Imaging of Cerebral Blood Flow with Technetium-99m-HMPAO and Technetium-99m-ECD: A Comparison

Susanne Asenbaum, Thomas Brücke, Walter Pirker, Uwe Pietrzyk and Ivo Podreka

Departments of Neurology and Nuclear Medicine, University of Vienna, Vienna; Neurological Department, K.A. Rudolfsstiftung, Vienna, Austria; and Max Planck Institute for Neurological Research, Cologne, Germany

Because ^{99m}Tc-HMPAO and ^{99m}Tc-ECD are both used for SPECT imaging of cerebral blood flow, the question arises whether there are any differences in their respective regional cerebral distribution. For that purpose, visual and semiquantitative comparisons between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD studies were performed. **Methods:** Seventeen patients (4 women; 13 men; age 45–89 yr; mean age 71 yr) with various neurological diseases, except acute/subacute stroke, were investigated twice with ^{99m}Tc-HMPAO and ^{99m}Tc-ECD using a triple-headed rotating SPECT camera. After image reorientation, the two studies were evaluated visually. Seventy regions of interest (ROIs) were drawn manually and the same set of ROIs was applied in both studies. Regional indices (RI) normalized to individual brain values were calculated and first compared between two random patient groups. Second, for all patients, RI for 70 and later for 27 regions (gained after summing values of corresponding regions in different brain slices) were compared by using a paired Student's t-test applying Bonferroni's correction. **Results:** Visual evaluation demonstrated relatively high ^{99m}Tc-ECD uptake in occipital and comparatively low uptake in mediotemporal regions. Calculation of RI revealed significantly higher values in the right cerebellum, brainstem, mediotemporal regions, right basal ganglia and the thalamus in the ^{99m}Tc-HMPAO SPECT studies and higher values in the occipital, supratemporal/inferior parietal and parietal cortex in the ^{99m}Tc-ECD SPECT studies, respectively. **Conclusion:** Significant differences in regional tracer distribution between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD could be detected, probably caused by different tracer kinetics. The results indicate that direct comparisons of studies performed with ^{99m}Tc-HMPAO and ^{99m}Tc-ECD are not possible and the use of either tracer can be favorable in different clinical questions.

Key Words: cerebral blood flow; technetium-99m-ECD; technetium-99m-HMPAO; SPECT

J Nucl Med 1998; 39:613–618

Over the past decade, several radiotracers for imaging cerebral blood flow (CBF) with SPECT have been developed, of which *d,l*-hexamethylpropyleneamine oxime (HMPAO) is most widely used (*1*). Later, another technetium-labeled blood flow tracer became available: ethyl cysteinate dimer (ECD, or bicisate) (*2,3*). It is thought that ECD has properties similar to HMPAO. Both tracers form a neutral complex with ^{99m}Tc and their distribution in the brain is proportional to CBF in a wide range (*4,5*). The tracer complexes are stable, lipophilic and of small size, they circulate with the blood to the brain and pass the blood-brain-barrier (BBB) rapidly. Intracellularly, the two tracers are metabolized and retained for a long time. Both tracers show a good extraction and retention rate (*6–9*).

ECD is transformed intracellularly by esterases from a diester into a diacid complex. This polar metabolite does not cross the cell membrane and therefore is trapped in the cell (*3,10*). The intracerebral distribution is similar to that of ^{14}C-iodoantipyrine (IAP) in monkeys (*3*). However in comparison to direct CBF measurements in primates using ^{14}C-IAP (*11*) and in humans using ^{133}Xe (*12,13*) or PET (*9,14,15*), ECD shows a nonlinear relationship to CBF. In high-flow areas, CBF is underestimated, while in low-flow areas, ECD uptake is comparatively high (*11,12*). ECD demonstrates a slow washout from brain that is independent of CBF and region (*5,16*) in addition to a negligible redistribution over 24 hr (*8*).

In contrast to ECD, a steric transformation of the HMPAO chelate linked to intracellular glutathione activity has been proposed (*7,17*), an influence of the redox state of the interstitial space has been discussed recently (*18*). Due to a CBF-dependent backdiffusion of unmetabolized lipophilic HMPAO from brain to the blood, poor image contrast between normal and hypoperfused areas (*19*) and underestimation of CBF in high flow regions (*20*) has been described. An algorithm has been proposed by Lassen et al. (*7*) for the correction of underestimated CBF values. A minimal and negligible redistribution has also been noted (*6,21*).

Technetium-99m-ECD is claimed to have at least two advantages in comparison to ^{99m}Tc-HMPAO: better in vitro stability (*1,16,22*) and rapid clearance from extracerebral tissue. This results in more favorable dosimetry (*23*) and a better brain-to-background ratio than ^{99m}Tc-HMPAO, therefore leading to better image quality (*3,16*). Previous reports, comparing SPECT investigations with ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in healthy volunteers (*22,23*) or patients (*14,24,25*), demonstrated a superior image quality for ^{99m}Tc-ECD.

Because both ^{99m}Tc-ECD and ^{99m}Tc-HMPAO are proposed as CBF tracers and several nuclear medicine departments worldwide use them in routine clinical practice, the question arose whether these two "flow" tracers really give comparable results. Because the regional distribution of the two tracers appeared not to be identical, we decided to compare ^{99m}Tc-ECD and ^{99m}Tc-HMPAO brain distribution in the same subject and initiated a comparative study, which is presented here.

