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Superiority of HMPAO Ictal SPECT to ECD Ictal SPECT in Localizing the Epileptogenic Zone

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Summary: *Purpose:* We examined diagnostic performances of Tc-99m hexamethylpropylene amine oxime (HMPAO) and Tc-99m electron capture detection (ECD) ictal single-photon emission computed tomography (SPECT) to localize the epileptogenic zones in mesial temporal lobe epilepsy (TLE) and neocortical epilepsy (NE).

Methods: Epileptogenic zones were identified by invasive EEG or surgical outcome. Ictal SPECT was performed with stabilized Tc-99m HMPAO (TLE, 17; NE, 23) and with Tc-99m ECD (TLE, 7; NE, 7). Single-blind visual interpretation was used to localize the epileptogenic zones. Asymmetric index was calculated. Subtraction ictal SPECT was coregistered to a magnetic resonance imaging (MRI) template.

Results: In TLE, the sensitivity of Tc-99m HMPAO SPECT was 82% (14 of 17) and that of Tc-99m ECD SPECT was 71% (five of seven). The asymmetric index (AI; 25 ± 10) of Tc-99m HMPAO SPECT was larger ($p = 0.05$) than the AI (13 ± 13) of Tc-99m ECD SPECT in patients with TLE. In NE, the sensitivity of Tc-99m HMPAO SPECT was 70% (16 of 23), but that of Tc-99m ECD SPECT was 29% (two of seven). The AI (15 ± 10) of Tc-99m HMPAO SPECT was significantly larger ($p = 0.02$) than the AI (4.8 ± 6) of Tc-99m ECD SPECT in patients with NE. Subtraction ictal SPECT coregistered to MRI supported the visual assessment.

Conclusions: We concluded that the sensitivity of Tc-99m ECD ictal SPECT is similar to that of Tc-99m HMPAO ictal SPECT in TLE; however, ictal hyperperfusion was higher with the Tc-99m HMPAO SPECT. In patients with NE, Tc-99m HMPAO ictal SPECT also was superior to Tc-99m ECD ictal SPECT in sensitivity and degree of hyperperfusion. **Key Words:** Epilepsy—Epileptogenic zones—Tc-99m HMPAO—Tc-99m ECD—Ictal perfusion SPECT.

Both Tc-99m hexamethylpropylene amine oxime (HMPAO) ictal single-photon emission computed tomography (SPECT) (1,2) and Tc-99m electron capture detection (ECD) ictal SPECT (3–6) were reported to be helpful for the localization of epileptogenic zones; however, there has been no report regarding the comparative diagnostic performance of these SPECT studies. As Tc-99m HMPAO was unstable (7,8) but Tc-99m ECD was stable after labeling (3,8), Tc-99m ECD was thought to have a distinct advantage of possible rapid injection at the time of ictus. Recently, however, $CoCl_2$ has been used as a stabilizer for HMPAO, and Tc-99m HMPAO matched Tc-99m ECD in terms of the rapidity of its injection at the time of ictus (9).

The diagnostic performance of ictal-perfusion SPECT was different for mesial temporal lobe epilepsy (TLE) and for neocortical epilepsy (1,2,10). According to a recent meta-analysis on ictal SPECT, the diagnostic sensitivity of mesial TLE was 97%; however, the diagnostic performance of neocortical epilepsy has not been determined (1).

The distribution patterns of Tc-99m HMPAO and Tc-99m ECD were found to be very similar, although the identified differences may be significant (11–13). When one considers the different cellular retention mechanisms of these compounds, a difference in the distribution at the ictus might be expected (14,15).

Because the same ictal episode could not be studied simultaneously by Tc-99m HMPAO and Tc-99m ECD on an ictal-perfusion SPECT, sequential ictal SPECT with Tc-99m HMPAO and Tc-99m ECD with different ictal episodes in the same patients might be the best method of elucidating the difference between the two. However, the patterns of increased perfusion were not the same for various ictal episodes in the same patient (16–18), which reflected the different clinical symptoms and the ictal electrical propagation of different episodes.

