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Original articles

Comparison of fluorine-18 deoxyglucose and O-15 water PET in temporal lobe epilepsy

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Abstract

This study reports a comparison of Fluorine-18 deoxyglucose positron emission tomography (FDG-PET) and O-15 water ($H_2^{15}O$) PET with regard to lateralization of the seizure focus in patients with complex partial epilepsy. The analysis of 35 patients who had an anterior temporal lobectomy for medically intractable seizures indicated that FDG- and $H_2^{15}O$-PET were highly correlated in demonstrating the epileptic focus. FDG- and $H_2^{15}O$-PET showed significant asymmetries in 83% and 77% of cases respectively. The lateralization with visual analysis of MRI was found to be lower than both FDG and blood flow imaging. Ictal electroencephalography (EEG) lateralizations were concordant with sites of blood flow and FDG-PET abnormalities. Thirty-three patients (94%) were seizure-free or improved significantly after surgery. In conclusion, blood flow PET yielded similar results compared to FDG-PET and can be a valuable modality in preoperative evaluation of patients with temporal lobe epilepsy.

Key words : Blood flow ; FDG ; positron emission tomography ; epilepsy ; MRI ; EEG.

Introduction

In a wide range of neurodegenerative conditions, characterized by neuronal loss, such as Alzheimer's disease, changes in blood flow and glucose metabolism are closely correlated (Postiglione *et al.,* 1993 ; Gilman *et al.,* 1995). Because chronic epilepsy shows similar neuronal loss characteristics, one is led to hypothesize that the pattern of changes in blood flow and FDG may also be comparable in seizure disorders. In this study, this hypothesis was tested by comparing preoperative FDG and blood flow PET scans in patients with temporal lobe epilepsy to assess the ability of these tracers to lateralize the seizure focus.

Interictal FDG-PET has been widely used and accepted as a standard reference for lateralization and localization of the epileptic focus in seizure disorders for presurgical evaluation of temporal lobe epilepsy (Franck *et al.* 1986 ; Abou-Khalil *et al.,* 1987 ; Henry *et al.,* 1990 ; Engel *et al.,* 1990). Interictal blood flow studies with PET or single photon emission tomography (SPECT) have not been utilized as commonly as FDG in temporal lobe epilepsy, likely stemming from the lower sensitivity and specificity reported by prior blood flow studies in epilepsy. Previous studies have compared the sensitivity of FDG-PET to interictal HMPAO-SPECT, and FDG-PET to O-15 water PET (Ryvlin *et al.,* 1992 ; Leiderman *et al.,* 1992 ; Coubes *et al.,* 1993 ; Theodore *et al.,* 1994 ; Gaillard *et al.,* 1995 ; Nagata *et al.,* 1995 ; Fink *et al.,* 1996 ; Breier *et al.,* 1997). In several of these reports, FDG and blood flow images were obtained on separate days and with different scanners. Two previous studies that compared FDG and O-15 water PET in epilepsy reported a sensitivity of about 50% for O-15 water PET (Leiderman *et al.,* 1992 ; Theodore *et al.,* 1994).

In order to reevaluate the benefit of blood flow PET scanning in temporal lobe epilepsy, the current study compared semi-quantitative blood flow and FDG images in patients who were scanned on the same day and using the same scanner. In addition, receiver-operating curves (ROC's) were constructed using data from a large number of control subjects. The optimum cut-off value was selected from the ROC curves in order to maximize the diagnostic accuracy of FDG and O-15 water PET.

Materials and Methods

PATIENTS

This study included 35 patients who underwent an anterior temporal lobectomy for complex partial seizures. These patients were referred by three different epilepsy centers where they had a comprehensive presurgical evaluation including a complete neurological examination, video electroencephalography (VEEG) monitoring with seizure recordings, magnetic resonance imaging (MRI), interictal EEG and PET scanning. Informed con-

sent was obtained from each patient before administration of PET tracers.

