Annals of Nuclear Medicine Vol. 18, No. 6, 489–494, 2004

Development of "super rapid dynamic SPECT," and analysis of retention process of ^{99m}Tc-ECD in ischemic lesions: Comparative study with ^{133}Xe SPECT

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To analyze the retention process of technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) in normal and ischemic lesions, we developed a super rapid dynamic SPECT system based on the CERASPECT (DSI, Inc., Waltham, MA, USA). The system made it possible to take a SPECT series every 2 seconds. Each SPECT series contains a maximum of 16 slices (6.6 mm slice interval) in a matrix size of 32 × 32. The sensitivity of this system is 175 kcps/MBq/ml/cm slice thickness, and resolution is 12 mm FWHM at the center of a 20 cmϕ water phantom.

Using the super rapid SPECT system, the kinetic behavior of the ^{99m}Tc-ECD during retention in normal and ischemic lesions was analyzed. Twenty patients with ischemic lesions that were clearly demonstrated by ^{133}Xe-rCBF (regional cerebral blood flow) SPECT but unclear on static ^{99m}Tc-ECD SPECT were examined. For the dynamic SPECT, 700 MBq of ^{99m}Tc-ECD was injected intravenously, and dynamic SPECT data were acquired every 2 seconds during a 90-second period. The serial dynamic SPECT and time-activity curves at some lesions with reduced rCBF and at the contralateral normal brain were analyzed. These dynamic SPECT data were compared with conventional static ^{99m}Tc-ECD SPECT and quantitative ^{133}Xe-rCBF SPECT.

All of mildly or moderately reduced rCBF lesions on the ^{133}Xe-rCBF SPECT were recognized as low activity regions only at the early phase (during about 2–20 sec or less), with the lesions then gradually vanishing. These lesions were not recognized on the conventional static SPECT taken after the dynamic study. The time-activity curve at the reduced rCBF lesion was lower than that of contralateral normal brain at the early phase, and overtook the activity in the normal region with a gradual increase.

The early phase images of ^{99m}Tc-ECD SPECT within 20 seconds by the super rapid dynamic SPECT were very useful to the same extent as the ^{133}Xe-rCBF SPECT for detecting mild or moderate ischemic lesions.

This study suggests that esterase activity, participating in the ECD retention mechanism, may be tolerable to mild or moderate ischemia. This tolerance may be the main cause of the nonlinear relationship between ECD accumulation and cerebral blood flow.

Key words: super rapid dynamic SPECT, kinetic behavior of ^{99m}Tc-ECD, ^{133}Xe SPECT

INTRODUCTION

The technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) is a neutral and lipophilic tracer, which rapidly crosses the blood-brain barrier (BBB) and remains in the brain tissue. The distribution of the ^{99m}Tc-ECD has been widely used in clinical practice to evaluate the regional cerebral blood flow with a single photon emission computed tomography (SPECT) system.

Received December 26, 2003, revision accepted May 12, 2004.

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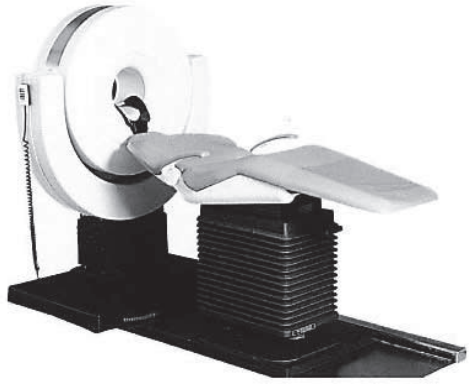

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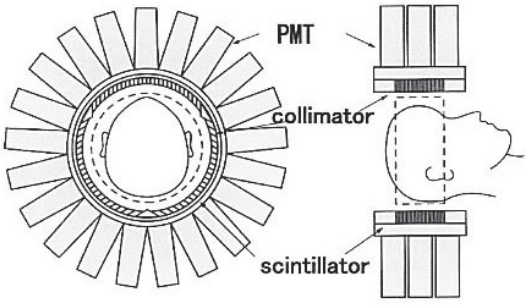

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Fig. 1 The appearance (a), and detector part (b) of the super rapid dynamic SPECT (CERASPECT).

