

# In Vivo $^{18}\text{F}$ -Fluorodeoxyglucose Positron Emission Tomography Imaging Provides a Noninvasive Measure of Carotid Plaque Inflammation in Patients

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<b>OBJECTIVES</b>	Given the importance of inflammation in atherosclerosis, we sought to determine if atherosclerotic plaque inflammation could be measured noninvasively in humans using positron emission tomography (PET).
<b>BACKGROUND</b>	Earlier PET studies using fluorodeoxyglucose (FDG) demonstrated increased FDG uptake in atherosclerotic plaques. Here we tested the ability of FDG-PET to measure carotid plaque inflammation in patients who subsequently underwent carotid endarterectomy (CEA).
<b>METHODS</b>	Seventeen patients with severe carotid stenoses underwent FDG-PET imaging 3 h after FDG administration (13 to 25 mCi), after which carotid plaque FDG uptake was determined as the ratio of plaque to blood activity (target to background ratio, TBR). Less than 1 month after imaging, subjects underwent CEA, after which carotid specimens were processed to identify macrophages (staining with anti-CD68 antibodies).
<b>RESULTS</b>	There was a significant correlation between the PET signal from the carotid plaques and the macrophage staining from the corresponding histologic sections ( $r = 0.70$ ; $p < 0.0001$ ). When mean FDG uptake (mean TBR) was compared with mean inflammation (mean percentage CD68 staining) for each of the 17 patients, the correlation was even stronger ( $r = 0.85$ ; $p < 0.0001$ ). Fluorodeoxyglucose uptake did not correlate with plaque area, plaque thickness, or area of smooth muscle cell staining.
<b>CONCLUSIONS</b>	We established that FDG-PET imaging can be used to assess the severity of inflammation in carotid plaques in patients. If subsequent natural history studies link increased FDG-PET activity in carotid arteries with clinical events, this noninvasive measure could be used to identify a subset of patients with carotid atherosclerosis in need of intensified medical therapy or carotid artery intervention to prevent stroke. (J Am Coll Cardiol 2006;48:1818-24) © 2006 by the American College of Cardiology Foundation

Current management of carotid atherosclerotic disease is guided primarily by determination of degree of carotid artery stenosis and does not take advantage of imaging techniques that could provide information about plaque composition and biological activity. Among the targets for imaging, detection of inflammation is likely to be of value because of the well-documented association between inflammatory processes and plaque rupture (1-6). A noninvasive method to characterize inflammation in carotid plaques may be of value for determination of prognosis, selection of appropriate medical or surgical therapy, and

assessment of novel therapies designed to stabilize atherosclerotic plaques.

Preliminary data from our group and others have demonstrated that positron emission tomography (PET) with  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) can identify inflamed atherosclerotic plaques in an animal model of atherosclerosis (7-9). Furthermore, Rudd et al. (10,11) demonstrated increased carotid uptake of FDG in patients with evidence of a recent ischemic cerebrovascular event. The same group demonstrated in ex vivo experiments that FDG co-localizes with macrophages within excised carotid specimens that are incubated with FDG (10). However, that ex vivo experiment used quantities of FDG that cannot be used in vivo in patients. Moreover, although it is evident that symptomatic vascular lesions can be detected using FDG-PET, it remains unknown if the imaging technique can be used to noninvasively characterize the severity of vascular inflammation in patients. Accordingly, in this study, we tested the hypothesis that inflammation

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#### Abbreviations and Acronyms

CEA	= carotid endarterectomy
FDG	= <sup>18</sup> F-fluorodeoxyglucose
hsCRP	= high-sensitivity C-reactive protein
PET	= positron emission tomography
SUV	= standardized uptake value
TBR	= target-to-background ratio

in human carotid arteries could be measured noninvasively, in vivo, using <sup>18</sup>F-FDG-PET.

## METHODS

**Patients.** Seventeen adult patients (11 men, 6 women) with severe carotid artery stenosis already scheduled to undergo carotid endarterectomy (CEA) were recruited. Eligibility criteria included a 70% to 99% stenosis of the internal carotid artery detected by carotid Doppler ultrasound, magnetic resonance angiography, or computed tomography angiography. All patients were expected to undergo CEA within 1 month of enrollment. The study protocol was approved by the local Human Research Committee, and informed consent was obtained from each subject.