The patients (17 males, 18 females) had complex partial epilepsy with a mean duration of 20 years. Seizures were characterized by aurae, staring, involuntary movements such as head turning, lip smacking, eye deviation and extremity movements, unconsciousness and inability of recalling the seizure event after the episode. The mean frequency of complex partial seizures per patient was 12 per month (range : 5-30). Most of the patients had occasional secondary generalized tonic-clonic seizures with an occurrence of one to four per year. The patients' age at surgery ranged from 18 to 52 years (mean 33 ; SD : 10). Of these patients, 14 were operated on the left and 21 on the right. The clinical follow up ranged from 1 to 5 years after surgery. An experienced neuropathologist (KKH) reviewed the specimens.

MRI

MRI scans were obtained with Elscint Prestige 2T and General Electric Medical System 1.5T and Philips Gyroscan ACS-II 1.5 T scanners. Patients underwent transaxial, sagittal, T1 and T2 weighted scans with coronal views perpendicular to hippocampus. The reports of scans were obtained from patients' charts. The criterion for mesial temporal sclerosis (MTS) was hippocampal atrophy with or without T2 signal changes.

EEG

Continuous VEEG monitoring was performed after tapering patients'antiepileptic medications to record seizures. Scalp electrodes were placed according to the 10-20 international system over the temporal regions with sphenoidal electrodes being used in approximately 25% of patients. In determining the lateralization or localization of the ictal focus, the site of the onset of discharges as well as their amplitude and semiology of the seizures were taken into account. Depth electrode VEEG monitoring or intraoperative recordings were obtained in 11 patients when clear lateralization of the seizure focus could not be established from other diagnostic modalities such as inconclusive ictal EEG, normal MRI or PET scans. Final localization of seizures was obtained by utilizing the data obtained from depth ictal, scalp ictal, and interictal EEG, seizure semiology, imaging findings and neurological examination. The patients underwent anterior temporal lobectomies after the final lateralization of seizures was made based on the convergent results of multiple tests. The standard of reference to calculate the performance of FDG and O-15 water PET in this study was the final surgical site.

PET Blood flow and glucose metabolism image acquisition

Scans were obtained with a GE/Scanditronix 4096 scanner with a field of view of 10.6 cm, 15 slices and an axial resolution of 6.5 mm full-width at half maximum. Transmission scans with a Germanium-68 source were obtained to measure and correct for attenuation. The emission images were reconstructed with a Hanning filter to a spatial resolution of 8 mm. Three blood flow scans every 12 to 15 minutes were acquired and averaged to improve the signal to noise ratio. A bolus of 2405-2960 MBq (65-80 mCi) ^{15}O-water was administered for each emission recording. Immediately after the completion of blood flow scans, 204 MBq (5.5 mCi) FDG was injected intravenously. Glucose metabolism scans were initiated 40 minutes after the FDG administration. FDG and ^{15}O-water scan acquisition times were 20 minutes and 90 seconds, respectively. All scans were acquired while the patient was in a resting state, eyes closed and without repositioning the patient. A thermoplastic mask to the face was applied throughout the study in order to minimize head motion.

Data Analysis

The data was analyzed semi-quantitatively by using asymmetry indices. Images were analyzed with regions of interests (ROIs) drawn on three mid and lower contiguous temporal lobe planes, containing more than 10×10 pixels. Whole brain ROI was created by an automated, threshold based shrink-wrap technique (DIPs station, Boulder, Colorado) and 30% of the maximum intensity value of all 15 slices was used as threshold to wrap the brain. The temporal lobe ROIs were then drawn manually to make a complete contour outlining the temporal lobes (Fig. 1). An asymmetry index (AI) was calculated from three consecutive temporal plane values by this formula : $100 \times$ (left - right)/(left + right)/2. An average functional asymmetry index value was calculated from three consecutive planes. Additionally, temporal to whole brain ratios (normalized regional values) were computed. The same analysis was performed on PET images of 100 control subjects (75 O-15 water, 25 FDG), who served as volunteers in other research studies, to create means and standard deviations of asymmetry indices and normalized regional values (NRV's). Since there was no statistically significant difference in mean AI between these two control groups ($p = 0.24$, two- sample t test), the standard deviation (SD) was calculated from the combined control group. In patients, the PET abnormalities were divided in three groups as mild, moderate and severe. The asymmetry indices between the temporal lobes ranged between 5 to 10% for mild, 10 to

