Systemic arterial inflammation, measured with ^{18}F FDG-PET, is common amongst subjects with both recent and prior cerebrovascular disease

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ABSTRACT

Objective: To compare systemic arterial inflammation in subjects with recent ischaemic stroke or TIA and controls with prior cerebrovascular disease.

Methods: Systemic arterial inflammation was prospectively measured by ^{18}F -fluorodeoxyglucose positron emission tomography in 11 cases with recent ischaemic stroke or TIA, and 11 sex matched controls with prior cerebrovascular disease.

Results: Hot spots (both carotid and non-carotid) of localised ^{18}F FDG uptake were found in more than half of all patients with either recent ($n=6$) or prior ($n=8$) cerebrovascular disease. There was no significant difference in the total number of hotspots, or hotspots at specific sites, in cases compared with controls. Mean standard uptake values (SUV) were similar in the carotid arteries and aorta of cases and controls, and showed a trend toward higher values in the femoral arteries of the controls (median 1.8; IQR 1.6–2.2) compared to cases (median 1.5; IQR 1.4–1.7).

Conclusion: Arterial inflammation was common, and appeared similar, in patients with recent stroke/TIA, and controls with stroke/TIA more than two years previously.

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1. Introduction

Inflammation contributes to the aetiology of cerebrovascular disease and is also associated with acute stroke. Systemic markers of inflammation correlate with the volume and outcome of focal brain infarction [1] and also with progression of small deep (lacunar) infarction [2]. However, it remains uncertain if inflammation in acute ischaemic stroke is a primary and/or secondary phenomenon. This is an important question because systemic inflammation is a potential therapeutic target in acute cerebrovascular disease.

Arterial inflammation can be imaged using ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F FDG-PET). Compared to serologic measures of inflammation, ^{18}F FDG-PET allows anatomic localisation of arterial inflammation. Inflammation of symptomatic carotid lesions appears to correlate with

the degree of carotid stenosis [3]. However these data have not been reproduced amongst patients with asymptomatic carotid lesions [4], suggesting that arterial inflammation may be an important aetiological factor independent of the degree of luminal stenosis.

On the basis of small uncontrolled studies [5,6], ^{18}F FDG-PET imaging has been proposed as a promising clinical investigation in acute ischaemic stroke. However availability of ^{18}F FDG-PET imaging is limited and the technique is associated with substantial radiation exposure [7] (about 7 mSv for PET alone, and about 25 mSv for PET/CT, compared to 0.1 mSv for a chest X-ray) and is costly. The role of ^{18}F FDG-PET imaging in the investigation of subjects presenting with acute ischaemic stroke thus remains uncertain.

Our hypothesis was that participants with recent ischaemic stroke would have greater carotid, and systemic, vascular inflammation than participants with prior cerebrovascular disease. We conducted this study to compare arterial inflammation, measured with ^{18}F FDG-PET imaging, amongst subjects with recent and prior cerebrovascular disease.

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2. Material and methods

This prospective case–control study, conducted in the acute stroke units and TIA clinics of two university teaching hospitals, was approved by the Royal Perth Hospital Ethics Committee. All participants provided written informed consent.

2.1. Subjects

Our subjects had a history of recent acute ischaemic stroke or TIA (within the previous 10 days) confirmed by standard clinical diagnostic criteria [8]. We excluded patients with blood glucose level >13 mmol L⁻¹ and those with diagnosed infection or malignancy. Sex and (when possible) age matched controls had a history of old ischaemic stroke or TIA (more than two years prior to the current study) and were placebo-treated participants of the vitamins to prevent stroke trial (VITATOPS) [9] who had taken part in a VITATOPS sub-study of arterial inflammation [10].

2.2. Measurements

Demographic and clinical data comprised cardiovascular risk factors, medication, the qualifying stroke syndrome, blood pressure and lipid profile. We measured inflammation within artery walls by ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) using a standard whole body imaging protocol on a Philips Allegro GSO scanner (Philips Medical Systems, USA), as described previously [10]. Briefly, whole body scans were performed on fasted participants from the base of skull to proximal thighs with attenuation correction.

The primary outcome measure was the standardised uptake value (SUV), corrected for body weight at six pre-specified sites (left and right common carotid arteries at the apex of the lung fields, the arch of the thoracic aorta, the abdominal aorta at the level of the first lumbar vertebra and the left and right femoral arteries at the level of the greater trochanter). SUV measurements were made by two investigators who reached consensus regarding all measurements. We selected the cross-sectional slice containing these landmarks and drew a circular region of interest (ROI) around the artery. We recorded the maximum SUV at each site and the mean maximum arterial FDG uptake for each participant was calculated as the average of these six maximum values. The secondary outcome measure was the number of discrete regions of increased FDG-uptake (“hot spots”) in the major vessels (left and right carotids, thoracic and abdominal aorta and left and right femoral arteries). A “hot spot” was defined as a discrete region with an SUV greater than a pre-specified cut-off value of 2.5 (compared with normal background activity which is in the order of SUV 1.0–1.5) [10].

