Filling Out Phenomenon with Technetium-99m HM-PAO Brain SPECT at the Site of Mild Cerebral Ischemia

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Although the distribution of [^{99m}Tc]hexamethylpropyleneamine oxime(HM-PAO) in the brain is said to be in a flow-related manner without temporal change, we present cases with leakage of [^{99m}Tc]HM-PAO (filling out phenomenon) in the delayed image of brain single photon emission computed tomography (SPECT) and clarify its clinical significance. The filling out phenomenon was observed in seven out of 21 cases of cerebrovascular disease and four cases of arteriovenous malformation. The leakage of [^{99m}Tc]HM-PAO was also confirmed by visual and semiquantitative analysis. In the pharmacokinetics of [^{99m}Tc]HM-PAO in the blood, the percent dose of plasma fraction at 4 hr was reduced to 54% of activity at 30 min. The percent dose of brain blood could be predicted as 3.36%/l at 30 min and 2.35%/l at 4 hr after correction with the hematocrit of the brain. The filling out phenomenon of [^{99m}Tc]HM-PAO was attributed to a significant reduction of blood activity of [^{99m}Tc]HM-PAO in the plasma. Since the initial image might mask reduced rCBF with an increase of rCBV, the late image would have an advantage in accurately evaluating rCBF from the clearance of [^{99m}Tc] HM-PAO bound to the plasma. Therefore, the filling out phenomenon of [^{99m}Tc]HM-PAO in late images of brain SPECT could show the area of mild cerebral ischemia accompanying cerebral vascular reserve.

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Lipophilic chelate of technetium-99m (^{99m}Tc) with d,l isomer of hexamethylpropyleneamine oxime (HM-PAO (*1*) can cross the blood-brain barrier with a high first-pass extraction fraction (*2*) and deposit in the brain in proportion to cerebral blood flow. The potential of [^{99m}Tc]HM-PAO was confirmed by the initial clinical findings (*3,4*). The maintenance of the regional distribution of [^{99m}Tc]HM-PAO with a very slow clearance from the brain provides ideal conditions for single photon emission computed tomography (SPECT) to obtain images of three-dimensional rCBF on a routine basis (*5*). However, we have reported leakage of [^{99m}Tc] HM-PAO in the late image at the site of mild cerebral ischemia (*6*), a finding also observed in regions of cerebral hyperemia described as "the filling out phenomenon" (*7*).

The aim of this study is to present cases which show the temporal change of "the filling out phenomenon" with [^{99m}Tc]HM-PAO brain SPECT and to explain its clinical meaning for evaluating cerebrovascular diseases after analyzing the temporal distribution of [^{99m}Tc]HM-PAO with brain SPECT visually and semiquantitatively and investigating the pharmacokinetics of [^{99m}Tc]HM-PAO in the blood.

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MATERIALS AND METHODS

Technetium-99m HM-PAO was prepared from a nonradioactive kit (Ceretec, Amersham Medical Limited). The vial was reconstituted with 3–4 ml of saline containing 20–35 mCi (740–1,295 MBq) of [^{99m}Tc]pertechnetate. Following ligand preparation, a solution of 15–25 mCi (555–925 MBq) of [^{99m}Tc]HM-PAO was withdrawn from the vial and injected intravenously within 5 min to the subject under investigation. After reconstitution, the radiochemical purity exceeded 90% when tested by chromatography (*8*).

CLINICAL STUDIES

The studies were carried out with a conventional rotating gamma camera (STARCAM, 400 AC/T, General Electric Co.,

Milwaukee, WI). Data were obtained from 64 projections for 15 sec into a 64 × 64 matrix, using a general all purpose collimator. The radiopharmaceutical was administered intravenously with a winged needle by bolus injection and flushing using 10 ml saline to avoid retention in a peripheral vein. Patients were supine with eyes closed by a mask for 15 min before and after injection.

In order to get the same plane of the SPECT image for comparing the initial image and late image, a right lateral planar image was taken for 15 sec with a mark on the right eye and the right external meatus by a hot spot of 3×10^{-1} mCi (11.1 MBq) ^{99m}Tc prior to SPECT, and the orbito-meatal line was determined. Data collection for the initial brain SPECT with [^{99m}Tc]HM-PAO (initial image) was started 15–30 min after the tracer was injected, then data on late brain SPECT with [^{99m}Tc]HM-PAO (late image) was collected after 4 hr. The acquisition time was 16 min, during which time the collected count exceeded 3.5 billion in the initial image and 2 billion in the late image using a general all purpose collimator.

