

Carotid plaque inflammation assessed with ^{18}F -FDG PET/CT is higher in symptomatic compared with asymptomatic patients

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Background Carotid artery plaque inflammation is thought to be an important marker of plaque vulnerability and increased stroke risk.

Aim The main aim of this study was to assess the level of agreement between 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F -FDG) uptake on PET (positron emission tomography) scan in carotid plaques, with cerebrovascular symptoms, carotid plaque ultrasound echogenicity and histological assessments of plaque inflammation.

Methods Thirty-six patients with $\geq 70\%$ carotid stenosis scheduled for carotid endarterectomy underwent a Colour Duplex ultrasound, ^{18}F -FDG PET/CT and blood tests less than 24 h prior to surgery. Plaques were defined as symptomatic when associated with ipsilateral cerebral ischemic symptoms within 30 days prior to inclusion. Plaques were assessed histologically following endarterectomy. The level of agreement between ^{18}F -FDG uptake (mean SUV_{max} and SUV_{max}), and target-to-background ratio, symptoms, plaque echolucency, and histological evidence of inflammation was assessed.

Results The amount of ^{18}F -FDG uptake in plaques and the amount of inflammation on histological assessment were significantly correlated ($r = 0.521$, $P = 0.003$). ^{18}F -FDG uptake was significantly higher in symptomatic plaques with median SUV_{max} 1.75 (1.26–2.04) in symptomatic, and 1.43 (1.15–2.28) in asymptomatic patients ($P = 0.03$). ^{18}F -FDG uptake was also positively correlated with echolucency on Doppler ultrasound ($P = 0.03$).

Conclusion ^{18}F -FDG uptake on PET/CT correlated with histological assessments of inflammation and was higher in patients with symptomatic compared with asymptomatic

carotid artery plaques. These results support the use of ^{18}F -FDG PET/CT in the detection inflammation in carotid atherosclerosis, which may be of help in the detection of vulnerable plaques.

Key words: carotid plaque echogenicity, carotid plaque, carotid stenosis, carotid ultrasound, ischemic stroke, positron emission tomography

Introduction

A significant proportion of strokes are thromboembolic, arising from a vulnerable atherosclerotic plaque at the carotid bifurcation. Such strokes have been shown to be effectively preventable by carotid endarterectomy (CEA) (1,2). In current clinical practice patient selection for revascularization primarily involves identification of the severity of luminal stenosis. It has, however, become increasingly clear that the degree of luminal stenosis alone is not the best predictor of stroke risk and the composition of an atherosclerotic plaque is considered more important. Owing to the process of arterial remodeling, the lumen of an artery may not be compromised despite the presence of a significant atherosclerotic burden with vulnerable plaques prone to rupture (3). Strokes may occur as a result of nonstenotic carotid disease, and conversely, a non-negligible proportion of patients with significant carotid stenosis may remain completely asymptomatic throughout their lifetime (3,4). Identifying markers of plaque destabilization is therefore central for improving treatment decisions and reducing the risk of embolic stroke for patients with carotid artery atherosclerosis. Inflammation is thought to be central in plaque destabilization and has been proposed as a major criterion for defining a high-risk vulnerable plaque (5–7). Due to the infiltration and retention of oxidized lipids in the arterial wall, vulnerable plaques contain a greater density of macrophages compared with asymptomatic plaques (8). Activated macrophages have a significantly increased metabolic rate and therefore increased 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F -FDG) uptake. Rudd *et al.* found increased ^{18}F -FDG in macrophage-rich regions of carotid plaques, removed at endarterectomy, in eight symptomatic patients compared with contralateral asymptomatic plaques in the same patients (9). Tawakol *et al.* demonstrated that *in vivo* ^{18}F -FDG uptake correlated with the degree of plaque inflammation in 17 patients when macrophage staining was assessed histologically (10).