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In this study, we exchanged Tc-99m HMPAO with Tc-99m ECD for a period of 3 months. During the 3 months, all of the ictal and interictal SPECT studies were performed with Tc-99m ECD. The diagnostic performances in localizing epileptogenic zones by visual assessment and by SISCOM and the degrees of hyperperfusion of the Tc-99m HMPAO ictal SPECT and the Tc-99m ECD ictal SPECT were compared. We tried to decide which radiopharmaceutical was better for ictal SPECT studies.

MATERIALS AND METHODS

Subjects

Tc-99m HMPAO ictal perfusion SPECT was performed in 40 patients, Of these, 25 were men and 15 were women; they were 23 ± 9.1 years old. Tc-99m ECD ictal perfusion SPECT was performed on 14 patients; 10 were men and four were women, and they were 28 ± 11 years old.

Among the HMPAO group, 17 had mesial TLE, and 23 had neocortical epilepsy. Neocortical epilepsy in this group included nine patients with lateral TLE, seven with frontal lobe epilepsy, four with occipital lobe epilepsy, and three with parietal lobe epilepsy. Among the ECD group, seven had mesial TLE, and seven had neocortical epilepsy. Neocortical epilepsy in this group included three patients with lateral TLE, three with frontal lobe epilepsy, and one with occipital lobe epilepsy.

Imaging and reconstruction of ictal-perfusion SPECT

Patients were admitted to epilepsy monitoring units for 1 to 18 days. Three to 20 ictal episodes (mean, six) were monitored. During one of these episodes, 1,110 MBq of Tc-99m HMPAO or Tc-99m ECD was injected. Tc-99m HMPAO was stabilized with $CoCl_2$. The injection delay of Tc-99m HMPAO SPECT was 52 ± 20 s. The injection delay of Tc-99m ECD SPECT was 42 ± 27 s.

The ictal perfusion SPECT was acquired 1–2 h after ictal injection by using a triple-head SPECT camera (Prism 3000; Picker International, Philips Medical Systems, Highland Heights, OH, U.S.A.) and fan-beam collimator for 18 min with 25 s per shoot with a 3-degree interval, with matrix size of 128 × 128. Projection files were reconstructed with the filtered backprojection method by using a Metz filter with x value of 1.5 to 2.0. In-plane resolution [full-width half maximum (FWHM)] was 9.7 mm. The attenuation was corrected by using Chang's method. Reconstructed images were reoriented to sagittal and coronal slices.

Asymmetric index calculation

A region of interest (ROI) was drawn over the most hyperperfused epileptogenic areas by using an ellipsoid ROI with 10 mm long diameter and another over the contralateral part of that slice, and total counts in these ROIs were measured. The asymmetric index (AI) was calculated by dividing the difference between the counts of these ROIs by the sum of the counts [AI = (Total count of the ipsilateral ROI – Total count of contralateral ROI)/(Total count of the ipsilateral ROI + Total count of the contralateral ROI) × 200].

Subtraction ictal SPECT coregistered to MRI (SISCOM)

Interictal SPECT was performed in all the patients. With these interictal SPECTs, SISCOM studies were performed. SPM 99 (Statistical Parametric Mapping 99; Institute of Neurology, University College of London, London, U.K.) implemented in Matlab 5.3 (The Mathworks Inc., Natick, MA, U.S.A.) was used to realign the ictal and interictal SPECT images, which were spatially normalized into standard templates (19). Spatially normalized images were smoothed by convolution with an isotropic gaussian kernel with a 10-mm FWHM. The pixel counts of the SPECT images were normalized to a mean pixel count of gray matter in each SPECT image.

The percentage-change map was calculated (20). Perfusion changes of >20% were regarded as significant, and the perfusion-change map containing significant pixels was superimposed on a T_1 MRI template (21–23).

Image interpretation

Ictal and interictal images were reviewed by two physicians who were unaware of the clinical history and the results of the other presurgical evaluations. Coronal, sagittal, and transaxial images were analyzed. The cerebral cortex was divided into the occipital lobe, medial temporal lobe, lateral temporal lobe, frontal lobe, and parietal lobes. When there was disagreement between the two examiners, an effort was made to develop a consensus. A decision was taken on all ictal SPECTs as to whether they were lateralized.

