Postictal switch in blood flow distribution and temporal lobe seizures

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Abstract
The ictal increase of regional cerebral blood flow has yet to be fully utilised in the investigation of focal seizures. Although single photon emission tomography (SPECT) is being increasingly used in the localisation of epileptic foci, the evolution and time courses of the peri-ictal perfusion changes have yet to be clarified. We performed serial SPECT studies in the interictal, ictal and immediate postictal states in 12 patients with refractory temporal lobe epilepsy to define the patterns and duration of peri-ictal cerebral blood flow changes. Visual analysis showed a constant pattern of unilateral global increases in temporal lobe perfusion during seizures which suddenly switched to a pattern of relative mesial temporal (hippocampal) hyperperfusion and lateral temporal hypoperfusion in the immediate postictal period. Quantitative analysis confirmed the visual assessment. Lateral temporal cortex ictal/normal side to side ratios were increased by mean 35·1% (95% confidence interval 21·8% to 48·4%) more in the ictal studies than in the interictal studies and mesial temporal cortex ratios increased by mean 30·8% (22·4% to 39·2%). In the postictal state, however, lateral temporal ratios were reduced by mean 7·7% (−15·8% to 0·4%) compared with interictal values, whereas mesial temporal perfusion was maintained compared with the interictal studies. These observations provide critical information for interpreting scans which can be used in the localisation of epileptic foci. This postictal switch in blood flow patterns may reflect the underlying metabolic processes of neuronal activation and recovery and have implications for understanding the neurobiology of human epileptic seizures.

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The abnormal synchronised discharge of a neuronal aggregate that characterises focal epileptic seizures is accompanied by focal hyperperfusion[1-5]and hypermetabolism.[6 7] Functional imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) has shown a variety of peri-ictal blood flow patterns,[5 8-13] presumably reflecting the rapid changes of blood flow accompanying focal seizures. Peri-ictal studies with PET can be performed only serendipitously when seizures happen to occur during the scan. SPECT radionuclides such as [99m]Technetium-hexamethyl propyleneamineoxime (HMPAO) rapidly cross the blood-brain barrier and reside in cerebral tissue for several hours. Isotope can thus be injected during an observed seizure and the patient can then be scanned within the next few hours, with the scan reflecting cerebral blood flow (CBF) at the time of injection.[14] These properties permit the prospective and serial evaluation of changes in CBF associated with focal seizures, which typically last less than two minutes.

We previously reported the early postictal perfusion changes with SPECT, which allowed accurate prediction of seizure focus in 69% of a series of patients with refractory temporal lobe epilepsy.[11-13] We have since sought to determine the diagnostic value of ictal and postictal SPECT scans by examining a series of ictal and postictal paired studies in the same patients with qualitative and quantitative image analysis. We found a remarkable difference in the ictal and postictal perfusion patterns, representing a postictal switch in blood flow distribution. This finding is important for clinical diagnosis of seizure localisation and for understanding the pathophysiology of temporal lobe epilepsy.

Methods
Twelve patients (mean age 28, (range 16–46) years; seven women) with intractable unilateral temporal lobe epilepsy diagnosed on clinical and EEG criteria, and MRI[15] and neuropsychological data were studied (table 1). Peri-ictal SPECT is a routine investigation for prospective therapeutic temporal lobectomy in our centre,[11-13] and the 12 patients analysed were selected because they had undergone paired SPECT studies for both ictal and postictal states.

An interictal study was performed when the patient had been seizure free for at least 24 hours, with full medication. The ^{99m}Tc-HMPAO was injected with the patient in the resting state (supine, eyes closed, and silent with a minimum of background noise). Patients were continuously monitored with video recording and EEG for periods of up to two weeks (with reduced medication) and underwent ^{99m}Tc-HMPAO injection as soon as possible after onset of the seizure. SPECT images derived from injections during or up to 30 seconds after the end of a seizure were

Table 1   Localisation data in 12 patients studied with ictal and postictal SPECT*

Patient	Ictal EEG	Interictal SPECT	Ictal SPECT	Postictal SPECT	MRI†	Pathology
1	Left temporal discharge‡	Not lateralised	Left	Not lateralised	Left HS	HS
2	Right hippocampal discharge§	Right	Right	Right	Right HS	HS
3	Left hippocampal discharge§	Left	Left	Left	Left HS	HS
4	Left temporal discharge‖	Not lateralised	Left	Left	Left tumour	Ganglioglioma
5	Left hippocampal discharge§	Left	Left	Left	Normal	Normal
6	Left temporal discharge‖	Left	Left	Left	Left HS	HS
7	Unlocalised. Active Right interictal	Not lateralised	Right	Right	Right HS	HS
8	Left temporal discharge‖	Left	Left	Left	Left dysplasia	Dysplasia
9	Left temporal discharge‖	Left	Left	Not lateralised	Left HS	HS
10	Right temporal discharge‖	Not lateralised	Right	Right	Right HS	Cortical gliosis¶
11	Right hippocampal discharge§	Right	Right	Not lateralised	Normal	Normal
12	Left temporal discharge‖	Left	Left	Left	Left HS	HS