^{18}F -FDG uptake has also been shown to correlate with factors that are associated with plaque vulnerability. Carotid plaques with decreased ultrasound echogenicity and patients with increased serum lipids have been found to have higher degrees of ^{18}F -FDG uptake on PET (11,12). Evidence from longitudinal studies also suggests that arterial ^{18}F -FDG uptake may be related to patient outcome. Figueroa *et al.* followed 513 patients without

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symptomatic cardiovascular disease for a mean of 4.2 years. They found that ^{18}F -FDG uptake within the wall of the ascending aorta was an independent predictor of future cardiovascular events (13). Results from The Dublin Carotid Atherosclerosis Stroke Study showed, in 44 patients, that carotid plaque inflammation, measured by ^{18}F -FDG PET, was associated with a high risk of early stroke recurrence, independent of the degree of stenosis (14).

Previous studies have, however, been limited by relatively small sample sizes and time delays of weeks or months from symptoms to ^{18}F -FDG PET imaging and histology following endarterectomy. There is therefore a possibility that plaque inflammation may have been modified by medications and lifestyle changes during time-delays from symptoms to imaging and histological assessments (15,16). Increased ^{18}F -FDG uptake must be closely correlated with ipsilateral ischemic cerebral events and higher in symptomatic compared with asymptomatic patients if this method is to be of value in the clinical management of these patients.

Aim

The main aim of this study was therefore to assess level of agreement between carotid plaque ^{18}F -FDG uptake on PET/CT and histological assessments of the degree of inflammation in plaques from symptomatic and asymptomatic patients.

Methods

Subjects

Consecutive patients with internal carotid artery stenosis $\geq 70\%$ scheduled for CEA were included in the study from April 2009 to November 2013. Plaques were defined as symptomatic when associated with ipsilateral cerebral ischemia (minor strokes, transitory ischemic attack or amaurosis fugax) within 30 days prior to inclusion. Exclusion criteria were prior CEA, stenting, carotid occlusion, vasculitis, malignancy, prior radiation therapy to the neck, treatment with immunomodulating drugs or oncological disease.

All patients underwent a clinical neurological examination and registration of the following cardiovascular risk factors: hypercholesterolemia, hypertension, coronary artery disease and diabetes. The Regional Committee for Medical and Health Research Ethics (REC) approved the study, and informed written consent was obtained from all patients.

Carotid ultrasound

Colour duplex ultrasound was performed with a General Electric Vivid 7 (General Electric, Horten, Norway) using a M12L probe (14 MHz) on both carotid arteries. The degree of stenosis was based on velocities according to consensus criteria of the Society of Radiologists in Ultrasound (17). Plaque echogenicity was assessed with the vessel lumen as the reference structure for defining echolucency, and the bright echo zone produced by the media-adventitia interface as the reference for defining echogenicity (18–20). Echogenicity was graded from 1 to 4 as: echolucent, predominantly echolucent, predominantly echogenic, or echogenic by an experienced examiner blinded for the PET results (18).

^{18}F -FDG PET/CT

Patients were examined with a hybrid PET/CT scanner (Siemens Biograph 64, Siemens Medical Systems, Erlangen, Germany). After an overnight fast (minimum six-hours), an ^{18}F -FDG PET/CT was performed from the base of the skull to the aortic arch, approximately 90 mins after the injection of 5 Mbq/kg ^{18}F -FDG. Blood glucose levels were measured. The PET data were reconstructed to 2 mm thick slices with a matrix size of 256 x 256 pixels (pixel size 2.67 mm) using the OSEM 2D algorithm with four iterations (i), eight subsets (s) (4i/8s), and Gaussian post-reconstruction filter with full-width at half maximum (FWHM) of 3.5 mm (21). A CT without contrast for attenuation correction was performed immediately before the PET scan with the patient in the same position. A contrast-enhanced CT of the carotid arteries was also performed on those patients that did not have a recent CT angiography available. The contrast-enhanced CT was used for localizing the carotid artery plaque. A specialist in nuclear medicine blinded for patient data placed the regions of interest (ROI). The contrast-enhanced CT angiography was used as a guide for drawing the ROI on the PET slice (fused with noncontrast CT). ROIs covering the whole plaque including vessel wall thickening and the lumen contrast-filling defect (22) were drawn on each axial slice from the most cranial to the most caudal slice of the plaque. The ROI was minimized to only cover parts of the plaque uptake when nearby ^{18}F -FDG activity, e.g. lymph nodes, paravertebral muscles or salivary glands could have influenced the measured ^{18}F -FDG activity in the ROIs. Four ROIs were placed in the lumen of the jugular vein close to the plaque for calculation of the target-to-background ratio (TBR). Maximum standardized uptake values (SUV_{max}); the highest activity concentration per injected dose per lean body mass (lbm – a factor derived from each patients height, weight and gender) after correction for decay in each ROI were measured. SUV normalized to lbm is an established parameter for the quantification of ^{18}F -FDG uptake (23). The following uptake parameters were used for the statistical analysis for each plaque: (1) SUV_{max} = the single highest SUV_{max} value, (2) Mean SUV_{max} = mean of all plaque SUV_{max} values, (3) TBR = mean SUV_{max} divided by mean SUV_{mean} in the four venous regions.

