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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 52–110 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...
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 $^{[11C]}$-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, bruist 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. All patients were known intolerance to iodinated contrast agent, inability to lie flat, age <25 or >80 years, and claustrophobia.

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 $^{[11C]}$-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 $^{[11C]}$-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 vertebral 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.

**Abbreviations and Acronyms**

- **CRP** = C-reactive protein
- **CT** = computed tomography
- **ESR** = erythrocyte sedimentation rate
- **FDG** = $^{[18F]}$-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

[11C]-PK11195 was prepared as described by Tomasi et al. (8). In brief, $^{[11C]}$-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 Ultracearb 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 $^{[11C]}$-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%.
when heterogeneously increased \([^{11}C]\)-PK11195 uptake was seen in areas corresponding to the aortic or carotid wall on CT angiography.

**Semiquantitative measurement of \([^{11}C]\)-PK11195 uptake.** CT images were reduced to a matrix size of 128 \(\times\) 128 \(\times\) 47 to match the size of the reconstructed PET images and superimposed to the PET images to help define the regions of interest (ROIs). Images were then re-sliced with a slice thickness of 1 mm to obtain cross-sections of the ascending, arch, and descending aorta, and ROIs were placed encompassing the wall of aorta and carotid arteries using dedicated software (MATLAB software, The MathWorks Inc., Natick, Massachusetts). The average volume of interest was 1.2 \(\pm\) 1.0 ml for the carotid arteries and 4.0 \(\pm\) 2.5 ml for the aorta. To quantify tracer uptake in the vessel wall, standardized uptake values (SUVs) were calculated as the mean tissue activity concentration in each volume of interest (in Bq/ml) divided by total injected activity per body weight (in Bq/g). A background SUV was obtained in a venous structure (superior vena cava, subclavian, or internal jugular vein), and arterial wall target-to-background ratios (TBRs) were calculated as arterial wall SUV divided by venous blood SUV.

**Statistical analysis.** Statistical analysis was performed with SPSS version 16.0.1 (SPSS, Inc., Chicago, Illinois). Quantitative variables are expressed as mean \(\pm\) SD. Categorical variables are expressed as frequencies (percentages). The Mann-Whitney \(U\) test was used for comparison of quantitative data. A \(p\) value \(< 0.05\) was considered statistically significant.

**Results**

**Patient characteristics.** Mean patient age was 52 \(\pm\) 16 years, and 13 patients were female. Five patients had TA, 4 had GCA, and 6 had SLE. All patients fulfilled American College of Rheumatology diagnostic criteria (11–13). For SLE patients, the mean Systemic Lupus Erythematosus Disease Activity Index was 6 \(\pm\) 5 (range 2 to 14). Individual patients’ characteristics and ongoing medications are described in Table 1.

A trend toward higher serum biomarker levels was seen in symptomatic patients versus asymptomatic patients (CRP, 24 \(\pm\) 46 mg/l vs. 4 \(\pm\) 6 mg/l; ESR, 42 \(\pm\) 43 mm/h vs. 33 \(\pm\) 22 mm/h; and white blood cell count, 9.7 \(\pm\) 5.5 \(\times\) 10\(^9\)/l vs. 7.4 \(\pm\) 2.9 \(\times\) 10\(^9\)/l (\(p\) = NS). Individual levels are given in Table 1.

**Visual PET/CT findings.** Average injected activity in our study population was 446 \(\pm\) 82 MBq. \([^{11}C]\)-PK11195 uptake was visually detected in 6 patients, all with symptoms suggesting active vasculitis. No evidence of significant atheroma was seen on CT angiography at the level of tracer uptake in all 6 patients. In 5 patients (Patients #1 to #3, #5, and #6), uptake was seen at the level of the aorta. Representative images are shown for all symptomatic patients in Figures 1 and 2. In 3 of these patients (Patients #1, #5, and #6), CT angiography showed diffuse thickening of the aortic wall (up to 4 mm), coincident with maximal tracer uptake with minimal calcification and no evidence of atheroma (Figs. 1 and 2). In 1 patient (Patient #4) with carotidynia, fever, and malaise, focal uptake was noted at the level of the

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<th>Table 1 Baseline Characteristics</th>
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Drug doses are expressed per day unless otherwise stated.

CRP = C-reactive protein (normal values \(<5\) mg/l); ESR = erythrocyte sedimentation rate (normal values 0 to 20 mm/h); GCA = giant cell arteritis; HyChlor = hydroxychloroquine; Mtx = methotrexate; NSAID = nonsteroidal anti-inflammatory drugs; Pred = prednisolone; SLE = systemic lupus erythematosus; TA = Takayasu’s arteritis; WBC = white blood cell count (normal values 4 to 11 \(\times\) 10\(^9\)/l).
left common carotid artery just proximal to the bifurcation. In this patient, CT angiography showed focal thickening of the common carotid artery wall (approximately 2 mm) at the level of tracer uptake in the absence of atheroma. An ultrasound study confirmed this finding, which corresponded with the region of maximal tenderness.

