Identification of Culprit Lesions After Transient Ischemic Attack by Combined $^{18}$F Fluorodeoxyglucose Positron-Emission Tomography and High-Resolution Magnetic Resonance Imaging

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Background and Purpose—Carotid endarterectomy is currently guided by angiographic appearance on the assumption that the most stenotic lesion visible at angiography is likely to be the lesion from which future embolic events will arise. However, risk of plaque rupture, the most common cause of atherosclerosis-related thromboembolism, is dictated by the composition of the plaque, in particular the degree of inflammation. Angiography may, therefore, be an unreliable method of identifying vulnerable plaques. In this study, plaque inflammation was quantified before endarterectomy using the combination of $^{18}$F fluorodeoxyglucose positron (FDG)-emission tomography (PET) and high-resolution MRI (HRMRI).

Methods—Twelve patients, all of whom had suffered a recent transient ischemic attack, had a severe stenosis in the ipsilateral carotid artery, and were awaiting carotid endarterectomy underwent FDG-PET and HRMRI scanning. A semiquantitative estimate of plaque inflammation was calculated for all of the lesions identified on HRMRI.

Results—In 7 of 12 patients (58%), high FDG uptake was seen in the lesion targeted for endarterectomy. In the remaining 5 patients, FDG uptake in the targeted lesion was low. In these 5 patients, 3 had nonstenotic lesions identified on HRMRI that exhibited a high level of FDG uptake. All 3 of the highly inflamed nonstenotic lesions were located in a vascular territory compatible with the patients’ presenting symptoms.

Conclusions—Our data suggest that angiography may not always identify the culprit lesion. Combined FDG-PET and HRMRI can assess the degree of inflammation in stenotic and nonstenotic plaques and could potentially be used to identify lesions responsible for embolic events. (Stroke. 2005;36:2642-2647.)

Key Words: atherosclerosis ■ carotid endarterectomy ■ inflammation ■ MRI ■ positron emission tomography

Patients who have suffered a recent transient ischemic attack (TIA) or stroke are currently selected for carotid endarterectomy (CEA) on the basis of an angiographically defined severe stenosis of the relevant carotid artery. Large, randomized, controlled clinical trials have shown that CEA reduces mortality and stroke by ~16% in those patients with >70% stenosis of the internal carotid artery.1 The Asymptomatic Carotid Surgery Trial also showed a statistically significant benefit for CEA in patients with severe asymptomatic carotid artery stenosis, but when compared with symptomatic patients, the absolute risk reduction over medical therapy was much reduced, at 7%.2 The discrepancy in absolute risk reduction after CEA in symptomatic and asymptomatic patients highlights the importance of factors other than plaque size and degree of luminal obstruction in determining risk. Histological studies have shown that plaque inflammation and, in particular, the degree of macrophage infiltration are important predictors of plaque rupture and embolic events.3 Macrophages are central to the inflammatory process within atherosclerotic plaque, helping to initiate, maintain, and sustain it. Uncontrolled inflammation causes breakdown of the extracellular matrix of the fibrous cap of the plaque and apoptosis of the vascular smooth muscle cells responsible for its synthesis.4,5 This ultimately leads to thinning of the cap and a reduction in its mechanical strength, rendering the plaque susceptible to rupture and subsequent thromboembolism.6 Despite the recognition that plaque composition is more important than plaque size in determining
outcome, x-ray angiography remains the technique of choice to target lesions for surgical intervention. However, angiography cannot identify inflamed plaques or nonstenotic plaques in positively remodeled vessels, which may be particularly prone to inflammation and plaque rupture.7

Advances in the understanding of plaque biology and the short comings of x-ray angiography have stimulated the development of novel imaging techniques to identify and quantify inflammation within atheromatous vessels. Our group has shown that 18F fluorodeoxyglucose (FDG) positron-emission tomography (PET) is capable of identifying and quantifying inflammation within human carotid plaques.8 In the same study, we demonstrated that FDG uptake was confined to areas of the plaque that are heavily infiltrated by macrophages,8 and others have demonstrated a highly significant correlation between FDG uptake and the degree of macrophage infiltration in a rabbit model of atherosclerosis.5 Thus, PET appears to be able to identify inflamed plaques. However, a major limitation of PET is the low level of anatomical detail that it provides. In the present study, we have combined FDG-PET and high-resolution MRI (HRMRI) to assess patients with recent ischemic symptoms ascribed clinically to stenotic carotid lesions targeted for CEA. We hypothesized that if the targeted lesion was responsible for the symptoms, then it would show evidence of inflammation on FDG-PET images.

