The usefulness of repeated ictal SPET for the localization of epileptogenic zones in intractable epilepsy

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Abstract. This study investigated whether repeated ictal single-photon emission tomography (SPET) is helpful in the localization of epileptogenic zones and whether it can provide information confirming that an area of increased perfusion is really the culprit epileptogenic lesion. Fifty-four repeated ictal SPET studies were performed in 24 patients with ambiguous or unexpected findings on the first ictal SPET study. These patients were enrolled from among 502 patients with intractable epilepsy in whom pre-operative localization of epileptogenic zones was attempted with a view to possible surgical resection. Video monitoring of ictal behaviour and EEGs was performed in all patients. Repeated ictal SPET was performed using technetium-99m hexamethylpropylene amine oxime (HMPAO) when there was no prominently hyperperfused area or when unexpected findings were obtained during the first study. Two ictal SPET studies were performed in 19 patients, three studies in four patients and four studies in one patient. The average delay between ictal onset and injection was 28 s for the first study and 22 s for the second, third and fourth studies. Using interictal SPET, ictal-interictal subtraction images were acquired and co-registered with the population magnetic resonance imaging (MRI) template. Invasive study and surgery were performed in 18 patients, and in these cases the surgical outcome was known. In the other six patients, epileptogenic foci were determined using MRI, positron emission tomography (PET) and ictal EEG findings. Two patients were found to have mesial temporal lobe epilepsy, two lateral temporal lobe epilepsy, eight frontal lobe epilepsy, three parietal lobe epilepsy and one occipital lobe epilepsy. The other eight had multifocal epilepsy. The first study was normal in 12 patients (group I) and indicated certain zones to be epileptogenic in the other 12 (group II). Among group I, the correct epileptogenic zone or lateralization was revealed at the repeated study in nine patients, while in the other three it was not. Among group II, six patients showed the same results at the second study, thus confirming that the initially identified zones were of epileptogenic significance. In the other six patients, different areas were identified on the first and second studies, and repeated ictal SPET corroborated multifocality of the ictal EEG findings in five. These results indicate that repeated ictal SPET is useful because it can yield new or additional information about the epileptogenic zones and can confirm that a region of interest is an epileptogenic zone or that the epilepsy is of multifocal origin.

Keywords: Epilepsy – Ictal SPET – Subtraction ictal SPET – ^{99m}Tc-HMPAO

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Introduction

Increased ictal regional cerebral blood flow is associated with increased ictal neuronal activity, which is reflected by ictal scalp rhythm [1]. Ictal single-photon emission tomography (SPET) has been reported to display excellent sensitivity in localizing epileptogenic zones in intractable temporal lobe epilepsy [2, 3]. In addition, it has been found to assist in the identification of epileptogenic

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zones in patients with cryptogenic epilepsy who have normal and symmetrical hippocampi [4, 5].

Video monitoring of ictal semiology and electroencephalography (EEG) is usually continued until several episodes of ictus have been documented [1]. This is because the start of the ictal discharge is often ambiguous on ictal scalp EEG, and the observation of multiple episodes improves the localization. Furthermore, multiple epileptogenic foci may be found on prolonged ictal EEG monitoring in an individual patient [6, 7, 8]; in these cases, observation of multiple episodes is mandatory. By contrast, ictal SPET is usually acquired only on one ictal episode.

Simultaneous video-EEG monitoring is essential when performing ictal SPET in order to determine the time between the onset of a seizure and tracer delivery [2]. On the basis of criteria as to what constitutes an acceptable delay prior to injection, it might be possible to select a good ictal SPET study. However, despite efforts to shorten the delay prior to injection, rapid peri-ictal propagation of seizure activity complicates the interpretation of hyperperfused areas [9, 10]. As a consequence of such peri-ictal propagation, an unexpected peri-ictal pattern of hyperperfusion may be seen on ictal SPET, and false lateralization can result. Moreover, not infrequently ictal SPET fails to reveal an area of significant hyperperfusion, giving rise to false-negative results. In order to overcome the possibility of false lateralization or lack of sensitivity due to rapid propagation, the propagation pattern of hyperperfusion needs to be observed sequentially. There is no way of doing this; however, repeated observation of the ictal perfusion pattern over several ictal episodes might yield information that complements the ictal scalp EEG findings. This is true especially in patients with multifocality.

In this study, we investigated whether repeated ictal SPET is helpful in the localization of epileptogenic zones and whether it can provide information confirming that an area of increased perfusion is really the culprit epileptogenic lesion.