Tissue processing and histological analysis

The plaques were removed en bloc (intact) at CEA, fixed in 4% formaldehyde, decalcified in ethylenediaminetetraacetic acid, and cut into 2–3 mm slices. After dehydration the slices were embedded in paraffin, and histological sections were cut at 5 μm and stained with hematoxylin and eosin. Plaques were assessed by a pathologist and a research physician blinded for clinical and ^{18}F -FDG PET findings. A section from each slice was evaluated with 120 times magnification and the percentage of inflammatory cells (macrophages and leukocytes) was estimated as the area with inflammatory cells as a percentage of the total area. The amount of inflammation per plaque was calculated as the sum of all areas with inflammatory activity divided by the total area of the sections to give a percentage of inflammatory cells per plaque. This method for evaluating and grading inflammation has been shown to have good to excellent intra- and inter-rater variability (24).

Histological assessments were made on 11 slices from three plaques on two occasions more than two-months apart to assess the reproducibility of the findings. For this analysis the percentage inflammatory cells per slice was classified into the following categories: 0–5%, 5–10%, 10–15% and 15–20% and the results assessed using Kappa statistics.

Statistical analysis

SPSS for Windows statistical software (version 18.0; SPSS Inc., Chicago, IL) was used for data analysis. Student's *t* test or Mann–Whitney *U*-test was used depending on the distribution of data. The chi-square test was used for analyzing contingency data. Coefficients of correlation were calculated by the Spearman correlation. All statistical results were considered significant when $P < 0.05$.

Results

Clinical characteristics

Thirty-six patients took part in the study. There were 26 men (66.8 ± 9 years) and 10 women (67.9 ± 7 years). Eighteen patients were symptomatic, and 18 patients asymptomatic. Plaques were not delivered for histology after endarterectomy due to practical reasons in six patients; four of these were in the symptomatic and two were in the asymptomatic group. All other data from these patients were retained in the analyses. Clinical characteristics of the patients are shown in Table 1. There were no statistically significant differences between the symptomatic and asymptomatic patients with respect to age or gender. Mean age was 67.5 years in the symptomatic group and 66.7 in the asymptomatic group. Thirteen patients (72.2%) were male in both groups. For symptomatic patients ($n = 18$), mean time from last symptom to CEA was 12 days ranging from 3 to 30 days. Although not reaching statistical significance, patients in the symptomatic group had higher average plasma leukocyte levels at $9.2 \times 10^9/L$ compared with $7.6 \times 10^9/L$ in the asymptomatic group ($P = 0.05$). Plasma levels of CRP, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and glucose were similar in the two groups.

Plaque inflammation on histological analysis and correlation to ^{18}F -FDG uptake and echogenicity on ultrasound

There was a significant correlation (Fig. 1) between the amount of inflammation on histology and all ^{18}F -FDG uptake parameters (mean SUV_{max} $P = 0.003$, SUV_{max} $P = 0.009$ and TBR $P = 0.002$).

Higher amounts of inflammation on histology were also significantly correlated with low echogenicity on carotid Doppler ultrasound ($P = 0.014$).

When the histopathological assessments were repeated on two occasions more than two-months apart we found that the amount of inflammatory cells was in the same 5% category at both assessment for 8 of 11 slices (73%, Kappa = 0.73).