**PET imaging.** FDG was administered (13 to 25 mCi) intravenously after an overnight fast. Three hours later, imaging was performed using a Siemens ECAT Exact HR+ system (Siemens, Knoxville, Tennessee), which provides 63 planes, a 15.5-cm field of view, and 4.2-mm intrinsic resolution. Data were acquired in 3-dimensional mode. The choice of time interval was based on our previous work in animals and on the work of Rudd et al. (10). Patients were imaged in the supine position using a head fixation device. Images were obtained over 20 min. Attenuation-corrected images were reconstructed using a Hanning filter with a conventional, filtered back-projection algorithm, yielding an effective resolution of 5 mm.

**Anatomic imaging, image co-registration, and measurement of FDG uptake.** Metabolic imaging with PET provides limited structural data. Accordingly, anatomic imaging with either multidetector computed tomographic imaging (MDCT) (n = 11 patients) or magnetic resonance imaging (MRI) (n = 6 patients) was performed using previously reported methods (12,13) for structural delineation of the carotid arteries and their atherosclerotic plaques.

The PET images were co-registered with the structural (MDCT or MRI) images using a workstation that enables multimodal standard (rigid) image fusion (REVEAL-MVS; Mirada Solutions, Oxford, United Kingdom). The PET and CT (or MR) images were manually co-registered by an investigator blinded to the histologic analysis using extravascular anatomic landmarks (such as brain, spinal cord, spine, and jaw) that were apparent on both images.

After co-registration of the images, carotid FDG uptake was measured along the length of the carotid vessel, starting at the bifurcation and extending inferiorly and superiorly

every 4 mm. Because the length of carotid plaque that would eventually be removed during endarterectomy was not known at the time of image analysis, the measurements were extended, at 4-mm intervals, to points 4 cm above and 2 cm below the carotid bifurcation. However, only those sections for which carotid histology was eventually obtained were used for analysis. At each axial plane along the length of the carotid, regions of interest (ROIs) (approximately 8 mm in diameter) were placed within the wall of the carotid vessel for determination of the standardized uptake value (SUV). The SUV is the decay-corrected tissue concentration of FDG (in kBq/ml) divided by the injected dose per body weight (kBq/g). The CT and MRI data were used to guide placement of the ROI within the plaque (area of greatest wall thickening) at each axial plane. In cases where the plaque occupied more than 180° of the vessel wall the SUV measurement was taken at the most metabolically active half of the vessel wall. To obtain a background value for FDG uptake, SUV was measured in a venous structure. To accomplish this, an ROI was placed within the center of a large vein (such as the subclavian or internal jugular vein) in an area devoid of significant spill-over activity. Afterward, a target-to-background ratio (TBR) was calculated as carotid plaque SUV divided by venous blood SUV, and an averaged value of TBR was calculated for each patient (mean TBR). Additionally, we calculated the plaque-to-blood SUV gradient as the difference between the carotid plaque SUVs and blood background SUV ( $\Delta$ SUV).

Blinding was maintained between investigators responsible for the registration of PET and structural images, and the determination of PET uptake, on the one hand, and those responsible for the histologic analyses of the CEA specimens, on the other hand. To determine the variability of the measurement (mean plaque TBR), images from 10 patients were twice co-registered and analyzed, several weeks apart in a blinded manner. The mean ( $\pm$  SD) intraobserver difference was  $8.9 \pm 9.0\%$ .

**Histology and immunohistochemistry.** At the time of CEA, the atherosclerotic plaques were immediately fixed in 10% buffered formalin and subsequently decalcified in the standard fashion. Specimens were transversely sectioned at 3-mm intervals. Each interval section was embedded face up in paraffin and cut at 5- $\mu$ m thickness to yield 4 slices for subsequent staining. For immunohistochemistry, sections were mounted on gelatin-coated slides and subsequently stained with a macrophage-specific, anti-CD68 monoclonal antibody (mAb KP-1; Dako, Glostrup, Denmark) and a smooth muscle cell-specific antibody (anti-smooth muscle cell alpha-actin antibody; Dako).