Methods

Patient Recruitment

We studied 12 patients with recent carotid-territory TIA and a “culprit” internal carotid artery stenosis of ≥65% who were awaiting carotid endarterectomy. In each patient, the diagnosis was made by a stroke specialist after the necessary investigations had been completed. Lipid studies, random glucose estimation, electrocardiography, carotid Doppler, and x-ray angiography were carried out on all of the patients. Patients were excluded if they had carotid artery occlusion or contraindications to MRI or PET imaging. At the time of enrolment, all of the patients were receiving aspirin and a statin, along with antihypertensive therapy at the discretion of the assessing doctor. The study was approved by the local ethics committee and the UK Administration of Radioactive Substances Advisory Committee. All of the patients gave written informed consent.

PET Imaging

PET imaging was carried out using a GE Advance PET scanner (GE Medical Systems) to acquire a dynamic set of PET images in 3D mode over a 120-minute period after the IV administration of 185 MBq of FDG. Before injection, blank and transmission scans were acquired with germanium-68 rod sources to allow measured attenuation correction. Emission images (128×128×35; voxel size 2.34×2.34×4.25 mm) were reconstructed using the PROMIS 3D filtered back projection algorithm with corrections applied for attenuation, isotope decay, dead time, scatter, and random coincidences. In order to identify FDG uptake into atheromatous plaque, emission data from the last 30 minutes of each scan were used, which allowed time for FDG to clear from the circulation and, hence, reduce the spillover of signal from blood into the plaque region because of the partial volume effect.10

HRMRI

HRMRI was performed on a 1.5 T whole body system (GE Medical Systems) using a customized 4-channel phased array coil (Flick Engineering Solutions BV) wrapped around the neck, to give coverage of ~2-cm proximal and 4-cm distal to the carotid bifurcation. Initially, a low-resolution T1-weighted sequence was used to provide an image of the whole head and neck. This was used to facilitate coregistration of HRMRI and PET images (see below). The following axial 2D, ECG-gated, blood-suppressed, fast spin echo pulse sequences were used: intermediate T2-weighted sequence using repetition time (TR) of twice the time interval between successive R waves on the ECG (RR interval), and an echo time (TE) of 46 ms both with and without fat saturation; T2-weighted sequence using TR of twice the RR interval and a TE of 100 ms; and an inversion recovery (STIR) sequence using a TR of twice the RR interval, a TE of 46 ms, and an inversion time of 150 ms. The slice thickness was 3 mm giving an overall voxel size of 0.4×0.4×3 mm.

PET/HRMRI Coregistration

Care was taken to position the patient in the same posture for both PET and MRI scans. This was facilitated by using the same foam headrest for both scans and by ensuring that the patient’s chin was adequately centered. A measurement was taken from the chin to the suprasternal notch on each patient to ensure the same degree of neck flexion on both scans. Coregistration of low-resolution and high-resolution MRI was performed by applying translational and rotational shifts using the software package MPI Tool (Max Planck Institute). The PET image was then coregistered to the low-resolution MRI image of the head and neck using anatomical landmarks present on both scans, such as spinal cord, submandibular glands, and soft tissue surrounding the skull and mandible (Figure 1). Finally, PET, HRMRI, and fused PET-HRMRI images were displayed using the MPI Tool.

Plaque FDG Uptake

A semiquantitative assessment of FDG uptake was carried out by a person blinded to the patient’s clinical details. For each patient, regions of interest were drawn around all of the atheromatous plaques seen on HRMRI and then transferred onto the corresponding coregistered PET image to enable FDG uptake values (kBq/mL) to be calculated. The same process was carried out for 5 segments of vessel wall with normal appearance on HRMRI. The uptake value for each plaque was then divided by the average of the normal vessel wall values to give an uptake ratio. This was done in order to normalize for interpatient variations in FDG delivery to the plaque and basal metabolism. Finally, to enable the plaque uptake to be classified as high or low, we determined the 3D of the 60 normal

Figure 1. Coregistered FDG-PET and low-resolution MRI images and image fusion. Some of the anatomical structures used to coregister the images are highlighted by arrows. Yellow arrows, sublingual glands; green arrows, tonsils; blue arrows, spinal cord; white arrows, submandibular gland.
vessel wall values after they had been normalized to the average value in the corresponding patient. Plaque FDG uptake was then defined as high if the uptake ratio was >2 SD above unity. This equated to an uptake ratio above 1.28.

**Results**

Details of the 12 patients are summarized in Table. Their mean age was 71 years (SD±10 years). The mean time from symptoms to imaging was 64 days (SD±43 days). No significant correlation was found between degree of FDG uptake and time from symptoms to imaging (Spearman rank order correlation: r = −0.41; P = 0.18).

In all of the patients, HRMRI defined the extent and morphology (eg, concentric or eccentric) of the stenotic atherosclerotic lesion targeted for endarterectomy (Figure 2). In the majority of patients, HRMRI also demonstrated plaque elsewhere in the carotid and/or vertebral circulation, most of which were nonstenotic and caused little or no angiographic stenosis (Figure 2).