^{18}F -FDG uptake and correlation to clinical symptoms

Figure 2 shows that the amount of ^{18}F -FDG uptake measured by mean SUV_{max} was significantly higher in symptomatic compared with asymptomatic plaques (Fig. 4). Median mean SUV_{max} in the symptomatic group was 1.75 (range: 1.26–2.04) compared with 1.43 (range: 1.15–2.28) in the asymptomatic group. This difference was statistically significant with $P = 0.03$. TBR was not significantly higher in the symptomatic compared with asymptomatic patients. The highest mean SUV_{max} 2.28 was measured in an asymptomatic patient.

^{18}F -FDG uptake and correlation to echogenicity on ultrasound

There was a positive correlation for mean SUV_{max} and low echolucency on carotid Doppler ultrasound ($r = 0.378$, $P < 0.03$) (Fig. 3). Mean SUV_{max} was significantly increased ($P = 0.028$) for echolucent plaques 1.67 (1.2–2.28) compared with echogenic plaques 1.5 (1.2–2.04). Mean SUV_{max} remained significantly higher in echolucent plaques compared with predominantly echolucent plaques ($P = 0.01$). Lower ultrasound echogenicity was associated with a higher TBR values ($P = 0.005$).

Table 1 Clinical characteristics of symptomatic and asymptomatic patients

	Symptomatic ($n = 18$)	Asymptomatic ($n = 18$)	<i>P</i>
Age, yrs; (mean \pm SD)	67.5 \pm 9.5	66.7 \pm 7.2	0.77
Gender, male; <i>n</i> (%)	13 (72.2)	13 (72.2)	1.00
Hypercholesterolemia, no of patients	13 (72.2)	14 (77.8)	0.60
Antihypertensive medication, yes	10 (55.6)	12 (66.7)	0.56
Coronary artery disease, no of patients	4 (22.2)	10 (55.6)	0.04
Diabetes, yes	2 (14.3)	3 (16.7)	0.68
Plasma levels: (mean \pm SD)			
Leukocytes, $10 \times 9/L$	9.2 \pm 2.4	7.6 \pm 1.9	0.05
CRP, mg/l	11.2 \pm 27	4.9 \pm 4.5	0.44
Cholesterol mmol/l	4.9 \pm 1.5	4.0 \pm 0.8	0.17
LDL, mmol/l	3.1 \pm 1.4	2.0 \pm 0.6	0.06
HDL, mmol/l	1.22 \pm 0.6	1.1 \pm 0.7	0.84
Glucose, mmol/l	5.9 \pm 0.8	6.5 \pm 2.2	0.33

CRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; HDL, high density lipoprotein.

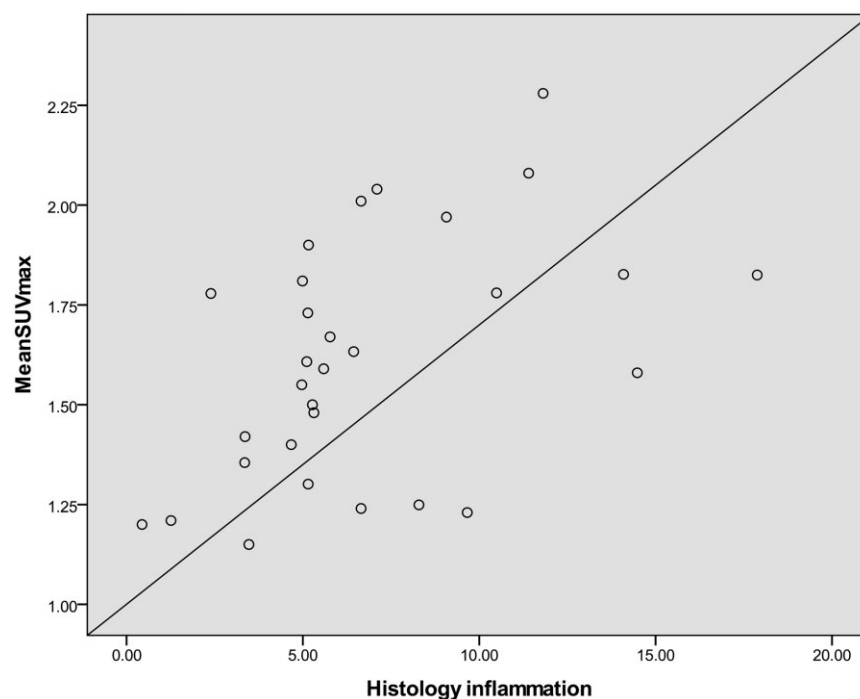


Fig. 1 Correlations between mean SUV_{max} values and percentage plaque inflammation on histology. $P = 0.003$. SD, standard deviation.