All data were corrected for an attenuation of 0.1 cm^{-1} and the tomographic data were reconstructed using a filtered back-projection algorithm. Based on the orbito-meatal line from the right lateral planar image, the slice planes of the transaxial section were determined. The slice of each section was 6 mm in thickness. Transaxial, coronal, and sagittal images of [^{99m}Tc]HM-PAO brain SPECT were examined by visual inspection and classified into four groups depending on temporal distribution. The criteria for classification were as follows (Fig. 1): Group Ia; normal perfusion in the initial image and no subsequent filling out phenomenon (FOP) in the late image, Group Ib; normal perfusion in the initial image and subsequent FOP in the late image, Group IIa; defect in the initial image and subsequent no FOP in the late image, Group IIb; defect in the initial image and subsequent peri-infarct FOP in the late image. For semiquantitative analysis, regions of interest (ROIs) were drawn on a transverse slice of the defect area and the normal area at the matched contralateral side by manual outlining, and the mean count rate per voxel was estimated in each ROI. The count density ratio of a defect area to a normal area (D/N ratio) was obtained (Fig. 1). A brain SPECT with [^{99m}Tc]pertechnetate was done within 1 wk interval of taking [^{99m}Tc]HM-PAO brain SPECT and reconstructed using the same algorithm.

Five-milliliter blood samples were taken 30 min and 4 hr after administering the tracer. Activity in whole blood and separated plasma was measured and expressed as a percentage of the injected dose per liter (percent dose). Counts of whole blood (=W), those of plasma (=P) and those of [^{99m}Tc]HM-PAO (=T) of the administered solution in 10^{-4}l were measured with a well scintillation counter (TDC-601, Aoka). From the administered volume of [^{99m}Tc]HM-PAO (V:ml) and hematocrit of the patient (Ht), percent administered dose per liter of whole blood (%WB), and plasma (%PL) also cell-bound (%CB) was obtained from the following equations.

$$\%WB = \frac{W \times 10^5}{V \times T},$$

$$\%PL = \frac{P \times (1 - Ht) \times 10^5}{V \times T},$$

$$\%CB = \%WB - \%PL.$$

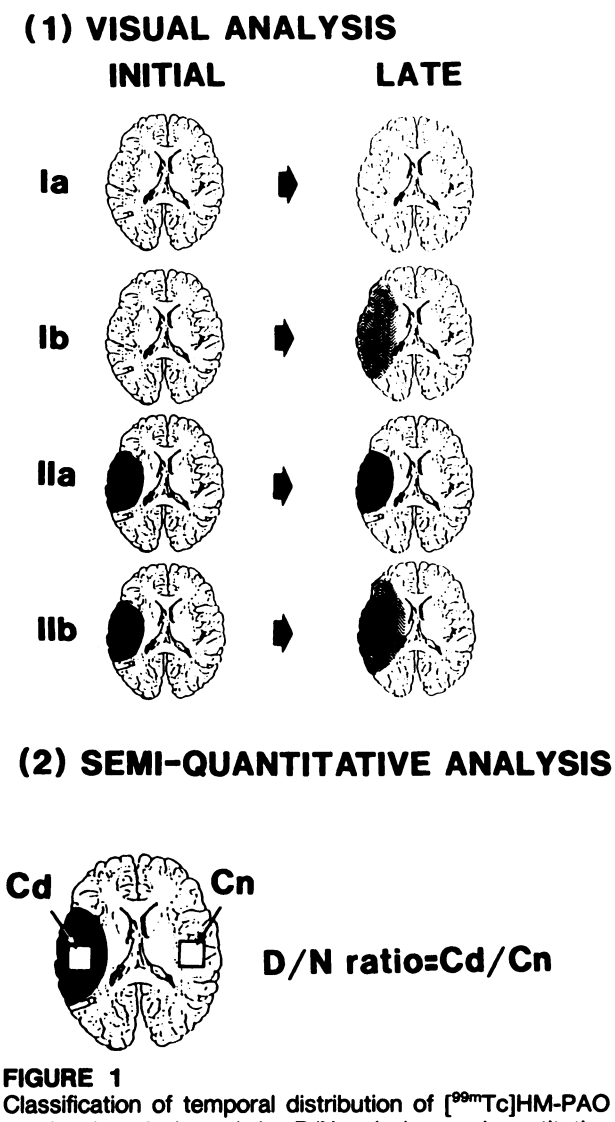

FIGURE 1
Classification of temporal distribution of [^{99m}Tc]HM-PAO by visual analysis and the D/N ratio by semiquantitative analysis. (D = Defect, N = Normal, Cd = Count in defect area, Cn = Count in normal area.)

