Ictal and Interictal Brain SPECT Imaging in Epilepsy Using Technetium-99m-ECD

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The aim of this study was to evaluate the use of ^{99m}Tc-ethyl cysteinate dimer (ECD), also known as ^{99m}Tc-bicisate, in the presurgical evaluation of patients suffering from medically intractable epilepsy. **Methods:** Twenty-three brain SPECT studies (8 ictally and 15 interictally) were performed on 16 patients with a high-resolution annular SPECT system (CERASPECT). For the ictal studies, the tracer was injected in the very early phase of the seizure. The delay between seizure onset and ^{99m}Tc-ECD injection was 2–20 sec. **Results:** Interictally, all patients showed circumscribed hypoperfusions. In four patients, the SPECT lesion represented only structural defects. Circumscribed increased tracer uptake was observed in all ictal studies. For all patients with temporal lobe epilepsy without significant mass lesion, in whom an interictal and ictal ^{99m}Tc-ECD-SPECT study could be obtained, the asymmetry index was 0.88 ± 0.03 for the interictal and 1.23 ± 0.08 for the ictal studies. **Conclusion:** The data suggest that ^{99m}Tc-ECD is an effective marker of cerebral perfusion imaging in epilepsy. In comparison to other tracers, it has a high in vitro stability and is therefore particularly useful for ictal studies in the very early phase after seizure onset.

Key Words: technetium-99m-ECD; brain SPECT; epilepsy

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In the presurgical evaluation of patients suffering from refractory complex partial seizures, functional imaging with SPECT and PET plays an important role in foci localization (*1–7*). Interictal brain SPECT has a sensitivity in the range of 50–70% (*1,3,4,7*), whereas the sensitivity of ictal studies ranges between 65 and 97% (*3,5,6*). Hexamethyl propyleneamine oxime (HMPAO), labeled with ^{99m}Tc, has the advantage of very rapid brain uptake and high in vivo stability in brain tissue with no major redistribution. This is particularly important in all clinical applications with only short-lasting blood flow alterations, such as the ictal phase in partial epilepsy. The disadvantage of ^{99m}Tc-HMPAO in epilepsy diagnosis is its low in vitro stability. Methods for rapid preparation and injection have been described recently (*6*). Nevertheless, in most cases, several vials are required in order to perform a tracer injection within the first few seconds of a seizure. The need to reconstitute HMPAO immediately prior to use makes injection within the first few seconds of a seizure impossible in patients with low seizure frequency.

Technetium-99m-ethyl cysteinate dimer (ECD), also known as ^{99m}Tc-bicisate, is a new agent for cerebral blood flow imaging with SPECT. ECD has the advantages of high radiochemical stability and rapid washout from extracerebral tissue (*8,9*). This radiopharmaceutical has been proven to be suitable in cerebrovascular diseases (*10,11*) and has been commercially available in Europe since December 1993. This paper presents our first experiences with ^{99m}Tc-ECD in presurgical epilepsy diagnosis, which is in part covered by a clinical trial on ^{99m}Tc-ECD.

METHODS

Patients

All patients suffering from medically intractable epilepsy who were admitted for presurgical evaluation since December 1993 were included in the study. Clinical data of the patients are given in Table 1. Three patients had been operated on before and had persisting seizures. The protocol for the clinical trial was approved by the local ethical committee, and written informed consent was obtained from each patient. The trial included 23 studies on 16 patients, 8 were performed ictally and 15 interictally. All patients underwent intensive EEG and video monitoring and MR imaging (except one patient who could not be investigated because of metal clips). MRI (Philips GYROSCAN ACS II, 1.5 Tesla) was performed including transaxial proton- and T2-weighted SE-sequences using temporal angulation (parallel to the long axis of the temporal lobes) and coronal T1-weighted IR- and T2-weighted TSE-sequences.

Tracer Preparation and Injection

Neurolite^{R}, a kit for the preparation of ^{99m}Tc-bicisate (Du Pont Pharma, Bad Homburg, Germany or Dupharm APS, Kastrup, Denmark), was labeled according to the study protocol and product information. First, 2 ml of $^{99m}TcO_4^-$ (3.7 GBq) were added to the buffer vial and then 1 ml of the reconstituted lyophilized ligand vial was added and allowed to stand for 30 min. Radiochemical purity was controlled by thin-layer chromatography (TLC) and

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the kit was used if the purity was ≥90%. The administered dose was 590–770 MBq.

