Hypofixation and Hyperfixation of ^{99m}Tc-Hexamethyl Propyleneamine Oxime in Subacute Cerebral Infarction

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The relationship between hypofixation and hyperfixation of ^{99m}Tc-hexamethyl propyleneamine oxime (^{99m}Tc-HMPAO) remains unclear. The purpose of this study was to compare ^{99m}Tc-HMPAO SPECT with regional cerebral blood flow (CBF) imaging using ^{133}Xe inhalation in patients with subacute cerebral infarction and to investigate the behavior of ^{99m}Tc-HMPAO in the infarct area using dynamic SPECT. **Methods:** ^{133}Xe and consecutive ^{99m}Tc-HMPAO SPECT studies, the latter of which consisted of dynamic and static scanning, were performed on 51 patients (22 women, 29 men; age range, 40–83 y; mean age, 61 y) with cortical infarction in the middle cerebral artery territory 13–15 d after stroke onset. One region of interest (ROI) was drawn in the infarct area. The control ROI was mirrored to the contralateral side, and the same set of ROIs was applied to all SPECT studies. Fractional fixation of ^{99m}Tc-HMPAO in the infarct area was evaluated relatively as the ratio of the infarct-to-control region in ^{99m}Tc-HMPAO static tomograms/the ratio of the infarct-to-control region in CBF images using ^{133}Xe inhalation and was classified as hyperfixation when this value was >1.1 and hypofixation when this value was <0.9. To investigate the behavior of ^{99m}Tc-HMPAO in the infarct area, the second (36–72 s after tracer injection) and eighth (252–288 s after tracer injection) of 8 dynamic scans were selected, and the washout rate was calculated using the formula: 1 − (mean count in the eighth scan/mean count in the second scan). **Results:** The infarct area showed hyperfixation of ^{99m}Tc-HMPAO when CBF in the area was 35 mL/100 g/min or less and showed hypofixation when CBF was >45 mL/100 g/min. The washout rate was usually negative when CBF imaging using ^{133}Xe inhalation was <20 mL/100 g/min but was positive when it was >45 mL/100 g/min. The washout rate was negative when the infarct area showed hyperfixation of ^{99m}Tc-HMPAO but was positive when it showed hypofixation. **Conclusion:** ^{99m}Tc-HMPAO SPECT underestimates CBF in high-flow regions and overestimates CBF in low-flow regions of subacute cerebral infarction. ^{99m}Tc-HMPAO hypofixation and hyperfixation are associated with backdiffusion from the brain to blood and gradual accumulation of hydrophilic metabolites, respectively. Dynamic images should be useful for discriminating between ^{99m}Tc-HMPAO hypofixation and hyperfixation.

Key Words: ^{99m}Tc-HMPAO; subacute stroke; brain SPECT

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A radiopharmaceutical that was developed for use in cerebral blood flow (CBF) imaging by SPECT is ^{99m}Tc-hexamethyl propyleneamine oxime (^{99m}Tc-HMPAO) (*1*). HMPAO is a stable, lipophilic, small molecule that circulates with the blood to the brain and rapidly passes through the blood–brain barrier, where it is metabolized intracellularly from the lipophilic form to a hydrophilic derivative. The exact mechanism of retention in brain cells is unknown. However, a steric transformation of the HMPAO chelate linked to intracellular glutathione activity has been proposed (*2*), and an effect of the redox state of the interstitial space has recently been discussed (*3*).

The distribution of ^{99m}Tc-HMPAO in the brain is proportional to CBF over a wide range (*4*). However, CBF-dependent backdiffusion of nonmetabolized lipophilic ^{99m}Tc-HMPAO from the brain to blood causes poor image contrast between normal and hypoperfused areas (*5*) and CBF underestimation in high-flow regions (*6*). Lassen et al. (*7*) have proposed an algorithm with which to correct underestimated CBF values.