Materials and methods

Subjects. Twenty-four patients with ambiguous or unexpected findings on the first ictal SPET were enrolled in this study (Table 1). These patients were selected from among 502 patients with intractable epilepsy in whom pre-operative localization of epileptogenic zones was attempted with a view to possible surgical resection. Standard presurgical evaluation included scalp video-EEG monitoring, brain magnetic resonance imaging (MRI), interictal EEG and fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET). When results were deemed inconclusive upon review by the Epilepsy board meeting at our institution, additional ictal SPET was performed. Nine of the patients were men and 15 women; their mean age was 19.2 years (range 5–35 years). Diagnosis was made by surgery and confirmation of surgical outcome in 18 patients and by scalp video-EEG monitoring, brain MRI and ^{18}F-FDG PET in six patients.

MRI scans were normal in 12 patients and abnormal in 12. Abnormal findings on MRI scan included hippocampal sclerosis in four patients, single or multiple cortical/subcortical lesions in seven and diffuse hemi-atrophy in one.

Pathology in 18 patients included 14 cases of focal cortical dysplasia, two cases of hippocampal sclerosis, one oligodendroglioma, one old infarct and one case of Sturge-Weber disease (Table 1). These patients were followed up for 20–81 months after neocortical resection or anterior temporal lobectomy. Outcome was assessed by the Engel class, as follows: class 1, seizure free; class 2, rare seizures; class 3, significantly improved; and class 4, not improved or worse. The outcome was Engel class 1 in ten patients, class 3 in six and class 4 in two.

Ictal ^{99m}Tc-HMPAO SPET. Ictal video scalp-EEG monitoring (Telefactor, Philadelphia, U.S.A.) was performed in all patients for 3–13 days. ^{99m}Tc-HMPAO was reconstituted and stabilized with $CoCl_2$. In this form, labelling efficiency was preserved for 3 h after reconstitution. 925 MBq of ^{99m}Tc-HMPAO was injected per ictus. The injection delay was 28±21 s for the first study and 22±10 s for the second, third and fourth studies.

Ictal SPET images were acquired on average 2 h after injection using a triple-head Prism3000 SPET camera (Picker International, Ohio, U.S.A.) with a low-energy high-resolution fan-beam collimator. The entire acquisition lasted 15 min. One hundred and twenty images were acquired at 20 s each using the step and shoot method with an interval of 3° and a 128×128 matrix. Transaxial images were reconstituted using filtered back-projection and a Metz filter (x=1.5~2.0). Attenuation was corrected using Chang's method. Transaxial images were re-aligned to yield sagittal and coronal images.

Interictal ^{99m}Tc-HMPAO SPET studies were acquired at least 3 days apart from the ictal SPET. In 19 patients, a second ictal SPET study was acquired during the same admission as for the first study. In the other five patients, the second and third (n=4) or even fourth (n=1) ictal SPET studies were acquired during separate admission.

Subtraction ictal SPET co-registered to MRI (SISCOM). Interictal SPET was performed in 18 of 24 patients. Using these interictal SPET studies, SISCOM studies were performed. SPM 99 (Statistical Parametric Mapping 99, Institute of Neurology, University College of London, UK) implemented in Matlab 5.3 (Mathworks Inc., USA) was used to re-align the ictal and interictal SPET images, which were spatially normalized into standard templates [11]. Firstly, ictal and interictal SPET images were re-aligned with each other. Secondly, individual ictal and interictal SPET images were spatially normalized into the SPET template using SPM software. Parameters for the spatial normalization were obtained from interictal SPET images and applied to both the ictal and the interictal SPET images. Spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel with a 10-mm full-width at half-maximum. The pixel count of the SPET images was normalized to a mean pixel count of grey matter in each SPET image, which was measured on a grey matter probability map (provided by SPM) using the following equation:

$$\frac{\sum_{i,j,k} I_{i,j,k} \times G_{i,j,k}}{\sum_{i,j,k} G_{i,j,k}}$$

where $I_{i,j,k}$ and $G_{i,j,k}$ are pixel counts of the SPET image and the grey matter probability map at (i, j, k)th pixel, respectively. The