MATERIALS AND METHODS

Patients

Seventeen patients (4 women, 13 men; age 45–89 yr; mean age 71 yr) with different neurological disorders except acute/subacute stroke were investigated twice with ^{99m}Tc-ECD and ^{99m}Tc-HMPAO. The two SPECT studies were performed within an interval of 2–21 days (mean 6.7 days). Between the two SPECT studies, no additional clinical symptoms developed. Hematocrit was also controlled both times and no significant differences were found (39.0% versus 38.1%).

Clinical data for the patients are listed in Table 1. Patients who had suffered neurological deficits attributable to the territory of the

Received Jan. 3, 1997; revision accepted Jul. 3, 1997.

For correspondence or reprints contact: Susanne Asenbaum, MD, PhD, Department of Neurology, University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria.

TABLE 1
Clinical Data

Patient no.	Age (yr)	Sex	Diagnosis	Time	cCT	SPECT	Delay (day)
1	65	M	Stroke, HP right	3.5 wk	Part MCA left	Vast hypoperfusion left, perfusion defect left temp.par	4
2	68	M	Stroke, HP right	3 wk	Basal ganglia left	Vast hypoperfusion left	5
3	72	M	Vertigo	7 yr	Normal	Frontal atrophy	2
4	83	F	Stroke, HP left	3 wk	Leukoaraiosis	Supratemporal right	8
5	80	M	CVD	3 wk	Leukoaraiosis	Cortical atrophy	4
6	73	M	CVD, ataxia	4 wk	Lacunar infarct, cerebral atrophy	Frontal, temporal right, cerebellum right	7
7	45	M	CPR	4 wk	Cerebral atrophy	Diffuse cortical hypoperfusion	2
8	61	F	Epilepsy	Since childhood	Small gliosis left parietal	Normal	14
9	63	M	Stroke, HP left	3 wk	Parietal right	Perfusion defect right tem.par	4
10	80	F	CVD	2 yr	Leukoaraiosis	Frontal atrophy	3
11	84	M	Stroke, HP left	3.5 wk	Lacunar infarct	Basal ganglia right, frontal and parietal left in HMPAO study	3
12	60	M	CPR	4.5 wk	Age corresponding	Diffuse cortical hypoperfusion	13
13	89	M	CVD	8 yr	Cerebral atrophy	Frontal atrophy	3
14	61	M	CHI	5 wk	Frontobasal Contusions	Defect frontobasal left+right	21
15	65	F	Stroke, HP right	3 yr	Part. MCA infarct left	Vast hypoperfusion left	2
16	77	M	CVD, HP left	0.5 yr	Part. MCA infarct right	Frontal right	6
17	76	M	Stroke, HP left	0.5 yr	Temporal right, cerebral atrophy	Vast hypoperfusion right	13

Time = time since disease onset; cCT = cerebral transmission computed tomography; HP = hemiparesis; delay = days between the two investigations; temp.par = temporoparietal; CVD = cerebrovascular disease; CPR = cardiopulmonary resuscitation; CHI = closed-head injury; part. = partial; MCA = middle cerebral artery.

middle cerebral artery at least 3 wk before the first study were classified as "stroke" (Patients 1, 2, 4, 9, 11, 15 and 17). Patients with "cerebrovascular disease" had memory deficits of vascular origin or frontal gait disorders (Patients 5, 6, 10, 13 and 16). The diagnosis was based on clinical history, neurological examination and the results of transmission CT and MRI, respectively. For the patient with epilepsy (Patient 8), the SPECT studies were performed more than 1 wk after the last seizure. At the time of tracer administration, there were no symptoms indicating epileptic activity. Patients 7 and 12 had been resuscitated after cardiac arrest more than 4 wk before the SPECT investigations, and Patient 14 was investigated 5 wk after a closed-head injury.

The study was approved by the local ethics committee and informed consent was obtained from each patient.

SPECT Imaging

SPECT studies were performed in a light- and sound-shielded room. After blockade of thyroid uptake by administration of 500 mg sodium perchlorate, patients were placed in a supine position and advised to close their eyes. Technetium-99m-HMPAO and ^{99m}Tc-ECD were prepared according to the manufacturer's recommendation and administered in random order on different days. Radiochemical purity, estimated by octanol extraction of the lipophilic fraction, was 78%–90% for ^{99m}Tc-HMPAO and 84%–92% for ^{99m}Tc-ECD.

Patients received a mean dose of 691 (±98) MBq of ^{99m}Tc-HMPAO and 581 (±82) MBq of ^{99m}Tc-ECD intravenously as a bolus. After tracer administration, data acquisition for the ^{99m}Tc-HMPAO study was started at least 10 min (mean 40 min) later and at least 60 min (mean 80 min) later for the ^{99m}Tc-ECD study, in accordance with the manufacturer's recommendation, to await the prolonged stable period of slow ^{99m}Tc-ECD clearance (*12,25*).

SPECT studies were performed with a triple-headed rotating scintillation camera (FWHM 9 mm) (Siemens Multispect 3, Des Plaines, IL) equipped with UHRES collimators and a dedicated computer system. Data acquisition lasted for 25 min (25 sec per frame, 180 frames in step-and-shoot mode). After prereconstructional filtering 3.5-mm thick cross-sections were reconstructed parallel to the canto-meatal plane by filtered backprojection in 128 × 128 matrices using a Butterworth filter (cutoff frequency 0.9, order 7). Attenuation correction (Chang's method) was then performed by using a uniform attenuation coefficient of 0.12/cm.