On the other hand, Sperling and Lassen (*8,9*) showed dissociation between increased ^{99m}Tc-HMPAO uptake in infarcted areas and relatively low-flow values using the reference method of CBF analysis (^{133}Xe). They indicated that ^{99m}Tc-HMPAO SPECT can overestimate reflow hyperemia after spontaneous reperfusion in patients with subacute ischemic stroke. Although hypofixation and hyperfixation of ^{99m}Tc-HMPAO—namely, the underestimation and overestimation of CBF—are conflicting phenomena, the relationship between the 2 has not been determined (*8*).

The purpose of this study was to compare ^{99m}Tc-HMPAO SPECT with regional CBF imaging using ^{133}Xe inhalation in patients with subacute cerebral infarction and to investigate the behavior of ^{99m}Tc-HMPAO in the infarct area using dynamic SPECT.

MATERIALS AND METHODS

Patients

Fifty-one patients (22 women, 29 men; age range, 40–83 y; mean age ± SD, 61 ± 9 y) with subacute cerebral infarction caused by cerebral embolism were admitted to Kohnan hospital between January 1995 and May 1996 and participated in this study. At Kohnan Hospital, local intra-arterial thrombolysis using recombinant tissue plasminogen activator is indicated as the treatment of choice for cerebral embolism according to 3 criteria: the patient is hospitalized within 6 h of onset; no regions of hypodensity are observed on the CT scan on admission; and sites of occlusion are in the middle cerebral artery (MCA). All patients who do not meet the criteria for this therapy receive only conservative systemic care. We never use medications that affect the function of thrombocytes or the coagulation–fibrinolysis system in order not to impair hemorrhagic transformation associated with delayed recanalization. For ischemic brain edema or hemorrhagic transformation, mannitol or glycerol is administered. When this treatment is ineffective and brain herniation is progressing, mild hypothermia or decompressive hemicraniotomy should be performed. The subjects of this study were patients who did not meet our criteria for local intra-arterial thrombolysis and did not require mild hypothermia or decompressive hemicraniotomy.

Cerebral angiography was performed on all patients within 24 h of the onset of symptoms. Sites of occlusion were the internal carotid artery in 17 patients, the horizontal segment of the MCA in 20 patients, and distal to the bi- or trifurcation of the MCA main trunk in 9 patients. Angiographic occlusions were not evident in 5 patients. CT scans performed 1 wk after stroke onset revealed massive cortical infarction in the MCA territories of all patients.

This study was performed according to the standards of good medical practice. Informed consent was obtained from all participants or their next of kin, and the ethics committee of Kohnan Hospital approved the study.

SPECT Imaging

A SPECT study was performed on all patients 13–15 d after stroke onset. SPECT images were obtained using a multidetector ring-type scanner, the detector array of which consists of 64 NaI crystals in a 38-cm-diameter circle. After tomographic reconstruction, the spatial resolution and slice thickness in the center of the plane were 9- and 16-mm full width at half maximum (FWHM), respectively, for static imaging and 20- and 25-mm FWHM, respectively, for dynamic imaging. The energy window in this study was 140 keV ± 15%. Projection data for static and dynamic imaging were processed with Ramachandran's filtered backprojection after introduction of a Butterworth prefilter. A 64 × 64 (^{99m}Tc-HMPAO static) or 32 × 32 (^{99m}Tc-HMPAO dynamic and ^{133}Xe) image matrix was used.

Patients inhaled 1480 MBq ^{133}Xe gas for 1 min, and sequence SPECT imaging was performed every min for 10 min using a high-sensitivity collimator. Quantitative CBF maps were reconstructed using the Kanno–Lassen method (*10*). ^{99m}Tc-HMPAO was prepared from a freeze-dried kit by addition of 1110 MBq freshly eluted pertechnetate in 5 mL saline solution immediately before injection. The radiochemical purity of ^{99m}Tc-HMPAO was tested according to the manufacturer's recommendations. In this study, only reconstituted kits with a radiochemical purity of >80% were used. Ten to 15 min after the ^{133}Xe SPECT scan, each patient received an intravenous bolus injection of 1110 MBq ^{99m}Tc-HMPAO. At the same time, dynamic scanning with a high-sensitivity collimator was begun and continued for a total of 288 s (8 scans) with a scan-time duration of 36 s. Static SPECT imaging with a high-resolution collimator proceeded 10 min after tracer injection. Tomographic data were obtained continuously over a 20-min period (Fig. 1).