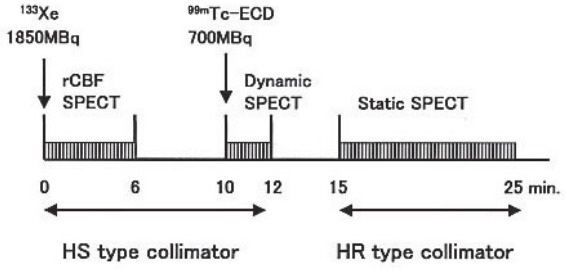


Fig. 2 Protocol for consecutive ^{133}Xe, dynamic and static ^{99m}Tc-ECD SPECT imaging.

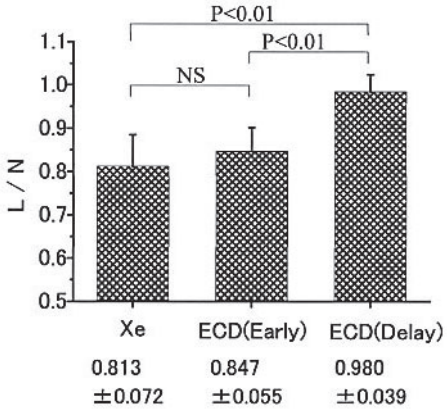
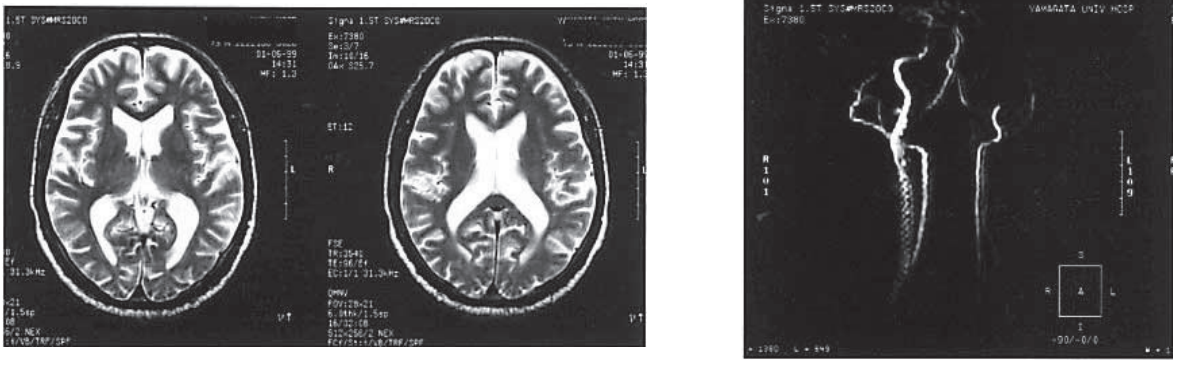


Fig. 3 The mean ratio of reduced lesion to normal brain (L/N ± SD) of the 20 patients on the ^{133}Xe-rCBF SPECT, the early and the conventional static ^{99m}Tc-ECD SPECT.



a b

Fig. 4 MR study in a 73-year-old male with transient ischemic attack (TIA). (a) MRI (T2-WT) shows almost normal image. (b) MR-angiography shows severe stenosis of the left IC.

Many investigators have described the nonlinear relationship between the accumulation of ^{99m}Tc-ECD and cerebral blood flow. The main cause of the non-linearity was reported to be due to back diffusion especially in high flow regions.[1] Some methods for correction of the non-linearity were also reported.[2–5] To ascertain the cause of the non-linearity, we analyzed the kinetic behavior during the retention of ^{99m}Tc-ECD using a newly developed "super rapid SPECT system."[6]

