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Cardiac Imaging

Imaging of Vascular Inflammation With [^{11}C]-PK11195 and Positron Emission Tomography/Computed Tomography Angiography

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Objectives We sought to investigate whether positron emission tomography/computed tomography (CT) angiography using [^{11}C]-PK11195, a selective ligand for peripheral benzodiazepine receptors expressed in activated macrophages, can be used to image vascular inflammation.

Background Activated macrophages and T lymphocytes are fundamental elements in the pathogenesis of large-vessel vasculitides.

Methods Fifteen patients (age 52 ± 16 years) with systemic inflammatory disorders (6 consecutive symptomatic patients with clinical suspicion of active vasculitis and 9 asymptomatic control patients) underwent positron emission tomography with [^{11}C]-PK11195 and CT angiography. [^{11}C]-PK11195 uptake was measured by calculating target-to-background ratios of activity normalized to venous blood.

Results Coregistration of positron emission tomography with contrast-enhanced CT angiography facilitated localization of [^{11}C]-PK11195 arterial wall uptake. Visual analysis revealed focal [^{11}C]-PK11195 uptake in the arterial wall of all 6 symptomatic patients, but in none of the asymptomatic controls. Although serum inflammatory biomarkers (C-reactive protein, erythrocyte sedimentation rate, white cell count) did not differ significantly between the 2 groups, symptomatic patients had increased [^{11}C]-PK11195 vascular uptake (target-to-background ratio 2.41 ± 1.59 vs. 0.98 ± 0.10; $p = 0.001$).

Conclusions By binding to activated macrophages in the vessel wall, [^{11}C]-PK11195 enables noninvasive imaging of vascular inflammation. Alternative longer-lived radioligands for probing peripheral benzodiazepine receptors are being tested for wider clinical applications. (J Am Coll Cardiol 2010;56:653–61) © 2010 by the American College of Cardiology Foundation

Large-vessel vasculitides such as giant cell arteritis (GCA) and Takayasu's arteritis (TA) are characterized by granulomatous pan-arteritis with focal leukocytic infiltration. The inflammatory infiltrates may cause thickening of the involved artery and lead to luminal narrowing and occlusion. Dilation, aneurysm formation, and thrombosis may also ensue (1,2). These patients are also at risk from accelerated atherosclerosis when compared with age-matched controls, further increasing their cardiovascular morbidity and mortality (2,3).

Activated macrophages and T lymphocytes are fundamental elements in the pathogenesis of GCA and TA (2). The ligand PK11195 binds to the peripheral benzodiazepine receptor (PBR), a protein that is highly expressed in activated cells of the mononuclear phagocyte lineage. Since the early 1980s, [^{11}C]-PK11195 has been used in combination with positron emission tomography (PET) to image inflammatory diseases in the human brain on the basis of the low expression of PBRs in normal brain tissue and high expression in activated microglia, the resident phagocytes in brain tissue, during neuroinflammation (4,5).

More recently, specific in vitro binding of [^{3}H]-PK11195 to macrophages has been shown in human carotid endarterectomy samples, suggesting its potential value as a specific marker of vascular inflammation (6). In view of the abundance of activated macrophages characteristic of GCA

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Abbreviations and Acronyms

CRP = C-reactive protein
CT = computed tomography
ESR = erythrocyte sedimentation rate
FDG = [^{18}F]-fluorodeoxyglucose
GCA = giant cell arteritis
HPLC = high-performance liquid chromatography
PBR = peripheral benzodiazepine receptor
PET = positron emission tomography
ROI = region of interest
SLE = systemic lupus erythematosus
SUV = standardized uptake value
TA = Takayasu's arteritis
TBR = target-to-background ratio

and TA, we hypothesized that patients with large-vessel vasculitides would be an ideal target for a proof of principle study to ascertain whether PET with [^{11}C]-PK11195 in combination with computed tomography (CT) angiography can be used to image vascular inflammation.

Methods

Study population. From Imperial College Healthcare National Health Service Trust rheumatology clinics, 15 patients with systemic inflammatory disorders (GCA, TA, and systemic lupus erythematosus [SLE]) were enrolled. Of these, 6 consecutive patients with large-vessel vasculitis were chosen due to a high clinical index of suspicion of active disease. Active vasculitis was defined as onset within the previous 3 months of any of the following symptoms: visual disturbance, headache, bruit or vascular pain/tenderness, new claudication, fever, night sweats, and/or arthralgia.