Among axial slices, 1 slice through the basal ganglia was selected. One 11.1-cm^2 region of interest (ROI) was drawn in the infarct area shown on CT scans. The control ROI was mirrored to the contralateral side, and the same set of ROIs was applied to all SPECT studies. Fractional fixation of ^{99m}Tc-HMPAO in the infarct area was evaluated relatively as the ratio of the infarct-to-control region in ^{99m}Tc-HMPAO static tomograms/the ratio of the infarct-to-control region in CBF images using ^{133}Xe inhalation and was classified as hyperfixation when this value was >1.1 and hypofixation when this value was <0.9. To investigate the behavior of ^{99m}Tc-HMPAO in the infarct area, the second and eighth of 8 dynamic scans were selected, and the washout rate was calculated using the formula: 1 − (mean count in the eighth scan/mean count in the second scan).

Statistical Analysis

Correlations among various parameters were determined by linear regression analysis and by computing regression equations and correlation coefficients. The Mann-Whitney *U* test was used to compare CBFs between groups. Statistical significance was set at the $P < 0.05$ level.

RESULTS

The ratio of the infarct-to-control region in ^{99m}Tc-HMPAO static tomograms was compared with that in ^{133}Xe-CBF, and the results are shown in Figure 2. The fit to the regression line was significant ($P < 0.0001$), with the correlation coefficient being 0.79. However, the ratios of the infarct-to-control region in ^{99m}Tc-HMPAO static tomograms were lower at high ratios of the infarct-to-control region and

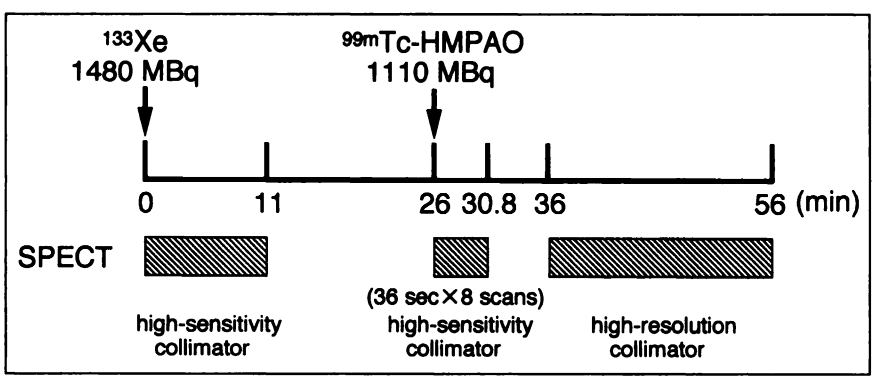

FIGURE 1. Protocol for consecutive ^{133}Xe and dynamic and static ^{99m}Tc-HMPAO SPECT imaging.

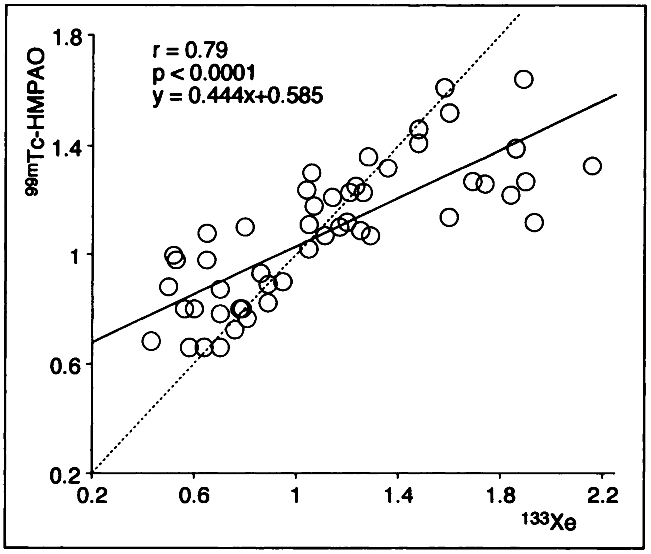

FIGURE 2. Relationship between ratio of infarct-to-control region in ^{99m}Tc-HMPAO static tomograms and that in ^{133}Xe tomograms. Dotted line represents line of identity.

