Different uptake of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in the same brains: analysis by statistical parametric mapping

In Young Hyun[1], Jae Sung Lee[2], Joung Ho Rha[3], Il Keun Lee[3], Choong Kun Ha[3], Dong Soo Lee[2]

[1] Department of Nuclear Medicine, Inha University College of Medicine, Incheon, Korea
[2] Department of Nuclear Medicine, Seoul National University College of Medicine, 28 Yungundong Chongnogu, Seoul 110-744 Korea
[3] Department of Neurology, Inha University College of Medicine, Incheon, Korea

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Abstract. The purpose of this study was to investigate the differences between technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) and technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) uptake in the same brains by means of statistical parametric mapping (SPM) analysis. We examined 20 patients (9 male, 11 female, mean age 62±12 years) using ^{99m}Tc-ECD and ^{99m}Tc-HMPAO single-photon emission tomography (SPET) and magnetic resonance imaging (MRI) of the brain less than 7 days after onset of stroke. MRI showed no cortical infarctions. Infarctions in the pons (6 patients) and medulla (1), ischaemic periventricular white matter lesions (13) and lacunar infarction (7) were found on MRI. Split-dose and sequential SPET techniques were used for ^{99m}Tc-ECD and ^{99m}Tc-HMPAO brain SPET, without repositioning of the patient. All of the SPET images were spatially transformed to standard space, smoothed and globally normalized. The differences between the ^{99m}Tc-ECD and ^{99m}Tc-HMPAO SPET images were statistically analysed using statistical parametric mapping (SPM) 96 software. The difference between two groups was considered significant at a threshold of uncorrected *P* values less than 0.01. Visual analysis showed no hypoperfused areas on either ^{99m}Tc-ECD or ^{99m}Tc-HMPAO SPET images. SPM analysis revealed significantly different uptake of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in the same brains. On the ^{99m}Tc-ECD SPET images, relatively higher uptake was observed in the frontal, parietal and occipital lobes, in the left superior temporal lobe and in the superior region of the cerebellum. On the ^{99m}Tc-HMPAO SPET images, relatively higher uptake was observed in the medial temporal lobes, thalami, periventricular white matter and brain stem. These differences in uptake of the two tracers in the same brains on SPM analysis suggest that interpretation of cerebral perfusion is possible using SPET with ^{99m}Tc-ECD and ^{99m}Tc-HMPAO.

Keywords: ^{99m}Tc-ECD – ^{99m}Tc-HMPAO – Brain SPET – Statistical parametric mapping

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Dong Soo Lee (✉)
Department of Nuclear Medicine,
Seoul National University College of Medicine,
28 Yungundong Chongnogu, Seoul 110-744 Korea
e-mail: dsl@plaza.snu.ac.kr
Tel.: +82-2-7602501, Fax: +82-2-7669083

Introduction

Technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD), a relatively new tracer for brain single-photon emission tomography (SPET) imaging, is a marker of regional cerebral blood flow (rCBF) [1, 2] and is increasingly being used in the diagnosis of various clinical diseases [3, 4, 5]. Many investigators have compared the differences between ^{99m}Tc-ECD and ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) from the point of view of image quality and pharmacokinetics [6, 7, 8, 9].

Patterson et al. [10] reported significant quantitative differences between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO uptake in a side-by-side comparison and a statistical parametric mapping (SPM) analysis. Different tracer kinetics has been regarded as the main reason for differences in the uptake of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO. However, Patterson's study was limited in that the comparisons of the two ^{99m}Tc-labelled tracers were not performed in the same subjects.

Other investigators [7, 11] have examined intra-individual differences, but these studies were not performed using SPM methods and so were subject to the inherent inaccuracy of region of interest methods. Comparative brain SPET studies of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO uptake in the same subjects, healthy or suffering from stroke, are important in order to determine the true differences between the tracers.

In order to identify the significant differences between these two ^{99m}Tc-labelled tracers, we investigated their uptake in the same brains of stroke patients without cortical infarction using a software package known as SPM 96.