To compare the corresponding cerebral structures in the two SPECT studies, the data were transferred to a SUN SPARK 10 workstation (Hamilton Computer AG, Bülach, Switzerland). Images were then precisely reoriented using an appropriate computer program (*26*). Subsequently consecutive summation of three adjacent cross-sections gave a set of overlapping 10.5-mm thick slices for further evaluation. Visual analysis of clinically relevant signs was performed by two of the authors.

Eight adjacent slices covering the whole brain were chosen and regions of interest (ROIs) were drawn manually for the ^{99m}Tc-HMPAO study over one hemisphere. This set of ROIs was mirrored to the contralateral side. Only in few cases minor adjustments were necessary. Seventy infra- and supratentorial ROIs were obtained by this procedure (Fig. 1). Identical sets of ROIs were transferred to the ^{99m}Tc-ECD study images.

To assess the regional distribution of both tracers, relative regional values normalized to individual whole brain values were obtained for both studies (regional index (RI): mean counts/voxel of one ROI/counts/voxel of all ROI).

For statistical evaluation, three approaches were chosen. First, we evaluated differences in tracer deposition between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in nine subjects (number 1–9). Based on the statistical results obtained, which showed significant differences in 38 ROIs, we formulated the hypothesis that ^{99m}Tc-HMPAO has a relatively higher retention than ^{99m}Tc-ECD in the cerebellum, brainstem, mediotemporal cortex and thalamus. In the supratemporal/inferior parietal cortex, the parietal lobe and occipital region, the opposite occurs with higher relative ^{99m}Tc-ECD uptake. To conform our hypothesis, an additional group of eight patients (Patients 10–18) was investigated using the same protocol and was compared with the first group. Second, we pooled the data of all 17 patients and evaluated relative tracer uptake in all 70 ROIs. Finally, we reduced the number of ROIs by summing the data of corresponding cerebral regions in adjacent slices to diminish the

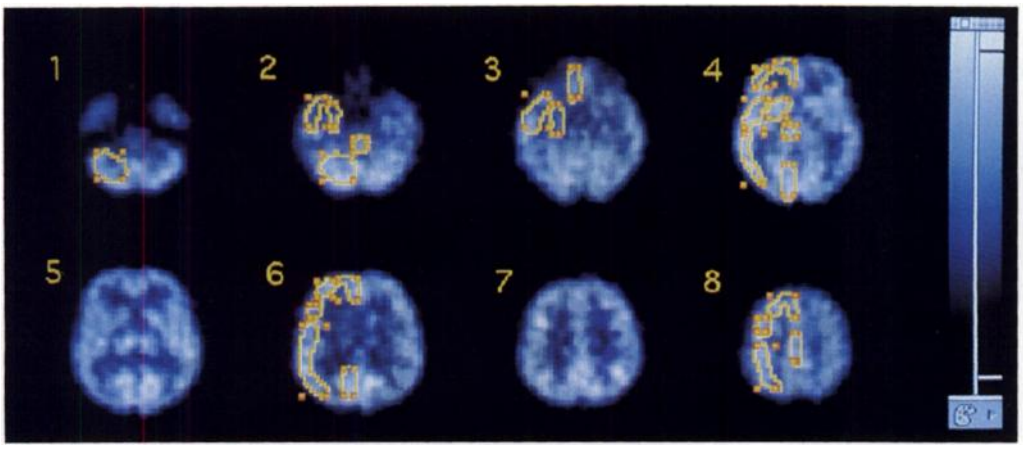

FIGURE 1. ROI: slice 1 = cerebellum I; slice 2 = laterotemporal I, mediotemporal I, cerebellum II, brainstem, slice 3= mediofrontal-frontobasal, laterotemporal II, mediotemporal II; slice 4 and slice 5 = mediofrontal I + II, inferior frontal I + II, insula I + II, supratemporal/inferior parietal I + II, occipital I + II, basal ganglia I + II, thalamus I + II; slice 6 and slice 7 = mediofrontal III + IV, laterofrontal I + II, central I + II, parietal I + II, parieto-occipital I + II; slice 8 = superior frontal, superior central, superior parietal, midline.

possibility of casually occurring significant results by obtaining 27 ROIs for comparison. In patients with the diagnosis of "stroke" (n = 7), an asymmetry index (AI) was also calculated in both studies (AI=[(mean counts/voxel of ROI of affected side minus mean counts/voxel of ROI of unaffected side)/(mean counts/voxel of ROI of affected side plus mean counts/voxel of ROI of unaffected side)/2]x100).

Corresponding RI and AI obtained in the two SPECT studies were compared using a paired Student's t-test (two-tailed) and, except for the first step and calculations of the AI ($p < 0.05$), the level of significance was adjusted by applying Bonferroni's correction for multiple comparisons.

