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Positron Emission Tomography and Magnetic Resonance Imaging of Cellular Inflammation in Patients with Abdominal Aortic Aneurysms

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WHAT THIS PAPER ADDS

Comparing these techniques identifies a modest correlation but some key differences related to the spatial distribution of ^{18}F-FDG and USPIO uptake. This may reflect the differing elements of macrophage activity detected by these modalities: glycolysis and phagocytosis. Further studies are needed to assess whether identification of this varying activity will influence aneurysm growth rates and the clinical outcome.

Objectives: Inflammation is critical in the pathogenesis of abdominal aortic aneurysm (AAA) disease. Combined ^{18}F-fludeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET-CT) and ultrasmall superparamagnetic particles of iron oxide (USPIO)-enhanced magnetic resonance imaging (MRI) are non-invasive methods of assessing tissue inflammation. The aim of this study was to compare these techniques in patients with AAA.

Materials and methods: Fifteen patients with asymptomatic AAA with diameter 46 ± 7 mm underwent PET-CT with ^{18}F-FDG, and T2*-weighted MRI before and 24 hours after administration of USPIO. The PET-CT and MRI data were then co-registered. Standardised uptake values (SUVs) were calculated to measure ^{18}F-FDG activity, and USPIO uptake was determined using the change in R2*. Comparisons between the techniques were made using a quadrant analysis and a voxel-by-voxel evaluation.

Results: When all areas of the aneurysm were evaluated, there was a modest correlation between the SUV on PET-CT and the change in R2* on USPIO-enhanced MRI ($n = 70{,}345$ voxels; $r = .30$; $p < .0001$). Although regions of increased ^{18}F-FDG and USPIO uptake co-localised on occasion, this was infrequent (kappa statistic 0.074; 95% CI 0.026–0.122). ^{18}F-FDG activity was commonly focused in the shoulder region whereas USPIO uptake was more apparent in the main body of the aneurysm. Maximum SUV was lower in patients with mural USPIO uptake.

Conclusions: Both ^{18}F-FDG PET-CT and USPIO-MRI uptake identify vascular inflammation associated with AAA. Although they demonstrate a modest correlation, there are distinct differences in the pattern and distribution of uptake, suggesting a differential detection of macrophage glycolytic and phagocytic activity respectively.

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INTRODUCTION

Recent advances in imaging modalities have generated considerable interest in novel molecular and cellular techniques. In contrast to anatomical and structural approaches, molecular and cellular imaging targets the activity of specific biochemical and cellular processes to provide insight into the aetiology, biology, and pathogenesis of diseased states. Moreover, this has the potential to refine the diagnosis and risk stratification of cardiovascular disease as well as to assess responses to specific therapeutic interventions.[1–5] A combination of morphological imaging with molecular imaging has proven a particularly useful approach.

^{18}F-Fludeoxyglucose (^{18}F-FDG) is used to image metabolically active cells with combined positron emission and computed tomography (PET-CT). ^{18}F-FDG accumulates in all

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cells and tissues that metabolise glucose, in direct proportion to their metabolic activity. In atherosclerotic arteries and those affected by vasculitides, ^{18}F-FDG uptake correlates with the degree of arterial inflammation and is reproducible.[6–8] Furthermore, ^{18}F-FDG uptake increases with the number of cardiovascular risk factors present, is predictive of future cardiovascular events,[9–11] and has been used as a biomarker to demonstrate the anti-inflammatory effects of statins and other novel therapies.[12–14] ^{18}F-FDG accumulates in the wall of abdominal aortic aneurysms (AAAs) and several studies have correlated uptake with aortic vessel wall inflammation on histology.[15–17] There is evidence to suggest that ^{18}F-FDG can discriminate between asymptomatic and symptomatic AAA, but its potential use as a marker of aneurysm expansion, progression, and rupture has yet to be established.[15–22]

Magnetic resonance imaging (MRI) with ultrasmall superparamagnetic particles of iron oxide (USPIO) is an alternative approach for detecting cellular inflammation.[23,24] Owing to their small particle size (diameter 10–30 nm), USPIO escape immediate recognition by the reticulo-endothelial system, persist in the bloodstream, and accumulate at sites of vascular inflammation. Here they undergo phagocytosis by tissue-resident macrophages within which they accumulate and are detectable on T2- and T2*-weighted MRI sequences. Within atheromatous plaques, USPIO uptake correlates with macrophage density, distinguishes stable from unstable carotid plaques, and is reduced following high-dose atorvastatin therapy.[25–27] USPIO uptake in the wall of AAAs has previously been demonstrated, where it co-localises with macrophages and is associated with a threefold higher AAA growth rate.[24]