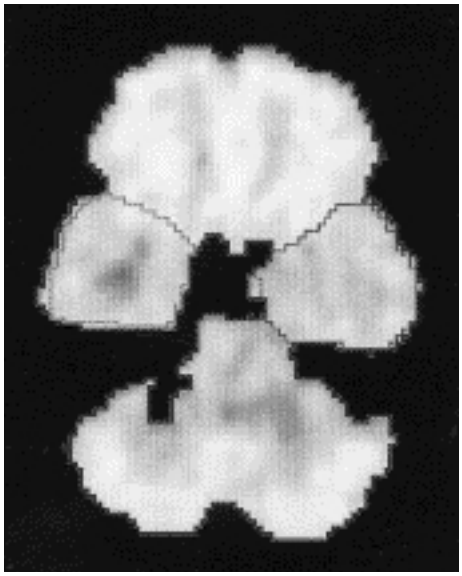

FIG. 1. — Illustration of the regions of interest (ROI) method. Thirty% threshold of maximum value of the whole brain is selected to wrap the brain contour. After thresholding, the slices were manually edited to exclude non-temporal regions. Temporal regions were drawn on three consecutive temporal planes.

20% for moderate and larger than 20% for severe disease (Fig. 2).

Results

The mean AI in 100 control subjects was -0.43 (SD : +/- 2.32). The mean NRV was 0.92 (SD : +/-0.045). The significant correlation of AI between FDG and blood flow in 35 patients is demonstrated in figure 3 (Spearman correlation coefficient, $r = 0.74$, $p < 0.000$). The mean AI of FDG (1.88, SD : +/- 10.98) and blood flow (1.08, SD : +/- 7.17) were not statistically different (paired t test ; $p = 0.47$). Receiver operating characteristics (ROC) analysis (Hanley *et al.,* 1990) was performed from asymmetry indices of FDG and O-15 water PET of 35 patients and 100 normal volunteers. Statistical analysis of FDG and blood flow PET was performed by comparison of the areas under the ROC curves ($p < 0.0004$). Although overall the blood flow PET is less sensitive, the shape of the ROC curves of both tracers is similar (Fig. 4). The optimum cutoff threshold value of asymmetry index was obtained from the ROC curve and ranged between 4 and 5%. For this study, 4.5% AI is chosen as a threshold in order to obtain optimum sensitivity values of blood flow and FDG PET. With 4.5% AI as a threshold, 29 out of 35 (83%) patients were correctly lateralized by FDG-PET, all matched with the surgical site, and 27 out of 35 (77%) patients were lateralized by O15-water PET. The results of FDG-PET, $H_2{}^{15}O$-PET, MRI, EEG, pathology and outcome data are summarized in Table 1.

Interestingly, in two patients (patient 2 and 18), the O-15 water and FDG-PET asymmetry indices, although statistically significant (above 5%), were in the opposite direction (Fig. 3). This result presumably reflects hyperperfusion of the temporal lobe during scanning. In these patients, the NRV values of the epileptic lobe were significantly elevated during blood flow scans (1.05) while FDG showed hypometabolism. Patient no. 18 was monitored with surface EEG during PET scanning and did not show a visible epileptiform activity during both blood flow and FDG scans (Fig. 5). Both patients' last clinical seizure episodes were within 24 hours prior to PET scan.