RESULTS

Visual Evaluation

Visual evaluation of the ^{99m}Tc-HMPAO and ^{99m}Tc-ECD studies revealed excellent agreement between clinical symptoms and both SPECT studies in patients with stroke and cerebrovascular disease, respectively. Except in one patient (Patient 11), no essentially new information could be obtained by comparing both tracers. However, in all ^{99m}Tc-ECD studies, different tissue compartments (extracerebral tissue, gray and white matter) were better delineated due to a higher contrast. Well-demarcated perfusion defects (Patients 1, 9 and 14) showed clearer contrast to normal brain tissue in the ^{99m}Tc-ECD study and therefore appeared smaller. In two patients (Patients 2 and 3), a difference between frontal and parietal tracer uptake in favor of the latter was only visible on the ^{99m}Tc-ECD SPECT studies. Clearly, higher tracer uptake of ^{99m}Tc-ECD was observed in the occipital region in six instances (Patients 1, 2, 3, 5, 11 and 12). A striking uptake difference for both tracers was also seen in the medial temporal lobe (Patients 1, 2, 3, 5, 11, 12, 14, 15 and 16) (Fig. 2). No signs of focal hyperperfusion were evident in the ^{99m}Tc-HMPAO studies.

Semiquantitative Evaluation

After a comparison of the two patient groups (Patients 1–9 versus 10–18) in the first evaluation step, corresponding results were obtained in 44 ROIs showing significantly different RIs of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in 17 of these ROIs: for example in the right cerebellum, brainstem, in two of four mediotemporal, mediofrontal-frontobasal and thalamic regions for ^{99m}Tc-HMPAO, and in all four occipital and two of four supratemporal/inferior parietal regions for ^{99m}Tc-ECD. As the

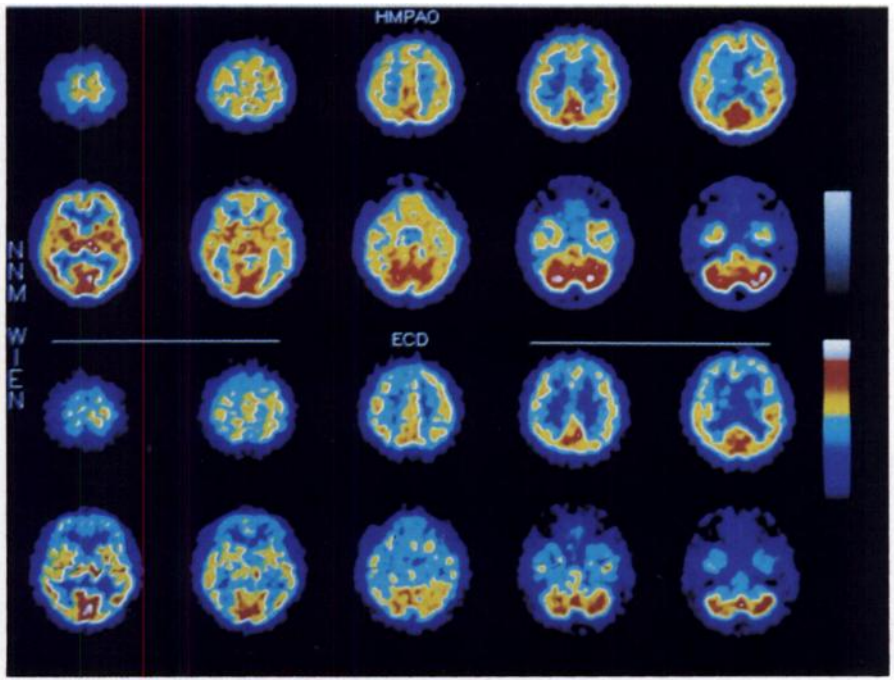

FIGURE 2. Row 1 + 2: ^{99m}Tc-HMPAO SPECT study (Patient 6); Row 3 + 4: ^{99m}Tc-ECD SPECT study of the same subject. Both studies are scaled to their own maximum. In contrast to the ^{99m}Tc-HMPAO SPECT study, ^{99m}Tc-ECD demonstrates relatively high tracer uptake in the occipital cortex and comparatively low tracer uptake in the mediotemporal regions, basal ganglia and thalamus, respectively.

TABLE 2
Technetium-99m-HMPAO Versus Technetium-99m-ECD: Significant Differences of Regional Index After Bonferroni's Correction Calculated for 70 ROIs

Region	t value	p value
Cerebellum I right	4.12	0.0008
Mediotemporal I left	5.09	0.0001
Mediotemporal II left	4.10	0.0008
Mediofrontal-frontobasal left	5.33	0.0001
Thalamus I right	7.58	0.0001
Thalamus I left	4.33	0.0005
Thalamus II right	4.65	0.0003
Occipital I left	−4.08	0.0008
Occipital II right	−4.79	0.0002
Occipital II left	−5.07	0.0001
Supratemporal/inf.par II right	−4.76	0.0002
Supratemporal/inf.par II left	−4.97	0.0001
Basal ganglia II right	5.2	0.0001
Superior central left	−4.74	0.0002
Brainstem	5.59	0.0001

inf.par = inferior parietal.