higher at low ratios of the infarct-to-control region of ^{133}Xe-CBF tomograms. The CBF of the control region on the contralateral side ranged from 19 to 41 mL/100 g/min (mean ± SD, 25.2 ± 5.0 mL/100 g/min), which was significantly ($P < 0.0001$) lower than the normal control value (mean ± SD, 46.1 ± 3.1 mL/100 g/min) obtained from 10 healthy volunteers (age range, 35–65 y; mean age, 52.3 y).

The relationships between ^{133}Xe-CBF, the relative fractional fixation of ^{99m}Tc-HMPAO, and the washout rate of ^{99m}Tc-HMPAO in the infarct area are shown in Figure 3. The correlation between relative fractional fixation and ^{133}Xe-CBF was significant ($r = -0.71$; $P < 0.0001$). The infarct area showed hyperfixation of ^{99m}Tc-HMPAO when ^{133}Xe-CBF was 35 mL/100 g/min or less and hypofixation when it was >45 mL/100 g/min. The correlation between the washout rate and ^{133}Xe-CBF was significant ($r = 0.83$; $P < 0.0001$). The washout rate was usually negative when the flow rate of ^{133}Xe-CBF was <20 mL/100 g/min but was positive when it was >45 mL/100 g/min. The correlation between the washout rate and the relative fractional fixation was significant ($r = -0.84$; $P < 0.0001$). The washout rate was negative when the infarct area showed ^{99m}Tc-HMPAO hyperfixation but was positive when it showed hypofixation.

Figures 4 and 5 show time–activity curves for dynamic SPECT typical of ^{99m}Tc-HMPAO hypofixation and hyperfixation, respectively.

DISCUSSION

The notion has prevailed since 1993 that patients with reperfusion in regions of subacute cerebral infarction always