Assessment of macrophage and smooth muscle cell staining was performed using the methods of Jander et al. (14). Computer-assisted planimetry was used to quantitate areas of staining. The sections were computerized as color-encoded digitized images (Sony CCD camera, Hamamatsu DVS video image processing unit, and National Institutes of Health image analyzing software on an Apple Macintosh

personal computer). Total section areas and areas of macrophage infiltration were outlined manually by comparing the computerized image with the microscopic image at 4× and 20× magnification. Macrophage staining was determined at each carotid slice and reported as the absolute area staining for macrophages (mm<sup>2</sup>) at each carotid level. Additionally, inflammation was recorded as percentage of plaque staining. In cases where the plaque occupied more than 180° of the vessel wall, the value for percentage plaque staining in the most inflamed half of the vessel wall (% CD68 staining) was reported. This was done for improved registration with the imaging findings, because the imaging values were derived from the most metabolically active half of the vessel wall at each axial section of the PET images. Smooth muscle cell staining was defined as the percentage of plaque staining for antismooth muscle cell antibody. Morphometric measurement of lipid area, cap thickness, and collagen content were performed.

**Co-registration and comparison of histologic and PET data.** The axial PET images were registered to histology sections on the basis of the distance from the common carotid bifurcation. The carotid bifurcation was defined as the apex of the luminal flow divider (which divides internal and external carotid artery) as identified on the CT (or MR) images as well as the pathologic specimens. Contraction (due to axial elastic recoil) of the endarterectomy specimen during histologic processing (between its relatively stretched state in vivo to a more contracted state ex vivo) was observed. To account for this change in tissue length, 25% contraction in the length of the specimens along the inferior-superior dimension was assumed, based on earlier experience of the lab.

**High-sensitivity C-reactive protein.** Serum high-sensitivity C-reactive protein (hsCRP) was measured using an automatic immunonephelometer with a sensitivity of 0.02 mg/dl (Behring, Deerfield, Illinois).

**Statistical methods.** Data were analyzed using SPSS for Windows version 13.0 (SPSS, Inc, Chicago, Illinois). Continuous parameters are reported as mean values ± SD. Spearman method was used to assess the correlation between the <sup>18</sup>FDG uptake (FDG TBR) and the histopathologic assessment of inflammation (% CD68 staining), as well as the correlation between mean FDG uptake (mean TBR) and the serum hsCRP level. A value of  $p < 0.05$  was considered significant. To correct for multiple tests, the alpha was adjusted using the Bonferroni method.

## RESULTS

**Patient characteristics.** Patient characteristics are displayed in Table 1.

**Imaging and histology.** The 17 carotid plaque specimens obtained during the course of the study yielded 107 plaque sections (7 ± 4 plaque sections/patient) after sectioning. There was a significant correlation between the PET signal

**Table 1.** Subject Characteristics

Characteristic	Mean (± SEM)
Age (yrs)	62 ± 6
Gender (M/F)	11/6
Symptoms (%)	24
Diabetes (%)	24
Smoking (%)	29
Statin Rx (%)	65
Aspirin Rx (%)	100
SBP (mm Hg)	137 ± 4
DBP (mm Hg)	68 ± 3
LDL cholesterol (mg/dl)	96 ± 9
CRP (mg/l)	3.6 ± 1.5

CRP = C-reactive protein; DBP = diastolic blood pressure; LDL = low-density lipoprotein; Rx = therapy; SBP = systolic blood pressure.