Materials and methods

Patient selection. Sixty patients with neurological symptoms on admission were investigated using the two tracers ^{99m}Tc-ECD and ^{99m}Tc-HMPAO. Brain magnetic resonance imaging (MRI) was performed in all patients with a 1.5-T General Electric Signa Horizon (GE, Medical System, Milwaukee, USA). Twenty patients (11 women, 9 men; age 34–75 years; mean age 62±12 years) were selected, excluding the 40 patients who had cortical infarction on follow-up MRI. These 20 patients did not have cortical infarction. However, ischaemic periventricular white matter lesions were observed in 13 patients. Lacunar infarction was observed in seven patients. Infarctions in the pons were observed in six patients, and infarction in the medulla in one patient. ^{99m}Tc-ECD and ^{99m}Tc-HMPAO SPET scans were performed during the subacute phase of the patients' strokes, less than 7 days after their onset.

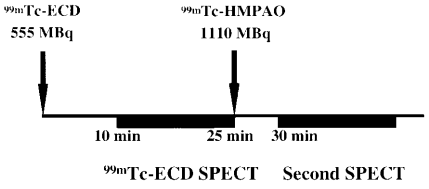

Fig. 1. Protocol of split-dose and sequential acquisition of ^{99m}Tc-ECD and second SPET. ^{99m}Tc-HMPAO SPET images were obtained by subtracting the first ^{99m}Tc-ECD SPET images from the second SPET images, performed without repositioning of the patient

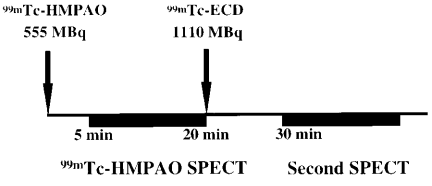

Fig. 2. Protocol of split-dose and sequential acquisition of ^{99m}Tc-HMPAO and second SPET. ^{99m}Tc-ECD SPET images were obtained by subtracting the first ^{99m}Tc-HMPAO SPET images from the second SPET images, performed without repositioning of the patient

SPET imaging protocol. The study was approved by the Ethics Committee of Inha College School of Medicine. Before the SPET scan was performed, all subjects had an intravenous line while they rested supine on the scanning bed with their eyes closed. The room was dimly lit and noise was minimized during two sequential SPET acquisitions. Each patient underwent assessment of cerebral perfusion using SPET with a triple-head camera (MultiSPET 3; Siemens, Ohio, USA) and low-energy, high-resolution fan-beam collimators (FWHM=9.7 mm). Each detector head acquired 40 projections, over 120°, with a 128×128 matrix. Transaxial, sagittal and coronal images were reconstructed by filtered back-projection using a Butterworth filter (cut-off frequency 0.32 cycles/pixel for the first SPET images and 0.37 cycles/pixel for the subtracted SPET images from the second SPET image) and employing Chang's first-order method with attenuation coefficient μ=0.12/cm.

We used a split-dose and sequential SPET protocol employing the two tracers ^{99m}Tc-ECD and ^{99m}Tc-HMPAO [12, 13]. The sequential ^{99m}Tc-ECD/^{99m}Tc-HMPAO (Fig. 1) and ^{99m}Tc-HMPAO/^{99m}Tc-ECD SPET (Fig. 2) schedules were used in 11 and 9 patients, respectively. A first dose of 555 MBq (15 mCi) ^{99m}Tc-ECD for the ^{99m}Tc-ECD/^{99m}Tc-HMPAO SPET schedule or ^{99m}Tc-HMPAO for the ^{99m}Tc-HMPAO/^{99m}Tc-ECD SPET schedule was administered in the supine position. Ten minutes after the administration of ^{99m}Tc-ECD or 5 min after the administration of ^{99m}Tc-HMPAO, the first SPET study with 20 s per step was performed. Without repositioning of the patient, a second dose of 1110 MBq