TABLE 3
Technetium-99m-HMPAO Versus Technetium-99m-ECD: Significant Differences of Regional Index Calculated for 27 Summed ROIs

Region	t value	Original p value	Significant after Bonferroni's correction
Cerebellum			
Right	4.18	0.0007	*
Left	2.86	0.011	
Brainstem	5.6	0.0001	*
Laterotemporal			
Right	2.21	0.042	
Left	1.84	0.084	
Mediotemporal			
Right	3.95	0.0011	*
Left	4.91	0.0002	*
Mediofrontal-frontobasal			
Right	2.7	0.0159	
Left	6.12	0.0001	*
Supratemporal/inf.par			
Right	−4.62	0.0003	*
Left	−4.93	0.0001	*
Occipital			
Right	−3.6	0.002	*
Left	−4.35	0.0005	*
Basal ganglia			
Right	5.12	0.0001	*
Left	1.76	0.09	
Thalamus			
Right	8.4	0.0001	*
Left	5.63	0.0001	*
Laterofrontal			
Right	−.004	0.99	
Left	−.83	0.42	
Central			
Right	−2.84	0.012	
Left	−2.59	0.02	
Superior frontal			
Right	−.33	0.75	
Left	−2.5	0.024	
Parietal			
Right	−3.92	0.001	*
Left	−4.98	0.0001	*
Superior parietal			
Right	−3.77	0.0017	*
Left	−6.28	0.0001	*

*Regions with significant t values.
inf.par = inferior parietal.

previously formulated hypothesis was confirmed to a great extent, data of all 18 patients and 70 ROIs were calculated together. The results of this second step are listed in Table 2, which also support this hypothesis.

Calculating a regional index for the 27 ROIs in the ^{99m}Tc-HMPAO and ^{99m}Tc-ECD SPECT studies, significant differences could be obtained in 16 areas supporting the aforementioned hypothesis of regional discrepancies in tracer deposition. Detailed results are listed in Table 3. In the right cerebellum, brainstem, mediotemporal cortex and thalamus on both sides, left-sided mediofrontal-frontobasal cortex and right basal ganglia, a significant higher RI in the ^{99m}Tc-HMPAO investigation was evident, whereas in the supratemporal/inferior parietal and occipital ROIs on both sides and in all four parietal regions, a higher RI was found in the ^{99m}Tc-ECD study.

An analysis of the AI revealed significant differences for the cerebellum (t = 3.05) and the parietal cortex (t = 4.32) with higher values in the ^{99m}Tc-ECD study.

DISCUSSION

ECD and HMPAO have been proposed as blood flow tracers with similar qualities for imaging cerebral perfusion. However, different uptake properties have been reported in acute stroke exhibiting "luxury perfusion," which in contrast to ^{99m}Tc-HMPAO was not shown by ^{99m}Tc-ECD (*5,14,15,27*). Together with the known different trapping mechanisms of both radioligands, which are responsible for tissue uptake, it is now postulated that ^{99m}Tc-ECD provides not only information on CBF but also on tissue metabolism. In addition, different cerebral uptake kinetics have been described (*8,28*). Therefore, the question arises whether the regional distribution of ECD in patients with chronic cerebral diseases can be compared unconditionally to that of HMPAO.

Only a few SPECT studies have been performed that directly compare ^{99m}Tc-HMPAO and ^{99m}Tc-ECD. In a study of healthy volunteers, Leveille et al. (*22*) and Demonceau et al. (*23*) noted superior image quality of ^{99m}Tc-ECD, but no regional analyses were made. Matsuda et al. (*24*) also emphasized the superiority of ^{99m}Tc-ECD over ^{99m}Tc-HMPAO in terms of lesion detection and contrast in patients with chronic cerebrovascular disease. In a comparison of ^{99m}Tc-HMPAO and ^{99m}Tc-ECD in Alzheimer's disease, Van Dyck et al. (*25*) reported greater contrast between affected and unaffected areas in the ^{99m}Tc-ECD study.

In this study, visual analysis of ^{99m}Tc-HMPAO and ^{99m}Tc-ECD images revealed no major differences concerning the detection of brain tissue lesions and hypoperfused regions. Both tracers demonstrated high sensitivity in imaging clinically relevant areas with impaired perfusion in stroke patients. Due to rapid extracerebral washout, better background-to-brain ratios were evident with ^{99m}Tc-ECD, which results in improved image contrast. Furthermore, ^{99m}Tc-ECD gave a higher lesion-to-normal tissue ratio compared to ^{99m}Tc-HMPAO. Similar observations have been made comparing ^{99m}Tc-ECD with ^{123}I-IMP (*29*). Gray-to-white matter differences were more pronounced with ^{99m}Tc-ECD. These findings are in agreement with previously published data (*14,22–24*) and have been explained by relatively larger, CBF-dependent backdiffusion of

unmetabolized ^{99m}Tc-HMPAO in comparison with ^{99m}Tc-ECD (*20,28*).

When the two SPECT studies were evaluated semiquantitatively by calculating a regional index with normalization to whole brain uptake, significant differences in relative tracer distribution became evident. The most striking difference was obtained in the parietal and occipital regions, which exhibited significantly higher ^{99m}Tc-ECD uptake when compared to ^{99m}Tc-HMPAO. On the other hand, ^{99m}Tc-HMPAO was trapped in a significantly higher proportion than ^{99m}Tc-ECD in mediotemporal areas. This was not only proven by calculation, but had already been indicated by prior visual analysis. Such a pattern of distribution with preferential uptake in occipital and parietal areas using ^{99m}Tc-ECD had been mentioned previously. Leveille et al. (*16*) and Pupi et al. (*30*) described the highest ^{99m}Tc-ECD uptake in the occipital regions. In a study of the distribution pattern of ^{99m}Tc-ECD and ^{14}C-IAP in monkeys, Walovitch et al. (*3*) did not find significant differences, but a relatively higher ^{99m}Tc-ECD uptake than ^{14}C-IAP binding was evident in the occipital cortex. In a direct comparison of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO, Huglo et al. (*31*) found higher uptake indices of ^{99m}Tc-ECD in the occipital and parietal areas. After comparing regional ^{99m}Tc-ECD distribution with CBF data obtained with ^{133}Xe, Huglo et al. (*13*) reported the highest relative ^{99m}Tc-ECD uptake in the occipital cortex followed by the parietal and anterior frontal cortices. Furthermore, significantly lower ^{99m}Tc-ECD uptake indices were observed for the temporal cortex in comparison with CBF values calculated from ^{133}Xe washout.

