions, some variability in the myocardial uptake of ^{18}F-FDG was observed). In 20 of the 32 patients (63%), myocardial suppression was good (12) or adequate (8) and scans were interpretable. Patients with good, adequate, and poor suppression had a maximal myocardial SUV of 2.8 ± 0.7, 5.0 ± 1.3, and 17.0 ± 9.7, respectively. Figure 1 shows representative images of ^{18}F-FDG myocardial uptake in patients with good, adequate, and poor suppression. Figure 2 depicts coronary tree ^{18}F-FDG uptake, with corresponding angiographic images. The SUVmax of the ^{18}F-FDG–positive vessel segments was 2.6 ± 0.64. For the negative-uptake vessel segments, SUVmax was 1.9 ± 0.46 ($P < 0.001$). Most of the uptake was in the left anterior descending and left circumflex coronary arteries; only 3 patients had uptake in the right coronary artery.

Correlation with Coronary Angiography

Coronary angiography findings were normal in 6 patients only. We were able to identify areas of ^{18}F-FDG uptake in 15 patients in 1 or more coronary segments, with angiographically apparent lesions of varying severity. A trend to significance in correlation between the presence of angiographic disease and signal in the vessel was demonstrated ($P = 0.07$; 80 vessels examined). In contrast, only 7 patients with significant coronary artery disease had aortic ^{18}F-FDG uptake. There did not appear to be a significant correlation between the presence of unstable symptoms or likelihood of intervention and ^{18}F-FDG uptake in the coronary arteries, with the limitation that our analysis was not powered to detect this correlation. Table 2 depicts the correlation of ^{18}F-FDG coronary uptake with presence of coronary lesions by angiography. Table 3 depicts the correlation of aortic ^{18}F-FDG uptake with presence of coronary lesions by angiography.

Myocardial and Brown Fat ^{18}F-FDG Uptake Suppression by High-Fat Preparation

Before undergoing the coronary study, patients who underwent ^{18}F-FDG PET/CT after an overnight fast were compared with patients on the described low-carbohydrate, high-fat preparation. During a 12-mo period, 1,229 patients underwent ^{18}F-FDG PET/CT after an overnight fast (at least 8 h). The mean age of the patients (52% men) was 58 ± 16 y, and all patients in this group had a blood glucose level of 109 ± 32 mg/dL. A subsequent group of 724 patients underwent ^{18}F-FDG PET/CT using an overnight low-carbohydrate, high-fat preparation over a 6-mo period. The mean age of patients in this group was 58 ± 15 y, 53% were male, and blood glucose level was 99 ± 43 mg/dL. Brown adipose tissue was evident on 6.3% of scans in the fasting group versus 2.8% in the low-carbohydrate, high-fat preparation group, a difference that was statistically significant ($P < 0.001$) (*14,15,17,18*). Furthermore, myocardial maximal ^{18}F-FDG uptake was 8.8 ± 3.6 in the fasting group and 2.5 ± 1.5 in the low-carbohydrate, high-fat group, again a difference that was statistically significant ($P < 0.001$)

DISCUSSION

To our knowledge, this preliminary pilot study provides the first indication that using ^{18}F-FDG PET/CT may enable imaging of coronary vasculature and possibly vulnerable and inflamed coronary plaques in patients. We were able to alter the myocardial metabolism and decrease the myocardial ^{18}F-

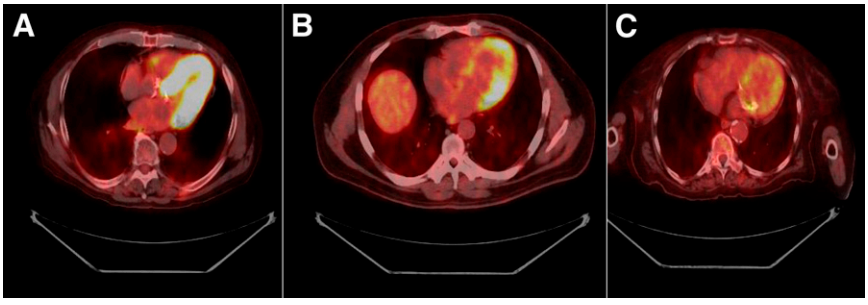

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FIGURE 1. Adequacy of myocardial suppression. Myocardial ^{18}F-FDG uptake in representative patients with poor (A), adequate or fair (B), and good (C) suppression.

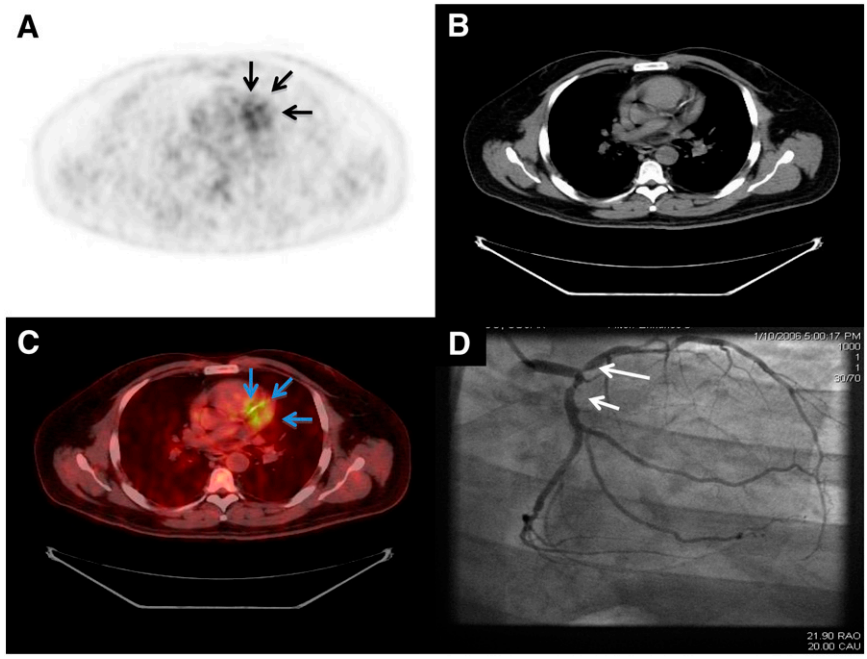

FIGURE 2. Representative images of ^{18}F-FDG PET (A), CT (B), PET/CT (C), and coronary angiography (D) from patient with good suppression with coronary ^{18}F-FDG uptake (arrows).