O-15 water PET scans were non-lateralizing in 8 patients. FDG-PET was non-lateralizing in 6 patients and 4 patients were not lateralized by either O-15 water or FDG-PET. In one case (patient no. 28), FDG and blood flow PET scans showed an insignificant asymmetry between the right and left temporal lobe (AI : 0.7 and 1.2). Bilateral disease was evident visually and was supported by the low normalized regional values (0.82) bilaterally on

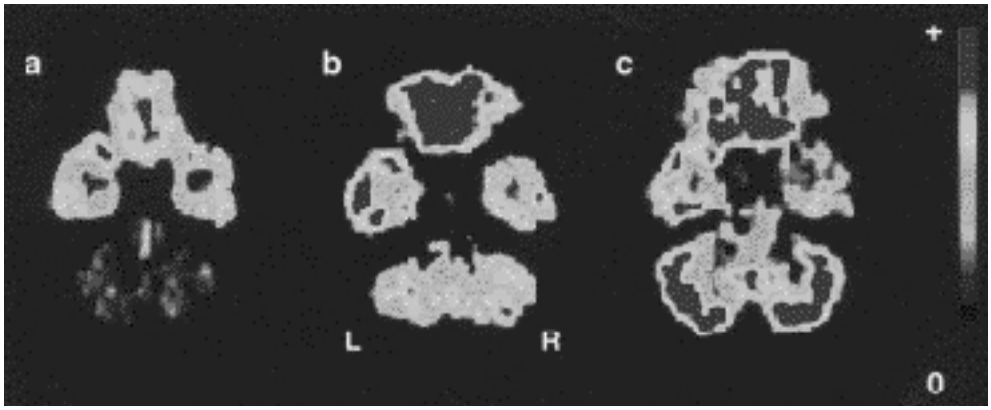

FIG. 2. — Illustration of mild, moderate, severe abnormality of the left temporal lobe in three epileptic patients. FDG tracer was utilized. From left to right, the asymmetry indices are 7%, 15%, and 22% respectively.

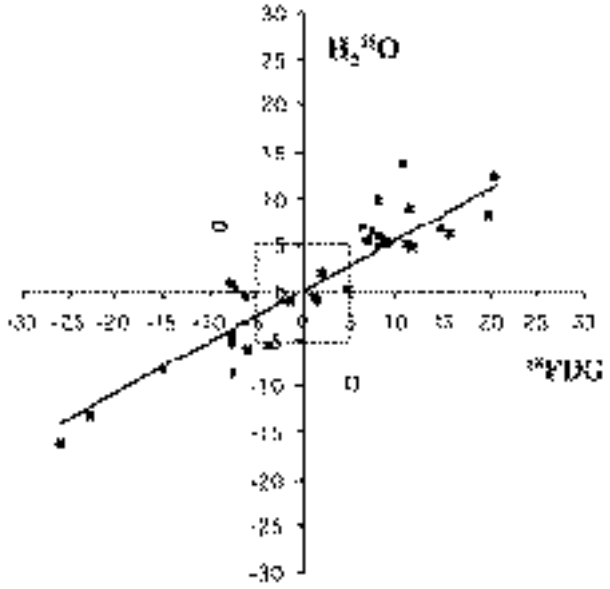

Fig. 3. — The relationship between the asymmetry indices (AI) for O-15 water and FDG-PET, illustrating a significant correlation between two tracers (Spearman correlation coefficient, r = 0.74, p < 0.000) with only two cases having asymmetry indices in the opposite direction (white squares). Square box represents 5% asymmetry index (approximately 2 standard deviations).