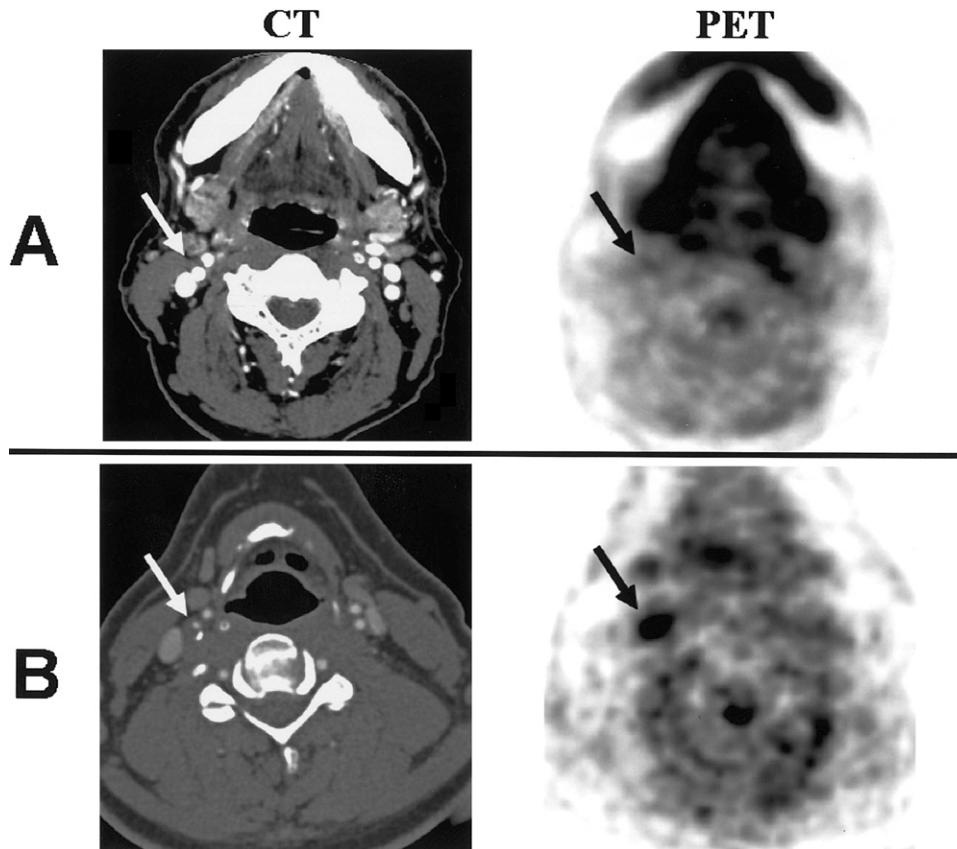
(judged as the ratio of target to background PET emissions, TBR) and macrophage staining, for both the absolute macrophage area ( $r = 0.68$ ;  $p < 0.0001$ ) and the % CD68 staining of the plaque sections ( $r = 0.70$ ;  $p < 0.0001$ ) (Figs. 1 to 3). A significant but somewhat weaker correlation was observed between absolute FDG uptake (absolute SUV) and both absolute macrophage area ( $r = 0.49$ ;  $p < 0.0001$ ), and the % CD68 staining ( $r = 0.58$ ;  $p < 0.0001$ ) of the plaque sections.

A stronger relationship was noted when mean values for FDG uptake (mean TBR) and histologic inflammation (CD68 staining) were generated for each of the 17 patients, for % CD68 staining, ( $r = 0.85$ ;  $p < 0.0001$ ; Fig. 4) as well as absolute macrophage area ( $r = 0.76$ ;  $p < 0.0001$ ). Concordant with those observations, there was a highly significant correlation between the plaque-to-blood SUV gradient ( $\Delta$ SUV) and plaque inflammation, measured as mean % CD68 staining ( $r = 0.88$ ;  $p < 0.001$ ) as well as absolute macrophage area ( $r = 0.80$ ;  $p < 0.001$ ). In contrast, there was no significant correlation between FDG uptake (mean TBR) and smooth muscle cell staining ( $r = 0.15$ ;  $p = 0.40$ ) (Fig. 5), collagen staining ( $r = -0.48$ ;  $p = 0.11$ ), plaque thickness ( $r = 0.15$ ;  $p = 0.49$ ), or plaque area ( $r = 0.00$ ;  $p = 0.99$ ). There was no correlation between either FDG uptake (mean TBR) or plaque inflammation (mean % CD68 staining) and the following variables: hsCRP, age, gender, blood pressure, serum lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides), statin use, presence of diabetes, body mass index, or smoking.