Table 1. Clinical summary and results of ictal SPET studies

Patient no.	Age/sex	Onset (yrs)	Diagnosis	Surgery	Follow-up (Engel class)	Pathology	1st ictal SPET		2nd ictal SPET		3rd ictal SPET		4th ictal SPET	
							Visual	SISCOM	Visual	SISCOM	Visual	SISCOM	Visual	SISCOM
1	15/M	4	R FLE	NR (F)	66 mo (class 3)	FCD	N	N	R FTP	N				
2	35/F	8	L PLE	NR (P)	20 mo (class 3)	FCD	N		N					
3	26/F	12	R mTLE	N.D.	–	–	N	N	R T	R T				
4	23/F	22	Multifocal	N.D.	–	–	R T		L T		R T			
5	12/M	9	Multifocal	R ATL	76 mo (class 4)	FCD	R T		L T		R F			
6	30/M	16	R TOLE	NR (T, O)	64 mo (class 1)	FCD	N	N	N	R TO				
7	16/F	10	R FLE	NR (F)	64 mo (class 1)	FCD	N	N	N	N	R F	R F		
8	15/M	4	L latTLE	L ATL, NR (T)	81 mo (class 1)	HS, FCD	L FP	L FP	L FP	L T				
9	13/F	6	L FLE	NR (F)	52 mo (class 4)	FCD	N		N					
10	34/M	7	Multifocal	R ATL, NR (F)	74 mo (class 3)	FCD	B T		L T					
11	9/M	5	R mTLE	R ATL	75 mo (class 1)	HS	N	N	R T	N				
12	17/F	14	L FLE	N.D.	–	–	L F	L F	R FT	N				
13	12/M	4	Multifocal	NR (T, P)	65 mo (class 1)	FCD, dyslamination	N		L F					
14	28/F	7	R PLE	NR (P)	62 m (class 1)	FCD	N	N	R T	R P				
15	22/F	13	Multifocal	N.D.	–	–	R T	R T	L T	L T				
16	18/F	11	R FLE	NR (F)	66 mo (class 3)	Old infarct	N	R T	R F	R T				
17	10/F	0	L FLE	NR (F)	47 mo (class 1)	FCD	L F	L F	L T	L P	L F	L F	L T	L F
18	5/F	2	R OLE	NR (O)	56 mo (class 1)	SW disease	N		R O					
19	5/F	1	L FLE	N.D.	–	–	L F	L F	L F	L F				
20	31/M	23	L PLE	NR (P)	66 mo (class 3)	FCD, microdysgenesis	L P	L P	L P	L P	N	N		
21	18/F	3	Multifocal	NR (P, F, T)	56 mo (class 1)	Oligodendroglioma	R P	N	R P	R P				
22	24/M	21	Multifocal	NR (T)	71 mo (class 3)	FCD, heterotopia	L FT	L FT	R T	R T				
23	18/F	18	Multifocal	N.D.	–	–	R FTP		L T					
24	24/F	9	L FLE	NR (F)	52 m (class 1)	FCD	N	N	L FTP	L FP				

M, Male; F, female; R, right; L, left; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; latTLE, lateral temporal lobe epilepsy; mTLE, medial temporal lobe epilepsy; TOLE, temporo-occipital lobe epilepsy; PLE, parietal lobe epilepsy; NR, neocortical resection; F, frontal; T, temporal; P, parietal; O, occipital; ATL, anterior temporal lobectomy; N.D., not done; FCD, focal cortical dysplasia; HS, hippocampal sclerosis; SW, Sturge-Weber disease; N, normal

Table 2. Visual interpretation of ictal SPET on the first and the repeated ictal SPET studies

1st ictal SPET study		Repeated ictal SPET (2nd, 3rd, 4th studies)	
No area of hyperperfusion (group I)	12	No area of hyperperfusion	3
		Lateralization only	4
		Localization possible	5
Any area of hyperperfusion (Group II)	12		
Localization possible	8	Concordant	6
Lateralization only	4	Similar to 1st study but equivocal	3
		Confirmed the localization on the 1st study	3
		Discordant	6
		Multifocality	5
		False lateralization	1

perfusion change map was calculated according to the following equation:

$$\frac{I_{ic} - I_{in}}{I_{in}} \times 100(\%)$$

where I_{ic} and I_{in} are the normalized ictal and interictal SPET images, respectively [12].

Perfusion changes of greater than 20% were regarded as significant, and the perfusion change map containing significant pixels was superimposed on the T1 MRI template [13, 14, 15].