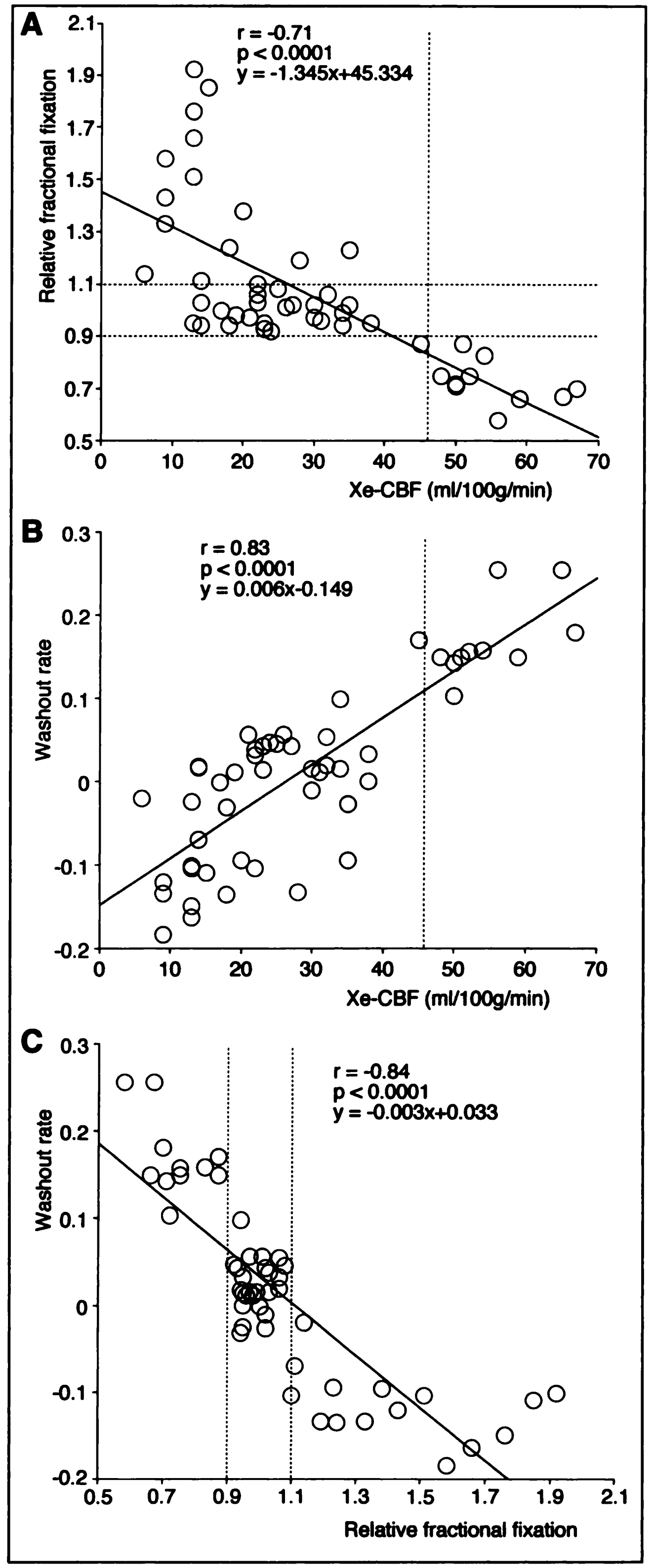

FIGURE 3. (A) Relationship between relative fractional fixation of ^{99m}Tc-HMPAO and CBF in infarct areas. (B) Relationship between washout rate of ^{99m}Tc-HMPAO and CBF in infarct areas. (C) Relationship between washout rate and relative fractional fixation of ^{99m}Tc-HMPAO in infarct areas. Relative fractional fixations >1.1 and <0.9 indicate hyperfixation and hypofixation of ^{99m}Tc-HMPAO, respectively (dotted vertical lines in C and dotted horizontal lines in A). Dotted vertical lines in A and B indicate mean CBF of healthy volunteers (control group).

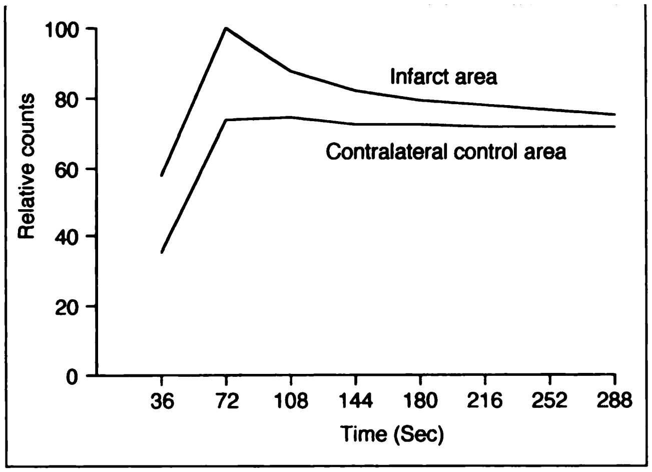

FIGURE 4. Example of hypofixation: 47-y-old man with cerebral infarction in right MCA territory. Time–activity curves for dynamic ^{99m}Tc-HMPAO SPECT reveal rapid decrease in tracer activity in infarct area.