2.3. Statistical analysis

Data were summarised descriptively. Log-normal data were log transformed prior to analysis. Non-normal data were analysed using non parametric tests. Categorical variables were assessed by chi square or Fisher's exact test. Data were analysed using SPSS 15.0.

3. Results

We recruited 11 patients with recent ischaemic stroke ($n=7$) or TIA ($n=4$), and 11 sex matched controls with an old ischaemic stroke or TIA (median 5 years, IQR 4–5 years). Table 1 shows demographic and clinical variables measured at the time of undergoing PET scanning, as well as the clinical syndrome of the qualifying cerebrovascular event.

Table 1

Qualifying stroke event, demographic and clinical variables.

	Recent stroke/TIA $n=11$	Stable disease $n=11$	<i>P</i>
Female gender, n (%)	3 (27%)	3 (27%)	1.0
Age at time of PET scan, years	63.7 $\pm$ 8.6	65.4 $\pm$ 9.4	0.18
Medical history			
Myocardial infarction	4 (36%)	1 (9%)	0.31
Hypertension	8 (73%)	10 (91%)	0.59
Hypercholesterolaemia	9 (82%)	9 (82%)	1.0
Diabetes	2 (18%)	1 (9%)	1.0
Smoking	4 (36%)	7 (64%)	0.2
Medical therapy			
Antihypertensive	6 (54%)	10 (91%)	0.15
Lipid lowering	8 (73%)	8 (73%)	1.0
SBP, mm Hg	140.5 $\pm$ 22.1	146.6 $\pm$ 18.4	0.51
DBP, mm Hg	78.6 $\pm$ 13.6	84.8 $\pm$ 8.4	0.24
Cholesterol, mmol L ⁻¹	4.8 $\pm$ 1.5	4.2 $\pm$ 0.6	0.22
Triglycerides, mmol L ⁻¹	1.5 $\pm$ 0.9	1.4 $\pm$ 0.8	0.76
HDL, mmol L ⁻¹	1.3 $\pm$ 0.2	1.2 $\pm$ 0.4	0.88
LDL, mmol L ⁻¹	2.7 $\pm$ 1.4	2.1 $\pm$ 0.5	0.30
Clinical syndrome			
PACI	5 (45%)	2 (18%)	0.18
LACI	2 (19%)	6 (55%)	
POCI	0	1 (9%)	
TIA	4 (36%)	2 (18%)	

Data are n (%) or $n \pm$ SD; S(D)BP: systolic (diastolic) blood pressure mm Hg; H(L)DL: high (low) density lipoprotein; PACI: partial anterior circulation; LACI: lacunar; POCI: posterior circulation; TIA: transient ischaemic attack.

Hot spots (carotid and/or non-carotid) of localised ¹⁸FDG uptake were found in more than half of all patients with either recent ($n=6$) or prior ($n=8$) cerebrovascular disease.

There was no significant difference in the total number of hotspots, or hotspots at specific sites, in cases compared with controls. Four cases had one or more carotid hot spots and 5 had non-carotid hot spots. Three of the control subjects had carotid hot spots and 8 had non-carotid hot spots.

Table 2

¹⁸FDG-PET results.

	Recent stroke/TIA $n=11$	Stable cerebrovascular disease $n=11$	<i>P</i>
Mean standard uptake value (SUV)	2.0 (1.9–2.1)	2.1 (1.8–2.4)	0.66
Carotid SUV	2.1 (1.7–2.2)	2.0 (1.7–2.2)	0.41
Aortic SUV	2.4 (2.2–2.7)	2.6 (2.2–2.9)	0.89
Femoral SUV	1.5 (1.4–1.7)	1.8 (1.6–2.2)	0.05
Total number of hot spots	1.1 $\pm$ 1.1	1.2 $\pm$ 1.1	0.86
Number of carotid hot spots	0.5 $\pm$ 0.7	0.2 $\pm$ 0.4	0.32
Number of non-carotid hot spots	0.6 $\pm$ 0.9	0.9 $\pm$ 0.7	0.33
Number with >1 hot spot present	6	8	0.66
Number with >1 carotid hot spots present	4	3	1.0
Number with >1 non-carotid hot spots	5	8	0.39
Number with >1 aortic hot spots	5	8	0.39
Number with >1 femoral hotspots	0	2	0.48
Maximum SUV of all hot spots	3.0 $\pm$ 0.6	2.8 $\pm$ 0.5	0.98

Values are n , mean $\pm$ SD or median (IQR).

Table 3
Clinical syndrome and hotspots in cases with recent stroke/TIA subjects.

Gender	Age	Syndrome	Lateralising signs	Hotspots
Female	65	TIA	Right amaurosis fugax	3 Aortic
Female	69	TIA	Left sided weakness	1 Aortic
Female	80	TIA	Right face and arm weakness	1 Right carotid 1 Aortic
Male	50	PACI	Left leg weakness	1 Right carotid 1 Aortic
Male	52	PACI	Left arm numbness	Nil
Male	61	TIA	Left face and arm weakness	Nil
Male	62	LACI	Right hemiparesis	Nil
Male	62	LACI	Right sided weakness	1 Left carotid 1 Aortic
Male	62	PACI	Left facial droop and hemiparesis- esthesia	Nil
Male	64	PACI	Right arm weakness	Nil
Male	71	PACI	Right sided weakness	1 Left carotid 1 Right carotid

Table 2 shows the mean standard uptake values (SUV). Mean SUV were similar in the carotid arteries and aorta of subjects with recent stroke/TIA compared to controls with prior cerebrovascular disease, and showed a trend toward higher values in the femoral arteries of the controls (median 1.8; IQR 1.6–2.2) compared to cases (median 1.5; IQR 1.4–1.7).