All results were expressed as mean ± s.d. The significance of difference was calculated using the paired t-test. A p value of <0.01 was considered to be significant.

After informed consent had been obtained, a total of 25 subjects were studied: Twenty-one patients with transient ischemic attack (TIA) or cerebral infarction (CI) confirmed by clinical history, physical examination, transmission computed tomography, or magnetic resonance imaging and angiography; four patients with arteriovenous malformation (AVM) including one patient associated with hemangioma who was diagnosed as having Sturge-Weber syndrome.

RESULTS

Visual Analysis

Twenty-one patients of TIA or CI were classified into four groups; Group Ia (normal without FOP) comprised five cases, Group Ib (normal with FOP) comprised four

cases, Group IIa (defect without FOP) comprised nine cases and Group IIb (defect with peri-infarct FOP) comprised three cases (Table 1).

Cases from Group Ib, Group IIa, and Group IIb are presented. Case 6 in Group Ib was a 57-yr-old male who exhibited left hemiparesis when he awoke after having been drunk. An enhanced computed tomographic (CT) scan showed a high density area in the right anterior limb of the internal capsule, but stenosis of the cerebral artery was not detected. Technetium-99m HM-PAO brain SPECT was done on the 28th day from onset; a defect in the right fronto-temporo-parietal area was detectable in the late image but not in the initial image of the brain SPECT (Fig. 2). He was discharged without neurologic deficit.

Case 10 in Group IIa was a 66-yr-old female who exhibited left hemiparesis when watching television. A CT showed a low density area (LDA) in the right temporo-parietal area. Angiographically, the right middle cerebral artery (M1 portion) was occluded. Technetium-99m HM-PAO brain SPECT was done on the 56th day from onset; the size of the defect in the late image was the same as that in the initial image (Fig. 3). She was discharged with left hemiparesis.

Case 19 in Group IIb was a 65-yr-old male who exhibited left hemiplegia. A CT showed LDA in the right fronto-temporal area. Ninety percent stenosis of the right middle cerebral artery (M1 portion) was detected. Technetium-99m HM-PAO brain SPECT was done on the 25th day from onset. The extent of the defect in the right fronto-temporal area in the late image was larger than that in the initial image of the [^{99m}Tc] HM-PAO brain SPECT. Subsequent [^{99m}Tc]pertechnetate brain SPECT revealed a hot uptake in the right fronto-temporal area, the size of which was in accord with that of defect in the initial image of the [^{99m}Tc] HM-PAO brain SPECT (Fig. 4).

In Case 23 of a 56-yr-old male, the arteriovenous malformation was identified in the left thalamic area with enhanced x-ray CT and vertebral angiography. The image of AVM was also demonstrated as being warm in the initial image and subsequently cold in the late image with [^{99m}Tc]HM-PAO brain SPECT (Fig. 5).

Semiquantitative Analysis

Comparing the initial image with the late image, the D/N ratio in Group Ia (from 0.97 ± 0.04 to 0.96 ± 0.04) was unchanged, however, those in Group Ib (from 0.92 ± 0.04 to 0.78 ± 0.02) dropped significantly. In addition, the D/N ratio of Group IIa in the infarct area (from 0.70 ± 0.15 to 0.70 ± 0.15) and in the peri-infarct area (from 0.92 ± 0.08 to 0.91 ± 0.07) did not