HS = hippocampal sclerosis.
*SPECT results derived from blinded visual assessment. Interictal SPECT localised by focal *hypo*perfusion, ictal SPECT by focal *hyper*perfusion, and postictal SPECT by mesial *hyperperfusion* with lateral *hypo*perfusion.
†MRI diagnosis of hippocampal sclerosis was made as previously described and validated.[15]
‡Surface EEG.
§Depth EEG.
‖Sphenoidal EEG.
¶Hippocampal tissue not found on pathology specimen.

called "ictal studies", as the appearances of scans in all cases were consistently similar. All 12 patients underwent an additional injection on another occasion more than 30 seconds after seizure end (postictal study; mean (SD) delay 1·46 (0·4) min). Exact timing of the injections was made possible by the timer linked to the video and EEG, which was read on playback of all seizures. The paired seizures studied were of a stereotyped pattern and similar length for each patient. Patients were scanned within two hours of injection, with a Starcam 400AC gammacamera (General Electric, Milwaukee, USA). Data acquisition, reconstruction, and display methods have been described previously.[12]

Scans were qualitatively interpreted by three blinded observers. The blood flow changes were quantitated by determining a ratio of counts, dividing the number in the epileptogenic side by that in the normal side, in the following regions of interest; mesial, lateral, and posterior temporal regions; lateral frontal and parietal cortices; basal ganglia; and cerebellar hemispheres. Three contiguous 3·2 mm transverse slices were summed and regions of interest were drawn using rectangular boxes. The volume studied was 4·9 cm³ (5 × 10 × 3 pixels) for all regions except for the cerebellum (7 × 7 × 3 pixels, 4·8 cm³) and basal ganglia (5 × 5 × 3 pixels, 2·5 cm³). Normal data were obtained from scans of 18 healthy male volunteers where L/R ratios were calculated for the same regions of interest. Mean ratios for each region of interest in the ictal, postictal, and interictal patient studies were compared with each other by using paired *t* tests and with control values by using multiple unpaired *t* tests. Conversion of ratios to logarithms was unnecessary as ratios varied beween 0·7 and 1·7.

Results

All patients were studied with ictal and postictal SPECT; the length of seizures was similar in each patient for the two studies (ictal, mean length 1 min 33 s, postictal, mean length 1 min 25 s). Ictal images in all 12 patients

showed a pronounced global increase in temporal lobe blood flow on the epileptogenic side (figure). This pattern was seen when injections were given during clinical and EEG ictal activity or up to 30 seconds after its cessation and was easily identified in all 12 cases by the three blinded observers independently (table 1). Postictal studies showed a switch in distribution of blood flow with hypoperfusion of the epileptogenic lobe and hemisphere in all 12 studies and residual hyperperfusion of the mesial temporal region in seven. The postictal changes were not always striking. In nine patients they were obvious to all three observers but in the three others they were not sufficiently clear for blinded lateralisation independent of other data.

Hypoperfusion of the frontal and parietal cortex was seen ipsilateral to the discharging focus in the ictal studies and persisted into the postictal period. One patient progressed to hemigeneralisation after his complex partial seizure. SPECT showed increased perfusion in the contralateral motor cortex in this case, in addition to the temporal lobe hyperperfusion.

Perfusion ratios for all regions of interest in the patients' interictal state did not differ from those in the control group, except for the mesial temporal region where there was a significant decrease on the side of the epileptic focus (table 2). Quantitative analysis of the ictal and postictal studies confirmed the qualitative interpretation of the images (table 3).