Additionally, radiochemical purity of the radiopharmaceutical was estimated again, with a modified solvent extraction method (*12*), after 24 hr in 16 cases and showed only minor changes (30 min after reconstitution: 94.9 ± 1.5%; 24 hr after reconstitution: 91.9 ± 2.5%). For the interictal studies, the tracer was injected in a seizure free patient. Such a patient had to be seizure free for at least 24 hr. The injections for the interictal studies were not performed under EEG monitoring. For the ictal studies, the radiopharmaceutical was administered under EEG monitoring via a prepared venous line within the first seconds after seizure onset. First clinical or EEG signs were defined as seizure onset. The delay between seizure onset and tracer injection was 2–20 sec. The duration of the seizures ranged between 20 sec and 3 min.

SPECT Technique and Evaluation

The patients, except Patient 5, were studied using an annular crystal camera (*13*). The detector consists of a stationary annular crystal/photomultiplier assembly. The only rotating part of the camera is the cylindrical collimator, which is divided into three parallel hole sections. The spatial resolution of this system is about 8 mm in the center of rotation. The axial field of view is 10.5 cm. (For further details see reference *13*.)

The acquisition was started not earlier than 30 min after tracer injection to allow a sufficient washout from extracerebral tissue. In some ictal studies, the delay was longer (up to 3 hr), because either the patients had to be brought from the EEG-monitoring unit to the nuclear medicine department or the camera was being used for other patients.

In five patients the acquisition of the ictal SPECT study was performed twice (41 ± 8 min delay) to measure the tracer washout from the hyperperfused areas and to compare it with washout values from other brain regions. The data of both SPECT studies were compared using a paired t-test (hyperperfused area versus total brain uptake).

The acquisition time was 30 min. Projections (120) were acquired using a 512 × 64 matrix (matrix of the crystal for three simultaneous projections). Two pulse-height analyzer windows were used, one for the photopeak (126 to 154 keV, and one for the scatter correction (112 to 126 keV). Scatter correction and back projection with a butterworth filter (cutoff frequency 0.9 cm) was performed. The transaxial slices (1.67 mm (1 pixel) thick) were attenuation corrected by Chang's method with an attenuation coefficient equal to 0.15 cm^{-1}. Coronal, sagittal and transaxial (parallel to the orbitomeatal line) slices were calculated from the original transaxial slices and summed in order to obtain 6.68 mm (4 pixel) thick slices. Additionally, thin slices of 1 pixel thickness and parallel to the long-axis of the temporal lobes were calculated for evaluation of the temporal lobes.

Initially, all images were evaluated visually by two readers who were blind to the clinical data, EEG findings or MRI, but were informed regarding whether the tracer was injected ictally or interictally. There were no discrepancies between the two readings.

All studies were quantified using a semiautomatic technique, developed by Pavics et al. (unpublished results, Fig. 1). The analysis was performed by a single blinded observer. Initially, 10 transaxial slices, parallel to the orbitomeatal line (5 pixels thick) were created. By an automatic contour-finding program the outline was defined by a 64-polygon line. The activity in the pixels within this border was ≥35% of the maximum of the whole