TABLE 1
Clinical Presentation and Brain SPECT Result

Patient no.	Age (yr)	Sex	Diagnosis	Neurologic symptom	Lesion in X-RAY-CT	HM-PAO
1	65	M	TIA	(—)	(—)	Ia
2	76	M	TIA	(—)	(—)	Ia
3	44	F	TIA	(—)	(—)	Ia
4	67	M	TIA	(—)	(—)	Ia
5	63	M	TIA	(—)	(—)	Ia
6	57	M	CI	L-hemiparesis	Internal capsule*	Ib
7	46	M	CI	L-hemiparesis	R-temporal (small)	Ib
8	58	M	CI	Difficulty in writing	(—)	Ib
9	59	F	CI	R-hemiparesis	L-periventricular	Ib
10	66	F	CI	L-hemiparesis	R-temporo-parietal	IIa
11	46	M	CI	L-hemiparesis	R-temporo-parietal	IIa
12	76	M	CI	R-hemiparesis	L-occipital	IIa
13	55	M	CI	Difficulty in writing	L-temporo-parietal	IIa
14	64	M	CI	(—)	R-fronto-temporal	IIa
15	39	M	CI	Aphasia, R-hemiparesis	L-temporo-parietal	IIa
16	73	M	CI	L-hemiparesis	R-temporo-parietal	IIa
17	60	M	CI	Difficulty in calculating	R-frontal + L-parietal	IIa
18	56	M	CI	L-hemiplesia	R-temporo-parietal	IIa
19	65	M	CI	L-hemiplesia	R-fronto-temporal	IIb
20	57	M	CI	Hypesthesia	L-parietal	IIb
21	58	M	CI	(—)	L-frontal	IIb
22	12	F	AVM, hemangioma	R-hemiplesia	L-hemisphere†	AVM
23	56	M	AVM	R-hemiparesis	L-thalamus	AVM
24	36	F	AVM	(—)	R-parietal	AVM
25	23	M	AVM	L-hemiparesis	R-parietal	AVM

M: Male; F: Female; R: Right; L: Left; TIA: Transient ischemic attack; CI: Cerebral infarction; AVM: Arteriovenous malformation; * Enhanced by contrast x-ray CT; † Calcified lesion; HM-PAO: Classification of temporal distribution with [^{99m}Tc]HM-PAO brain SPECT.