Table 2   Side to side perfusion ratios in the interictal state,* Values are means (SD)

Region of Interest	Controls	Patients	p Value
Lateral temporal	98 (2·5)	100 (4·39)	NS
Mesial temporal	101 (1·9)	94 (6·24)	< 0·05
Posterior temporal	101 (2·5)	100 (3·04)	NS
Lateral frontal	99 (2·3)	99 (3·31)	NS
Parietal	99 (1·7)	101 (3·92)	NS
Cerebellum	100 (1·9)	99 (3·75)	NS
Basal ganglia	99 (2·1)	100 (2·0)	NS

*Side to side ratios (multiplied by 100) calculated from left or right side counts for controls, and ictal or normal side for patients, were compared in each region of interest by using unpaired *t* tests.
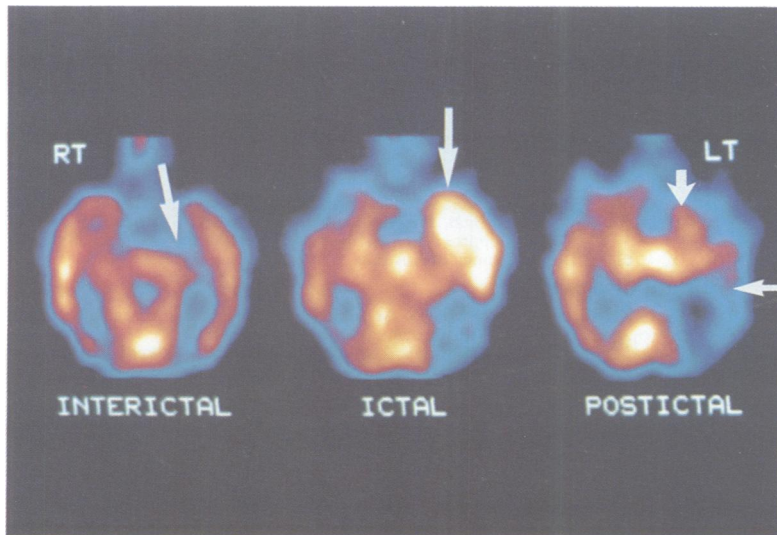
Transverse images through the temporal lobes for interictal, ictal, and postictal studies of patient 6 (left temporal lobe seizures). Colour scale from white to red to blue represents a spectrum of high to low counts. In the interictal study there is a small region of hypoperfusion in the left mesial temporal lobe (arrow). The ictal study shows a pronounced global increase in temporal perfusion (large arrow). The 1·5 minute postictal study shows lateral temporal hypoperfusion (horizontal arrow) with residual mesial hyperperfusion (vertical arrow) on the left.

firmed the suspected hippocampal sclerosis. All patients underwent temporal lobectomy on the side of the ictal SPECT focus (table 1). Pathology was found in 10 cases (seven showed hippocampal sclerosis, and there were individual cases of ganglioglioma, neocortical gliosis and dysplasia). All but one were seizure free (class 1 of Engel[16]) during a mean follow up of 15 (range 4–32) months. Patient 11 had a pronounced improvement in seizure frequency (class 3 of Engel[16]), although no pathology was suspected on MRI or found on histological examination.

Discussion

We analysed the relative blood flow changes in the peri-ictal period as seen in the side to side differences of brain perfusion, by qualitative and quantitative comparisons of cerebral blood flow patterns in the interictal, ictal, and post-ictal phases. This was done because the determination of absolute CBF by SPECT requires an accurate attenuation correction technique which is not routinely available. It also requires an accurate arterial input function for the tracer, which requires elaborate and time consuming preparations similar to those for PET. Such an approach to blood flow measurement is not currently feasible in the investigation of unpredictable events such as spontaneous seizures.

Ictal scans in all patients showed significant relative global increases in blood flow in the discharging temporal lobe. The SPECT images produced from ^{99m}Tc-HMPAO injection during or within 30 seconds of the end of the seizure suggests that the ictal temporal hyperperfusion persists beyond the termination of EEG discharge for 60–90 seconds, as most of the HMPAO that crosses the blood brain barrier does so in the first 60 seconds after the intravenous injection.[14] This distribution period may be shorter, given the tachycardia that often accompanies seizures.[17]

Injection after this time showed a switch in blood flow patterns, with hypoperfusion of the lateral temporal cortex frequently associated with preserved perfusion or hyperperfusion of the mesial temporal structures. The sequence of changes was thus a significant relative increase in mesial and lateral temporal lobe blood flow with ipsilateral depression of frontal cortex perfusion during the seizure, followed by a reduction in perfusion of the epileptogenic hemisphere with relative preservation of mesial temporal blood flow in the immediate postictal state. Our previous observations[11–13] suggest that postictal blood flow changes gradually return to normal within 10–30 minutes.

