Imaging Atherosclerotic Plaque Inflammation With [18 F]-Fluorodeoxyglucose Positron Emission Tomography

J.H.F. Rudd, MD, MRCP; E.A. Warburton, MD, DM; T.D. Fryer, PhD; H.A. Jones, PhD; J.C. Clark, DSc; N. Antoun, MD, FRCP, FRCR; P. Johnström, PhD; A.P. Davenport, PhD; P.J. Kirkpatrick, MSc, FRCS; B.N. Arch, PhD; J.D. Pickard, MD, FRCS; P.L. Weissberg, MD, FRCP

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
Details of Patients Who Underwent 18FDG–PET Imaging

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Symptoms</th>
<th>Net 18FDG Accumulation Rate ($\times 10^{-5}$ sec$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptomatic</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>66</td>
<td>R amaurosis $\times 2$</td>
<td>5.88</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>71</td>
<td>Aphasis $\times 3$</td>
<td>8.05</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>48</td>
<td>R hemiparesis</td>
<td>7.59</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>68</td>
<td>L amaurosis $\times 2$</td>
<td>8.44</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>52</td>
<td>L hemiparesis $\times 6$</td>
<td>8.38</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>63</td>
<td>L hemiparesis $\times 2$</td>
<td>5.77</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>69</td>
<td>L hemisensory</td>
<td>10.87</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>71</td>
<td>R hemiparesis</td>
<td>8.65</td>
</tr>
</tbody>
</table>

Female (%) Mean age Mean (SEM) Mean (SEM)
25 63.5 7.95 ($\pm$0.96)

The values in the "Symptomatic" and "Asymptomatic" columns are the net 18FDG accumulation rates for symptomatic and asymptomatic plaques, respectively. The absent values in the asymptomatic column represent patients with 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.

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 Histology
After imaging, carotid endarterectomy samples from all 8 patients imaged were fixed and stained with hematoxylin and eosin. Immunohistochemistry was performed using anti-macrophage antibodies (CD68, Dako, Elys, UK).

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×$10^{-3}$ 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×$10^{-3}$ 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 18FDG 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 18FDG-PET may be capable of imaging and potentially quantifying plaque inflammation. This raises the possibility that 18FDG-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 18FDG 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 18FDG 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 18FDG-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.

Acknowledgments

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References

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