## DISCUSSION

The primary finding of this study is that noninvasive PET imaging can be used to assess the degree of inflammation in carotid atherosclerotic plaques in vivo as documented by correlations in patients undergoing CEA.

**<sup>18</sup>FDG uptake in vascular inflammation.** Several groups have established that inflamed blood vessels have increased uptake of <sup>18</sup>FDG. This <sup>18</sup>FDG enhancement by vascular inflammation has been demonstrated in animal models of atherosclerosis (15) and verified in human studies of patients



**Figure 1.** Axial positron emission tomographic (PET) images and the co-registered computed tomographic (CT) images from 2 patients, 1 (patient A) who manifested low  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) uptake in the region of the carotid plaque and 1 (patient B) with high FDG uptake in the region of the carotid plaque. The region of the excised carotid plaque is noted with arrows. (A) Carotid plaque specimen taken from the patient with low FDG uptake (patient A). The corresponding trichrome-stained histologic specimen demonstrates a collagen-rich plaque with low lipid content, and CD68 staining on the high-powered images demonstrates limited macrophage infiltration. These histologic features are consistent with a metabolically stable and potentially clinically stable plaque. (B) Carotid plaque specimen taken from the patient with high FDG uptake (patient B). The corresponding trichrome-stained histologic specimen demonstrates a complex plaque with a necrotic core, and the CD68 staining demonstrates intense macrophage infiltration. These histologic features are consistent with a metabolically unstable plaque which is vulnerable to rupture.

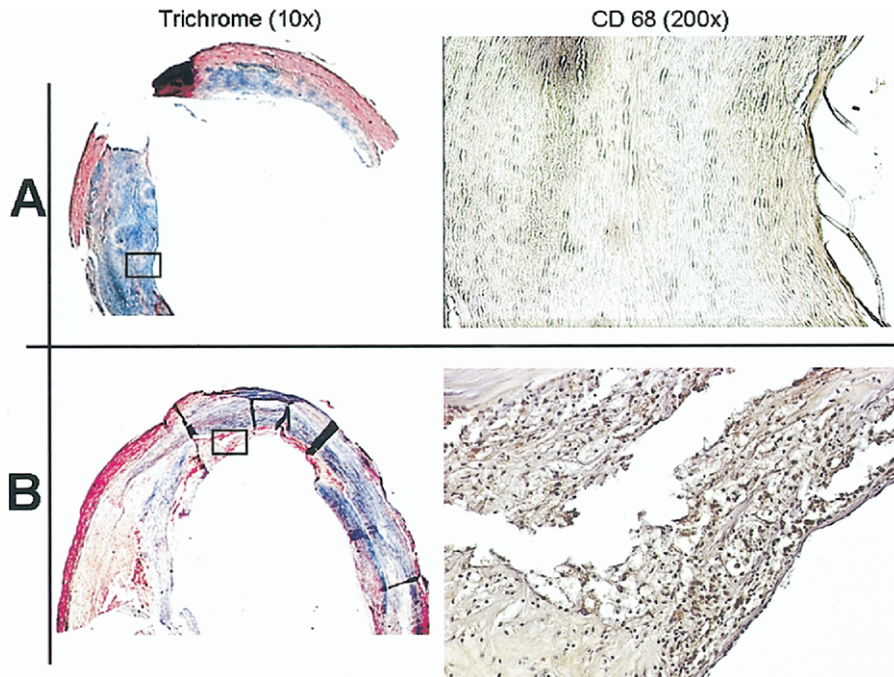
with Takayasu's arteritis, giant cell arteritis, polymyalgia rheumatica, and nonspecific aortitis (16–19). More recently,  $^{18}\text{F}$ FDG uptake was shown to be greater in carotid plaques obtained from patients with clinical evidence of carotid plaque instability (10). However, in that study, the relationship between inflammation and imaging findings was not established.