Given that both ^{18}F-FDG PET and USPIO-enhanced MRI have been used to assess vascular inflammation in patients with AAA, the aim of this study was to compare ^{18}F-FDG PET and USPIO-enhanced MRI in patients with AAAs. Specifically, the spatial distribution and intensity of the inflammatory process using both techniques was assessed to determine whether they provided complementary or distinct insights into the pathology of AAAs.

MATERIALS AND METHODS

Subjects

Patients with asymptomatic AAA (diameter 30–55 mm on duplex ultrasound examination) were recruited from the aneurysm surveillance clinic at the Royal Infirmary of Edinburgh. Exclusion criteria were age $<$ 50 years, active systemic inflammatory or malignant disease, renal dysfunction (estimated glomerular filtration rate $<$ 30 mL/min, because of the risks of contrast induced renal dysfunction), hepatic cirrhosis (Child–Pugh score B or C, because of the contrast agent not having been studied in this group of patients), planned AAA surgery within 6 months of screening, any contraindication to MRI and insulin-dependent diabetes mellitus (due to the confounding of ^{18}F-FDG uptake with variable blood glucose concentrations). Studies were performed with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of each participant.

All patients underwent a comprehensive baseline clinical assessment, including evaluation of their cardiovascular risk factor profile and recording of an abdominal ultrasound scan. ^{18}F-FDG PET-CT and USPIO-MRI data acquisition procedures are detailed in Methods I of the Supplementary Material.

Image analysis

Registration of PET and MRI images. The accuracy of PET-CT to Computed Tomography Aortogram (CTA) registration was confirmed by visual assessment, and minor intra-scan patient movement was corrected using a semi-automatic rigid 3D voxel registration protocol (Analyze 11.0, Mayo Clinic, Rochester, MN, USA). Registration of the MRI data allowed the excellent anatomical detail on the T2W images and the high sensitivity of T2*W images for iron to be utilised. All MR images were registered to the pre-contrast T2W image. The CTA and T2W MRI datasets were also co-registered. At the end of the registration process, the pre-USPIO T2*W MRI, the post-USPIO T2*W MRI, the CTA, and the PET-CT were all co-registered to enable direct comparison. All steps of registration used a semi-automatic rigid 3D voxel registration protocol that has been previously validated and published.[24] All outputs were manually checked and optimised as necessary. Two independent trained observers, who were experienced vascular surgeons who had developed the image analysis techniques, undertook the analyses. There was excellent inter-observer agreement with kappa statistics between 0.84 and 0.89, for all steps.

^{18}F-FDG quantification. The maximum standardised uptake value (SUV_{max}) was used to assess ^{18}F-FDG uptake in the aneurysm. The SUV is the decay-corrected tissue uptake divided by the injected dose per unit body weight and is a semi-quantitative dimensionless unit that has been previously validated and is a commonly used measure of tissue ^{18}F-FDG uptake.[5,28] The SUV in vascular structures can be heavily influenced by variability of ^{18}F-FDG activity in the blood pool. Therefore, the tissue-to-background ratio (TBR) was also calculated by dividing the tissue SUV_{max} by an averaged mean SUV in the blood pool, derived from five circular regions of interest in the centre of the inferior vena cava. An area of ^{18}F-FDG uptake was defined as positive if the SUV_{max} or TBR was $>$ 125% of the value obtained from an averaged SUV_{max} from five randomly selected regions in the non-aneurysmal descending thoracic aorta.[29,30]

USPIO quantification. Using validated in-house software built in the Matlab environment (Mathworks, Natick, MA, USA), all four echoes in the multi-echo T2*W sequence were combined to generate a T2* map in which the magnitude of each voxel represented the T2* value ($S(t) = S(0)\exp - (t/T2^*)$). USPIO uptake was detected using the change in T2* (or R2*; R2* = 1/T2*) following USPIO administration. We applied a validated image analysis