The relatively lower ^{99m}Tc-ECD uptake indices in the thalamic areas, as demonstrated in this study, parallel the observations of Huglo et al. (*13,31*), who described a significantly lower thalamic index for ^{99m}Tc-ECD in comparison with ^{99m}Tc-HMPAO (*31*) or ^{133}Xe (*13*). On the other hand, Heiss et al. (*32*) reported on a relatively high ^{99m}Tc-HMPAO uptake in the striatum and thalamus compared with CBF values obtained with ^{18}F-fluoromethane. Similar to our findings, high cerebellar ^{99m}Tc-HMPAO uptake which overestimated CBF in relation to forebrain values also was derived. Heiss et al. (*32*) explained their observation of a relatively high cerebellar ^{99m}Tc-HMPAO uptake to the higher capillary density in the cerebellum. In contrast to these findings, Devous et al. (*12*) reported substantial agreement between ^{99m}Tc-ECD and ^{133}Xe in regional tracer distribution.

The calculation of an AI in patients with stroke showed higher values in the ^{99m}Tc-ECD study in the parietal regions and the cerebellum. For parietal areas, these findings could be explained by the reported higher lesion-to-normal tissue ratio in a previous study (*29*) as well as in this study, because the parietal cortex was the most affected area. Huglo et al. (*13,31*) found a strong correlation of the AI between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO SPECT, respectively, and the ^{133}Xe study. However, they noted a higher asymmetry in ischemic areas in the ^{99m}Tc-ECD SPECT images. Matsuda et al. (*24*) also described a higher AI for detected lesions in patients after stroke in the ^{99m}Tc-ECD than in the ^{99m}Tc-HMPAO study. The different AI of cerebellar areas in the present investigation may be related to relatively more pronounced cerebellar diaschisis in ^{99m}Tc-ECD SPECT investigations.

An explanation of the differences in regional tracer uptake found in our study might be the different kinetic properties of ECD and HMPAO in normal subjects. Technetium-99m-ECD was reported to possess a higher overall retained fraction than ^{99m}Tc-HMPAO (*7,8,28*) with a lower, not CBF-dependent backdiffusion of the lipophilic complex (*5,15*). This is in contrast to ^{99m}Tc-HMPAO, which demonstrates a CBF-dependent backdiffusion (*7,20,28*). Both tracers underestimate true CBF in high-flow regions, but ^{99m}Tc-ECD was considered to fit CBF more closely than ^{99m}Tc-HMPAO (*8*). Accordingly, in another study, Orlandi et al. (*33*) described nonlinearity between ^{99m}Tc-ECD uptake and true CBF measured with radiolabeled microspheres at flow values above that of the cerebellum (i.e., in the caudate and thalamus). When they compared their data with a study of Yonekura et al. (*19*) who had used ^{99m}Tc-HMPAO SPECT and $C^{15}O_2$ PET, respectively, they concluded that the nonlinearity of ^{99m}Tc-HMPAO started at flow values of 50% of that of the cerebellum, which resulted in underestimation of CBF at already lower flow rates. Furthermore, for ^{99m}Tc-ECD, a lower conversion rate from lipophilic-to-hydrophilic tracer, but a higher relative intracellular fixation rate than ^{99m}Tc-HMPAO (*7,8*), a negligible hydrophilic-to-lipophilic conversion (*8*) but apparently existing backdiffusion of the hydrophilic complex (*8,9*) were found. On the other hand, the first-pass brain extraction of ^{99m}Tc-HMPAO was reported to be higher than that of ^{99m}Tc-ECD (*8,20,34*). However, differences of the kinetic properties of ECD and HMPAO are mostly determined by the CBF-dependent washout of HMPAO corresponding to a higher k_2 value of HMPAO (*7–9,28*). Discrepancies in regional distribution of ^{99m}Tc-HMPAO and ^{99m}Tc-ECD may therefore be due to the more pronounced washout of ^{99m}Tc-HMPAO in regions with relatively higher CBF (except the cerebellum) and the higher overall retained fraction of ^{99m}Tc-ECD, which might influence the regional RI to a different extent.

Other factors influencing cerebral uptake might be the different radiochemical purity of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO, which is lower for ^{99m}Tc-HMPAO (*23,34*) and influences first-pass extraction from blood to brain (*34*), as well as the different dosage of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO used in this study. Regionally varying conversion rates from lipophilic-to-hydrophilic components as proposed by Lear (*35*) for HMPAO, regionally different "membrane trapping" of ECD (*36*) due to changing proportions of membrane and cytosolic esterase activity (*10*), or different trapping mechanisms of the tracers in archicortical (mediotemporal structures) and neocortical brain tissue could theoretically account for differences in regional tracer uptake, especially in patients with brain diseases. Furthermore, an influence of the underlying neurological disease on the kinetic parameters cannot be excluded.