High FDG uptake was seen in only 7 of 12 (58%) carotid lesions targeted for CEA (Figure 3a). The remaining 5 (42%) exhibited low uptake (Figure 3b). In the 5 patients in whom FDG uptake into the targeted lesion was classified as low, 3 (25%) had nonstenotic lesions identified on HRMRI that exhibited a high level of FDG uptake. Two of the 3 nonstenotic lesions with high FDG uptake were found in the same arterial territory as the lesion targeted for CEA (Figure 4), with the remaining nonstenotic lesion located in the contralateral vertebral artery (Figure 5).

**Discussion**

It has recently become apparent that risk of plaque rupture, and, therefore, risk of a downstream embolic event, is determined more by plaque composition than plaque size or degree of stenosis.11 In addition, autopsy studies of the coronary circulation have confirmed that arteries can remodel to accommodate large atherosclerotic plaques and preserve lumen diameter.12 Such lesions cannot readily be detected by angiography, yet, in the cerebral circulation, endarterectomy aimed at preventing stroke is currently guided solely by angiographic appearance on the assumption that the most stenotic lesion visible at angiography is likely to be the lesion from which future embolic events will arise. Given the

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M indicates male; F, female; R, right; L, left; RIC, right internal carotid; LIC, left internal carotid; RCC, right common carotid; LCC, left common carotid; RVA, right vertebral artery. *Lesion targeted for endarterectomy. †No. represents FDG uptake in plaque divided by that in normal arterial wall; ≤1.28 = low; >1.28 = high.
diffuse nature of atherosclerosis in the cerebral circulation, it is likely that the culprit lesion will frequently fail to be identified by angiography.

In this study, using combined FDG-PET and HRMRI, we identified inflamed plaques in 10 of 12 patients who had recently suffered a presumed cerebral embolic episode in a vascular territory consistent with their clinical presentation. In 7 of 12, the inflammation localized to the stenotic internal carotid lesion that was presumed to have caused the clinical event and was targeted for surgery. However, in the remaining 5 patients, 2 had inflamed nonstenotic lesions in the same arterial territory, and 1 had inflamed atheroma in a vertebral artery. All of the patients in our study were presumed to have suffered an anterior circulation embolic event at the time of entry into the study. However, a retrospective review of their symptoms revealed that the patient with inflamed vertebral artery disease (patient 2 in Table) had suffered a visual event compatible with a posterior circulation TIA.

Our study provides 2 novel observations. The first is that in a significant minority of patients, the index clinical event may not have arisen from the stenotic internal carotid lesion targeted for surgery. The second is that in the majority of patients studied, an actively inflamed plaque could be identified in a vascular location compatible with the clinical

Figure 2. HRMRI scans of the neck demonstrating the diffuse nature of atherosclerosis. a, Patient 1: the red arrow highlights a large eccentric plaque causing a severe stenosis of the right internal carotid artery. A large stenotic plaque can be seen in the contralateral, asymptomatic internal carotid artery (green arrow). b, Patient 7: a moderate-sized eccentric plaque can be seen in the right internal carotid artery (red arrow). An eccentric nonstenotic plaque can be seen in the contralateral internal carotid artery (green arrow).

Figure 3. a, HRMRI and FDG-PET images from patient 7, who suffered a right carotid territory stroke. The HRMRI image shows a large stenotic right internal carotid artery plaque (green arrow), which was subsequently excised surgically. The plaque demonstrated a high level of FDG uptake (blue and red arrows). b, HRMRI and FDG-PET scans from patient 6, who had suffered a recent stroke and was due to undergo carotid endarterectomy. Despite the presence of a highly stenotic left internal carotid artery caused by the presence of concentric atheroma (yellow arrow), there is no discernable FDG uptake (white and black arrows), suggesting a low level of inflammatory activity within this plaque.

Figure 4. HRMRI and FDG-PET scans taken from patient 1 after a right carotid territory stroke. a, Transaxial images taken at the level of the proximal right internal carotid (RIC) artery. There is a large atherosclerotic plaque in the RIC artery causing severe luminal stenosis (green arrow). Despite its size, only low FDG uptake is demonstrated (blue and red arrows). b, Axial images taken at the level of the proximal common carotid arteries (CCA). The yellow arrow highlights a nonstenotic plaque in the wall of the right CCA. The white arrow points to an area of high FDG uptake, the location of which is confirmed on the fused scan as the right CCA (black arrow).