Visual and SISCOM image interpretation. Ictal and interictal images were reviewed by two physicians who were unaware of the clinical history and the results of the other presurgical evaluations. Coronal, sagittal and transaxial images were analysed. The cerebral cortex was divided into the occipital, medial temporal, lateral temporal, frontal and parietal lobes.

Each examiner was requested to analyse ictal SPET images in a blind fashion without knowing whether these images belonged to the same patient or not. When there was disagreement between the two examiners, an effort was made to reach a consensus regarding localization. A decision was taken on all ictal SPET studies as to whether they were lateralized or not when hyperperfused areas extended beyond one lobe. Patients were assigned to group I when no area of hyperperfusion was observed on the first ictal SPET and to group II when there was an area of hyperperfusion on the first ictal SPET (Table 2).

The same physicians interpreted SISCOM images while blinded to the previous results, including the ictal and the interictal SPET findings.

Statistical analysis. The McNemar test was used to compare the sensitivity of the first SPET study and the repeated SPET studies.

Results

SPET findings on the first and subsequent ictal studies

A total of 54 ictal SPET studies were performed in the 24 patients. On the initial ictal SPET study, areas of ictal hyperperfusion could not be found in 12 patients (group I) but were found in the other 12 (group II). In 19 patients, a second ictal SPET study was performed; in four patients, a third study was also performed; and in one patient, four studies were performed (Table 1).

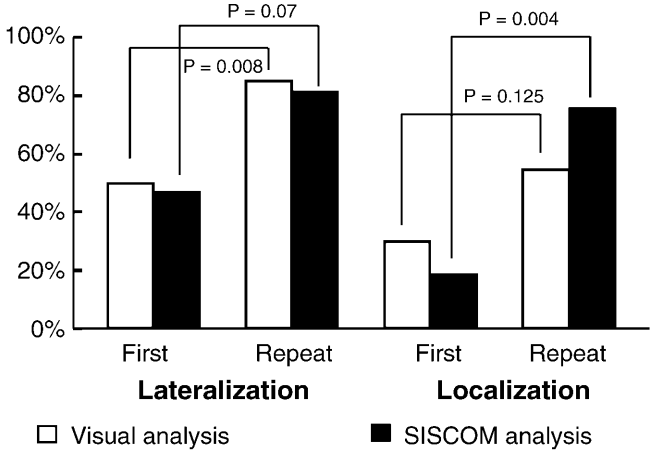

Fig. 1. Lateralization and localization rates of the first and repeated ictal SPET studies by visual assessment of ictal (and interictal) SPET and by SISCOM image interpretation. The patient number was 24 for visual analysis and 16 for SISCOM. Significant differences were found in the localization rates of the repeated studies by both visual and SISCOM analysis

Among the group I patients without any area of hyperperfusion on initial ictal SPET, eight showed ictal hyperperfusion at the second study (Table 2). In four of these eight patients, the hyperperfused area on the second SPET indicated the correct epileptogenic zones. Lateralization only was possible in the other four patients on the second ictal SPET study. A third SPET study was performed in one of the four patients with normal ictal SPET findings on the first and second studies, and this third study resulted in the correct localization of the epileptogenic zone (case 7 of Table 1).

Among the 12 group II patients with an area of hyperperfusion on initial ictal SPET, six had concordant results on repeated ictal SPET and the other six had discordant results (Table 2). Among the concordant group, a second study showed hyperperfused areas in three patients, which confirmed that those areas were of epileptogenic significance. In the other three, the degree of hyperperfusion was still equivocal on the second study. Among the discordant group, five patients were found to have multifocal epilepsy, which was suggested by concordant ictal

scalp EEG findings and later confirmed by subsequent invasive EEG studies using subdural electrodes. In the remaining patient, the finding of the first SPET study was correct and the repeat study indicated a false area.

The sensitivity of the first ictal SPET was 50% (12/24) for lateralization and 33.3% (8/24) for seizure focus localization. On the repeated SPET studies, additional information indicating the correct localization or suggestive of multifocality was obtained in 16 patients. Taking into account the results of repeated ictal SPET, the sensitivity increased to 83% (20/24) for lateralization (P=0.008) and to 54% (13/24) for localization (P=0.125) of the epileptic focus (Fig. 1).