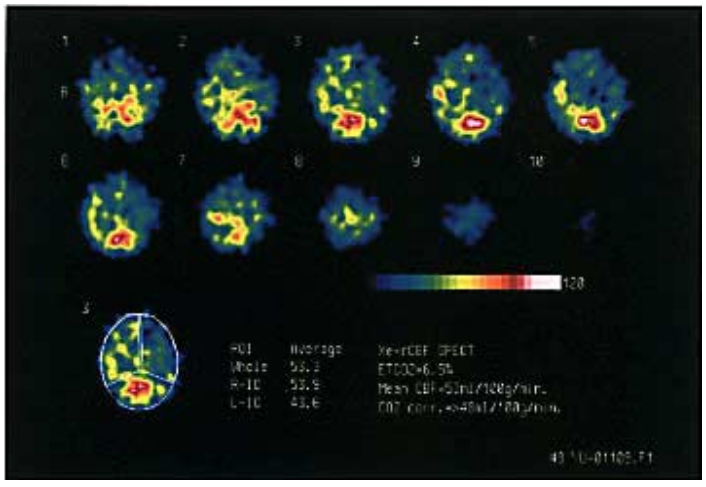


Fig. 5a

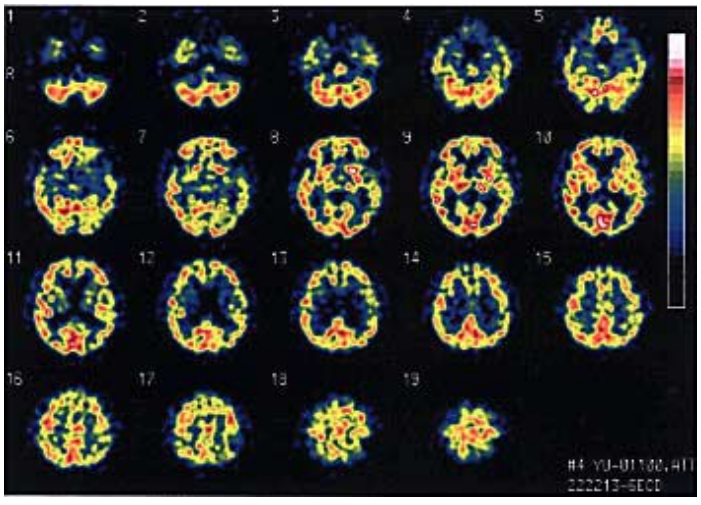


Fig. 5b

Fig. 5 Comparison between ^{133}Xe-rCBF SPECT and ^{99m}Tc-ECD SPECT. (a) Reduction in rCBF at the L-IC territory is clearly seen by the method of ^{133}Xe-rCBF SPECT. (b) But static ^{99m}Tc-ECD SPECT did not demonstrate this reduction.

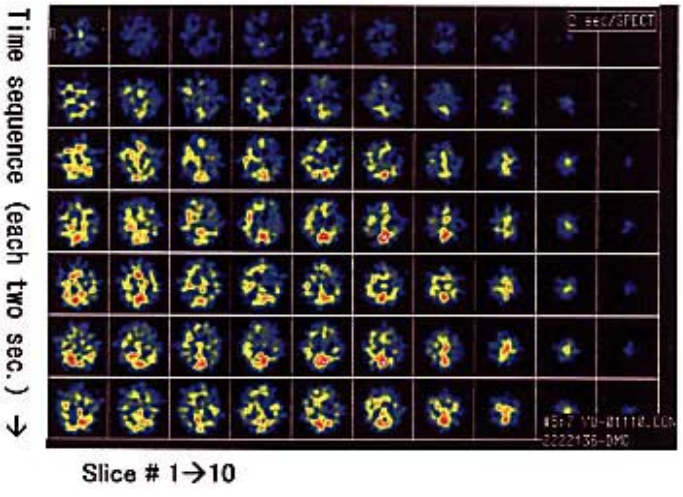


Fig. 6a

Fig. 6 Dynamic study: (a) sequential images every 2 seconds of the dynamic SPECT. The reduced lesion at the L-IC territory was seen only at the early phase. (b) The time-activity curves at the right & left IC territory and the whole slice. (c) Region of interests (ROI) to generate the time-activity curves.