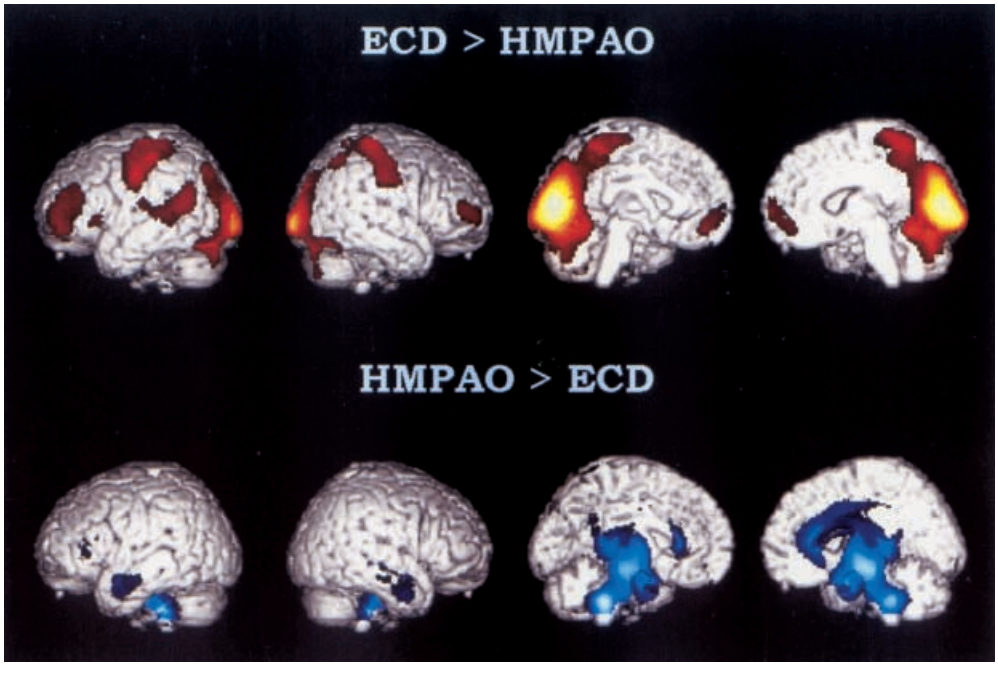

Fig. 3. SPM analysis revealed the areas of the same brains that showed significantly different uptake of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO