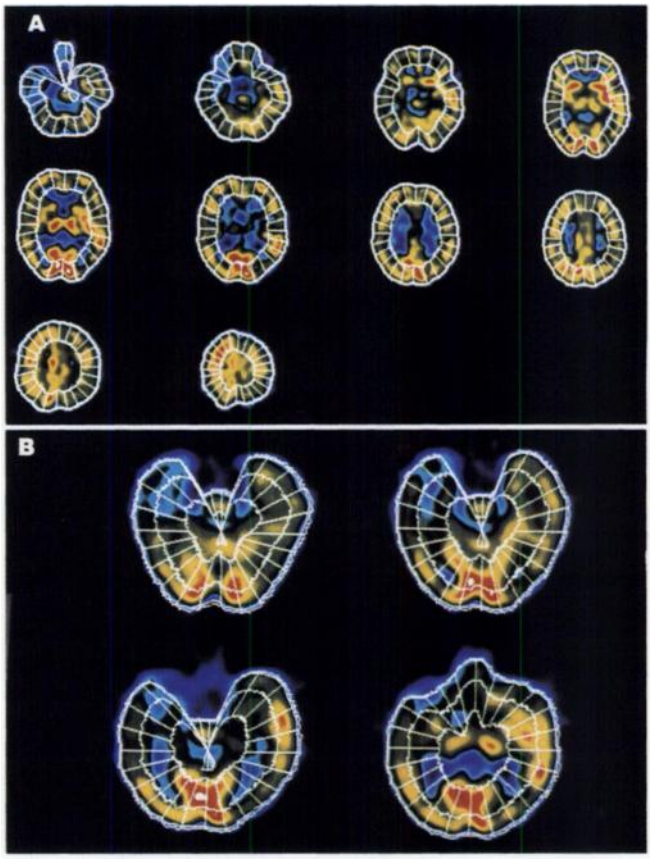

FIGURE 1. Automatic ROI positioning for the slices parallel to the orbitomeatal line (A) and the temporal lobes (B) using a 35% threshold for outline definition and a 17/10-pixel thick ring for cortical and temporolateral structures, (A, B) respectively, and a 14-pixel thick ring for the temporomesial structures (B).

SPECT study. A second polygon line was drawn in 17 pixels distance. The space between both polygon lines was divided into 24 parts (15-degree angles). Additionally, four slices parallel to the long axis of the temporal lobes were calculated (5 pixels thick). For the evaluation of these slices, again a 35% threshold outline was created and two additional lines were drawn in 10 and 24 pixels distances. Each ring was again divided into 24 parts. For all ictal and interictal studies, the asymmetry index (side of predominant EEG focus/contralateral side) was calculated for the ROIs covering the most marked SPECT lesion.

RESULTS

Visual Evaluation

The results are presented in Table 1. The ^{99m}Tc-HM-PAO-SPECT study of Patient 7 was not included for further analysis. In the interictal studies, circumscribed hypoperfusions were observed in all patients (Figs. 2 and 3). MRI/CT abnormalities were identified in 13 of these 16 patients and in 4 cases the lesions in the ^{99m}Tc-ECD SPECT represented the structural abnormality. In the other patients, the SPECT lesions were larger or the SPECT showed additional lesions. In 13 of 15 cases, the interictal SPECT result agreed with the EEG result.

In the ictal studies, all patients presented circumscribed increased tracer uptake (Figs. 2 and 3). In six of eight

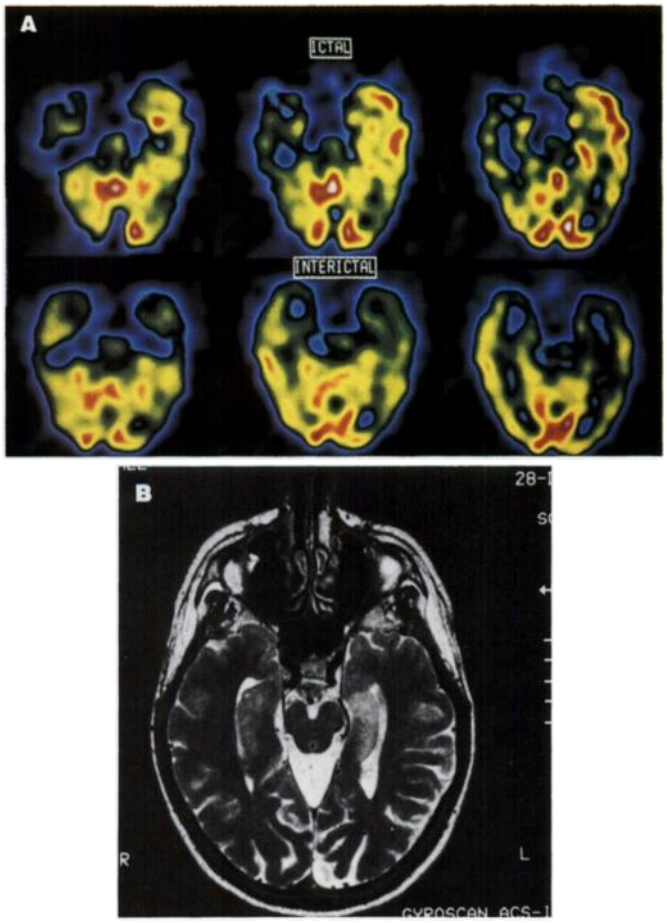

FIGURE 2. Interictal and ictal perfusion pattern in a 38-yr-old woman with bilateral EEG foci and suspected left temporal lobe sclerosis (Patient 9). The ^{99m}Tc-ECD-SPECT (A) (slices angulated parallel to the long-axis of the temporal lobes) shows decreased perfusion of the left temporal lobe interictally and markedly increased perfusion in the left temporolateral and temporopolar region and also a slightly increased perfusion in the mesial structures during the seizure. The MRI scan (B) (T2-weighted TSE-sequence, temporal angulation, slice thickness 2 mm/0.2 mm) shows an increased signal within the left hippocampus (typical sign of hippocampal sclerosis).

patients the results of the ictal SPECT agreed with EEG. In the remaining two patients, the ictal SPECT agreed with the ictal onset zone but showed additional hyperperfused zones.