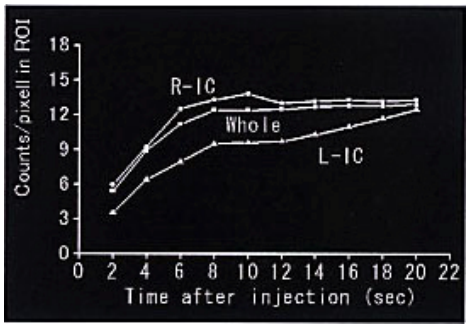


Fig. 6b

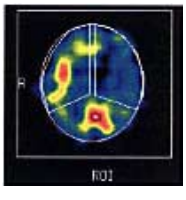


Fig. 6c

METHODS AND MATERIALS

Development of "super rapid SPECT"

We newly developed a super rapid SPECT system, which made it possible to take a SPECT series every 2 seconds as a dynamic imaging. This system was originally designed based on the "CERASPECT" (DSI, Inc., Waltham, MA, USA). The appearance and detector of the SPECT system are shown in Figure 1. The detector system is composed of a cylindrical scintillation crystal and 63 photomultiplier tubes (PMT). A high-sensitive type collimator was specially designed to have many holes with 25 mm of length, 3.14 mm of diameter consisting of 0.48 mm thick lead. The sensitivity of this system was 175 kcps/MBq/ml/cm slice thickness, and resolution was 12 mm FWHM at the center, 5.5 mm FWHM at 9 cm from the center of the 20 cmϕ water phantom. Each series of the SPECT images contains a maximum of 16 slices (6.6 mm thickness) in a matrix size of 32 × 32. The trial maximum dynamic rate was 1.7 seconds for each SPECT series. The dynamic rate was limited by the mechanical limitation of the collimator-rotation.

Patients: Twenty patients with chronic ischemic lesions due to arterial occlusion and/or stenosis that were detected clearly only by the quantitative ^{133}Xe-rCBF SPECT but unclear on static ^{99m}Tc-ECD SPECT were selectively analyzed. The ratio of the reduced region in cerebral blood flow to the contralateral region on the ^{133}Xe-rCBF SPECT ranged from 0.71 to 0.89 (mean = 0.813 ± 0.072). Informed consent was obtained from all subjects, and the study was approved by the Ethics Committee of Yamagata University.

Study protocol: The protocol for consecutive ^{133}Xe-rCBF SPECT, dynamic and static ^{99m}Tc-ECD SPECT is shown in Figure 2. After the ^{133}Xe-rCBF SPECT study using 1,850 MBq of ^{133}Xe, 700 MBq of ^{99m}Tc-ECD was injected intravenously, and dynamic SPECT data were acquired every 2 seconds during a 90-second period. Then the collimator was changed to a high-resolution type, and static SPECT data were acquired for 10 min.

Xe-rCBF SPECT: ^{133}Xe-rCBF SPECT study was performed by the ^{133}Xe gas bolus inhalation method[7] using the high-sensitive type (HS) collimator. Dynamic SPECT data of every 30 seconds were acquired during a 1.5 min inhalation phase and 4.5 min washout phase. The ^{133}Xe-rCBF SPECT image was constructed by the method of Kanno-Lassen.[8]

Dynamic SPECT: Just after the intravenous injection of 700 MBq ^{99m}Tc-ECD, dynamic data were acquired as a sequential SPECT every 2 seconds during 90 seconds. The matrix size was 32 × 32 × 10 slices.

Static SPECT: After the dynamic data acquisition, the collimator was changed to the high-resolution type (HR). Then static SPECT data were acquired in a matrix size of 128 × 128 × 64 slices. The SPECT image was displayed as a summation of three slices.

Data analysis: The serial dynamic SPECT images were constructed. Regions of interest (ROI) were set on the ischemic lesion and contralateral normal brain. The time-activity curves at several ROI were generated. The time-course of the tracer retention at the ischemic lesion and the normal region were analyzed, and compared with the static ^{99m}Tc-ECD SPECT and the ^{133}Xe-rCBF SPECT.

RESULTS

On the dynamic serial SPECT, all of 20 patients with mildly or moderately reduced rCBF lesions on the ^{133}Xe-rCBF SPECT were recognized as having a low activity region only at the early phase (during about 2–20 sec), with the reduced rCBF lesion gradually vanishing. Then these reduced uptake lesions were not detected on the conventional static SPECT taken after the dynamic study. Therefore time-activity curves at the reduced rCBF lesion were lower than those of contralateral normal brain at the early phase, and gradually overtook the activity in the normal region. The mean ratios of reduced lesion to normal brain (L/N ± SD) of the 20 patients were 0.813 ± 0.072, 0.847 ± 0.055 and 0.980 ± 0.039 on the ^{133}Xe-rCBF SPECT, the early ^{99m}Tc-ECD SPECT and the conventional static ^{99m}Tc-ECD SPECT respectively. No significant difference was seen between ^{133}Xe-rCBF SPECT and early ^{99m}Tc-ECD SPECT. The differences between static ^{99m}Tc-ECD SPECT and ^{133}Xe-rCBF SPECT, and also early ^{99m}Tc-ECD SPECT were significant ($p < 0.01$) (Fig. 3).