The present study for the first time demonstrates that FDG uptake, determined noninvasively with PET, correlates strongly with the degree of plaque inflammation. Accordingly, this study provides histologic validation in humans that carotid uptake of  $^{18}\text{F}$ FDG may be useful for noninvasive measurement of atherosclerotic plaque inflammation.

Several additional, potentially important, observations were made. It is apparent that the imaging method enables the characterization of inflammation within a range of carotid inflammation that has been shown to be clinically relevant. The study by Jander et al. (14) previously demonstrated that carotid plaques from patients with symptomatic carotid disease are more severely inflamed ( $18 \pm 10\%$  CD68 staining) compared with plaques removed from patients with asymptomatic carotid stenosis ( $11 \pm 4\%$  stain-

ing). Crisby et al. (20) demonstrated that plaques taken from symptomatic patients subjected to modest lipid lowering (40 mg/day pravastatin for 3 months) are less inflamed than plaques from patients that did not receive lipid-lowering therapy ( $15.0 \pm 10.2\%$  vs.  $25.3 \pm 12.5\%$  CD68 staining;  $p < 0.05$ ). Further, others demonstrated that plaques taken from predominantly asymptomatic patients subjected to aggressive lipid lowering (80 mg/day atorvastatin for 1 month) are less inflamed than plaques from patients that did not receive lipid-lowering therapy (2.5% [0.1 to 5.2] vs. 9.7 [3.1 to 15.5] % CD68 staining) (21). In the present study, we analyzed the ability to characterize plaques that fall into groups that bear relevance to the levels of inflammation shown to be important in the aforementioned histologic studies (<5%, 5% to 15%, and >15%), and found a significant difference between the 3 groups, suggesting that the imaging method may prove useful for the identification of plaques that may become symptomatic, and for following the response to plaque stabilization strategies such as lipid lowering therapy (Fig. 6).

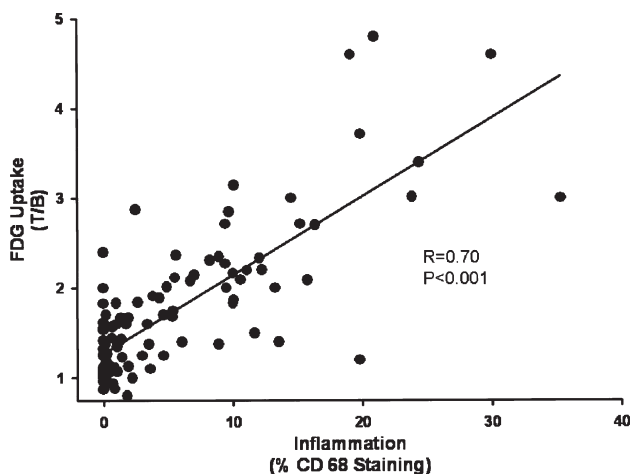
**Clinical implications.** Based on the results of large clinical trials, carotid revascularization is strongly recommended for



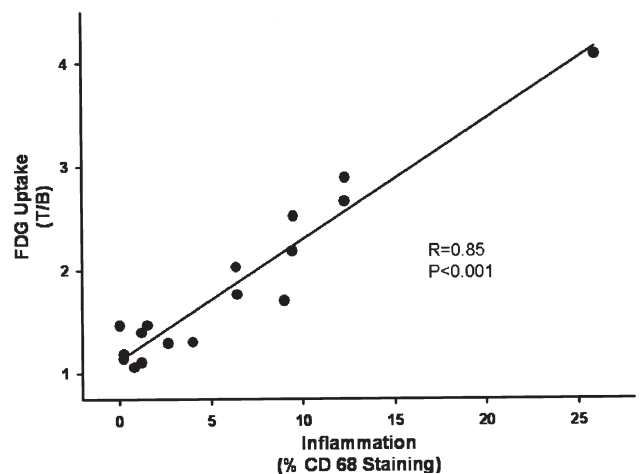
**Figure 2.** Trichrome- (10× magnification) and CD68-stained (200× magnification) carotid specimens that correspond to the images in Figure 1. The boxes in the trichrome-stained images indicate the regions corresponding to the high-powered CD68 stains. (A and B) As described in Figure 1.

cases of severe symptomatic stenoses, whereas for cases of moderate symptomatic or severe asymptomatic stenoses, the benefit in terms of stroke risk reduction is modest and revascularization is often limited to select cases in surgical centers with high experience (22-24). The findings of the present study suggest that PET studies of the carotid arteries could aid in the risk stratification of patients with less stenotic or asymptomatic lesions by identifying inflamed plaques that may be associated with a higher risk of a clinical event.