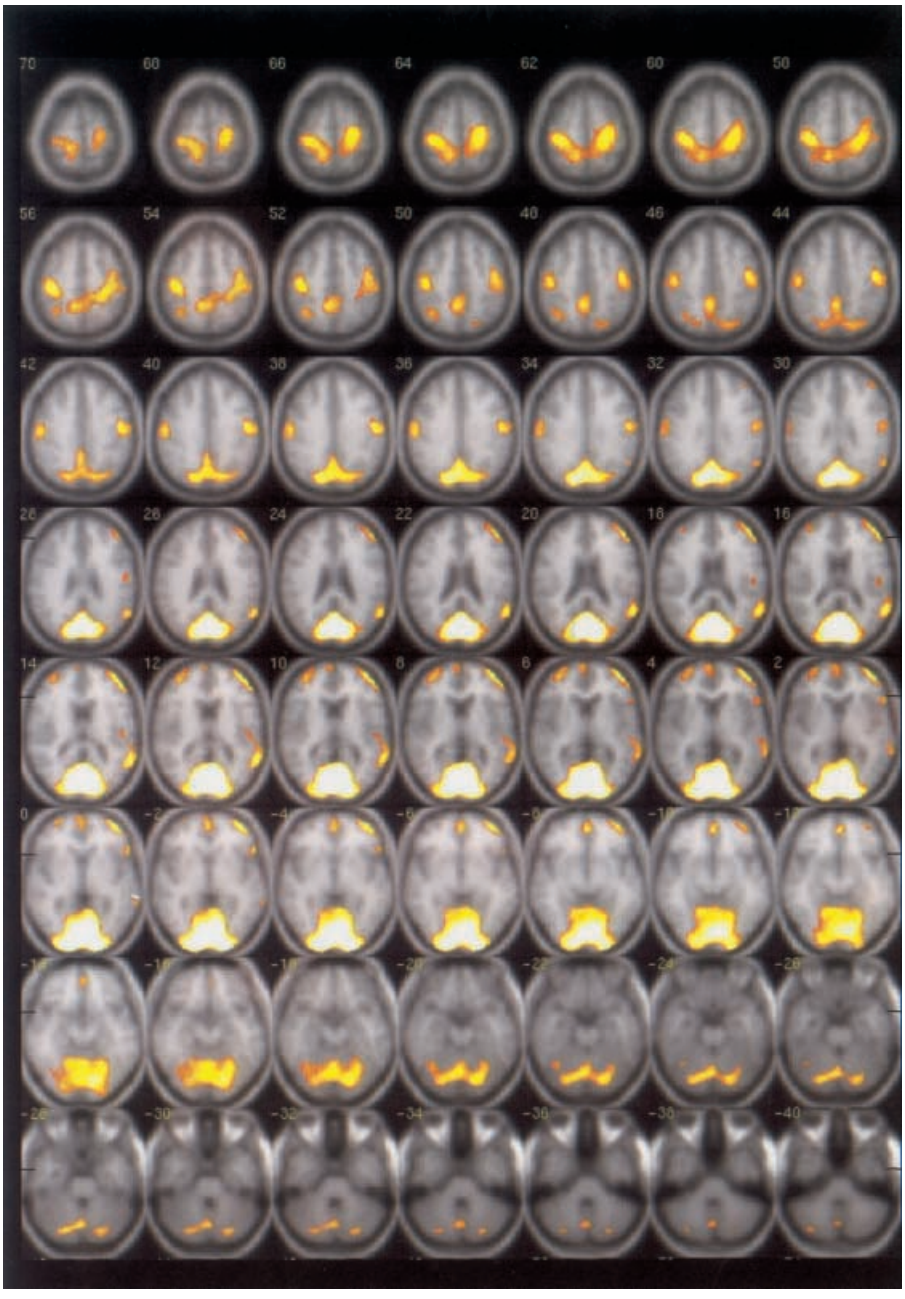

Fig. 4. Transverse ^{99m}Tc-ECD SPET images: compared with transverse ^{99m}Tc-HMPAO SPET images, relatively higher uptake was observed in the frontal, parietal and occipital lobes, the superior region of the cerebellum, and the left temporal lobe

(30 mCi) ^{99m}Tc-HMPAO for the ^{99m}Tc-ECD/^{99m}Tc-HMPAO SPET schedule or ^{99m}Tc-ECD for the ^{99m}Tc-HMPAO/^{99m}Tc-ECD SPET schedule was injected immediately after the first SPET acquisition. Five minutes after the injection of ^{99m}Tc-HMPAO or 10 min after the injection of ^{99m}Tc-ECD, another SPET study of 20 s per step was started.

Statistical parametric mapping analysis. SPM was used to determine the quantitative differences between the ^{99m}Tc-ECD and ^{99m}Tc-HMPAO SPET images. The image data were analysed using SPM 96 (Statistical Parametric Mapping 96, Institute of Neurology, University College of London, UK) implemented in Matlab (Mathworks Inc., USA) [14, 15]. Prior to statistical analysis, all of the images were spatially normalized into the MNI (Montreal Neurological Institute, McGill University, Calif., USA) standard template to remove the inter-subject anatomical variability [16, 17, 18, 19]. Affine transformation was performed to determine the 12 optimal parameters with which to register the brain on the template. Subtle differences between the transformed image and the template were removed using the elastic deformation method. The deformation was constrained to consist of a linear combination of the pre-defined smooth basis functions used in discrete cosine transformation. 3-D basis function was chosen as the lowest frequency component of the transformation because of the low spatial resolution of the SPET image. Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 16-mm full-width at half-maximum. The aim of smoothing was to increase the signal-to-noise ratio and to account for the variations in subtle anatomical structures. The count of each voxel was normalized to the total count of the brain (proportional scaling in SPM) to remove the differences in global CBF between the individuals.

Table 1. Areas with significantly higher uptake on ^{99m}Tc-ECD SPET, and their spatial coordinates and Z-scores

Brain area	*x*	*y*	*z*	Z-value
Right				
Pre-frontal area	36	50	8	3.16
Sensorimotor cortex	36	–26	58	5.31
Occipital lobe	4	–80	10	7.13
Left				
Pre-frontal area	–40	56	6	4.03
Superior temporal	–58	–56	18	3.88
Sensorimotor cortex	–24	–30	60	3.63
Occipital lobe	–4	–78	6	7.42
Central-frontal area	0	50	–8	3.27

After spatial and count normalization, significant differences between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO SPET images were estimated at every voxel using *t* statistics. The voxels with a *P* value of less than 0.01 were considered to be significantly different. For the sake of easy interpretation, the *t* values were transformed into the standard Gaussian distribution (Z-score).