Lee et al noted in two of their ictal studies that cortex surrounding the hyperperfused area was underperfused and suggested that a "steal" phenomenon may be responsible.[8] Alternatively, there may be a depression of neuronal activity in the corical zones adjacent to the disharging temporal lobe and a consequent reduction in the demand for blood flow to those relatively inactive areas. Other ictal studies using SPECT have shown

The lateral temporal, mesial temporal, and basal ganglia ratios were significantly increased in the ictal studies in comparison to the interictal, postictal and control data. The increase over interictal values was 35·1% (95% confidence interval 21·8% to 48·4%) (p < 0·0005) for the lateral temporal area and 30·8% (22·4% to 39·2%) (p < 0·0001) for the mesial temporal region. Comparison of the postictal to the interictal scans showed that the postictal mesial temporal ratios were unchanged, whereas the posterior and lateral temporal ratios were reduced (although the lateral temporal change just failed to reach significance). Frontal and parietal ratios were significantly decreased in the postictal state, confirming the visual interpretation of the scans.

No discrepancies were found between SPECT and EEG with regard to side of ictal activity. In patient 7, ictal EEG data were not useful in localizing the seizure focus, but because clinical, interictal EEG, SPECT, MRI, and neuropsychological data concurred on the localisation, a temporal lobectomy was performed; pathological examination con-

Table 3   Relative regional cerebral blood flow changes in the ictal and postictal states compared to the interictal condition*

Region of interest	Ictal studies Mean % change (95% confidence interval)	p Value	Postictal studies Mean % change (95% confidence interval)	p Value
Lateral temporal	35·1 (21·8 to 48·4)	< 0·0005	−7·7 (−15·8 to 0·4)	0·058
Mesial temporal	30·8 (22·4 to 39·2)	< 0·0001	2·0 (−6·3 to 10·3)	NS
Posterior temporal	11·1 (−3·5 to 25·7)	NS	−8·5 (−14·0 to −3·0)	< 0·01
Lateral frontal	−5·7 (−13·9 to 2·5)	NS	−12·3 (−17·6 to −7·0)	< 0·0005
Parietal	1·2 (−7·5 to 9·9)	NS	−7·7 (−13·9 to −1·5)	<0·05
Basal ganglia	9·6 (2·7 to 16·5)	< 0·02	−0·2 (−4·3 to 3·9)	NS
Cerebellum	−2·3 (−5·2 to 0·6)	NS	0·6 (−1·7 to 2·9)	NS

*Percentage differences in mean ratio changes (epileptic side/normal side) from interictal to ictal and from interictal to postictal studies in 12 patients

increased temporal lobe perfusion, but these did not include observations of frontal and parietal cortex hypoperfusion or the motor strip hyperperfusion observed during hemi-generalisation.[5 9 10] The motor strip hyperperfusion found during hemigeneralisation is consistent with the expected haemodynamic response to spread of neuronal discharge to the central region. The agreement of peri-ictal SPECT data with ictal EEG localisation shows the reliability of side and site localisation of SPECT in temporal lobe seizures. The ratio method of quantitation we used confirmed the visual interpretations and allowed a relative measure of the magnitude of changes in CBF.

The hippocampus is the site of seizure generation in most cases of temporal lobe epilepsy.[18 19] In the present study ictal mesial temporal (hippocampal) hyperperfusion persisted into the postictal period in some cases. This is consistent with the findings previously reported in a larger series of patients, in which depth electrode EEG studies showed total cessation of ictal activity at the time of HMPAO injection.[12 13] Two factors may underlie the ictal and postictal mesial hyperperfusion seen in our SPECT studies. Experimentally, the extracellular cations (H^+ and K^+) responsible for the peri-ictal increases in cerebral microflow take some minutes to decline after the end of the seizure.[20] Secondly, peri-ictal regional CBF may be coupled to increased non-oxidative glucose metabolism, which reflects hippocampal metabolic activity in physiological neural activation in humans[21] and experimental hippocampal seizures.[22]

We conclude that the blood flow patterns in temporal lobe epilepsy as shown by SPECT with HMPAO change within a short time frame, with global temporal hyperperfusion switching rapidly (within 90 seconds of seizure end) to hypoperfusion with relative preservation of mesial temporal blood flow. Ictal SPECT images with global temporal hyperperfusion are striking and readily interpretable, whereas the postictal scans show more subtle but characteristic changes that require knowledge of the postictal switch in blood flow. Clinically, therefore, accurate documentation of the time of injection with respect to the video-EEG recording is crucial for proper interpretation. The peri-ictal perfusion patterns provide further evidence that the hippocampus is the generator for most seizures arising in that region. The association of an abnormal synchronised hippocampal electrical discharge with the characteristic rapidly changing blood flow patterns described here may be

a pathophysiological hallmark of temporal lobe epilepsy. SPECT has expanded the understanding of pathophysiological events that accompany focal seizures in humans.

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