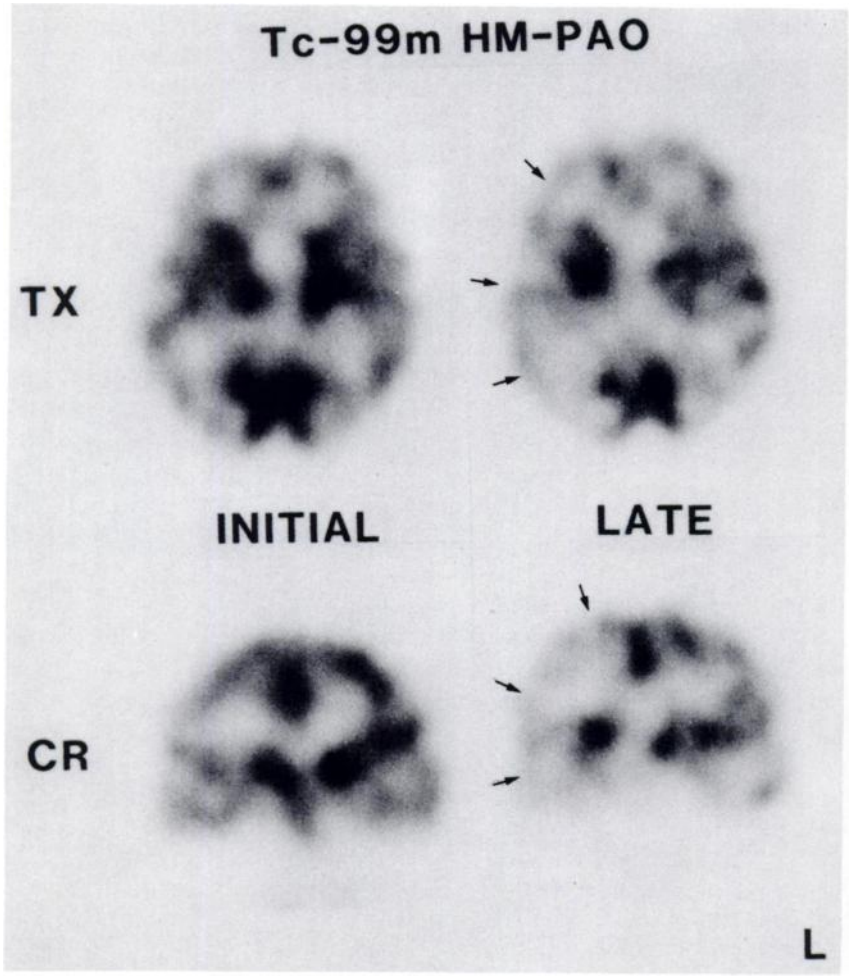

FIGURE 2
Case 6 of Group Ib; [^{99m}Tc]HM-PAO brain SPECT in the late image detects perfusion defect (↗) in the right fronto-temporoparietal area. (INITIAL = the initial brain SPECT image of [^{99m}Tc]HM-PAO, LATE = the late brain SPECT image of [^{99m}Tc]HM-PAO, TX = Transaxial section of brain SPECT, CR = Coronal section of brain SPECT, L = Left.)

change significantly. The D/N ratio of Group IIb in the infarct area (from 0.62 ± 0.13 to 0.62 ± 0.13) did not change significantly; however, those of Group IIb in the peri-infarct area (from 0.95 ± 0.04 to 0.81 ± 0.02) and those of the vascular component of AVM (from 0.85 ± 0.06 to 0.56 ± 0.06) did drop significantly (Fig. 6).

Temporal Change of Activity of [^{99m}Tc]HM-PAO in the Blood

In temporal activity, percent dose of plasma fraction at 4 hr was reduced to 54% of the initial activity at 30 min (1.66 ± 0.33%/l at 30 min to 0.89 ± 0.18%/l at 4 hr), however, those of the cell-bound fraction did not change significantly (from 1.87 ± 0.48%/l at 30 min to 1.70 ± 0.48%/l at 4 hr). Reduction of activity in the plasma reflected that in the whole blood. Hematocrit in the brain blood was estimated to be 31.3% using SPECT which was a relatively lower value than that in the peripheral vein (*9*). Since the mean value of hematocrit from the peripheral vein in our cases was 40.0%, we could predict 3.36%/l at 30 min and 2.35%/l at 4 hr as a percent dose in the brain blood after correction with the hematocrit of the brain, showing 30% loss of activity of [^{99m}Tc]HM-PAO in the brain blood, instead of 27% loss of activity in the peripheral blood, when taking the late image compared with the initial image (Fig. 7).

DISCUSSION

Since [^{99m}Tc]HM-PAO of the brain showed the same distribution as that of microspheres in laboratory animals (*10,11,12*) and clinically that of xenon-133 (^{133}Xe) (*5*) or of iodine-123 (^{123}I)amine (*13*), this radiopharmaceutical is expected to be a accurate marker of regional cerebral blood flow (rCBF) and offers the prospect of routine imaging of rCBF. However, in a positron emission tomographic study using ^{15}O of CO_2 or H_2O, brain SPECT with [^{123}I]IMP was said to be a more sensitive marker than that with [^{99m}Tc]HM-PAO to detect mild cerebral ischemia as a result of the relative low contrast between the defect area and the normal area (*14*). We investigated whether [^{99m}Tc]HM-PAO could be a truly flow-related radiotracer to detect mild cerebral ischemia, and the meaning of the filling out phenomenon of [^{99m}Tc]HM-PAO.