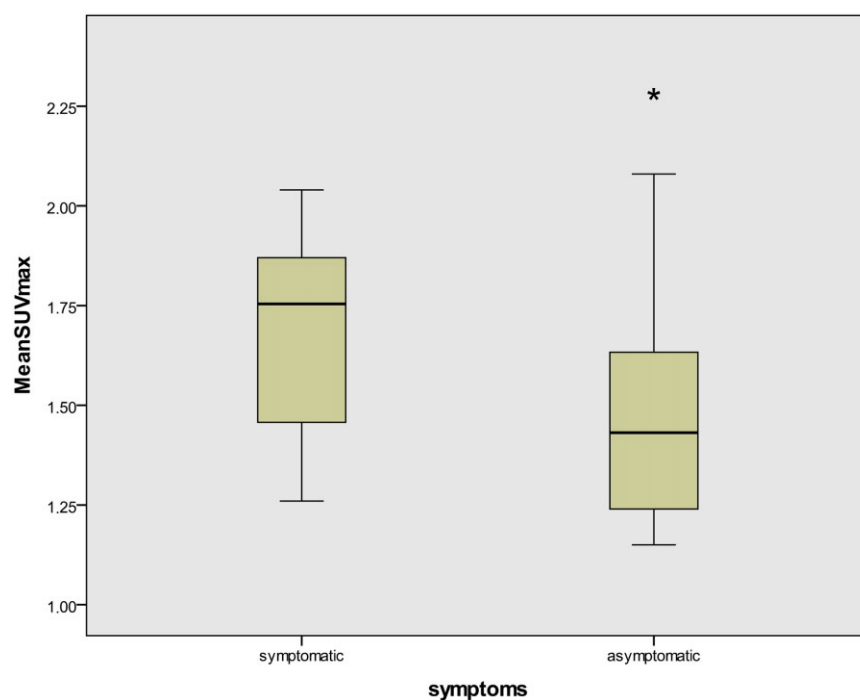


Fig. 2 Box plot showing distribution of FDG uptake values (median mean SUV_{max}) in symptomatic and asymptomatic patients. The bottom and top of the box represent the first and third quartile. Horizontal lines in boxes represent the median value (second quartile) and the whiskers the range limits. Median mean SUV_{max} was 1.68 (range 1.26–2.04) in symptomatic compared with 1.52 (1.15–2.28) in asymptomatic patients ($P = 0.03$). The P -value is from a Mann–Whitney U -test. *Represents the outlier in the asymptomatic patient group.