Results

There were no hypoperfused areas on either ^{99m}Tc-ECD or ^{99m}Tc-HMPAO SPET images by visual analysis.

SPM analysis showed significant differences in uptake between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO images in the same brains (Fig. 3). ^{99m}Tc-ECD SPET images dis-

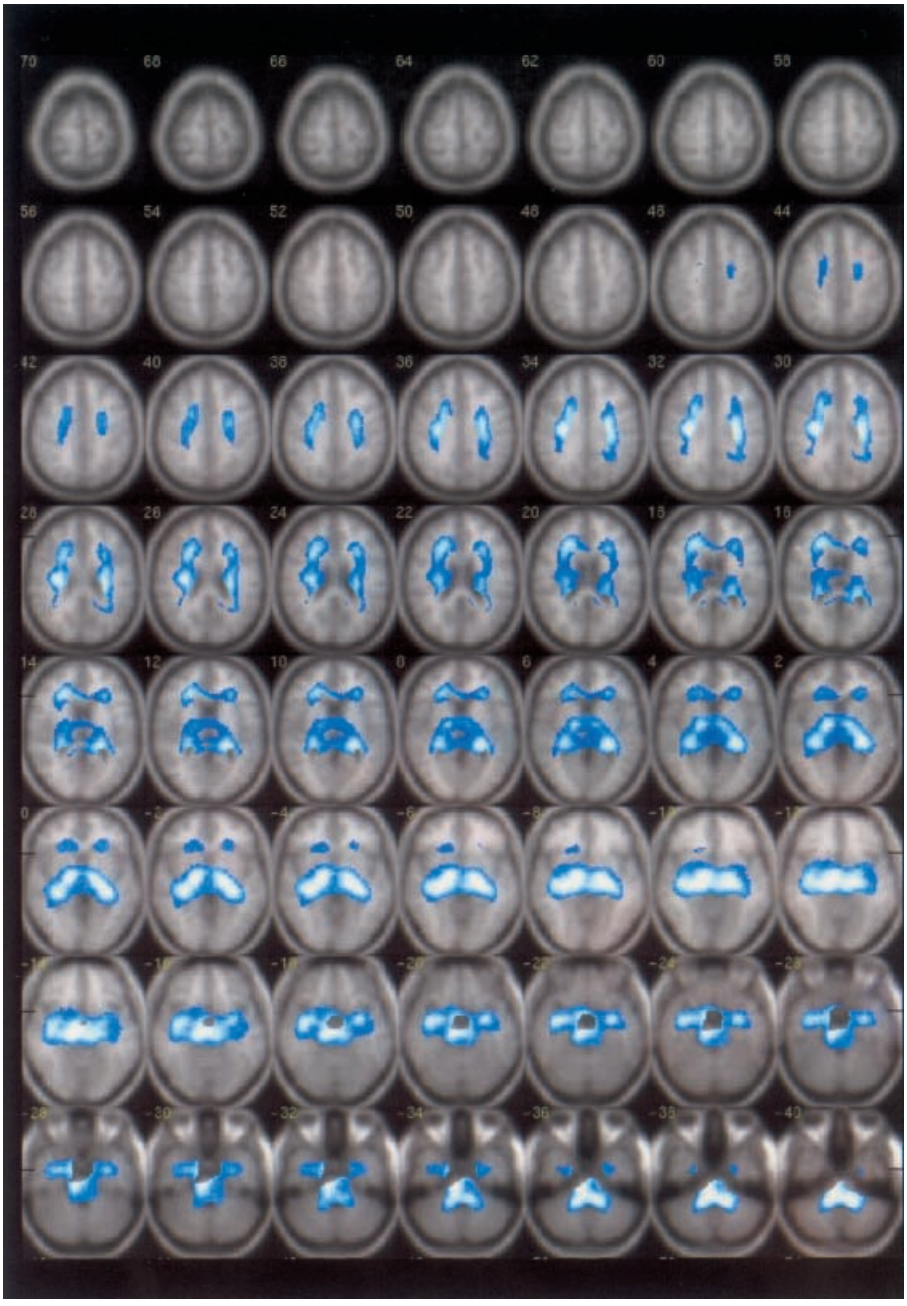

Fig. 5. Transverse ^{99m}Tc-HMPAO SPET images: compared with transverse ^{99m}Tc-ECD SPET images, relatively higher uptake was observed in the medial temporal lobes, thalami, periventricular white matter and brain stem