SISCOM images were analyzed again independently by the same physicians who were blinded to the previous results, including the ictal and the interictal SPECT findings.

Diagnosis of epileptogenic zones

The diagnosis was made by standard presurgical evaluation at our hospital; evaluation techniques included scalp video-EEG monitoring, brain MRI, interictal EEG, and positron emission tomography (PET). When results were inconclusive, additional intracranial EEG monitoring was performed. Patients were selected when the surgical outcome was good.

Anterior temporal lobectomy was performed in 20 of the 24 patients with mesial TLE. After 2 to 5 years of follow-up, 17 were Engel class 1, two were Engel class 2, and one was Engel class 3. Neocortical resection was

performed in 19 of the 30 patients with neocortical epilepsy. After 1 year 8 months to 3 year 4 months of follow-up, 13 were Engel class 1, and six were Engel class 3. Four mesial TLE patients who were not operated on showed hippocampal atrophy on MRI and temporal hypometabolism on F-18-fluorodeoxyglucose (FDG) PET. Eleven neocortical epilepsy patients who were not operated on did not show hippocampal atrophy on MRI and were diagnosed as having neocortical epilepsy according to F-18-FDG PET, ictal EEG, and invasive EEG using subdural grids and strip (four frontal lobe epilepsy, three lateral TLE, two parietal lobe epilepsy, two occipital lobe epilepsy).

Temporal pattern of uptake of Tc-99m ECD ictal SPECT

In three further patients with TLE (two mesial TLE, one lateral TLE), Tc-99m ECD ictal SPECT was acquired 3 times at 30 min, 2 h, and 4–7 h after injection, respectively. The uptake in the hyperperfused area was examined visually, and the AIs of the three SPECT images were compared.

Statistical analysis

The sensitivities of Tc-99m HMPAO and Tc-99m ECD ictal SPECT were compared by using Fisher's Exact test in patients with mesial TLE or neocortical epilepsy. AIs of Tc-99m HMPAO and Tc-99m ECD ictal SPECT were compared by using the Mann–Whitney *U* test for patients with mesial TLE and neocortical epilepsy. SPSS for Windows, version 7.5, was used.

RESULTS

Diagnostic performance of Tc-99m HMPAO and Tc-99m ECD ictal SPECT in patients with mesial TLE

The sensitivity of Tc-99m HMPAO ictal SPECT in patients with mesial TLE was 14 (82%) of 17. Postictal SPECT was performed in one patient among the three false negatives. In two of 14 positive patients, perfusion was increased in the contralateral side. One was bilateral independent TLE (correct), and the other was proven to be TLE of the contralateral side by invasive studies (incorrect). Thus the localization rate of epileptogenic zones of Tc-99m HMPAO ictal SPECT was 13 (76%) of 17.

Sensitivity of Tc-99m ECD ictal SPECT was five (71%) of seven. No significant difference was found between the sensitivity of Tc-99m HMPAO ictal SPECT and Tc-99m ECD ictal SPECT ($p > 0.05$). Injection delay was not different between Tc-99m HMPAO and Tc-99m ECD SPECT ($p > 0.05$). On SISCOM images, the findings were the same as those of the visual side-by-side interpretation.

Diagnostic performance of Tc-99m HMPAO and Tc-99m ECD ictal SPECT in patients with neocortical epilepsy

The sensitivity of Tc-99m HMPAO ictal SPECT was 16 (70%) of 23. Exact localization was not possible, and lateralization was possible in only eight of these 16 patients, as perfusion was increased in multiple lobes in the remaining eight patients. Thus the localization rate of epileptogenic zones of Tc-99m HMPAO ictal SPECT was eight (35%) of 23.

The sensitivity of Tc-99m ECD ictal SPECT was two (29%) of seven. The sensitivity of Tc-99m HMPAO ictal SPECT was significantly better than that of the Tc-99m ECD ictal SPECT ($p = 0.03$). Injection delay was not different between Tc-99m HMPAO and Tc-99m ECD SPECT ($p > 0.05$). On SISCOM images, the findings were the same as those of the visual side-by-side interpretation.