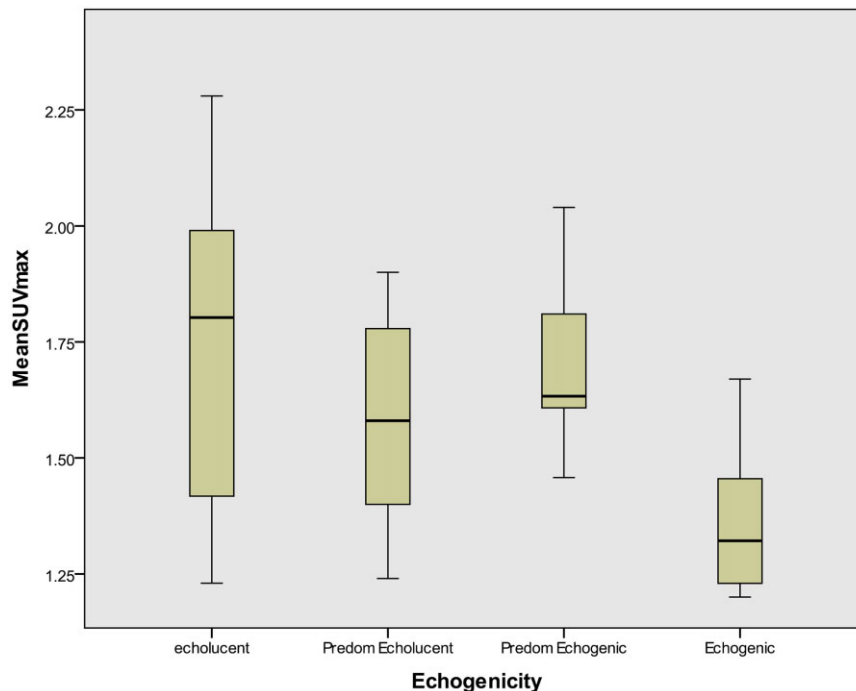


Fig. 3 Correlation of mean SUV_{max} and plaque ultrasound echogenicity. Box plot showing distribution of FDG uptake values (median mean SUV_{max}) and ultrasound echogenicity. Horizontal lines in boxes represent the median value and the whiskers the range limits. Mean SUV_{max} was significantly increased ($P = 0.028$) for echolucent plaques; 1.67 (1.2–2.28) compared with echogenic plaques; 1.5 (1.2–2.04). Echolucent vs. Echogenic plaques ($P = 0.028$). SUV, standardized uptake value; Predom, predominantly.

Discussion

In this study we found a significantly higher ^{18}F -FDG uptake in carotid artery plaques from symptomatic compared with those from asymptomatic patients. There was also a significant correlation between the amount of inflammation on plaque histology and ^{18}F -FDG uptake.

The findings of increased ^{18}F -FDG uptake in symptomatic carotid artery plaques in this study confirm the results of previous reports (9–11). Rudd *et al.* found higher ^{18}F -FDG uptake-values in carotid plaques obtained from patients with clinical evidence of plaque instability (9). In this small study histological assessments of the degree of plaque inflammation were not carried out and the relationship between inflammation and ^{18}F -FDG uptake was therefore not established. This association was first demonstrated by Tawakol *et al.* who found that histological evidence of plaque inflammation correlated with the degree of ^{18}F -FDG uptake (10). However, the time from the ^{18}F -FDG examinations and the histological assessments in this study was up to one-month and a change in the inflammatory status of the plaques during this time interval can therefore not be excluded.

To our knowledge, this is the first study, which has, in addition to demonstrating higher ^{18}F -FDG uptake values in plaques from symptomatic compared with asymptomatic patients also found a correlation between ^{18}F -FDG uptake and the degree of plaque inflammation on histological assessment. Higher ^{18}F -FDG uptake was demonstrated in plaques from symptomatic patients for both mean SUV_{max} and SUV_{max} values. These results show the potential of ^{18}F -FDG PET for evaluating carotid atherosclerosis with higher

^{18}F -FDG uptake in vulnerable plaques, which have a higher risk of causing embolic stroke. There are at present no established ^{18}F -FDG uptake limits that can be used to detect vulnerable carotid artery plaques. In this study, the range of SUV_{max} values, although significantly higher in symptomatic patients, overlapped in the two groups with the highest mean SUV_{max} uptake being recorded in a patient without symptoms. This patient was imaged 100 mins after ^{18}F -FDG injection and the increased ^{18}F -FDG uptake can therefore not be explained by longer circulation time of ^{18}F -FDG. Despite not reporting cerebrovascular symptoms, this patient had findings on magnetic resonance imaging (MRI) consistent with a small cerebral infarction in the ipsilateral cerebral hemisphere. This plaque had also low ultrasound echogenicity and a high inflammatory content on histology, which increases the probability that this was a vulnerable plaque. White matter lesions on cerebral MRI are known to indicate higher risk of stroke (25). Labeling carotid plaques as vulnerable in asymptomatic patients when the patient has ipsilateral silent brain infarcts on cerebral MRI imaging should therefore be considered in future studies where the aim is to identify unstable plaques.