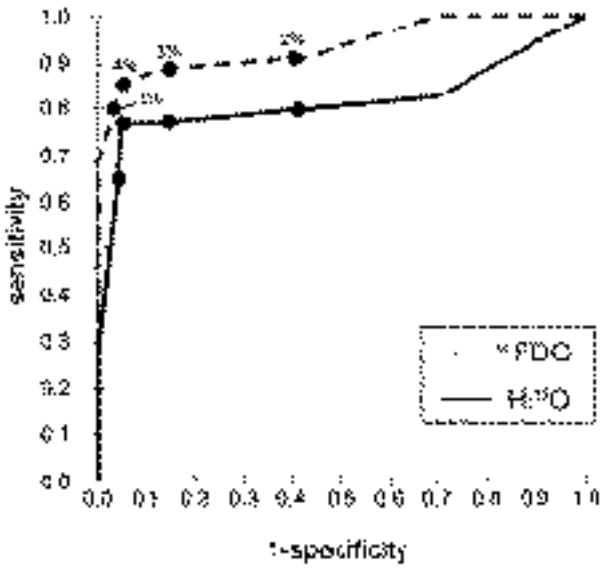

Fig. 4. — A receiver characteristic (ROC) curve illustrates the accuracies of FDG and blood flow tracers along a spectrum. Asymmetry indices are shown on the graph. The area index in ROC curve for FDG was 0.91 (SE : 0.03), and for O-15 water was 0.81 (SE : 0.05). Statistical comparison of areas under both curves demonstrated overall FDG having a higher performance than O-15 water (paired t test, p < 0.0004). The shapes of the curves are similar. Optimal diagnostic cut-off value of AI is determined to be 4 to 5%. At 4-5% threshold, the performance of ROC curves is not different (paired t test, p = 0.2).

PET scan. The patient had independent bitemporal epileptiform discharges by surface interictal EEG recordings and non-lateralized video EEG monitoring results, and a normal MRI. The patient underwent right temporal lobectomy as his depth electrode recordings demonstrated more prominent discharges emanating from the right hippocampus.

MRI

MRI was negative in 14 of 35 patients (40%). In one patient, who had a left temporal lobectomy (patient 33), the MRI was interpreted as right temporal lobe atrophy. The sensitivity and specificity of qualitative MRI was 60% and 97%. Out of 14 patients with normal MRI, FDG-PET and blood flow PET was abnormal in 11 patients (78%), and 9 patients (64%), respectively. O-15 water PET was superior to MRI for the detection of abnormal temporal lobes.

EEG

VEEG monitoring lateralized the majority of patients (77%), although the VEEG lateralized less foci than FDG-PET (83%). The ictal VEEG lateralizations were concordant with sites of blood flow and FDG PET abnormalities. Eight patients (23%) were not lateralized by VEEG. In 10 out of 11 patients, who had depth electrode or intraoperative recordings, the site of discharges was concordant with the blood flow and FDG-PET abnormalities. One patient (no. 6) had independent bilateral discharges by depth recordings (Table 1). FDG and blood flow PET showed more severe hypometabolism and hypoperfusion in the left temporal lobe.

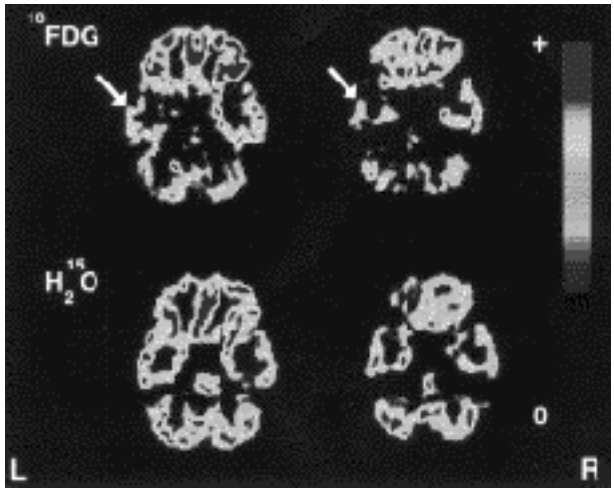

Fig. 5. — Upper arrows indicate left temporal lobe hypometabolism. Lower row demonstrates postictal persistent hyperperfusion of the same epileptic temporal lobe evidenced by elevated NRV's (1.05). Asymmetry indices were reversed. (FAI for FDG : -8.9, blood flow : +6.81). The patient's last clinical seizure was 24 hours prior to PET scan. The patient underwent left temporal lobectomy based on the ictal EEG and FDG-PET results.