Comparison of AI in patients with mesial TLE

AI of Tc-99m HMPAO ictal SPECT was 25 ± 10 (range, 1.9~45). AI of Tc-99m ECD ictal SPECT was 13 ± 13 (range, 0~35). AIs obtained by using Tc-99m HMPAO ictal SPECT were larger than those from Tc-99m ECD ictal SPECT ($p = 0.05$; Fig. 1).

Comparison of AI in patients with neocortical epilepsy

AI of the epileptogenic zones in Tc-99m HMPAO ictal SPECT was 15 ± 10 (range, –7~30). AI of Tc-99m ECD ictal SPECT was 4.8 ± 6 (range, –1.3~14). AIs of Tc-99m HMPAO ictal SPECT were significantly larger than those of Tc-99m ECD ictal SPECT ($p = 0.02$; Fig. 2).

Case examples

Perfusion increased in the left temporal lobe with Tc-99m HMPAO ictal SPECT in a 22-year-old patient with left mesial TLE, whose AI was 26 (Fig. 3A). The SISCOM image revealed left temporal lobe hyperperfusion. Left hippocampal sclerosis was found on MRI, and metabolism was decreased in the left temporal lobe with F-18-FDG-PET; therefore, a left anterior temporal lobectomy was performed, which resulted in a good surgical outcome (Engel class 1) after 4 years.

Perfusion increased in the right temporal lobe with Tc-99m ECD ictal SPECT in a 51-year-old patient with right mesial TLE, whose AI was 36 (Fig. 3B). The SISCOM image revealed right temporal lobe hyperperfusion. MRI and F-18-FDG-PET findings were compatible with right mesial TLE. This patient was seizure free (Engel class 1) for 4 years and 1 month after the operation.

Perfusion was increased in the left frontal lobe of a 16-year-old patient with left frontal lobe epilepsy, whose

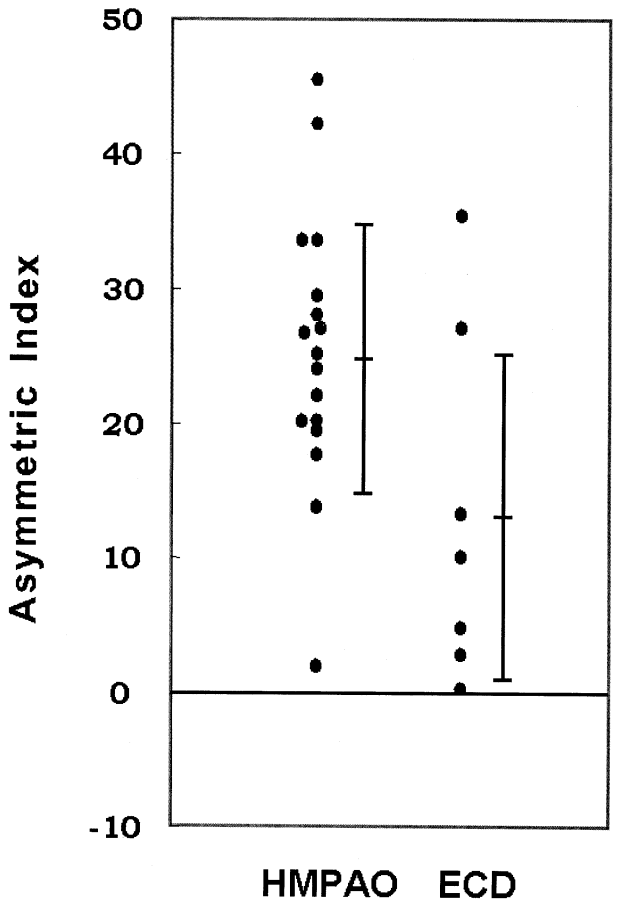

FIG. 1. Asymmetric indices (AIs) of epileptogenic zones and contralateral areas were calculated on Tc-99m hexamethylpropylene amine oxime (HMPAO) ictal single-photon emission computed tomography (SPECT) and Tc-99m electron capture detection (ECD) ictal SPECT in the patients with medial temporal lobe epilepsy. AIs of Tc-99m HMPAO ictal SPECT were larger than those of Tc-99m ECD ictal SPECT ($p = 0.05$).