In current studies different measurements of uptake are being used to quantify arterial ^{18}F -FDG uptake (9,10,12,26). In this study, blood background corrected TBR assessments of ^{18}F -FDG uptake did not show an association between FDG uptake and symptoms. This may be due to the early timing of PET/CT imaging in this study relative to the time of ^{18}F -FDG injection. Previous studies have found that TBR was a reliable and reproducible parameter when quantifying arterial ^{18}F -FDG uptake in late (>90 mins) acquisitions, but not for early imaging within

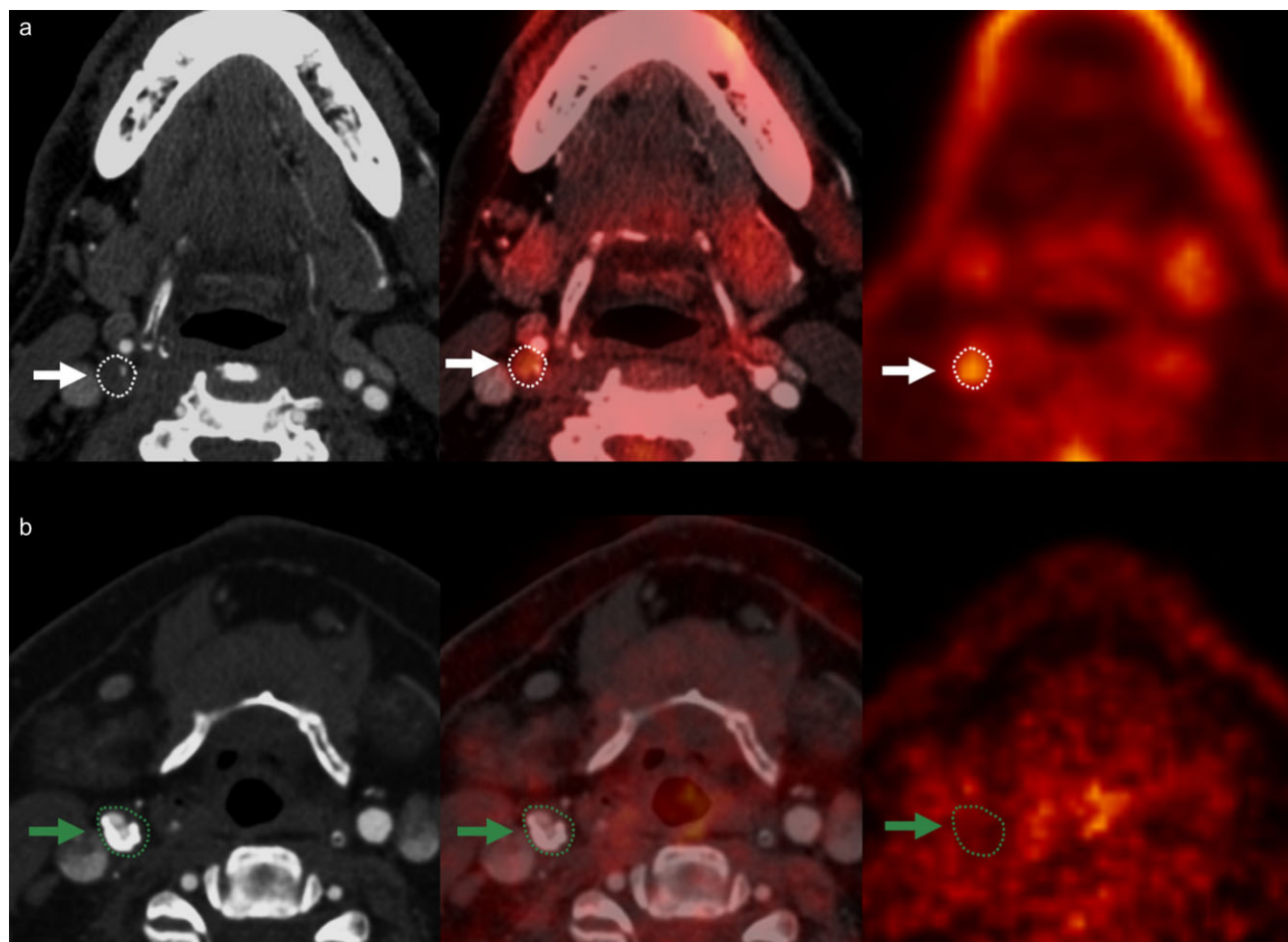


Fig. 4 ^{18}F -FDG PET/CT images of carotid artery plaques from symptomatic (a) and asymptomatic (b) patients. From left to right the images shown are contrast-enhanced CT, co-registered PET/CT and PET. Patient a has a noncalcified plaque with a high degree stenosis in the right internal carotid artery (white circle). The small white spot inside the circle on the CT image is contrast media in the stenotic ICA. The plaque had a high focal ^{18}F -FDG uptake (orange spot on PET images). The plaque was also echolucent on ultrasound and showed a large amount of inflammation on histology. Patient b has a calcified plaque in the right bifurcation (green circle) with no focal ^{18}F -FDG uptake. The plaque was echogenic on ultrasound and showed a small amount of inflammation on histology.

90 mins of ^{18}F -FDG injection (22). Graebe *et al.* compared ^{18}F -FDG uptake at one-hour and three-hours after ^{18}F -FDG injection in 19 patients and concluded that TBR measurements, using venous blood pool activity as background were not accurate for early scans (imaging <90 mins of ^{18}F -FDG injection) because of a mismatch observed in the relative ^{18}F -FDG plaque uptake between the two time-points; TBR values generally increases over time as blood pool activity decreased (22).

The method used in our histological evaluations allows the assessment of the total amount of inflammatory cells in the plaque, including both macrophages and leucocytes. Several methods have previously been described for estimating plaque inflammation histologically. These have included counting labeled macrophages (9–11). Leukocytes are also hypermetabolic cells that increase ^{18}F -FDG uptake. We therefore assessed both macrophage and leukocyte activity, as we believe that this is more accurate when comparing histological evidence of inflammation with ^{18}F -FDG uptake. All methods that are used to correlate histological findings with ^{18}F -FDG uptake on PET/CT imaging have, however, potential weaknesses. Despite careful removal of the