Findings on SISCOM images

SISCOM images were generated in 16 of the 24 patients (two with medial temporal lobe epilepsy, three with multifocal epilepsy and 11 with neocortical epilepsy). Two SISCOM images were generated in 13 patients, three SISCOM images in two patients and four SISCOM images in one patient. Nine of the first SISCOM images were normal, while lateralization was possible in the other seven, and localization in three of these seven (Table 3). On the second SISCOM images obtained in the aforementioned nine patients with normal initial SISCOM images, epileptogenic zones were localized in six patients while images were still ambiguous in the other three. Epileptogenic zones were localized on the repeated SISCOM images in three of the four patients in whom only lateralization was possible on the initial images.

Localization was possible in 14 of 16 patients on the second or repeated the SISCOM studies, thereby corroborating the visual findings. Lateralization and localization rates obtained using the SISCOM images on the first and the repeated SPET studies are shown in Fig. 1. No difference was apparent between the rates achieved with visual (n=24) and SISCOM (n=16) assessment. A high level of agreement was observed between visual assessment of ictal and interictal SPET side by side and SISCOM image interpretation, with a kappa value of 0.573 (Table 4).

Table 3. Interpretation of SISCOM images on the first and the repeated studies

1st SISCOM		Repeated SISCOM	
Normal	9	Normal again	3
		Localization	6
Lateralization only	4	Localization	3
		Equivocal	1
Localization	3	Localization	3

Case examples

Figure 2 shows an example of a group I patient without any area of increased perfusion on the first ictal SPET

Table 4. Comparison of ictal SPET and SISCOM results

Ictal SPET	SISCOM			Total
	Normal	Lateralization only	Correct localization	
Normal	9	1	1	11
Lateralization only	1	3	2	6
Correct localization	2	2	14	18
False lateralization	1			1
Total	13	6	17	36

36 studies (16: 1st; 16: 2nd; 3: 3rd; 1: 4th) in 16 patients
Kappa=0.573

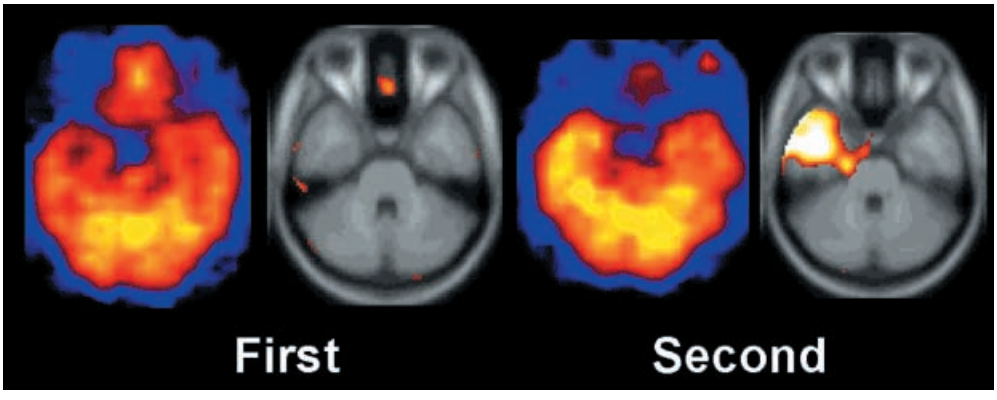

Fig. 2. The epileptogenic zone was found on the second ictal SPET study. This patient had right lateral temporal lobe epilepsy and a hyperperfused area was prominent on the second study. The SISCOM image showed similar findings

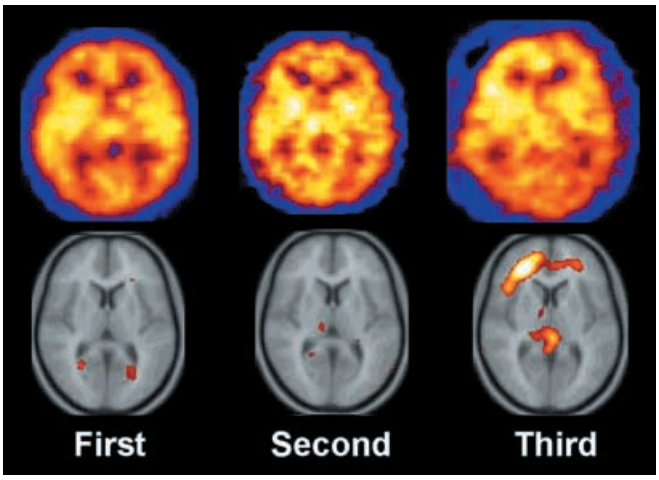

Fig. 3. The hyperperfused area was found only in the third ictal SPET study in this patient with right frontal lobe epilepsy. Corresponding SISCOM images are shown in the *lower row*