A representative case: 73-year-old male with transient ischemic attack (TIA)

MRI (T2-WT) shows an almost normal image (Fig. 4-a). MR-angiography shows severe stenosis of the left IC (Fig. 4-b). Obvious reduction in rCBF at the L-IC territory is seen by the method of ^{133}Xe-rCBF SPECT (Fig. 5-a). The reduced ratio to the contralateral side was 0.81. But the reduced lesion was not noted on the static ^{99m}Tc-ECD SPECT (Fig. 5-b), while the reduced lesion at the L-IC territory was seen only at the early phase on the dynamic SPECT (Fig. 6-a). The time-activity curve on the L-IC territory revealed lower activity than that of the contralateral region until 12 seconds, and increased gradually until 20 seconds after the first SPECT (Fig. 6-b). The reduced ratio to the contralateral side at the early phase is about 0.8 which corresponded to the ratio by the method of ^{133}Xe-rCBF SPECT.

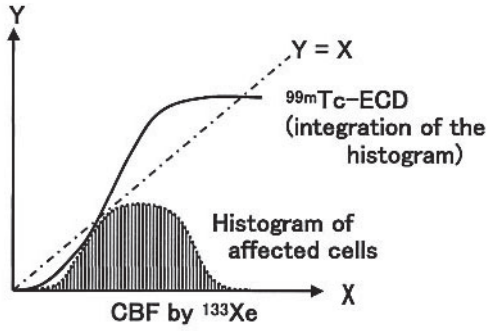


Fig. 7 Various tolerant levels to ischemia make a Poisson like histogram of affected cells. The integration of the histogram may be a survival (tolerated cells) curve corresponding to radioactive density of the ECD.

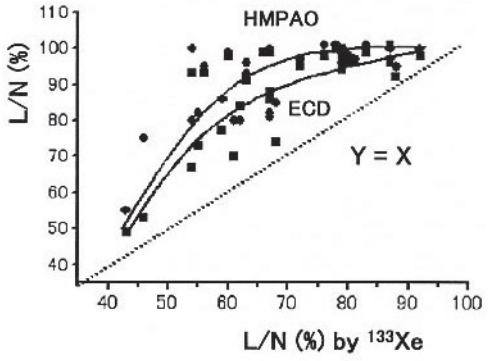


Fig. 8 Relations between ECD (or HMPAO) and Xe-133 in the ratio of ischemic lesion (L) to the contralateral normal region (N).

DISCUSSION

The usefulness of the early image on the dynamic ^{99m}Tc-ECD SPECT in patients with subacute cerebral infarction was reported by Ogasawara et al.[9] Their dynamic SPECT data were acquired with a scan-time duration of 36 seconds. The first 36 second SPECT showed close imaging contrast with rCBF by Xe-133 and revealed reflow hyperemia in areas of subacute stroke, which ^{99m}Tc-ECD static SPECT failed to show. Our newly developed dynamic SPECT has a dynamic rate with a scan-time duration of 2 seconds, with this dynamic rate far more rapid as compared with their system. So we were able to analyze the kinetic behavior of ^{99m}Tc-ECD just during the tracer retention. The mildly or moderately reduced rCBF lesions on the ^{133}Xe-rCBF SPECT were recognized as a low activity region only at the quite early phase (during about 2–20 sec or less), and gradually normalized the reduced lesion on the ^{99m}Tc-ECD dynamic SPECT. Also the time-activity curve at the reduced rCBF lesion was lower than that of contralateral normal brain at the early phase, and gradually overtook the activity of the normal region. The ratio of the radioactivity at the just early phase reflected the ratio of cerebral blood flow. So the initial retention corresponded to the cerebral blood flow. The gradual increasing phase is considered to reflect the retention process of ^{99m}Tc-ECD in the brain tissue. After the initial accumulation, the retention may progress gradually in the ischemic lesion. The cerebral blood flow in the gradually increasing lesion may be over the threshold-level for failure of ECD retention. We speculate that esterase activity of the neural cells, which changes the lipophilic ^{99m}Tc-ECD into hydrophilic form, has various threshold-levels to the same ischemic level. Therefore the quantity of additional affected cells according to reduction in blood-flow makes a Poisson like histogram. The integration curve of the histogram may be the total quantity of surviving residual cells according to the blood flow reduction. Then the integration curve may correspond to the radioactive density of the ECD (Fig. 7). The various tolerant levels may be one of the important background factors accounting for the non-linearity in the correlation between ^{99m}Tc-ECD accumulation and cerebral blood flow as shown in Figure 8.[10]