Summarizing a comparison of the regional distribution pattern of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in patients with various neurological disorders except acute/subacute stroke revealed significant differences in regional uptake values normalized to whole brain uptake. The relative ^{99m}Tc-ECD uptake was higher than that of ^{99m}Tc-HMPAO in the occipital and parietal regions and lower in the cerebellum, mediotemporal regions, basal ganglia and thalamus, respectively. These findings might be explained by a combination of the CBF-dependent washout of ^{99m}Tc-HMPAO in regions with relatively high CBF values and the higher overall retained fraction of ^{99m}Tc-ECD.

CONCLUSION

Technetium-99m-ECD and ^{99m}Tc-HMPAO are regarded as CBF tracers, although they have different cerebral retention mechanisms. The knowledge of different cerebral distribution patterns is therefore important for evaluation of SPECT studies in daily routine as these peculiarities have to be considered in visual analysis and make direct comparisons of semiquantitative measurements impossible. Furthermore, data obtained with both tracers in a certain condition cannot be pooled together for

scientific evaluation. The use of one of the two tracers might be of advantage in certain indications, as for instance, in temporal lobe epilepsy, ^{99m}Tc-HMPAO will be the more appropriate tracer due to the better visualization of mediotemporal regions. On the other hand, in acute stroke, ^{99m}Tc-ECD can clearly demonstrate hypoperfused areas (*27,37*). Due to the described differences, each nuclear medicine department should define its preference for one of the two tracers according to its main emphasis; or even use both of them for different well-specified neurological diseases. In addition, further studies have to be performed to explore the behavior of the two tracers in other acute diseases such as acute head injury, inflammatory diseases, brain tumors or epileptic seizures to provide further recommendations for choosing between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO.