exhibit hyperfixation on ^{99m}Tc-HMPAO SPECT (*11–14*). All authors who have described this phenomenon have used the term "hyperfixation" to indicate ^{99m}Tc-HMPAO uptake in the infarct region exceeding that in the corresponding region of the contralateral hemisphere (*11–14*). However, Sperling and Lassen (*8*) originally used this term to describe ^{99m}Tc-HMPAO retention exceeding what could be explained by CBF alone—that is, side-to-side asymmetry in ^{99m}Tc-HMPAO uptake clearly exceeding that for CBF. Therefore, the method of quantitative CBF analysis should be referred to when testing for hyperfixation of ^{99m}Tc-HMPAO. According to Sperling and Lassen (*9*), who analyzed a series of paired ^{133}Xe and ^{99m}Tc-HMPAO studies, 13 of 14 patients with subacute cortical infarction exhibited hyperfixation in the infarct area: The side-to-side asymmetry index of the ^{99m}Tc-HMPAO counting rate exceeded that of ^{133}Xe-CBF by 9%–30%. They also stressed that ^{99m}Tc-HMPAO SPECT overestimates even reflow hyperemia with ^{133}Xe-CBF equal to or higher than that in the control region on the contralateral side (*8,9*). Our finding that ^{99m}Tc-HMPAO SPECT underestimated CBF in high-flow infarct areas appears to be inconsistent with their results. Meyer et al. (*15*) reported bilateral reduction of hemispheric CBF in patients with unilateral cerebral infarction and concluded that unilateral hemispheric damage with reduced metabolism caused transhemispheric reduction of metabolism and a consequent reduction in blood flow on the contralateral side. Indeed, CBF of the control region on the contralateral side of our patients was considerably lower than the mean CBF of healthy volunteers (control group). Therefore, although CBF in the infarct region was the same as or higher than that in the control region on the contralateral side, it might have been below normal levels in the patients with hyperfixation observed by Sperling and Lassen.

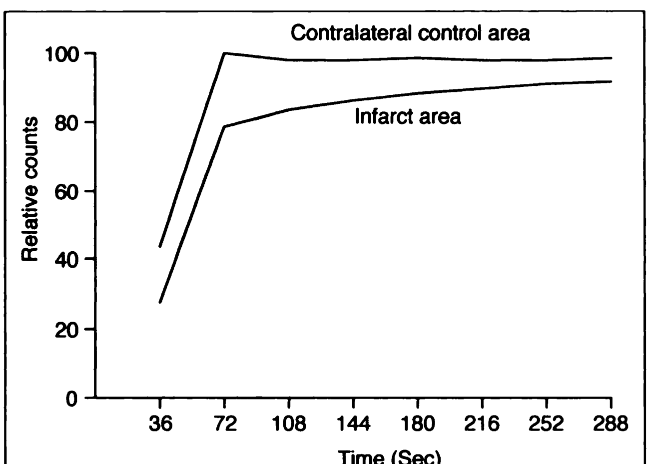

FIGURE 5. Example of hyperfixation: 60-y-old man with cerebral infarction in left MCA territory. Time–activity curves for dynamic ^{99m}Tc-HMPAO SPECT reveal gradual increase in tracer activity in infarct area.

In this study, the ^{99m}Tc-HMPAO washout rate increased with decrease in the fractional fixation of ^{9m}Tc-HMPAO in the infarct area. These findings confirmed that the underestimation of CBF in ^{99m}Tc-HMPAO SPECT images in subacute cerebral infarction with high-flow regions is associated with increased backdiffusion from the brain to blood, as observed in patients with chronic disease (*16*).

On the other hand, the washout rate in low-flow infarct areas with ^{99m}Tc-HMPAO hyperfixation was negative, indicating a gradual increase in tracer activity. Hyperfixation of ^{99m}Tc-HMPAO is observed only during the subacute stage (10–28 d after stroke onset), when damaged cerebral tissue undergoes repair with the formation of new capillaries and granulation tissue in the infarct area (*9*). Our finding therefore suggests that the excess ^{99m}Tc-HMPAO uptake was associated with the gradual accumulation of hydrophilic metabolites in new capillaries or granulation tissue resulting from alteration of the blood–brain barrier. In high-flow infarct areas, a similar ^{99m}Tc-HMPAO phenomenon should also be present, but its effect on fractional fixation is probably negligible compared with that of backdiffusion from the brain to blood.