FDG uptake with a low-carbohydrate, high-fat diet rather than a fasting protocol, which, in our experience, does not provide adequate suppression (*14,17,18*). We have previously described a dietary preparation consisting of a low-carbohydrate, high-fat meal and the use of a vegetable oil drink, which suppresses myocardial uptake of ^{18}F-FDG (*14–18*). Adequate suppression was defined as an SUVmax of 5.0 or less, retrospectively.

Most acute myocardial infarctions are caused by plaques that are not seen to be obstructive on invasive coronary angiography. These plaques usually occupy greater than 70% of the vessel lumen but have histologic features of so-called vulnerable plaques. These features include a thin fibrous cap greater than 65 μm and large lipid core (>40% of the plaque), are macrophage-rich, and have endothelial denudation. There are no accepted gold standard techniques to identify such plaques by noninvasive means (*7,20–26*). Invasive means such as intravascular ultrasound, optical coherence tomography (*27*), thermography (*28–30*), or angioscopy (*31*) and invasive cardiac catheterization all have their limitations, from resolution to depth of penetration (optical coherence tomography). Multidetector CT, especially with the newer scanners that have dual sources and 256 slices or more, promises to better characterize plaque morphology but has not yet been validated and requires contrast administration, which is prohibitive in patients with renal insufficiency (*32–34*). ^{18}F-FDG PET/CT, if proven, may offer an attractive alternative to vulnerable plaque imaging in some patients. The ability of this method to reliably measure aortic and carotid active plaque has been now demonstrated in several studies (*4,35,36*). Coronary imaging has been limited, however, by the myocardial uptake. We have previously demonstrated that we were able to overcome this limitation with our low-carbohydrate, high-fat dietary preparation (*14,15,17,18*). In the present study, we demonstrated that as a result of this myocardial suppression it may be possible to image coronary and possibly vulnerable coronary plaque. In addition, we demonstrated the superiority of a low-carbohydrate, high-fat preparation in the suppression of myocardial ^{18}F-FDG uptake. Given the need for fasting and a low-carbohydrate preparation at this time, we excluded insulin-dependent patients from our protocol.

^{18}F-FDG PET/CT of the coronary arteries can identify patients at risk (so-called vulnerable patients) and their cholesterol levels and biomarkers such as highly sensitive C-reactive protein. Such information in clinical practice may

TABLE 2. Correlation of Coronary ^{18}F-FDG Uptake with Angiographic Disease (Per-Patient Analysis)

^{18}F-FDG uptake in the coronary tree	Coronary artery disease by angiography	
	Negative	Positive
Negative	1	2
Positive	2	15

TABLE 3. Correlation of Aortic ^{18}F-FDG Uptake with Angiographic Coronary Disease (Per-Patient Analysis)

Aortic ^{18}F-FDG uptake	Coronary artery disease by angiography	
	Negative	Positive
Negative	2	10
Positive	1	7

allow for more aggressive statin and antiinflammatory treatment, the effectiveness of which can be assessed with endpoints such as decrease in ^{18}F-FDG PET/CT uptake and confirmed by reduction in hard endpoints of major adverse cardiovascular events.

The retrospective nature of this study is a clear limitation, particularly because many of the patients did not comply with the dietary preparation. The ^{18}F-FDG PET/CT scan was acquired within 3 mo of the angiogram, which may have weakened our ability to correlate the signals in the 2 studies, as ^{18}F-FDG plaque uptake can vary greatly in the same patient with time. In addition, no respiratory or cardiac gating was performed in these patients, which affects greatly the temporary and spatial resolution. However, it is expected that this group of patients would be on β-blockers (which would result in the heart being imaged primarily during diastole) and that during the quiet breathing part of the PET/CT study, the patients would be primarily in end expiration. In our current prospective study, we are performing both cardiac and respiratory gating. Because the volume of the vessel wall is much smaller than are the myocardial regions of interest, partial-volume averaging in the ungated studies of ^{18}F-FDG–negative and –positive vessel segments may explain why ^{18}F-FDG–positive diseased coronary segments have an SUVmax of 2.6 and the SUVmax for the background myocardial uptake for well-suppressed patients is 2.8.

In addition, we are concurrently conducting a study of patients undergoing clinically indicated CT angiography to detect coronary artery disease as the etiology of chest pain symptoms, and we are performing ^{18}F-FDG PET/CT in these patients within several days of the initial study. We hope that the 3-dimensional anatomic nature of CT angiography and its ability to look at plaque morphology or characteristics will allow us to better correlate plaque burden on CT angiograms and uptake on ^{18}F-FDG PET/CT scans.

CONCLUSION

^{18}F-FDG PET/CT with myocardial suppression may provide a novel method to image the coronary vasculature and potentially identify vulnerable (inflamed) plaque. Further studies of controls and patients with stable and unstable coronary syndromes are needed; such studies are ongoing in our center. In addition, correlation with traditional markers of inflammation and clinical outcomes are necessary to establish the clinical significance of this imaging modality.

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