Table 2. Areas with significantly higher uptake on ^{99m}Tc-HMPAO SPET, and their spatial coordinates and Z-scores

Brain area	*x*	*y*	*z*	Z-value
Right				
Brain stem	11	–38	–38	4.98
Thalamus	14	–12	–8	5.31
Medial temporal	40	–6	–20	4.69
Left				
Brain stem	–14	–42	–40	5.59
Thalamus	–24	–20	–6	5.21
Medial temporal	–30	–2	–22	4.67

played relatively higher uptake in the frontal and occipital lobes, in the sensorimotor cortex, and in the left superior temporal lobe and superior region of the cerebellum (Fig. 4, Table 1). In the frontal lobes, higher uptake of ^{99m}Tc-ECD was observed in both pre-frontal and central-frontal cortices. By contrast, ^{99m}Tc-HMPAO SPET images displayed relatively higher uptake in the medial temporal lobes, thalami, periventricular white matter and brain stem (Fig. 5, Table 2).

Discussion

This study compared ^{99m}Tc-ECD and ^{99m}Tc-HMPAO uptake in the same normal-looking brains. In this study protocol, SPET imaging was performed in stroke patients without cortical infarction during the subacute phase. In the subacute phase of stroke, luxury perfusion tends to be present, being reflected as maintained or increased cerebral ^{99m}Tc-HMPAO uptake relative to rCBF. However, visual interpretation of this study showed no hyperperfused areas on ^{99m}Tc-HMPAO SPET or hypoperfused areas on ^{99m}Tc-ECD SPET images. Semiquantitative techniques employed in analysing brain SPET images use a 10%–13% difference in counts between contralateral regions of interest as a threshold for the diagnosis of blood flow deficits [20]. Stapleton et al. [21] reported that visual interpretation of cerebellum detected a 5%–10% decrease in counts in the context of a receiver operating characteristic (ROC) study. Given that visual interpretation has an equivalent threshold for the detection of blood flow deficits to that of semiquantitative techniques, we assumed that foci of luxury perfusion or hypoperfused areas were not present in our patients.

In our study, ^{99m}Tc-ECD and ^{99m}Tc-HMPAO SPET imaging was performed in stroke patients with subcortical or brain stem infarctions. Ipsilateral cerebral or crossed cerebellar diaschisis due to functional deafferentation is a common finding in these patients [22, 23]. In this study, visual analysis showed no hypoperfused areas or asymmetric cerebral perfusion in either ^{99m}Tc-ECD or ^{99m}Tc-HMPAO SPET images, and we excluded the possibility that cerebral perfusion was influenced by functional deafferentation due to subcortical or brain stem infarctions.

SPM analysis demonstrated significant quantitative differences in the uptake of the two tracers. As indicated above, significantly higher ^{99m}Tc-ECD uptake was exhibited in the frontal, parietal and occipital lobes, the left superior temporal lobe and the superior region of the cerebellum. ^{99m}Tc-ECD uptake was relatively higher than ^{99m}Tc-HMPAO uptake in the sensorimotor cortex of both parietal lobes, in the pre-frontal cortex of both frontal lobes, and in the central-frontal area. On the other hand, ^{99m}Tc-HMPAO uptake was significantly higher in the medial temporal lobes, thalami and periventricular white matter.

These findings, with the exception of a higher ^{99m}Tc-ECD uptake in the superior region of the cerebellum, are in agreement with previously published data [10, 11, 24]. The differences in the cerebral uptake of the tracers are mainly due to variations in the mechanisms responsible for their cerebral accumulation. Both tracers underestimate true CBF in high-flow regions, but ^{99m}Tc-ECD uptake is considered to reflect CBF more closely than does ^{99m}Tc-HMPAO uptake [6]. Relatively higher ^{99m}Tc-ECD uptake in the occipital, parietal and frontal lobes 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 [24].

