Imaging Atherosclerotic Plaque Inflammation With $[^{18}F]$-Fluorodeoxyglucose Positron Emission Tomography

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**Background**—Atherosclerotic plaque rupture is usually a consequence of inflammatory cell activity within the plaque. Current imaging techniques provide anatomic data but no indication of plaque inflammation. The glucose analogue $[^{18}F]$-fluorodeoxyglucose ($[^{18}F]$FDG) can be used to image inflammatory cell activity non-invasively by PET. In this study we tested whether $[^{18}F]$FDG-PET imaging can identify inflammation within carotid artery atherosclerotic plaques.

**Methods and Results**—Eight patients with symptomatic carotid atherosclerosis were imaged using $[^{18}F]$FDG-PET and co-registered CT. Symptomatic carotid plaques were visible in $[^{18}F]$FDG-PET images acquired 3 hours post-$[^{18}F]$FDG injection. The estimated net $[^{18}F]$FDG accumulation rate (plaque/integral plasma) in symptomatic lesions was 27% higher than in contralateral asymptomatic lesions. There was no measurable $[^{18}F]$FDG uptake into normal carotid arteries. Autoradiography of excised plaques confirmed accumulation of deoxyglucose in macrophage-rich areas of the plaque.

**Conclusions**—This study demonstrates that atherosclerotic plaque inflammation can be imaged with $[^{18}F]$FDG-PET, and that symptomatic, unstable plaques accumulate more $[^{18}F]$FDG than asymptomatic lesions. (*Circulation. 2002;105:2708-2711.*)

**Key Words:** atherosclerosis ■ imaging ■ nuclear medicine

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**Methods**

**Patient Recruitment**

We recruited 8 patients who had experienced a recent carotid-territory transient ischemic attack and had an internal carotid artery stenosis of at least 70%. Patients were excluded if they had either carotid artery occlusion or diabetes. The study protocol was approved by the local ethics committee and the UK Administration of Radioactive Substances Advisory Committee. All patients gave written informed consent.

**PET Protocol**

PET was carried out using a GE Advance PET scanner (GE Medical Systems). We administered 370 MBq $[^{18}F]$FDG intravenously over 60 seconds. PET images (as 4×5 minute frames) were acquired in 3D mode, at 190 (±6) minutes after $[^{18}F]$FDG administration. This time-point was chosen after preliminary dynamic studies indicated that late imaging provided optimal contrast between the $[^{18}F]$FDG concentration in plaque and the main background region, namely blood. A stiff cervical collar was worn to minimize patient movement. PET images were reconstructed using the 3D reprojection algorithm, with corrections applied for attenuation, dead time, scatter, and random coincidences. Rigid body co-registration with CT was performed, using a combination of fiducial markers and internal anatomical landmarks (spinal cord and muscles of the jaw and neck). This resulted in co-registration typically to within 1 mm in each dimension around the stenosis. To estimate plaque $[^{18}F]$FDG concentration, three-dimensional volumes of interest (VOI) were drawn.
around the area of stenosis on the contrast CT scan using the Analyze software package (AnalyzeDirect).7 These regions were then placed onto the co-registered PET images to produce mean 18FDG concentration values (kBq/mL). The mean VOI size was 148 mm3. To determine the plasma 18FDG concentration up to the scan time (input function), venous blood was sampled throughout the PET study. The estimated net 18FDG accumulation rate was determined by dividing the mean decay-corrected plaque VOI 18FDG concentration by the integral of the decay-corrected input function, and is expressed in units of sec−1.

CT Protocol
Using a GE Hispeed Advantage CT scanner (GE Medical Systems), helical contrast CT angiograms were acquired from skull base to 3 cm below the level of the carotid bifurcation.

Plaque Autoradiography
In a separate autoradiographic study, 3 carotid plaques from symptomatic patients were incubated whole with 50 μCi tritiated deoxyglucose (an in vitro analogue of 18FDG) in 5 mL Medium 199 (Sigma) for 60 minutes at 37° C. Paraffin sections of 5 μm thickness were coated with autoradiographic emulsion (LM-1, Amersham), exposed for 6 weeks, developed, and counterstained with hematoxylin and eosin. Control slides were prepared without radioactivity.

Statistical Methods
Results are expressed as mean±SEM with 95% CI in brackets. The paired t test was used to compare net 18FDG accumulation rates in symptomatic and asymptomatic carotid plaques in the same patients.