The remaining 9 patients were consecutive asymptomatic patients (defined as absence of symptoms of active disease) who attended the clinic for routine follow-up. For SLE, the Systemic Lupus Erythematosus Disease Activity Index was used to assess disease activity (7). Exclusion criteria for all patients were known intolerance to iodinated contrast agent, inability to lie flat, age <25 or >80 years, and claustrophobia. In all patients, blood samples were obtained within a week of PET/CT imaging to measure C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count. The study protocol was approved by the local research ethics committee, and all patients gave written informed consent. Radiation exposure was licensed by the U.K. Administration of Radioactive Substances Advisory Committee.

Radiotracer synthesis. [^{11}C]-PK11195 was prepared as described by Tomasi et al. (8). In brief, [^{11}C]-methyl iodide was incubated with 1.0 mg of desmethyl-PK11195 (ABX, Radeberg, Germany) and 1.0 mg of powdered potassium hydroxide in 200 μl of dimethyl sulfoxide for 1.5 min at 90°C. The crude product was purified on a semi-preparative Phenomenex Ultracarb 7μ ODS 250 × 10-mm column using 70% ethanol, 30% water as the high-performance liquid chromatography (HPLC) solvent. After evaporation of the HPLC solvent, the purified product was formulated in 0.9% saline with 5% ethanol and filtered through a 0.22-μm sterile filter. Measurement of concentration and radiochemical purity of [^{11}C]-PK11195 batches was performed by HPLC using an analytical Luna C8 150 × 4.6-mm column (Phenomenex), a UV detector set at 277 nm, and a radioactivity detector in series. Radiochemical purity was >99.5%.

PET/CT imaging. Imaging was performed using a 16-slice PET/CT scanner (Discovery RX, GE Healthcare, Milwaukee, Wisconsin) with a 15-cm field of view. After acquisition of the localizer, a low-dose CT scan was acquired in helical mode for attenuation correction with the following parameters: 120 kV, 20 mAs, 8 × 2.5-mm slice thickness, pitch of 1.675, 0.5-s rotation time. A line passing 2 cm below the carina was used as lower limit of the PET field of view, which thus encompassed the aortic arch, common carotid arteries, and carotid bifurcations. After injection of 6.85 MBq/kg of [^{11}C]-PK11195, PET emission data were acquired over 60 min in list mode format and rebinned into 18 temporal frames (30-s background, 1 × 15 s, 1 × 5 s, 1 × 10 s, 1 × 30 s, 4 × 60 s, 7 × 300 s, and 2 × 600 s).

After the PET scan, CT angiography was performed with the same field of view as the PET scan. A bolus of 70 ml of contrast (Ultravist 370, Schering, Berlin, Germany) was injected at a rate of 3.5 ml/s into an antecubital vein. A bolus tracking technique was used to synchronize the arrival of contrast in the ascending aorta with the CT angiography scan. The CT angiography acquisition parameters were 120 kV, 180 mAs, 16 × 0.625-mm slice thickness, pitch of 1.0, 0.5-s rotation time. Using these parameters, scan times for CT angiography were in the range of 12 to 16 s. The effective dose of CT (including localizer, attenuation correction, and CT angiography) was estimated from the product of the dose-length product and an organ-weighting factor for the chest (0.014 mSv × mGy^{-1} × cm^{-1}) as proposed by the European Working Group for Guidelines on Quality Criteria in CT (9,10).

Image reconstruction. All emission scans were normalized and corrected for randoms, dead time, scatter, and attenuation and were reconstructed using an ordered subset expectation maximization algorithm with 2 iterations and 21 subsets. Frames 10 to 14 were added to obtain the image for visual analysis and uptake measurement.

Reconstruction parameters for CT angiography were 0.625-mm slice thickness, 0.625-mm increment, 30-cm-wide reconstruction field of view, window width of 300 Hounsfield units, and window level of 30 Hounsfield units.

Image coregistration and visual analysis. Using a dedicated workstation (Advantage Workstation 4.2, GE Healthcare), images were inspected visually for [^{11}C]-PK11195 uptake by 1 operator unaware of patient history, ongoing medications, and biomarker results. In the event of misalignment between the CT and the PET datasets, images were realigned manually using anatomical landmarks such as the vertebrae and the sternum, which showed marked tracer uptake. Visual analysis was performed on axial source slices, and sagittal, coronal, and oblique reformations of the ascending, arch, and descending aorta. The aorta or carotid arteries were considered positive for active inflammation