In 1 symptomatic patient with GCA (Patient #1) (Fig. 1), [11C]-PK11195 PET/CT images were obtained before and after a 20-week course of oral corticosteroids. The PET scan after treatment demonstrated that [11C]-PK11195 uptake in the wall of the aortic arch was markedly reduced, and TBRs decreased from 1.63 to 0.87. The reduction in [11C]-PK11195 uptake was paralleled by a distinct improvement in symptoms and a decrease in his serum inflammatory markers (ESR 124 mm/h vs. 67 mm/h and CRP 118 mg/l vs. 22 mg/l, respectively).

In the remaining 9 asymptomatic patients, no uptake was appreciable on visual analysis (Fig. 3). In 1 (Patient #15) of the patients with no evidence of focal tracer uptake, minor bilateral calcification was noted at the level of the carotid bifurcations. This patient had type 2 diabetes mellitus and was on treatment with oral antidiabetic drugs. The aorta was regular in diameter, and there were no ulcerated plaques.

Estimated mean effective radiation doses were 6.0 ± 0.5 mSv for CT and 2.1 ± 0.2 mSv for [11C]-PK11195 PET, and the mean total effective dose was 8.1 ± 0.6 mSv. Individual patient doses are given in Table 2.

**Semiquantitative measurement of [11C]-PK11195 uptake.** Individual TBRs for ROIs are shown in Table 2. TBR was significantly higher in symptomatic compared with asymptomatic patients (2.41 ± 1.59 vs. 0.98 ± 0.10; p = 0.001) (Fig. 4). None of the asymptomatic patients had a TBR >1.20, whereas none of the symptomatic patients had a TBR <1.20.

**Discussion**

In the present study, we demonstrate the value of PET with [11C]-PK11195 for detecting vascular inflammation in patients with GCA and TA. An increased tracer uptake was
noted in the arterial wall of patients with active vasculitis (defined by the presence of typical systemic symptoms) compared with asymptomatic controls. Hence, PET with [11C]-PK11195 may be used to distinguish active inflammation in patients with large-vessel vasculitis, characterized by a macrophage-rich infiltrate, from nonactive or more quiescent disease, where inflammatory changes are mild or absent (2).

In this proof of principle study, we used patients with large-vessel vasculitis as a model for vascular wall inflammation. In this context, the amount and density of the inflammatory infiltrate is directly linked to local disease activity. Patients with large-vessel vasculitis may present with marked vascular infiltration and high local and systemic inflammatory activity, leading to disruption of structural components of the vessel wall and ultimately stenosis, dilation, or occlusion of the involved arteries (1). Additionally, they have an increased cardiovascular risk compared with healthy individuals of comparable age as a consequence of accelerated atherosclerosis (2). Therefore, patients with large-vessel vasculitis constitute a suitable population for testing the value of [11C]-PK11195 to assess vascular inflammation in vivo.

Inflammation plays a key role in acute destabilization of atherosclerotic plaques, and dense inflammatory infiltrates are usually found at the site of plaque rupture in patients dying from acute myocardial infarction and stroke (14,15). Therefore, molecular imaging techniques targeting activated macrophages as a means of noninvasive detection of plaque vulnerability have been proposed (16). Several reports have
shown the value of [18F]-fluorodeoxyglucose (FDG) for imaging vascular inflammation in patients with large-vessel vasculitis (17–19), and many studies have established FDG as a useful tool to assess intraplaque inflammatory activity in atherosclerotic disease (20–24). Additionally, the observation that FDG uptake in atherosclerotic plaques is highly reproducible (25) paved the way for the first clinical drug trials using FDG uptake as a surrogate marker for plaque inflammation (26). However, the glucose analogue FDG is taken up by any metabolically active tissue, limiting its specificity for detecting inflammatory cells. In fact, microautoradiography studies of aortic sections of ApoE−/− mice

Figure 3 Representative [11C]-PK11195 PET/CT Reconstructions With Corresponding PET Images in Controls (Patients #7 to #15)

For each patient, [11C]-PK11195 positron emission tomography (PET)/computed tomography (CT) reconstructions are shown in the top panel and corresponding PET images are shown in the bottom panel. Note absence of [11C]-PK11195 uptake in the wall of the large arteries. In contrast, high [11C]-PK11195 could be observed in the bone marrow (*) and the salivary glands (white arrowheads). In Patient #13, an asymmetrically enlarged thyroid gland with increased [11C]-PK11195 was noted.
have shown that [14C]-FDG uptake into atherosclerotic plaques correlates poorly with fat content and selective macrophage staining with anti-CD68 (27). Moreover, despite its utility as a diagnostic tool (17–19), some concerns have recently been raised regarding the role of FDG-PET in the follow-up of patients with large-vessel vasculitis. In GCA, it has been suggested that FDG-PET may fail to identify those at risk of relapse (28), whereas Arnaud et al. (29) reported a poor correlation between FDG uptake and disease activity in TA. It remains unclear whether persistent vascular FDG uptake in otherwise clinically inactive patients reflects persistent granulomatous vasculitis or, alternatively, vascular remodeling or metabolically active tissue in the vicinity of the vessel wall.