REFERENCES

1. Neirinckx RD, Canning LR, Piper IM, et al. Technetium-99m d,l-HMPAO: a new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion. *J Nucl Med* 1987;28:191–202.
2. Cheeseman EH, Blanchette MA, Ganey MV, Maheu LJ, Miller SJ, Watson AD. Technetium-99m-ECD: ester-derivatized diaminedithiol Technetium complexes for imaging brain perfusion [Abstract]. *J Nucl Med* 1988;29(suppl):788.
3. Walovitch RC, Hill TC, Garrity ST, et al. Characterization of technetium-99m-*l,l*-ECD for brain perfusion imaging. Part 1: pharmacology of technetium-99m-ECD in nonhuman primates. *J Nucl Med* 1989;30:1892–1901.
4. Inugami A, Kanno I, Uemura K, et al. Linearization correction of ^{99m}Tc-labeled hexamethyl-propylene amine oxime (HM-PAO) image in term of regional CBF distribution: comparison of $C^{15}O_2$ inhalation steady-state method measured by positron emission tomography. *J Cereb Blood Flow Metab* 1988;8:S52–S60.
5. Shishido F, Uemura K, Murakami M, et al. Cerebral uptake of ^{99m}Tc-bicisate in patients with cerebrovascular disease in comparison with CBF and $CMRO_2$ measured by positron emission tomography. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S66–S75.
6. Lassen NA, Andersen AR, Friberg H, Neirinckx RD. Technetium-99m-d,l-HMPAO as a tracer of cerebral blood flow distribution: a kinetic analysis [Abstract]. *J Cereb Blood Flow Metab* 1987;7(suppl 1):S535.
7. Lassen NA, Andersen AR, Friberg L, Paulson OB. The retention of [^{99m}Tc]-d,l-HMPAO in the human brain after intracarotid bolus injection: a kinetic analysis. *J Cereb Blood Flow Metab* 1988;8:S13–S22.
8. Friberg L, Andersen AR, Lassen NA, Holm S, Dam M. Retention of ^{99m}Tc-Bicisate in the human brain after intracarotid injection. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S19–S27.
9. Ishizu K, Yonekura Y, Magata Y, et al. Extraction and retention of technetium-99m-ECD in human brain: dynamic SPECT and oxygen-15-water PET studies. *J Nucl Med* 1996;37:1600–1604.
10. Jacquier-Sarlin MR, Polla BS, Slosman DO. Cellular basis of ECD brain retention. *J Nucl Med* 1996;37:1694–1697.
11. Greenberg JH, Araki N, Karp A. Correlation between ^{99m}Tc-bicisate and regional CBF measured with iodo-[^{14}C]antipyrine in a primate focal ischemia model. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S36–S43.
12. Devous MD, Payne JK, Lowe JL, Leroy R. Comparison of technetium-99m-ECD to xenon-133 SPECT in normal controls and in patients with mild-to-moderate regional cerebral blood flow abnormalities. *J Nucl Med* 1993;4:754–761.
13. Huglo D, Rousseaux M, Leys D, Fialdes P, Steinling M. Regional cerebral blood flow imaging: a quantitative comparison of ^{99m}Tc-bicisate with ^{133}Xe using single-photon emission computed tomography. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S76–S83.
14. Tsuchida T, Nishizawa S, Yonekura Y, et al. SPECT images of technetium-99m-ethyl cysteinate dimer in cerebrovascular diseases: comparison with other cerebral perfusion tracers and PET. *J Nucl Med* 1994;35:27–31.
15. Yonekura Y, Tsuchida T, Sadato N, et al. Brain perfusion SPECT with ^{99m}Tc-bicisate: comparison with PET measurement and linearization based on permeability-surface area product model. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S58–S65.
16. Leveille J, Demonceau G, DeRoo M, et al. Characterization of technetium-99m-*l,l*-ECD for brain perfusion imaging. Part 2: biodistribution and brain imaging in humans. *J Nucl Med* 1989;30:1902–1920.
17. Neirinckx RD, Burke JF, Harrison RC, Forster AM, Anderson AR, Lassen NA. The retention mechanism of technetium-99m-HM-PAO: intracellular reaction with glutathione. *J Cereb Blood Flow Metab* 1988;8:S4–S12.
18. Jacquier-Sarlin MR, Polla BS, Slosman DO. Oxido-reductive state: the major determinant for cellular retention of ^{99m}Tc-HMPAO. *J Nucl Med* 1996;37:1413–1416.
19. Yonekura Y, Nishizawa S, Mukai T, et al. SPECT with ^{99m}Tc-d,l-hexamethyl-propylene amine oxime (HMPAO) compared with regional cerebral blood flow measured by PET: effects of linearization. *J Cereb Blood Flow Metab* 1988;8:S82–S89.
20. Andersen AR, Friberg HH, Schmidt JF, et al. Quantitative measurements of cerebral blood flow using SPECT and ^{99m}Tc-d,l-HM-PAO compared to xenon-133. *J Cereb Blood Flow Metab* 1988;8:S69–S81.
21. Sharp PF, Smith FW, Gemmell HG, et al. Technetium-99m-HMPAO stereoisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies. *J Nucl Med* 1986;27:171–177.
22. Leveille J, Demonceau G, Walovitch RC. Intrasubject comparison between technetium-99m-ECD and technetium-99m-HMPAO in healthy human subjects. *J Nucl Med* 1992;33:480–484.
23. Demonceau G, Leveille J, De Roo M, et al. Comparison of Tc-99m-ECD and Tc-99m-HMPAO: first human results. *J Nucl Med* 1988;29:747.
24. Matsuda H, Li YM, Higashi S, et al. Comparative SPECT study of stroke using Tc-99m ECD, I-123 IMP and Tc-99m HMPAO. *Clin Nucl Med* 1993;18:754–758.
25. Van Dyck CH, Lin CH, Smith EO, et al. Comparison of technetium-99m-HMPAO and technetium-99m-ECD cerebral SPECT images in Alzheimer's disease. *J Nucl Med* 1996;37:1749–1755.
26. Pietrzyk U, Herholz K, Fink G, et al. An interactive technique for three-dimensional image registration: validation for PET, SPECT, MRI and CT brain studies. *J Nucl Med* 1994;35:2011–2018.
27. Lassen NA, Sperling B. Technetium-99m-bicisate reliably images CBF in chronic brain disease but fails to show reflow hyperemia in subacute stroke: report of a multicenter trial of 105 cases comparing ^{133}Xe and ^{99m}Tc-bicisate (ECD, Neurolite) measured by SPECT on same day. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S44–S48.
28. Murase K, Tanada S, Inoue T, et al. Kinetic behavior of Tc-99m-ECD in the human brain using compartment analysis and dynamic SPECT: comparison with ^{99m}Tc-HMPAO. [Abstract]. *J Nucl Med* 1992;33(suppl):909.
29. Moretti J-L, Defer G, Tamgac F, Weinmann P, Belin C, Cesaro P. Comparison of brain SPECT using ^{99m}Tc-bicisate (L,L-ECD) and [^{123}I]IMP in cortical and subcortical strokes. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S84–90.
30. Pupi A, De Cristofaro MTR, Passeri A, et al. Quantification of brain perfusion with ^{99m}Tc-bicisate and single SPECT scan: comparison with microsphere measurements. *J Cereb Blood Flow Metab* 1994;14(suppl 1):S28–S35.
31. Huglo D, Rousseaux M, Amegassi F, Steinling M. Quantitative comparison of ^{99m}Tc-ECD cerebral uptake with ^{99m}Tc-HMPAO using single-photon emission computed tomography. *Eur J Nucl Med* 1992;19:731.
32. Heiss WD, Herholz K, Podreka I, Neubauer I, Pietrzyk U. Comparison of [^{99m}Tc]HMPAO SPECT with [^{18}F]fluoromethane PET in cerebrovascular disease. *J Cereb Blood Flow Metab* 1990;10:687–697.
33. Orlandi C, Crane PD, Platts SH, Walovitch RC. Regional cerebral blood flow and distribution of [^{99m}Tc]ethyl cysteinate dimer in nonhumans primates. *Stroke* 1990;21:1059–1063.
34. Matsuda H, Yagishita A, Tsuji S, Hisada K. A quantitative approach to technetium-99m ethyl cysteinate dimer: a comparison with technetium-99m hexamethylpropylene amine oxime. *Eur J Nucl Med* 1995;22:633–637.
35. Lear JL. Initial cerebral HM-PAO distribution compared to LCBF: use of a model which considers cerebral HM-PAO trapping kinetics. *J Cereb Blood Flow Metab* 1988;8:S31–S37.
36. Walovitch RC, Franceschi M, Picard M, et al. Metabolism of ^{99m}Tc-L,L-ethyl cysteinate dimer in healthy volunteers. *Neuropharmacology* 1991;30:283–292.
37. Moretti JL, Caglar M, Weinmann P. Cerebral perfusion imaging tracers for SPECT: which one to choose? *J Nucl Med* 1995;36:359–363.