Figure 5. HRMRI and FDG-PET scans taken from patient 2, diagnosed with a right carotid territory stroke after a transient visual field disturbance in conjunction with a stenosis of the right internal carotid (RIC) artery on x-ray angiography. a, Transaxial images at the level of the proximal RIC artery. The green arrow points to the RIC artery plaque targeted for endarterectomy. However, there is only a low-level FDG signal seen on the FDG-PET and fused scans (blue and red arrows). b, Transaxial scans taken 3 cm above those shown in “a.” The vertebral arteries (yellow arrows) can be clearly identified on the HRMRI (fat-saturated sequence). The white arrow on the FDG-PET highlights an area of high FDG signal, which, on the fused scan, lies over the right vertebral artery (black arrow). A highly inflamed right vertebral artery plaque could be the cause of this patient’s presenting symptoms.
presentation. These findings, if confirmed, have important implications for the management of patients with cerebrovascular disease. One is that PET could be used to target surgery only to those stenotic carotid lesions likely to have been responsible for an embolic event, thereby limiting surgery only to those most likely to benefit and reducing the risk:benefit ratio of the procedure. Secondly, by combining PET with HRMRI, it is possible that angiographically insignificant lesions and lesions that are not amenable to surgery can be identified and followed during treatment with plaque-stabilizing agents, such as statins.

The validity of these implications depends on the robustness of the association between the imaging data and true risk of a clinical event, which the current study could not address. Evidence that PET can identify actively inflamed lesions is growing. We have previously shown, in ex vivo experiments, that FDG accumulates predominantly in carotid plaque macrophages, and Ogawa et al. have shown, in a rabbit model of atherosclerosis, that FDG accumulation is proportional to plaque macrophage content. Vascular hot spots have also been identified on FDG-PET scans performed on cancer patients known to be at high risk for atherosclerosis.

In this study, we are unable to rule out the possibility that the time interval between the index clinical event and imaging may have had an effect on the degree of FDG uptake seen within the lesion targeted for endarterectomy. For example, it is plausible that a highly inflamed stenotic internal carotid lesion could be the cause of a stroke, but with the passage of time and after treatment with antiplatelet and cholesterol-lowering therapy, could become less inflamed, with other lesions becoming more so. Therefore, quantification of inflammatory levels within plaques cannot provide conclusive evidence of causality. Furthermore, although there is a close histological association between macrophage content and plaque rupture, no one has yet confirmed that plaques that accumulate most FDG are most likely to cause an embolic event. Studies currently underway in our group are addressing the correlation between FDG uptake and microembolic signals detected by transcranial Doppler.

The noninvasive nature of both PET and HRMRI gives them an obvious advantage over x-ray angiography, which, in this group of patients, carries a 1% to 2% risk of stroke. Unlike x-ray angiography, HRMRI can identify nonstenotic plaques, which, as shown in this study, can be highly inflamed and may well be a grossly underestimated cause of stroke. HRMRI can also define other important anatomical characteristics, such as size of lipid core and fibrous cap thickness, which, in conjunction with the degree of inflammation, could be used to refine the risk of plaque rupture and stroke. PET also allows for sophisticated quantification of physiological pathways, such as glucose metabolism in the case of FDG-PET. However, this is usually a demanding process, often requiring dynamic data acquisition and the measurement of arterial blood tracer activity. In this study, we opted to use a semiquantitative measure of FDG uptake that, by comparing uptake into plaque with that into normal vessel wall, goes some way to correcting for interpatient differences in the quantity of FDG injected, volume of distribution, renal clearance, and basal metabolic rate.

Although combined PET and HRMRI provides considerably more information than angiography on atherosclerotic plaques on which to make clinical decisions, PET has some notable drawbacks. First, it relies on ionizing radiation. However, since the publication of our first study, we have been able to halve the injected FDG activity to 185 MBq. This equates to a patient dose of 3.5 mSv, which is equivalent to that of a computed tomography chest scan. With additional refinements, it may be possible to reduce the radiation dose still further. Second, FDG is not specific for plaque macrophages and is taken up by other metabolically active cells, for example, in tumors, salivary glands, and the spinal cord. In the absence of coregistration with HRMRI, such uptake could be mistaken for inflammation within plaque and vice versa. Other, more macrophage-specific tracers are currently under evaluation in our laboratory. Third, the limited spatial resolution of PET (~6 mm in this study) renders images subject to partial volume errors that lead to under/overestimation of tracer accumulation in small objects, such as the atherosclerotic plaque, with high/low uptake, respectively. Partial volume correction algorithms, originally developed for brain PET, which use anatomical detail in MRI images coregistered to PET, could be adapted to significantly reduce the impact of this problem in atheromatous plaques. We are currently in the process of developing partial volume correction algorithms for plaque imaging in the neck.

One needs to remain cautious regarding the interpretation of results from a small study such as this one. However, our study does expand on our previous observation that FDG accumulates in inflamed human atherosclerotic lesions and points to the potential use of combined PET and HRMRI to identify lesions responsible for embolic events.

Acknowledgments

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