PK11195 binds with high affinity to activated cells of the mononuclear phagocyte lineage. In experimental rat brain studies, PET with [11C]-PK11195 detected increased PBR expression in activated microglia after ischemic injury (5). These findings have been confirmed in patients with neuroinflammation (4,30). Laitinen et al. (31) used [3H]-PK11195 in a murine model of atherosclerosis and demonstrated increased tracer uptake in inflamed plaques, although they also observed nonspecific uptake in the healthy vessel wall. It is worth noting, however, that PBR expression in the cardiovascular system varies considerably across species, and results obtained in rodents may not necessarily be translated into humans. PBRs are abundantly expressed in vascular smooth cells of rodents (32), but are absent in humans (33). More recently, Fujimura et al. (6) demonstrated specific binding of [3H]-PK11195 to macrophages in specimens of human carotid atherosclerotic plaques, but no uptake in vascular smooth muscle cells was seen. In our study, a more than 2-fold increase of TBR was found in patients with active disease, which compares well with FDG uptake reported in patients with atherosclerosis (21). Conversely, in our control subjects, TBR was 0.98 (i.e., equal to background activity), underlining the specificity of [11C]-PK11195.

In some minor lesions in patients with active vasculitis, the [14C]-PK11195 signal may not be strong enough to be easily detected on PET alone. A previous report by Kobayashi et al. (18) using FDG-PET showed that coregistration of PET with contrast-enhanced CT angiography
increased the sensitivity for the detection of vascular inflammation in patients with TA compared with PET alone. The morphological information provided by CT angiography, in addition to allowing better delineation of the vessel wall, permits characterization of arterial remodeling and the exclusion of atherosclerotic disease.

Preliminary findings in patients with carotid atherosclerosis suggest that $[^{11}C] $-PK11195-PET might hold promise for the detection of intraplaque inflammation. In Figure 5 we show images from 2 patients in whom $[^{11}C] $-PK11195 PET could distinguish between a recently symptomatic (i.e., unstable) and an asymptomatic (i.e., stable) carotid plaque. Whether these findings can be confirmed in a larger population is the subject of ongoing research.

**Study limitations.** We acknowledge the relatively limited sample size in this study. Nonetheless, the study was designed to assess the feasibility of $[^{11}C] $-PK11195 PET imaging in vivo, and albeit limited, this number of patients provided meaningful interpretation of vascular tracer uptake.

In 3 of our symptomatic patients, PET/CT imaging was performed after initiation of systemic steroid therapy. The humoral mechanisms regulating PBR expression in immune cells are poorly understood, and it is therefore difficult to know how steroid therapy affected our imaging results. In Patient #1, we found a decrease in vascular $[^{11}C] $-PK11195 uptake after a 20-week course of steroids (Fig. 1). However, this was a single case, and we did not assess whether reduced $[^{11}C] $-PK11195 uptake was secondary to a decrease in cellular PBR density or a decreased homing of monocytes and consequently lower cell density in inflamed vascular wall.

The proximity of the blood pool and limited thickness of the arterial wall can result in spillover and partial volume effects. However, this should affect asymptomatic and symptomatic patients to the same extent and is unlikely to account for any of the differences observed between the 2 groups. Correction for spillover and the quantification of receptor kinetics should overcome these potentially confounding factors, and further quantitative studies are warranted.

The short physical half-life of $[^{11}C] $-labeled compounds mandates an onsite cyclotron facility, thus limiting its clinical applicability. It also precluded performing a rectilinear whole-body scan after dynamic data acquisition and, therefore, restricted PET axial coverage to a 15-cm field of view. However, the introduction of new $[^{18}F] $-labeled PBR ligands, which are currently under pre-clinical investigation and have shown high affinity across species in the brain, may overcome some of these limitations (34).

Finally, the added radiation exposure from PET and CT remains an important concern, particularly if repeated studies are performed to assess inflammatory activity before and after treatment. The total effective radiation dose in our patients was well below 10 mSv, which is comparable to a standard cardiac FDG scan (35). Additionally, we rather overestimated CT doses, because we used a “chest” weighting factor to estimate doses, whereas a substantial portion of the scan field of view consisted of “neck,” for which the weighting factor is 3 times lower.

**Conclusions**

PET with $[^{11}C] $-PK11195 can be used to assess arterial inflammatory activity in patients with large-vessel vasculitis and may help to stratify patients with active and inactive disease. Coregistration with contrast-enhanced CT angiog-
raphy improves detection of $^{[11C]}$-PK11195 uptake in the vascular wall while providing anatomical information on vessel wall thickening and excluding atherosclerotic disease. These findings provide a basis for further studies to evaluate the potential role of $^{[11C]}$-PK11195 PET/CT for the detection of vascular inflammation in atherosclerotic disease.

Acknowledgments
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