Heiss et al. [25] described higher ^{99m}Tc-HMPAO uptake in the cerebellum owing to higher capillary density. However, the results of our SPM analysis showed that ^{99m}Tc-ECD uptake was relatively higher than ^{99m}Tc-HMPAO uptake in the superior region of the cerebellum. This is at variance with the results of previous studies [10, 24, 26]. Although one may regard this relatively higher ^{99m}Tc-ECD uptake in the cerebellum as a finding specific to this study, care should be exercised in its interpretation. Since the spatially normalized SPET images were smoothed with a 16-mm FWHM kernel, the activity in the superior region of cerebellum was contaminated by the activity in the neighbouring occipital cortex. Therefore, the difference in the relative uptake of the two tracers in the cerebellum might be caused by the higher ^{99m}Tc-ECD uptake in the occipital regions.

The relatively higher ^{99m}Tc-HMPAO uptake in the medial temporal lobes, thalami and periventricular white matter demonstrated in this study parallels the findings of other investigators [10, 24, 26]. Oku et al. [11] postulated that the non-uniform cortical distribution of glutathione and non-specific esterase activity, and the lower regional glucose metabolic rate of the hippocampus compared with grey matter, lead to the higher ^{99m}Tc-HMPAO uptake in the medial temporal lobes. The fact that uptake of ^{99m}Tc-ECD represented more sensitively the regional metabolic rate, especially in the hippocampus, could be another cause of the different uptake be-

tween these two tracers in the same normal-looking brains.

Koyama et al. [26] reported that high radioactivity of ^{99m}Tc-ECD or ^{99m}Tc-HMPAO in the cerebral cortex was not apparent on rCBF positron emission tomography (PET) images, and concluded that neither ^{99m}Tc-HMPAO nor ^{99m}Tc-ECD SPET images directly reflect rCBF. However, the specific pattern of uptake of each tracer revealed in this study will help identify areas with increased or decreased uptake as a reference for clinical diagnoses.

We obtained ^{99m}Tc-ECD and ^{99m}Tc-HMPAO SPET images in stroke patients without cortical infarction. As we compared the uptake of the two tracers intra-individually and without repositioning of the patient, the cortical rCBF in the same brains cannot have changed during the two SPET acquisitions. Thus, the difference in the uptake of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO reflected the difference in uptake mechanism irrespective of regional perfusion.

We used split-dose and sequential SPET imaging. This technique has been validated in patients with cerebrovascular disease after acetazolamide administration [27]. Two SPET acquisitions were performed within 60 min after the first injection of ^{99m}Tc-ECD or ^{99m}Tc-HMPAO. According to Ohnishi et al.'s report [27], washout of ^{99m}Tc-ECD within 60 min is negligible, and we presumed that the ^{99m}Tc-ECD uptake in the brain was the same in the second SPET acquisition as in the first. Thus, ^{99m}Tc-HMPAO SPET images obtained by subtracting the first ^{99m}Tc-ECD SPET images from the second SPET images reflected purely the uptake of ^{99m}Tc-HMPAO. Neurobiological effects on the distribution of rCBF could not have affected the results of our study because we randomly chose the sequence of tracer administration.

Our group has previously reported preliminary results in patients with cortical infarction during the subacute phase using the same split-dose and sequential SPET technique [28, 29, 30]. More hypoperfused areas were observed on ^{99m}Tc-ECD SPET images than on ^{99m}Tc-HMPAO images. These preliminary results in patients with cortical infarction were similar to the findings of the present study in terms of the discrepancies in uptake between the two tracers. On the other hand, in temporal lobe epilepsy, Lee et al. [31] reported that the degree of ictal hyperperfusion was higher and localization was better with ^{99m}Tc-HMPAO than with ^{99m}Tc-ECD. Therefore, differences in the regional uptake of these two tracers may be used to determine which tracer is preferable for the detection of a specific neurological disease. For instance, ^{99m}Tc-ECD has the advantage of better visualization of hypoperfused areas in acute or subacute stroke, while ^{99m}Tc-HMPAO has the advantage of better localization of epileptogenic zones.

In conclusion, uptake of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in the same normal-looking brains was significantly different on SPM analysis. The selective use of ^{99m}Tc-ECD or ^{99m}Tc-HMPAO in brain SPET imaging appears especially valuable for the interpretation of cerebral perfusion. Further investigation is necessary to determine which is more accurate for diagnosing different clinical conditions.

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