Results
We performed 18FDG-PET and CT scanning in 8 patients between 48 and 71 years of age (Table). The median time between symptoms and PET study was 3.5 months, and between PET and carotid endarterectomy was 43 days. In all patients, co-registered PET images acquired around 3 hours revealed 18FDG accumulation at the site of the symptomatic plaque (Figure 1).

Six of the 8 patients had contralateral asymptomatic stenoses ranging from 35% to 75%. A comparison was made between the net 18FDG accumulation rate in symptomatic plaques and contralateral asymptomatic lesions. In all cases, symptomatic lesions had higher estimated 18FDG accumulation rates than asymptomatic lesions; the mean symptomatic net accumulation rate was 7.95×10−5±0.58×10−5 sec−1 (95% CI: 6.58 to 9.32×10−5), with a mean difference between symptomatic and asymptomatic of 2.10×10−5±0.45×10−5 sec−1 (95% CI 0.94 to 3.26×10−5, P=0.005).

The 2 remaining patients had angiographically normal arteries on the asymptomatic side, in whom there was no significant accumulation of 18FDG compared to background plasma. The bottom row of the table summarises the overall findings. M indicates male; F, female; R, right; and L, left.

Discussion
Anecdotal reports of “hot spots” in blood vessels of patients at high risk of atherosclerosis undergoing whole body 18FDG-PET studies, along with a single study in cholesterol-fed rabbits,8 have suggested that 18FDG can accumulate in atherosclerotic plaques.
By combining PET and CT imaging, we have confirmed that $^{18}$FDG accumulates in human carotid artery atherosclerotic plaques, with significantly higher uptake in symptomatic lesions than in asymptomatic lesions. Furthermore, we have demonstrated that the majority of deoxyglucose accumulates in macrophage-rich areas of the plaque. These findings suggest that inflammation is present to a greater degree in symptomatic plaques than asymptomatic plaques.

Taken together, these results suggest strongly that $^{18}$FDG-PET may be capable of imaging and potentially quantifying plaque inflammation. This raises the possibility that $^{18}$FDG-PET could be used to predict the risk of future plaque rupture, and therefore to target surgery to high-risk carotid stenoses regardless of angiographic appearance. Perhaps more importantly, it might be used to monitor the effectiveness of systemic atheroma-modifying treatments because it is likely that any measurable effects of treatment on inflammation in carotid atheroma will reflect similar changes in other vascular beds, including the coronary arteries.

Before this potential can be realized, further studies are required to determine the precise relationship between $^{18}$FDG uptake, plaque macrophage activity, and risk of plaque rupture, and more macrophage-specific PET ligands will be required to image vessels in metabolically active tissues such as the heart and brain. Although PET has limited spatial resolution ($\approx 5$ mm FWHM for GE Advance), we have demonstrated that co-registration with CT can localize the $^{18}$FDG signal to individual atherosclerotic lesions. Because CT angiography cannot accurately measure plaque volume (because remodeling can accommodate large plaques with little impact on lumen diameter), however, we were unable to apply partial volume correction to our data in this study. We are confident, however, that this will be achievable with high-resolution carotid MRI.

In summary, this early study provides the first direct evidence that human atherosclerotic plaque inflammation can be assessed non-invasively by $^{18}$FDG-PET, and paves the way for a new approach to atheroma imaging that reflects the cellular pathology of the disease process rather than its anatomical consequences.

Figure 1. The upper row (from left to right) shows PET, contrast CT, and co-registered PET/CT images in the sagittal plane, from a 63-year-old man who had experienced 2 episodes of left-sided hemiparesis. Angiography demonstrated stenosis of the proximal right internal carotid artery; this was confirmed on the CT image (black arrow). The white arrows show $^{18}$FDG uptake at the level of the plaque in the carotid artery. As expected, there was high $^{18}$FDG uptake in the brain, jaw muscles, and facial soft tissues. The lower row (from left to right) demonstrates a low level of $^{18}$FDG uptake in an asymptomatic carotid stenosis. The black arrow highlights the stenosis on the CT angiogram, and the white arrows demonstrate minimal $^{18}$FDG accumulation at this site on the $^{18}$FDG-PET and co-registered PET/CT images.

Figure 2. Tritiated deoxyglucose autoradiography of symptomatic carotid artery plaque. The larger panel shows typical plaque architecture, whereas the inset shows that silver grains have accumulated at the lipid core/fibrous cap border region, predominately within macrophages. Magnification $\times 10$ and $\times 20$.
ment of Pathology at Papworth Hospital for their kind assistance with this project.

References

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Circulation. 2002;105:2708-2711; originally published online May 20, 2002;
doi: 10.1161/01.CIR.0000020548.60110.76

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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