The CBF-dependent backdiffusion and gradual accumulation of ^{99m}Tc-HMPAO in subacute stroke might interfere with the ability to obtain accurate CBF images in static SPECT. Dynamic images should be useful for discriminating between ^{99m}Tc-HMPAO hypofixation and hyperfixation because the correlation between the washout rate and the fractional fixation was significantly negative and that between the washout rate and CBF was significantly positive. These findings also suggest that ^{99m}Tc-HMPAO dynamic images permit CBF in infarct areas to be quantified.

CONCLUSION

^{99m}Tc-HMPAO SPECT underestimates CBF in high-flow regions and overestimates CBF in low-flow regions of subacute cerebral infarction. ^{99m}Tc-HMPAO hypofixation and hyperfixation are associated with backdiffusion from the brain to blood and gradual accumulation of hydrophilic metabolites, respectively. Dynamic images should be useful for discriminating between ^{99m}Tc-HMPAO hypofixation and hyperfixation.

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. Neirinckx RD, Burke JF, Harrinson 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(suppl):S4–S12.
3. 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.
4. Inugami A, Kanno I, Uemura K, et al. Linearization correction of ^{99m}Tc-labeled hexamethyl-propylene amine oxime (HM-PAO) image in terms 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(suppl):S52–S60.
5. Yonekura Y, Nishizawa S, Mukai T, et al. SPECT with [^{99m}Tc]-d,l-hexamethyl-propylene amine oxime (HM-PAO) compared with regional cerebral blood flow measured by PET: effects of linearization. *J Cereb Blood Flow Metab.* 1988; 8(suppl):S82–S89.
6. Andersen AR, Friberg HH, Schmidt JF, Hasselbalch SG. 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(suppl):S69–S81.
7. Lassen NA, Andersen AR, Friberg L, Paulson OB. The retention of [^{99m}Tc]-d,l-HM-PAO in the human brain after intracarotid bolus injection: a kinetic analysis. *J Cereb Blood Flow Metab.* 1988;8(suppl):S13–S22.
8. Sperling B, Lassen NA. Hyperfixation of HMPAO in subacute ischemic stroke leading to spuriously high estimates of cerebral blood flow by SPECT. *Stroke.* 1993;24:193–194.
9. Sperling B, Lassen NA. Unreliability of rCBF-SPECT in subacute ischemic stroke [letter]. *Stroke.* 1993;24:1099–1100.
10. Kanno I, Lassen NA. Two methods for calculating regional cerebral blood flow from computed tomography of inert gas concentrations. *J Comput Assist Tomogr.* 1979;3:71–76.
11. Papatheofanis FJ, Shirazi P, Gupta AS. Tc-99m HMPAO hyperfixation and reversal on cerebral SPECT imaging after subacute ischemic infarction. *Clin Nucl Med.* 1995;20:82–83.
12. Shintani S, Tsuruoka S, Satoh Y. Spurious hyperfixation of hexamethylpropyleneamine oxime in acute embolic stroke. *AJNR.* 1995;16:1532–1535.
13. Shintani S, Tsuruoka S, Shiigai T. Paradoxical hyperfixation of hexamethylpropyleneamine oxime in cerebral infarction. *AJNR.* 1997;18:1905–1908.
14. Toyama H, Takeshita G, Shibata K, et al. Evaluation of the clinical usefulness of super dynamic ^{99m}Tc-HM-PAO SPECT in ischemic cerebrovascular disease [in Japanese]. *Kaku Igaku.* 1996;33:521–529.
15. Meyer JS, Shinohara Y, Kanda T, Fukuuchi Y, Ericsson AD, Kok NK. Diaschisis resulting from acute unilateral cerebral infarction. *Arch Neurol.* 1970;23:241–247.
16. Murase K, Tanada S, Fujita H, Sakaki S, Hamamoto K. Kinetic behavior of technetium-99m-HMPAO in the human brain and quantification of cerebral blood flow using dynamic SPECT. *J Nucl Med.* 1992;33:135–143.