AI was 16 (Fig. 4A). The SISCOM image revealed left frontal lobe hyperperfusion. Invasive electroencephalography (EEG) was performed with subdural grids and strip. After corticectomy, surgical outcome was Engel class 1 after 3.6 years. No area of increased perfusion was found in a 23-year-old female patient, whose AI was 0 (zero) (Fig. 4B). The SISCOM image did not reveal any hyperperfused area. Ictal semiology was the supplementary sensorimotor type, and cerebromalacia was found in left frontal lobe on MRI, hypometabolism in the left frontal lobe on F-18-FDG-PET, and ictal discharge at F3/C3 was found on ictal EEG. Left frontal lobe epilepsy was suspected, but no operation was carried out.

In a 24-year-old female patient, both Tc-99m HMPAO ictal SPECT and Tc-99m ECD ictal SPECT were performed (Fig. 5). No area of increased perfusion was found by Tc-99m ECD ictal SPECT. However, on Tc-99m HMPAO ictal SPECT, a wide area of increased perfusion was found in the left frontoparietal lobes. The SISCOM image supported visual side-by-side interpretation. No structural abnormality was found on MRI, but metabolism had decreased in the frontal lobe on F-18-FDG-PET. Ictal EEG revealed ictal discharge emanating from F7. Invasive EEG using strip and grids proved the left inferior frontal lobe to be an epileptogenic zone and corticectomy was performed. Surgical outcome was excellent with Engel class 1 at 3 year and 6 months.

Temporal characteristics of ictal hyperperfusion on Tc-99m ECD ictal SPECT

No differences were found in hyperperfusion at epileptogenic zones on Tc-99m ECD ictal SPECT acquired 30 min, 2 h, and 4–7 h after injection. Figure 6 shows a 28-year-old patient with right mesial TLE. Right hippocampal atrophy was found on MRI, and the ictal discharge came from T_2. Visual grading of hyperperfusion and AI were identical on the 30-min, 2-h, and 4-h SPECT images. She awaits surgical resection.

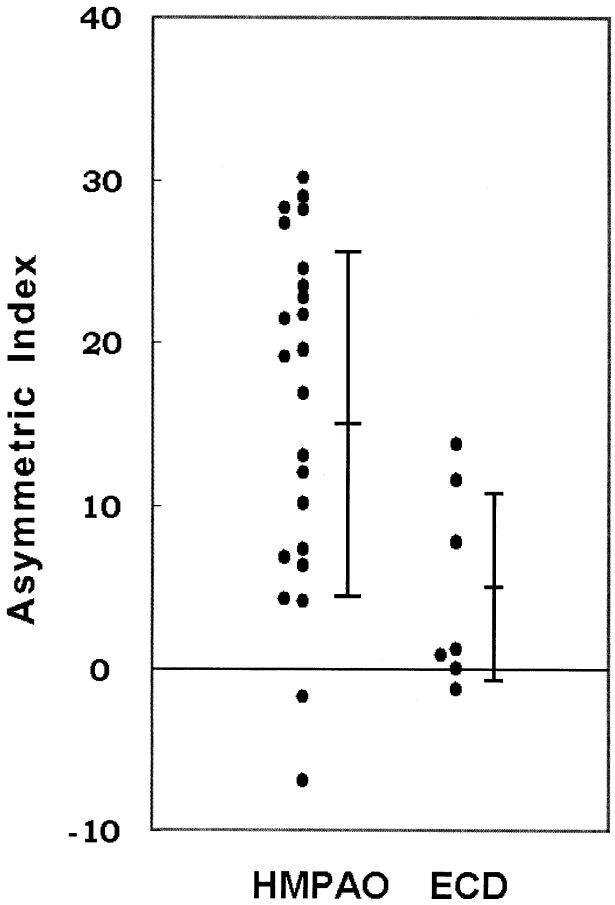

FIG. 2. Asymmetric indices (AIs) of epileptogenic zones and contralateral areas were calculated on Tc-99m hexamethylpropylene amine oxime (HMPAO) ictal single-photon emission computed tomography (SPECT) and Tc-99m electron capture detection (ECD) ictal SPECT of patients with neocortical epilepsy. AIs of ictal Tc-99m HMPAO SPECT were larger than those of ictal Tc-99m ECD SPECT ($p = 0.02$).