(case 11 of Table 1). This patient suffered from complex partial seizures with secondary generalization. On ictal scalp EEG he showed rhythmic theta activity on the T2 electrode. On second ictal SPET, perfusion was increased in the right temporal lobe. The SISCOM image also revealed right temporal lobe hyperperfusion. MRI was equivocal and metabolism was decreased in the right temporal lobe on ^{18}F-FDG PET. After depth EEG study, which revealed a right medial temporal origin, right anterior temporal lobectomy was performed, which resulted in a good surgical outcome (Engel class 1) after 6 years.

In a patient with right frontal lobe epilepsy (case 7 of Table 1), perfusion was normal on the first and the second ictal SPET studies despite an appropriate injection time. On ictal scalp EEG monitoring, rhythmic 3-Hz spike-and-wave was found on the F8 electrode. MRI was normal but metabolism was decreased in the right frontal lobe. On the third ictal SPET study, perfusion was increased in the right frontal lobe (Fig. 3). The SISCOM image also revealed right frontal lobe hyperperfusion. This patient was seizure-free (Engel class 1) for more than 5 years after the operation.

In a 24-year-old male patient (case 22 of Table 1), multifocality was suggested both by ictal scalp EEG and by repeated ictal SPET studies (Fig. 4). On the first ictal SPET study, perfusion was increased in the left frontotemporal lobe. Ictal scalp EEG also showed left temporal rhythmic spike-and-wave. However, on the second ictal SPET study, perfusion was increased in the right temporal lobe. Ictal scalp EEG showed a right temporal abnormality at this time. SISCOM images supported visual side-by-side interpretation. No structural abnormality was found on MRI and PET was not performed. Invasive subdural grid/strip EEG recording revealed left posterior temporal onset. Left temporal corticectomy was performed but surgical outcome was Engel class 3 after 6 years.

Discussion

Ictal SPET is considered to be useful for the localization of epileptogenic zones in surgical candidates with intractable epilepsy [2, 3]. A delayed injection time [16, 17] and propagation of ictal blood flow increase to nearby brain regions [9,18] are the prime suspected causes of failure to localize the epileptogenic zones. Injection times of less than 60 s from the onset of ictal discharge

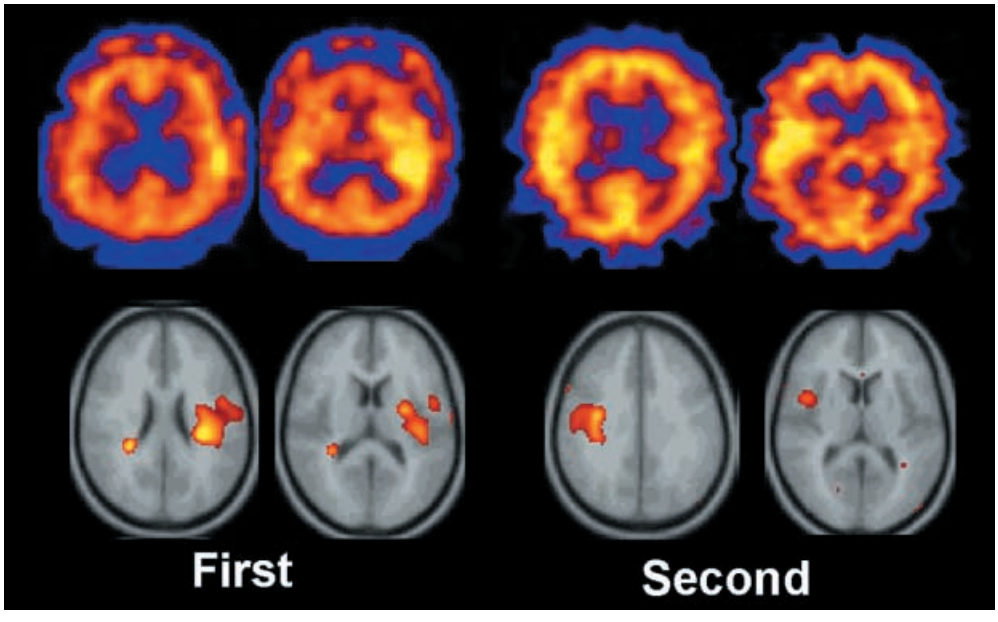

Fig. 4. An example of multifocal epilepsy proven by repeated SPET. On the first ictal SPET study, the left temporal lobe showed a hyperperfused area, while the right temporal lobe showed a hyperperfused area during the second SPET study. Concurrent SISCOM images identified the same areas