Quantitative Analysis

In Table 1, the asymmetry index is given for the area which showed the most markedly decreased uptake in the interictal study and the most markedly increased tracer uptake in the ictal study during visual inspection. For all patients with temporal lobe epilepsy without significant mass lesion, in whom an interictal and ictal ^{99m}Tc-ECD SPECT study could be obtained (Patients 5, 6, 8, 9, 12), the asymmetry index was 0.88 ± 0.03 for the interictal and 1.23 ± 0.08 for the ictal study.

In the patients on whom the ictal study could be performed twice, the washout from the hyperperfused areas was slightly lower, but statistically significant, than from other brain areas. It was 8.9% ± 2.3% for the hyperperfused areas and 13.5% ± 1.6% for the total brain uptake ($p < 0.01$) (values uncorrected for physical decay).

DISCUSSION

The purpose of this study was to investigate if ^{99m}Tc-ECD is a suitable tracer for presurgical diagnostic assessment in epilepsy. We studied whether or not ^{99m}Tc-ECD shows interictally decreased and ictally increased uptake in the epileptic focus, as does ^{99m}Tc-HMPAO.

During presurgical evaluation of patients with medically intractable focal epilepsy, functional and morphological investigations have to be carried out in order to delineate the epileptogenic zone and to estimate the patient's outcome as to seizure frequency and memory function (*1–7,14–16*). PET and SPECT are able to contribute to the decision about surgical intervention, and are important particularly in cases with normal MRI/CT findings. During the course of evaluation, both methods can help to plan diagnostic steps, such as electrode positioning. In some patients, EEG recording with cortical or depth electrodes might become unnecessary if the SPECT/PET data show clear results and agree with other clinical data.

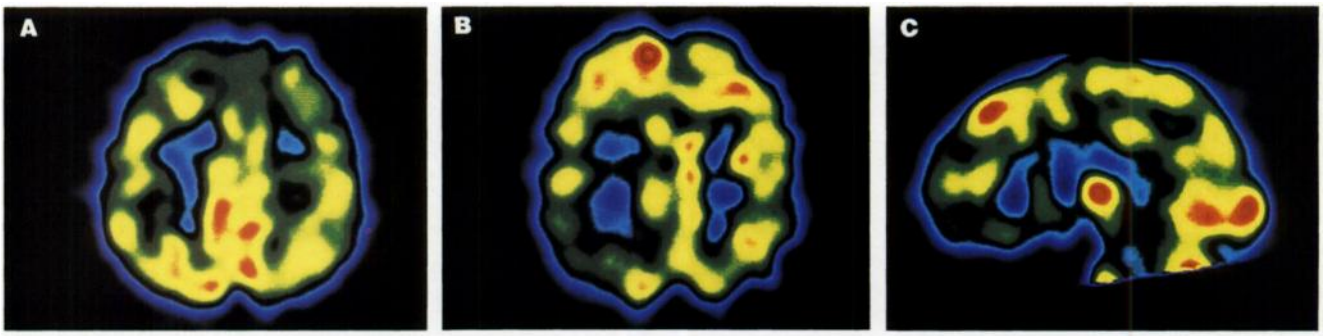

FIGURE 3. Interictal (A) and ictal (B, C) perfusion pattern in a 34-yr-old man with a suspected EEG focus in the right frontal lobe and normal MRI findings (Patient 4). The interictal study (A, transaxial slice) shows a mild hypoperfusion of both frontal lobes, more pronounced on the right side. The ictal study reveals a circumscribed increased tracer uptake in the right frontal lobe (B = transaxial slice; C = sagittal slice).