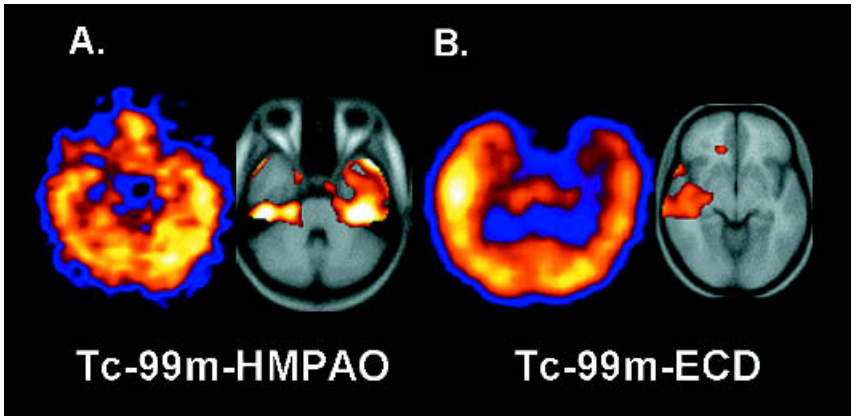

FIG. 3. **A:** Tc-99m hexamethylpropylene amine oxime (HMPAO) ictal single-photon emission computed tomography (SPECT) and the corresponding SISCOM image in a patient with left mesial temporal lobe epilepsy. **B:** Tc-99m electron capture detection (ECD) ictal SPECT and corresponding SISCOM image in a patient with right mesial temporal lobe epilepsy.

DISCUSSION

Sensitivity of HMPAO and ECD SPECT

The sensitivity of Tc-99m HMPAO ictal SPECT in mesial TLE by meta-analysis was reported as 97% (1). The confidence interval of this sensitivity ranged from 74 to 100% (1). The sensitivity of neocortical epilepsy has not been determined yet; however, it averaged ~60% (24). The difference of the sensitivity of ictal SPECT between mesial TLE and neocortical epilepsy has been considered to be due to their different ictal discharge propagation.

During the 30 s needed before technetium compounds are taken up in a hyperperfused area, ictal discharge could have already been propagated to adjacent lobes beyond the epileptogenic zones (16). If the injection delay was <60 s from the electrical onset of ictus on the video monitor of ictal scenes and the EEG, ictal hyperperfusion was almost always found in mesial TLE (25,26). However, if these compounds were injected between 2 and 15 min, decreased perfusion was observed in the epileptogenic zones (27). Shorter injection delays did not help to increase the performance of ictal SPECT if injection was within 60 s (16,18).

After the adoption of a stabilizing agent, $CoCl_2$, for Tc-99m HMPAO, stable Tc-99m ECD and stabilized Tc-99m HMPAO could easily be injected within 60 s from ictal onset, in most epilepsy-monitoring units (3,5,9,17).

During preparation of this article, O'Brien et al. (28) reported that the diagnostic performance of Tc-99m ECD ictal SPECT was better than that of unstabilized Tc-99m HMPAO ictal SPECT. They had collected a huge group of patients, 49 for each tracer. As Tc-99m HMPAO was not stabilized in their study, the median injection delay of HMPAO group was 80 s and far longer than that of the ECD group, and postictal injection also occurred more often with the HMPAO group. Although the percentage of increased uptake at the seizure focus was similar on SISCOM images between the two groups, the localization rate of Tc-99m ECD ictal SPECT was better than that of unstabilized Tc-99m HMPAO ictal SPECT.