have been found to be sufficient to catch ictal hyperperfusion at the epileptogenic zones [16, 17]. Careful analysis of the ictal EEG pattern on video-monitored ictal EEG before and after tracer injection, and the various patterns of spread of ictal EEG before injection, suggests that ictal SPET may often be misleading, in that it may lateralize false regions [1]. This is because the extent and contrast of an area of increased perfusion on ictal SPET in comparison with nearby or contralateral regions vary considerably; sometimes the result is convincing and on other occasions it is very subtle. Despite the application of subtraction ictal SPET co-registered to MRI [15, 19, 20, 21], one can be confronted with an ambiguous or an unexpected finding on the first ictal SPET study.

Ictal SPET has certain limitations. Injection is usually done a short time after the ictal EEG onset, and there is also a time lapse before maximal tracer uptake in the brain. These factors influence the perfusion pattern revealed on ictal SPET. Acknowledgement of this fact might lead to wider recognition of the potential role of repeated ictal SPET as a complementary technique, in much the same way as ictal episodes are observed repeatedly by video monitoring of the ictal scalp EEG and semiology. Among a total of more than 500 patients monitored during the last 5 years, we identified 24 with ambiguous or unexpected findings on the first ictal SPET. In most of these patients, repeated ictal SPET was performed during the same admission period, but in some, repeated studies were performed during a subsequent admission.

In a previously reported reproducibility study [14], peri-ictal SPET results were reproducible in most of the patients investigated, and this was corroborated by quantitative SISCOM images. However, in that study, peri-ictal SPET images repeatedly showed areas of decreased perfusion at the epileptogenic zones, and this was considered to be a reproducible finding. In fact, ictal SPET results are generally considered to be unhelpful when they reveal only an area of decreased perfusion instead of hyperperfused areas. SPET showing decreased perfusion is postictal SPET, and postictal SPET has its own sensitivity [3]. Thus, we suggest that every effort be made to shorten the injection delay in these cases. In our study, although the injection delay was not significantly shortened at the repeated study, repeated ictal SPET did provide incremental information.

Our series included no patients with pseudo-seizure, as was confirmed by EEG progress on the first and the repeated SPET studies, which revealed a truly ictal discharge character in each case. One patient who showed postictal hypoperfusion with a delayed injection time of 120 s on the first ictal SPET study was excluded from our series.

One-half of our patients showed no abnormal increase in perfusion during the initial visual assessment. Interpretation of the SISCOM images corroborated this result, with no area of perfusion difference exceeding 20% between the ictal and interictal studies. Because of these findings, and despite the ictal EEG showing ictal discharge, the second SPET studies were performed. On the second (or repeated) ictal SPET study, prominently increased perfusion was found and this was compatible with the final or provisional diagnosis. In other words, the hyperperfused area was found on the repeated ictal SPET study or the confidence in localization of epileptogenic zones was enhanced by acquisition of similar or more prominent findings on repeated ictal SPET.

In the other cases, we found that the first and second or the first, second and third studies showed different epileptogenic zones of multifocal epilepsy [6, 7, 8]. In these patients, ictal SPET studies reflected the ictal discharge of each episode (Fig. 4). Five patients with multifocality were operated on and showed a good surgical outcome. Among the total of 18 patients who underwent surgery in our series, ten were subsequently seizure free and six improved, but the other two did not. This study is limited in that patients with relatively poor outcomes were included.

The diversity of ictal episodes in a patient ranges from clinical semiology to EEG progress and finally to the ictal pattern of increased perfusion. In view of the diagnostic importance of ictal SPET and the diversity of ictal hyperperfusion, we recommend repeated ictal SPET when the first SPET study looks ambiguous or when it does not reveal an area of hyperperfusion expected on the basis of the findings of either ictal EEG or other imaging modalities.

In conclusion, repeated ictal SPET was found to be useful because it yielded new or additional information about the epileptogenic zones and confirmed that a region of interest was an epileptogenic zone or that the epilepsy was of multifocal origin. We suggest that ictal SPET be repeated when the appearance on the first SPET study is ambiguous. Subtraction ictal SPET co-registered to MRI corroborated visual interpretation but was not a surrogate for repeated study.

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