TABLE 1
Assymmetry Index of Interictal and Ictal Studies Showing the Most Marked Decreases and Increases in Uptake

Patient no.	Age/Sex	State	Delay after seizure onset	SPECT result	Asymmetry index	EEG focus	MRI
1	18/M	inter	—	L tempormesial/polar ↓	0.84	L temporal lobe	sclerosis L temporal lobe
2	29/F	inter	—	L frontal lobe ↓ (lesion)*	0.81	L frontal lobe	lesion L frontal lobe (postsurg.)
3	28/M	inter	—	R temporal lobe ↓	0.88	parietocentral	cavernoma R parietal lobe
4	34/M	inter	—	R frontal lobe ↓	0.93	R frontal lobe	normal
		ictal	6 sec	R frontal lobe ↑	1.15		
				and L occipital lobe	1.17		
5	34/F	inter	—	L temporal ↓	0.92	multiple foci;	normal
		ictal	3 sec	L temporolateral ↑	1.30	predominant	
				and R frontal lobe ↓	0.81	B frontotemporal	
6	28/M	inter	—	R temporal lobe ↓	0.87	R temporal lobe	normal
		ictal	2 sec	R temporolateral ↑	1.10		
7	28/F	inter	(^{99m}Tc-HMPAO)	L temporal lobe ↓ (lesion)*	0.47	L temporoparietal	CT: lesion L temporal lobe (postsurg.)
		ictal	5 sec	L frontotemporal ↑	1.22		
				L temporal lobe ↓ (lesion)*	0.37		
8	57/F	inter	—	R temporomesial ↓	0.87	R temporomesial	sclerosis R temporal lobe
		ictal	5 sec	R temporomesial/polar ↑	1.22		
9	38/F	inter	—	L temporal lobe ↓	0.87	B temporal lobes;	sclerosis L temporal lobe
		ictal	20 sec	L temporolateral/polar ↑	1.30	predominant L	
				R temporal lobe ↓	0.74	temporal lobe	
10	42/M	inter	—	R temporomesial/lateral ↓	0.89	L frontal lobe	cavernoma R temporal lobe
11	35/M	inter	—	L parietal lobe ↓ (lesion)*	0.49	L parietal lobe	cyst L parietal lobe
12	27/M	inter	—	L temporomesial ↓	0.91	L temporal lobe	sclerosis L temporal lobe + atrophy
		ictal	3 sec	L temporal lobe ↑	1.25		
				R frontoparietal ↑	1.13		
13	40/M	inter	—	L temporal lobe ↓ (lesion)*	0.75	L temporal lobe	cavernoma L temporopolar (postsurg.)
14	28/M	inter	—	L frontal lobe ↓ (lesion)*	0.56	L frontoorbital/	L frontal and (in part) temporal lobe:
				L temporal lobe ↓	0.77	L temporal	postencephalitic lesion
		ictal	2 sec	L temporomesial/polar ↑	1.23		
				L frontal lobe ↓ (lesion)*	0.64		
15	10/F	inter	—	L temporal lobe ↓	0.91	L temporal lobe	sclerosis L temporal lobe
16	34/F	inter	—	R temporal lobe ↓	0.93	R temporal lobe	R hippocampal atrophy

*Indicates that on ^{99m}Tc-ECD SPECT image the lesion represents only a morphological defect.

The sensitivity of interictal perfusion SPECT studies is about 50%–70%, depending on the radiopharmaceutical used and the spatial resolution of the acquisition system (*1,3,4,7*). Ictal studies with ^{99m}Tc-HMPAO are supposed to have a higher sensitivity of up to 97% (*1,6*) and are able to differentiate epileptic and nonepileptic seizures (*17,18*). The disadvantage of the true ictal investigations is the high logistic demand, since a staff member must stand next to the patient and a new vial of the radiopharmaceutical must be used every 30 min. This causes difficulties, particularly in patients with low seizure frequency, and increases costs. Recently, attempts have been made to stabilize ^{99m}Tc-HMPAO for longer than 30 min, such as by the addition of cobalt chloride hexahydrate (*19*). Alternatively postictal studies can be performed, but their sensitivity which seems to be higher than in interictal studies (*20*), decreases with the time lag between seizure end and injection (*1,20,21*). Technetium-99m Tc-ECD, however, has the advantage of

a high in vitro stability for up to 8 hr and has to be labeled only once for the preparation of an ictal study (*8*). The ^{99m}Tc-ECD brain uptake and retention curve is very similar to that of ^{99m}Tc-HMPAO (*22*).

Interictal PET has been proven to be more sensitive and specific in partial epilepsy than SPECT, due to better spatial resolution, quantification and the capability of measuring more parameters, such as glucose utilization. However, one advantage of SPECT is it allows freezing of cerebral perfusion patterns in ictal studies within seconds. This renders possible acquisition under resting conditions using ^{99m}Tc-HMPAO as tracer (*23*).