Details of the presenting clinical syndromes and hot spots detected amongst the 11 patients with recent stroke or TIA are shown in Table 3. Nine of the 11 recent cases had symptoms consistent with a carotid arterial lesion. Of these 9 cases, 3 had carotid hot spots. However, of these three patients, one had bilateral hot spots and one had an ipsilateral hot spot. Five of the 9 cases with carotid territory symptoms had aortic lesions, but the subject with the most aortic lesions ($n=3$) had a carotid syndrome (amaurosis fugax). Of 2 patients with lacunar syndromes, one had a carotid hot spot.

4. Discussion

This is the first study of systemic, rather than local (carotid), arterial inflammation measured with ^{18}F FDG-PET in people with recent stroke or TIA. Hot spots (both carotid and non-carotid) of localised ^{18}F FDG uptake were found in more than half of patients with either recent or prior cerebrovascular disease. Thus our data show that systemic arterial inflammation, as measured by ^{18}F FDG-PET, is common in patients with both recent acute and a history of prior cerebrovascular disease more than two years previously. Arterial inflammation remained common amongst control subjects with prior cerebrovascular disease despite frequent use of anti-hypertensive and lipid lowering therapy to treat underlying vascular risk factors.

Carotid FDG uptake is common in patients with carotid stenosis and symptoms of stroke/TIA. It has been proposed that ^{18}F FDG-PET may help to target surgical therapies [5,6]. However, previous studies have tended to be small, and are limited by the absence of a control group. Thus the clinical utility of ^{18}F FDG-PET in the investigation of acute stroke/TIA remains uncertain. Our data suggest that caution should be exercised in interpreting the aetiological significance of isolated hotspots. Hot spots detected amongst acute stroke subjects may often not relate to the acute presentation. The

relevance of carotid inflammation may be uncertain unless the aortic arch is also imaged simultaneously and other sources of embolism are thoroughly excluded. The value of ^{18}F FDG-PET in predicting future cerebrovascular events is also uncertain. The presence of carotid hotspots in patients with recent TIA/stroke may have little additional predictive value. Risk stratification based on clinical variables may be of greater clinical utility [11].

The strengths of our study are that the measures of arterial wall inflammation are likely to be valid. ^{18}F FDG-PET is generally considered a sensitive and reproducible method for assessing arterial wall inflammation in humans [12–14]. Although there are some apparently conflicting animal data [15], these may be influenced by a range of methodological factors [16]. We did our studies much more rapidly after the index event than some previous reports. In a recent study enrolling patients with TIA/minor stroke, who had both ipsilateral and contralateral carotid stenoses, significant differences in PET imaging results were present only when analysis was restricted to participants imaged within 38 days [17]. Our scans, done within ten days, are thus more likely to have detected arterial inflammation that was not persistent, than earlier studies with much longer intervals to imaging (often around three months) [5,6]. Our study also included a control group, which has been a limitation of previous studies.

The major weakness of our study is the potential for random error, and limited generalisability, because of the small number of participants, a feature shared with other publications dealing with this topic [5,6]. For example we had no participants with very large (total anterior circulation syndrome) strokes, and it is plausible that arterial inflammation may vary amongst subjects with stroke of different sub-types. Furthermore, there is potential for selection biases as the cases and controls were drawn from hospital and clinical trial populations, respectively, and non-consecutive sample of patients were screened (as our centres recruit to multiple trials simultaneously). Medical therapies may also influence inflammation. Although there was similar frequency of use of lipid lowering therapies in both groups, it is uncertain what proportion of the control group had long term high dose statin therapy, and it thus remains possible that their medical therapy may have been inadequate to influence systemic arterial inflammation. The window we used to define “recent” stroke/TIA may have been too wide, causing failure to detect arterial inflammation which was not persistent. Potential survivorship bias, incomplete matching of cases and controls (for age and clinical event), the cross-sectional design, and the methodology employed further limit interpretation of the data. However, these biases would tend to decrease the likelihood of finding inflammatory lesions in controls. Co-registration with CT or MRI is now more widely available and may increase reproducibility of PET measures [18,19]. Novel imaging targets (such as matrix metalloproteinases) are also being evaluated [20].

5. Conclusion

Systemic vascular inflammation is common (and appears similar) in patients with recent stroke or TIA and those with prior cerebrovascular disease more than two years previously. PET scanning may have utility in assessing the burden of vascular inflammation in patients with recent and prior cerebrovascular disease. Caution needs to be exercised in interpreting the aetiological significance of isolated hot spots in patients presenting with acute ischaemic stroke or TIA.

Conflicts of interest

The authors declare that they have no conflicts of interest or disclosures relevant to this work.

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