We present the contrasting results on a group of patients in whom ictal SPECT was performed with the same technique by the same personnel and also with the similar length of injection delay. We believe that the better performance of our Tc-99m HMPAO study resulted from the fact that we used stabilized Tc-99m HMPAO instead of unstabilized Tc-99m HMPAO.

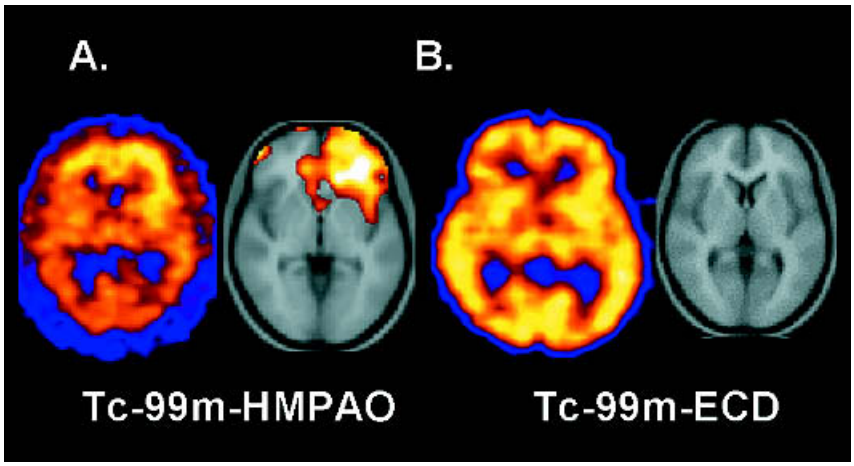

FIG. 4. **A:** Tc-99m hexamethylpropylene amine oxime (HMPAO) ictal single-photon emission computed tomography (SPECT) and SISCOM image in a patient with left frontal lobe epilepsy. **B:** Tc-99m electron capture detection (ECD) ictal SPECT and SISCOM image in a patient with left frontal lobe epilepsy.

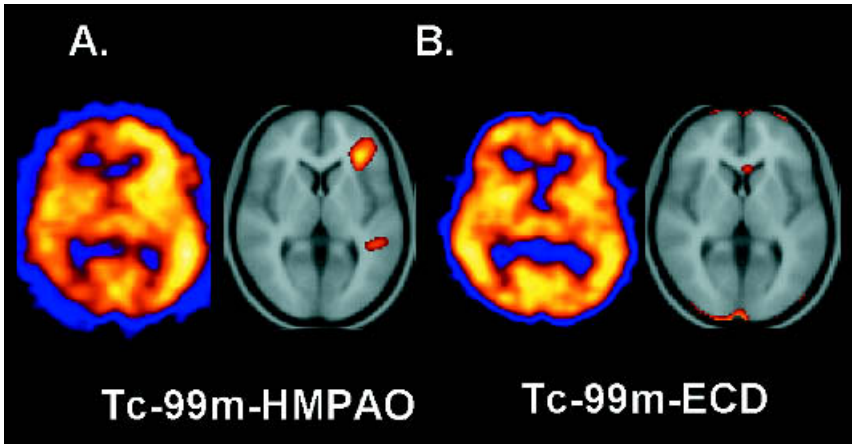

FIG. 5. A 24-year-old woman with left frontal lobe epilepsy whose Tc-99m electron capture detection (ECD) ictal single-photon emission computed tomography (SPECT) was normal, but Tc-99m hexamethylpropylene amine oxime (HMPAO) ictal SPECT showed increased perfusion at left frontoparietal lobes. SISCOM images showed the same findings.

Different mechanisms of HMPAO and ECD uptake

Tc-99m HMPAO is known to reflect tissue perfusion, but Tc-99m ECD reflected both the perfusion and the metabolism (14,15). If only these differences were taken into account, Tc-99m HMPAO might be more likely to reveal hyperperfused areas in the epileptogenic zones than was Tc-99m ECD. However, because of its back-diffusion characteristics, Tc-99m HMPAO was less sensitive to represent perfusion in high-flow areas than was Tc-99m ECD (29–31). Tc-99m HMPAO would perhaps be less likely to perform better than Tc-99m ECD in revealing hyperperfused areas in the epileptogenic zones. The effects of different mechanisms of HMPAO and ECD on the uptake at the epileptogenic zones needs experimental validation.