The distribution of ^{99m}Tc-ECD is different from that of ^{99m}Tc-HMPAO even in normal subjects. For example the accumulation of ^{99m}Tc-ECD is relatively high in the occipital lobe, but relatively low in the medial temporal region, while the accumulation of ^{99m}Tc-HMPAO in the cerebellum is relatively high. The different distribution between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO may not be caused by rCBF distribution, but mediated by the distribution of the activity of esterase or glutathione with retention of ^{99m}Tc-ECD or ^{99m}Tc-HMPAO respectively. Namely, not only cerebral blood flow but also the potency of the retention mechanism affects the tracer distribution. So the potency of the retention mechanism might reflect on the model for quantitative rCBF estimation.

CONCLUSION

All of mildly or moderately reduced rCBF lesions on ^{133}Xe-rCBF SPECT were recognized as low activity regions only at the early phase (about 2–20 sec), with the lesion then vanishing gradually. These lesions were not recognized as abnormal reduced regions on the conventional static SPECT taken after the dynamic study.

This study suggests that esterase activity is tolerate to the mild or moderate ischemia. The various tolerant levels of retention may be one of the important background factor accounting for the non-linearity in the correlation of ECD accumulation with cerebral blood flow.

REFERENCES

1. Kundsen GM, Andersen AR, Somnier FE, Videbaek C, Hasselbalch S, Paulson OB. Brain extraction and distribution of Tc-99m bicisate in human and rats. *J Cereb Blood Flow Metab* 1994; 14 (Suppl 1): S12–S18.

2. Crone C. The permeability of capillaries in various organs as determined by use of the "indicator diffusion" method. *Acta Physiol Scand* 1963; 58: 292–305.
3. Raichle ME, Eiching JO, Straatmann MG, Welch MJ, Larson KB. Blood-brain barrier permeability of C-11-labeled alcohols and O-15-labeled water. *Am J Physiol* 1976; 230: 543–552.
4. Yonekura Y, Tsuchida T, Sadato N, Nishizawa S, Iwasaki Y, Mukai T, et al. Brain perfusion SPECT with Tc-99m-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.
5. Tsuchida T, Yonekura Y, Nishizawa S, Sadato N, Tamanki N, Fujita T, et al. Nonlinearity correction of brain perfusion SPECT based on permeability-surface area product model. *J Nucl Med* 1996; 37: 1237–1241.
6. Komatani A, Sugai Y, Hosoya T. Development of super rapid dynamic SPECT, and analysis of ^{99m}Tc-ECD dynamics in ischemic lesion. *Eur J Nucl Med* 2001; 28 (Suppl): S1223.
7. Komatani A, Akutsu T, Yamaguchi K. Xennon-133 rCBF SPECT by newly designed bolus inhalation method. *KAKU IGAKU (Jpn J Nucl Med)* 1994; 31: 637–641.
8. Kanno I, Lassen NA. Two methods for calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 1979; 3: 71–76.
9. Ogasawara K, Ogawa A, Ezura M, Konno H, Doi M, Kuroda K, et al. Dynamic and static ^{99m}Tc-ECD SPECT imaging of subacute cerebral infarction: Comparison with ^{133}Xe-SPECT. *J Nucl Med* 2001; 42: 543–547.
10. Komatani A, Sugai Y, Watanabe N, Yamaguchi K, Kawakatsu S. Discrepancy between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD in Alzheimer's disease: Does the retention mechanism depend on the disease? *KAKU IGAKU (Jpn J Nucl Med)* 1998; 35: 715–720.