plaque at surgery, fragmentation of the CEA specimen is sometimes unavoidable resulting in a reduction of the observed amount of inflammation on histology.

We found that ^{18}F -FDG uptake was higher in plaques with low ultrasound echogenicity compared with those with high ultrasound echogenicity. This is in agreement with previous reports that have found that echolucent plaques are associated with both an increased risk of ipsilateral cerebrovascular events and increased presence of plaque macrophages on histology, independent of the degree of artery stenosis (18,27). Graebe *et al.* also found that echolucency on ultrasound correlated with ^{18}F -FDG uptake on PET (26). We did not find more patients who had plaques with low echogenicity in the symptomatic compared with the asymptomatic group. This may be explained by the sample size, which was underpowered to show such a difference.

Patients in the symptomatic group had higher LDL levels compared with patients in the asymptomatic group (mean 3.1 vs. 2.0 mmol/l), approaching statistical significance ($P=0.06$). The number of patients on statin therapy was, however, comparable for the two groups with 13 patients in the symptomatic group

taking statins, compared to 14 in the asymptomatic group. Chronin *et al.* found that increased ^{18}F -FDG uptake was associated with increased LDL, cholesterol and triglycerides and decreased high-density lipoprotein values. They suggested that increased LDL and cholesterol contribute to plaque inflammation (12). LDL and cholesterol are key mediators of inflammation, and studies have found that increased ^{18}F -FDG uptake correlated with an atherosclerotic lipid core, macrophage infiltration and matrix metalloproteinase immunoreactivity (10,28). Modifying atherosclerosis with statins and other anti-atherogenic therapy may also reduce plaque ^{18}F -FDG uptake (15).

In conclusion this study provides further evidence supporting the use of ^{18}F -FDG PET/CT for the detection of inflammation in vulnerable atherosclerotic plaques. Confirmation of this method in larger prospective clinical studies is, however, needed to clarify if ^{18}F -FDG PET/CT may be used to predict outcome in atherosclerotic carotid artery disease, especially in asymptomatic subjects and patients with less severe stenosis.

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