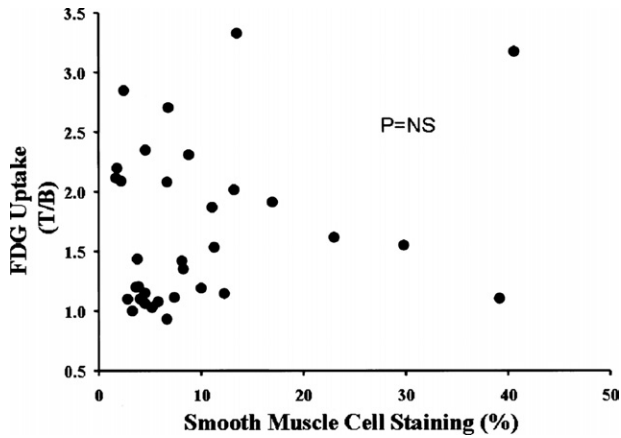
The important role of inflammation in the pathophysiology of atherosclerosis has been well established (1,2). Both histopathologic and epidemiologic data demonstrate the crucial role of inflammation in plaque formation and rupture. Plaques that have ruptured are often found to have extensive macrophage infiltrates (25-31). The macrophages are capable of destabilizing plaques by release of enzymes which degrade matrix proteins and inhibit collagen formation. Therefore, the use of <sup>18</sup>F-FDG-PET imaging to char-



**Figure 3.** Noninvasive positron emission tomography (PET) measurement of <sup>18</sup>F-fluorodeoxyglucose (FDG) uptake versus macrophage staining. The PET measurement of carotid plaque FDG uptake (target-to-background ratio [T/B]) in patients was compared with histologic assessment of inflammation in the corresponding sections taken during carotid endarterectomy. There was a significant correlation between T/B and macrophage density.



**Figure 4.** Mean within-patient <sup>18</sup>F-fluorodeoxyglucose (FDG) uptake versus inflammation in carotid endarterectomy patients. For each of the 17 subjects, all histologic sections were averaged to generate a mean per-patient value for percentage macrophage staining. Likewise, the corresponding imaging data were combined to generate a mean target-to-background ratio (T/B) for each patient. There was a significant correlation between mean T/B and mean inflammation ( $r = 0.85$ ;  $p < 0.001$ ). The correlation remained significant ( $r = 0.82$ ;  $p < 0.001$ ) even after the outlier with the highest plaque inflammation was removed from the analysis.



**Figure 5.** Positron emission tomography (PET) measurement of  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) uptake versus smooth muscle cell staining. The PET measurement of FDG uptake (target-to-background ratio [T/B]) in patients was compared with histologic assessment of smooth muscle cell staining (anti-SMA stain) in the corresponding sections taken during carotid endarterectomy. There was no correlation between FDG uptake and smooth muscle cell staining ( $r = 0.15$ ;  $p = 0.54$ ).

acterize plaques according to the degree of inflammation adds functional to anatomic data and might eventually prove useful for predicting which patients are at greatest risk of experiencing progression of disease or a clinical event. Natural history studies will be needed to determine whether such metabolic imaging will aid in risk assessment.

**Study limitations.** A concern regarding this study is that inflammation is likely to be a dynamic process which can develop and regress with time. Therefore, the inflammatory state observed on the day of noninvasive imaging may not be indicative of the degree of inflammation present on the day of endarterectomy. To minimize this potential effect, the time from imaging to obtaining histologic specimens was limited to <1 month in the present study. Changes in inflammation during the interval between imaging and surgery could have decreased the statistical power of the study. Despite this delay, highly significant correlations were observed.