Because acquisition of Tc-99m HMPAO ictal SPECT and Tc-99m ECD ictal SPECT of the same ictal episode is not possible, the second-best method of investigating differences in diagnostic performance involved conducting both studies in separate, unbiased populations. We selected a certain 3-month period and performed Tc-99m ECD ictal SPECT on every patient. The performance of Tc-99m ECD ictal SPECT during this period was compared with that of Tc-99m HMPAO ictal SPECT acquired before this period. Patient characteristics of the two populations were compared thoroughly to find, if any, significant biases. The proportions of mesial TLE, surgical treatment, and the proportion of patients with normal MRI findings or surgical outcomes were similar in the two groups. Most important, time delays of injection also were similar.

Whereas the diagnostic performance of Tc-99m HMPAO ictal SPECT was similar to that of Tc-99m ECD ictal SPECT in mesial TLE, the visual degree of hyperperfusion or the AIs obtained from Tc-99m HMPAO ictal SPECT were larger than those from Tc-99m ECD ictal SPECT. SISCOM images corroborated these findings. In neocortical epilepsy, the detection rate of the hyperperfused area and the degree of hyperperfusion on the Tc-99m HMPAO ictal SPECT, as well as the sensitivity, were larger than those from the Tc-99m ECD ictal SPECT. Tc-99m-HMPAO showed a more prominent uptake at epileptogenic zones visually, on SISCOM images, and quantitatively, regardless of mesial TLE or neocortical epilepsy.

Late washout of Tc-99m ECD not as the possible cause

As a possible mechanism of less contrast of ictal epilepsy, the hypothesis was examined that reduced Tc-99m ECD retention causes a reduction in Tc-99m ECD uptake in epileptogenic zones. We could not find any difference of Tc-99m ECD uptake in epileptogenic zones between the images acquired serially after injection. In addition,

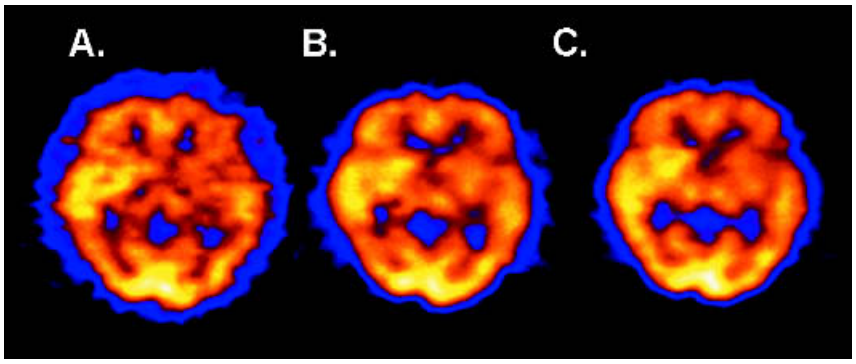

FIG. 6. A 28 year-old woman with right mesial temporal lobe epilepsy was studied with ictal Tc-99m electron capture detection (ECD) single-photon emission computed tomography (SPECT). Images were acquired after single ictal injection **(A)** 30 min after injection, **(B)** 2 h after injection, and **(C)** 4 h after injection. Right temporal hyperperfusion was consistent between the three images, and the asymmetry index was 10 on 30-min SPECT, 12 on 2-h SPECT, and 12 on 4-h SPECT.

their AIs also were nearly identical. No evidence suggested a differential washout or redistribution of Tc-99m ECD from epileptogenic zones later than 30 min. From these findings, we suggest that the lower activity of Tc-99m ECD at the epileptogenic zones is due to the lower uptake of Tc-99m ECD.

The diagnostic performance and contrast of hyperperfused areas at the epileptogenic zones of Tc-99m HMPAO ictal SPECT were better than those of the Tc-99m ECD ictal SPECT in our group of patients. To reconfirm the findings of this study, a head-to-head comparison in the same patients is warranted.

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