Table 1

Patients' summary

Patient	Age/ gender	FDG	BF	MRI	VEEG	Depth EEG	Surgical site	Pathology	Outcome
1	37 F	N	N	N	L	none	L	negative	SF
2	45 M	R	R	N	non-lateralized	R	R	hippocampal microdysgenesis	SF
3	27 M	R	R	N	R	R (intraoperative)	R	mild hippocampal sclerosis	SI
4	47 M	N	L	L MTS	Bilateral	L	L	white matter heterotopia	SI
5	27 M	R	R	R temporal heterotopic grey matter	R	R	R	hippocampal sclerosis	SF
6	31 F	L	L	N	non-lateralized	bilateral	L	neocortical microdysgenesis & dysplasia, hippocampal gliosis	NSI, on vagal stimulator
7	32 F	R	R	N	non-lateralized	none	R	white matter heterotopia	SI
8	19 M	L	L	L MTS	L	L		mesiotemporal sclerosis	SF
9	28 M	R	R	R MTS	non-lateralized	none	R	negative	SF
10	35 M	R	R	R temporal atrophy	R		R	negative	SF
11	27 F	L	L	L MTS	L		L	negative	SF
12	37 F	R	R	N	R		R	white matter heterotopia	SI
13	26 M	R	R	R MTS	R		R	white matter heterotopia	SI
14	26 M	R	R	R MTS	R		R	cortical gliosis	SI
15	31 F	R	R	R temporal atrophy and dysplasia	R		R	neocortical dysplasia	SI
16	29 M	L	N	N	L		L	negative	SI
17	30 F	R	R	R inferior temporal dysplasia	R		R	hippocampal cortical dysplasia & neocortical dysembryoplastic neuroepithelioma	SF
18	34 M	L	L	L temporal atrophy	L		L	neocortical & hippocampal gliosis	SF
19	28 F	L	L	N	L		L	hippocampal sclerosis & neocortical microdysgenesis	SF
20	52 F	L	L	L MTS	non-lateralized	L	L	hippocampal sclerosis	SF
21	50 F	N	N	N	R		R	mild diffuse neuronal heterotopia	SI
22	51 F	R	R	N	R	R	R	mesiotemporal sclerosis	SI
23	52 F	L	N	L MTS	L		L	hippocampal gliosis	SI
24	24 M	R	R	R MTS	R	R (intraoperative)	R	hippocampal sclerosis	SF
25	20 M	R	R	R MTS	R	R	R	hippocampal sclerosis	SF
26	18 F	R	N	N	R		R	microdysgenesis, cortical dyplasia of hippocampus & lateral temporal lobe	NSI, non-compliant, with meds
27	32 F	L	N	L MTS	L		L	inferomesial temporal lobe gliosis	SF
28	28 M	N	N	nonlateralized	R	L	R	hippocampal sclerosis	SF
29	41 F	R	R	R MTS	R	R		hippocampal sclerosis	SF
30	21 M	R	R	R MTS	non-lateralized	R	R	hippocampal sclerosis	SF
31	26 F	L	L	L MTS	L		L	hippocampal sclerosis	SF
32	20 F	L	L	L MTS	L		L	hippocampal sclerosis	SF
33	35 M	N	L	mild R temporal atrophy	L		L	hippocampal gliosis	SF
34	48 F	N	N	N	R		R	hippocampal microdysgenesis	SI
35	41 M	R	R	N	R		R	hippocampal sclerosis	SI

MTS = mesiotemporal sclerosis SF = seizure free
SI = significantly improved NSI = not significantly improved

Pathology

Histopathologic abnormalities were present in 30 (86%) patients. Fifteen patients (43%) had hippocampal sclerosis. Other pathological diagnoses included hippocampal or neocortical gliosis, heterotopia, dysplasia, and microdysgenesis. Both neocortical and hippocampal abnormalities were present in the same specimen in several cases (Table 1).

Outcome

After temporal lobectomy, 20 patients (57%) were seizure free. Thirteen patients (37%) had significant improvement in seizure frequencies having less than 3 seizures per year and 90% reduction in seizures within the 1 to 5 year follow-up. Two patients (6%) did not improve significantly. One of these patients with bilateral epilepsy was implanted with a vagal nerve stimulator after the left

temporal lobectomy (patient no. 6). Her preoperative PET scan showed hypometabolism and hypoperfusion of both temporal lobes, which were more severe on the left. The second patient was non-compliant with medications (patient no. 26). Her preoperative PET scan showed right temporal lobe glucose hypometabolism and non-lateralizing $H_2{}^{15}O$ PET.