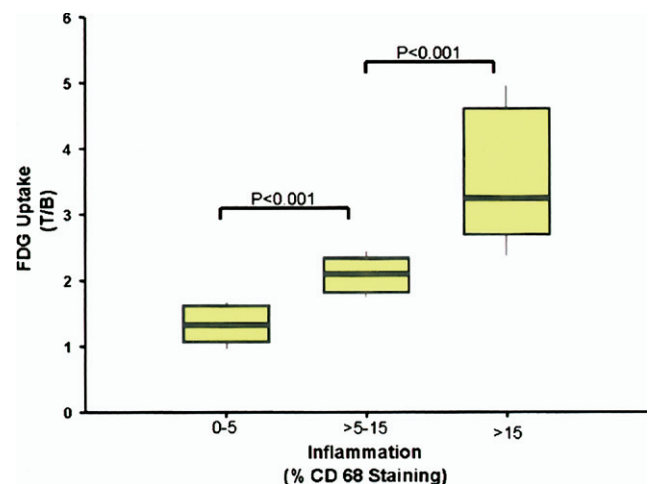
Another concern is that the method for co-registering the imaging and histologic sections is imperfect. There is potential error in the registration of the PET images with the histology. Although plaque specimens were carefully removed and marked to preserve orientation, several specimens were macerated or fractured, and varying degrees of recoil of the specimens was anticipated (perhaps depending on plaque composition). Such factors could have caused misregistration between the plaque specimens and images and may therefore have reduced the correlation coefficient between the individual imaging data and histology. In anticipation of this potential registration error, we calculated the average FDG uptake measured for each patient (average TBR for each patient) and compared it with the average inflammation seen in all of that patient's histologic sections (thereby removing the potential for misregistra-

tion). With this approach, the observed correlation was especially strong ( $r = 0.85$ ;  $p < 0.001$ )

**Future research directions.** In addition to the imaging of extracardiac vessels,  $^{18}\text{F}$ FDG may potentially be used to characterize coronary arterial plaques. Although small vessel size, mobility, and high myocardial uptake of  $^{18}\text{F}$ FDG (32-34) are potential obstacles to coronary imaging, several possible solutions exist. These include techniques to reduce myocardial uptake of  $^{18}\text{F}$ FDG and the use of combined PET-CT cameras to improve localization of tracer activity. Furthermore, novel intravascular positron-sensitive catheters can detect vascular FDG out of proportion to myocardial FDG, and may develop into a clinically useful imaging modality. Novel radiopharmaceuticals with greater macrophage specificity may further enhance the method.

**Conclusions.** We demonstrated that FDG-PET imaging can determine macrophage content of carotid plaques in vivo. This observation has important implications for drug development and, if supported by natural history studies, for the clinical care of patients at risk of stroke.

For drug development, this capability can assist in the clinical assessment of pharmaceutical agents designed to reduce macrophage activity in atherosclerotic plaques. It can do so by identifying patients with macrophage-rich plaques who could be randomly assigned to the agent of interest and by providing a surrogate end point for assessment of therapeutic efficacy. The direct impact of FDG-PET imaging on clinical care would require successful outcome of a natural history study demonstrating that a positive image was associated with an increased risk of neurologic symptoms. Such a study may demonstrate that nonstenotic but



**Figure 6.** Distribution of  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) uptake in patients grouped by average plaque inflammation. Patients were grouped according to the average amount of inflammation in their carotid specimens and the average FDG uptake determined for each group. The ranges assigned to these groups reflect the levels of inflammation shown to be important in previous histologic studies (14,20,21). The box plot shows mean values (thick lines) and 25th and 75th percentile values (upper and lower box boundaries). The length of the whiskers from the box boundaries represents standard error of the mean. The mean FDG uptake value for each group was significantly different. T/B = target-to-background ratio.

inflamed plaques, which would not be identified for intervention by the current stenosis-based screening method, are likely to cause events. If a link between FDG-PET imaging and events was established, this noninvasive measure could be used to identify patients in need of intensified medical therapy, carotid stenting, or CEA so that initial strokes might be prevented.

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