Imaging Atherosclerotic Plaque Inflammation With \(^{18}\text{F}\)-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 \(^{18}\text{F}\)-fluorodeoxyglucose (\(^{18}\text{FDG}\)) can be used to image inflammatory cell activity non-invasively by PET. In this study we tested whether \(^{18}\text{FDG}-\text{PET}\) imaging can identify inflammation within carotid artery atherosclerotic plaques.

**Methods and Results**—Eight patients with symptomatic carotid atherosclerosis were imaged using \(^{18}\text{FDG}-\text{PET}\) and co-registered CT. Symptomatic carotid plaques were visible in \(^{18}\text{FDG}-\text{PET}\) images acquired 3 hours post-\(^{18}\text{FDG}\) injection. The estimated net \(^{18}\text{FDG}\) accumulation rate (plaque/integral plasma) in symptomatic lesions was 27% higher than in contralateral asymptomatic lesions. There was no measurable \(^{18}\text{FDG}\) 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 \(^{18}\text{FDG}-\text{PET}\), and that symptomatic, unstable plaques accumulate more \(^{18}\text{FDG}\) than asymptomatic lesions. (*Circulation, 2002;105:2708-2711.*)

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

Inflammation is important in both the pathogenesis and outcome of atherosclerosis. \(^1\) Plaques containing numerous inflammatory cells, in particular macrophages, have a high risk of rupture, whereas those with few inflammatory cells are at lower risk. \(^2,3\) The current “gold standard” imaging technique for atherosclerosis is x-ray contrast angiography, which provides high-resolution definition of the site and severity of luminal stenoses, but no information about plaque inflammation.

There is a need to quantify plaque inflammation to predict the risk of plaque rupture and to monitor the effects of atheroma-modifying therapies. This is important because recent experimental and clinical studies strongly suggest that hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) promote plaque stability by decreasing plaque macrophage content and activity without substantially reducing plaque size and therefore angiographic appearance. \(^4\)

\(^{18}\text{F}\)-fluorodeoxyglucose (\(^{18}\text{FDG}\)) is a glucose analogue that is taken up by cells in proportion to their metabolic activity. \(^5\) We tested the hypothesis that plaque inflammation could be visualized and quantified non-invasively using \(^{18}\text{FDG}-\text{PET}\) in patients with symptomatic carotid artery disease.

**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 \(^{18}\text{FDG}\) intravenously over 60 seconds. PET images (as 4×5 minute frames) were acquired in 3D mode, at 190 (±6) minutes after \(^{18}\text{FDG}\) administration. This time-point was chosen after preliminary dynamic studies indicated that late imaging provided optimal contrast between the \(^{18}\text{FDG}\) 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 reprojecion algorithm,\(^6\) 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 \(^{18}\text{FDG}\) concentration, three-dimensional volumes of interest (VOI) were drawn.

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around the area of stenosis on the contrast CT scan using the Analyze software package (AnalyzeDirect). 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 mm$^3$. 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, with no significant uptake of 18FDG into those vessels; the 18FDG concentration in a VOI around the carotid bifurcation did not differ significantly from that measured in plasma (wall-to-plasma 18FDG concentration ratio=0.9±0.1).

Histological examination of the excised symptomatic plaques from all the patients who had undergone imaging revealed heavy macrophage infiltration.

Carotid plaque autoradiography with tritiated deoxyglucose demonstrated uptake in macrophage-rich areas of plaques, predominately at the lipid core/fibrous cap border of the lesions. There was little or no uptake in other areas of the plaques (Figure 2). Control sections showed no development of silver grains.

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, 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.9

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 (≈ 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.10

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.

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References

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