Technetium-99m-ECD proved to be a brain perfusion marker similar to ^{99m}Tc-HMPAO in many cases. Nevertheless, differences were demonstrated between both these radiopharmaceuticals in subacute stroke with luxury perfusion (*9,24*). This points out different retention mechanisms in the brain, at least in infarcted tissue. This characteristic of ^{99m}Tc-ECD might be useful to evaluate tissue viability in subacute infarction (*25*).

Whereas interictally decreased tracer uptake in the epileptic focus could be expected, the ictally increased uptake in the focus and its possible washout was particularly interesting in this study. In the patients examined twice in this study, the washout from the hyperperfused areas was significantly lower than the decrease of the total brain uptake. This observation might be due to methodological aspects. It also has been described by Walovitch et al. (*26*) for healthy volunteers in whom the washout calculated from small cortical regions is significantly lower than that from the whole brain. For clinical application, it is decisive that the image contrast (focus to other brain regions) in ictal studies is not decreasing further with time after tracer injection. Overall, the washout values were in the same range as reported by Leveille et al. (*9*) for healthy human subjects. In contrast, Pupi et al. (*27*) did not observe a significant tracer washout from the brain in patients affected by probable Alzheimer's disease or chronic cerebrovascular diseases.

All interictal studies showed focally decreased perfusion, 11 in the temporal, 2 in the frontal, 1 in the parietal, and 1 in frontal and temporal lobe.

All patients showed circumscribed hyperperfusions in the ictal state, the tracer injection being performed not longer than 20 sec after seizure onset. In 6 patients the increased uptake was observed in the temporal lobe, in 1 patient in the frontal lobe, and in 1 patient in the temporal and contralateral frontoparietal region. In 13 of 15 interictal studies and 6 of 8 ictal studies ^{99m}Tc-ECD-SPECT agreed with the EEG focus. If the results of both studies were evaluated using the criterion of circumscribed hyperperfusion in the ictal state and circumscribed hypoperfusion in the interictal state, the focus could be identified correctly by ^{99m}Tc-ECD-SPECT in 7 of 8 cases. The remaining patient had multiple foci in the EEG and data were inconclusive as to the depiction of the predominant zone of seizure origin.

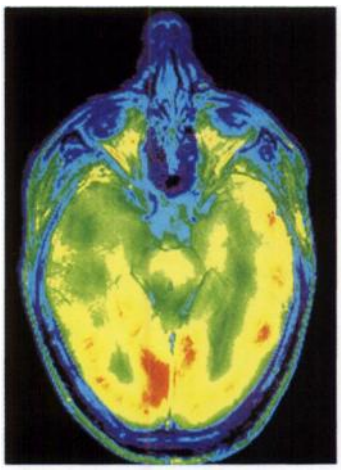

FIGURE 4. Superimposition of MRI and ^{99m}Tc-ECD-SPECT (slices angulated parallel to the long-axis of the temporal lobes).

Superimposition of MRI and SPECT (Fig. 4) renders better anatomical landmarking for functional lesions and allows a distinction between morphological and functional defects. Where both interictal and ictal studies are available, the evaluation of patients with morphological lesions is much easier. Decreased uptake in the interictal phase cannot be caused by only morphological alterations, if the ictal study shows a hyperperfusion in this area.

In those patients suffering from temporal lobe epilepsy, who did not show significant structural defects, the asymmetry index was 0.84–0.93 for the interictal studies, which is in the same range as reported by Rowe et al. for ^{99m}Tc-HMPAO and interictal studies (*3*). In the ictal studies, the asymmetry index in these patients was much higher (1.10–1.30), due to the high amount of blood flow increase during a short duration seizure.

CONCLUSION

Our first results show ^{99m}Tc-ECD to be a suitable radiopharmaceutical in the presurgical evaluation of patients suffering from partial epilepsy. Besides its rapid washout from extracerebral tissue, it has the advantage of high in vitro stability rendering possible tracer injection in the early ictal state. Particularly in patients suffering from frontal lobe epilepsy, in whom functional imaging has a higher rate of inconclusive results (*28*), a very rapid tracer injection is essential for a true ictal SPECT study (*29*). For the development of prepared devices which are linked to a seizure detection computer and allow for a rapid automatic tracer injection after seizure onset (*30*), a radiopharmaceutical with a high in vitro stability as ^{99m}Tc-ECD is essential.

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