Discussion

The main finding of this study is that the results of bloodflow imaging highly correlate with those for FDG for lateralizing the epileptic focus. The FDG and O-15-water PET demonstrated a statistically significant concordant hypometabolism and hypoperfusion ($r = 0.74$, $p < 0.000$) (Fig. 3).

Only two cases demonstrated a combination of hyperperfusion and hypometabolism. The cause of this discordance is uncertain. Postictal and interictal hyperperfusion of epileptogenic focus has been reported previously by several investigators (Lang *et al.,* 1988 ; Devous *et al.,* 1998 ; Tatlidil, 2000) and has been seen in approximately 5% of blood flow studies. The hyperperfusion seen in these two patients may be secondary to a temporary subclinical ictal activity in an epileptic focus unrecognized by surface EEG, uncoupling of blood flow and glucose metabolism during interictal spike activity or the enhancement of the blood flow due to anaerobic metabolic products such as lactate (Gaillard *et al.,* 1995 ; Yanai *et al.,* 1997 ; Bruehl *et al.,* 1998 ; Bittar *et al.,* 1999). If the discordance in these two patients is a result of a subclinical ictal state, then specificity of O-15 water is calculated as 100% ; however, if the discordant results are considered to be due to interictal state then specificity is 94% for seizure focus localization.

An asymmetry index calculated from temporal lobe regions is a sensitive index depicting abnormality in patients with unilateral disease. Applying this method, a 60 to 90% incidence of interictal glucose hypometabolism was previously reported. Typically, AI indices of 10 to 20% have been previously reported as a cut-off threshold in lateralization of epileptic focus (Abou-Khalil *et al.,* 1987 ; Henry *et al.,* 1990 ; Theodore *et al.,* 1994). In this report, by using a large number of controls and utilization of ROC analysis in choosing the approximate threshold of 4 to 5% for the AI index, higher sensitivity was obtained especially with bloodflow PET (80%), compared to previous studies (Leiderman *et al.,* 1992 ; Theodore *et al.,* 1994). In general, the abnormalities on FDG scan were more marked than those of blood flow scans as has been observed in previous studies (Leiderman *et al.,* 1992 ; Gaillard *et al.,* 1995 ; Breier *et al.,* 1997) (Fig. 3). These differences may be due to the diffusion limitation of O-15 water, uncoupling of blood flow and glucose metabolism or the differences in postictal dynamics of blood flow and glucose metabolism (Herscovitch *et al.,* 1987 ; Fink *et al.,* 1996 ; Breier *et al.,* 1997 ; Bruehl *et al.,* 1998 ; Bittar *et al.,* 1999).

In patients with normal MRI, FDG and blood flow PET yielded a sensitivity of 78% and 64%, respectively. Visually analysed MRI had a sensitivity of 60%, in lesion detection. It has been previously reported that the quantitative MRI with hippocampal volumetric measurements yielded higher sensitivities compared to qualitative MRI. (Reuters *et al.,* 1993 ; Cendes *et al.,* 1993).

This study demonstrated the usefulness of semi-quantitative blood flow PET as compared to widely accepted FDG scan in epileptic focus lateralization in complex partial seizures of temporal lobe origin. In addition to quick scan time, the advantage of blood flow PET includes the potential use of O-15 water ictally, when the patient has seizures during scanning although this may be difficult to achieve practically. Following seizures acquiring serial O-15 water scans can be useful to follow the time course of dynamic changes of blood flow in the epileptic focus. Hemispheric language mapping can potentially be made within the same imaging session by using various language activation tasks (Tatlidil *et al*., 2000 ; Tatlidil, 2000). In addition, both blood flow and FDG PET can obviate the use of invasive depth electrode recording for seizure focus lateralization in majority of cases.

In conclusion, O-15 water PET can be an alternative to FDG-PET in presurgical evaluation of patients with complex partial seizures, with comparable results. When concordant with other studies of preoperative evaluation, $H_2{}^{15}O$ PET may add confidence to the localization of the epileptogenic site. Prospective studies in larger numbers of patients will be helpful in further demonstrating the usefulness of blood flow PET in complex partial seizures of temporal lobe origin.

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