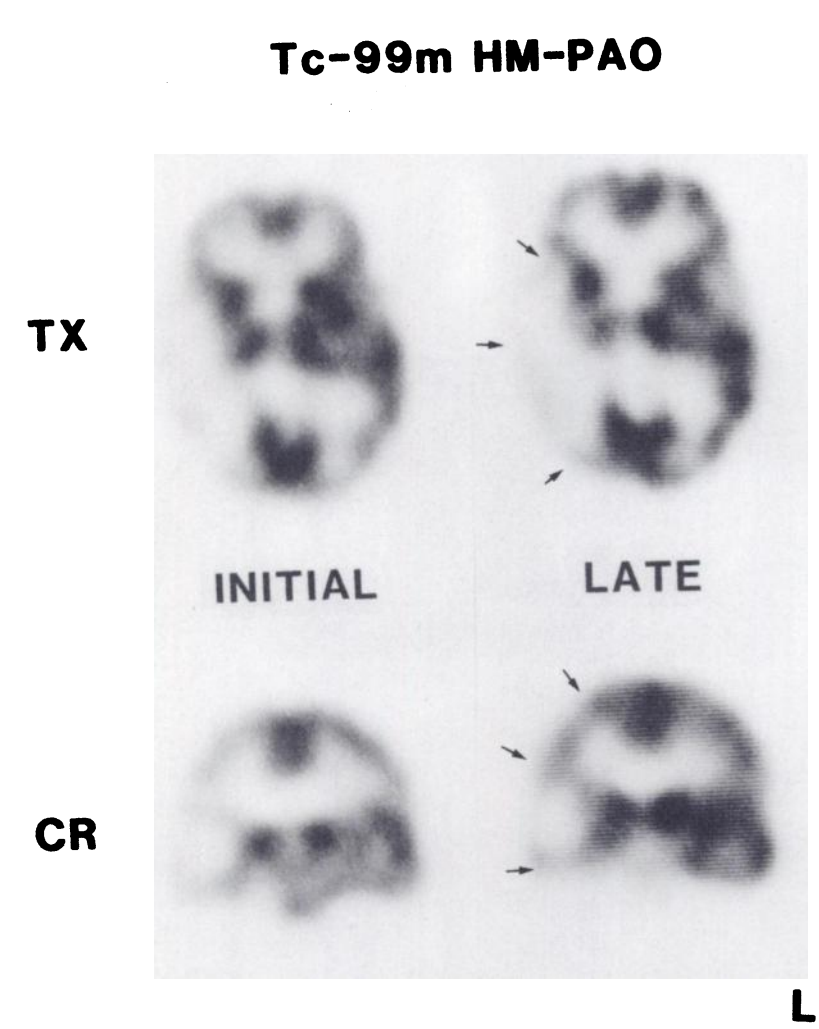

FIGURE 3
Case 10 of Group IIa; The size of defect in temporoparietal area (↗) with [^{99m}Tc]HM-PAO brain SPECT in the late image is the same as that in the initial image (abbreviations as in Fig. 2).

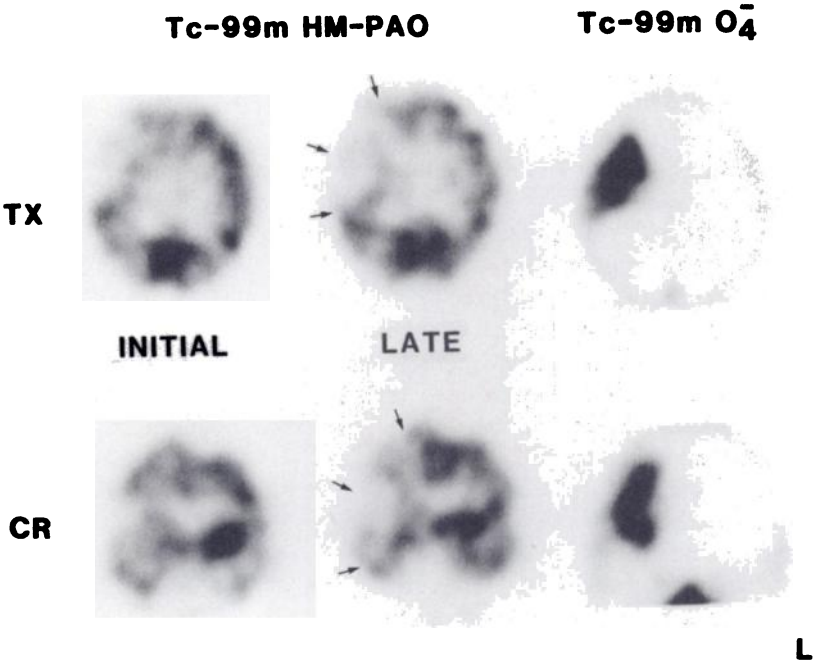

FIGURE 4
Case 19 of Group IIb; The extent of the defect in fronto-temporal area (↗) with [^{99m}Tc]HM-PAO brain SPECT in the late image is larger than that in the initial image. The size of the defect in the initial image with [^{99m}Tc]HM-PAO brain SPECT was in accord with the area of hot uptake of [^{99m}Tc]pertechnetate brain SPECT. ([^{99m}Tc]O_4^- = [^{99m}Tc]pertechnetate brain SPECT, other abbreviations as in Fig. 2).

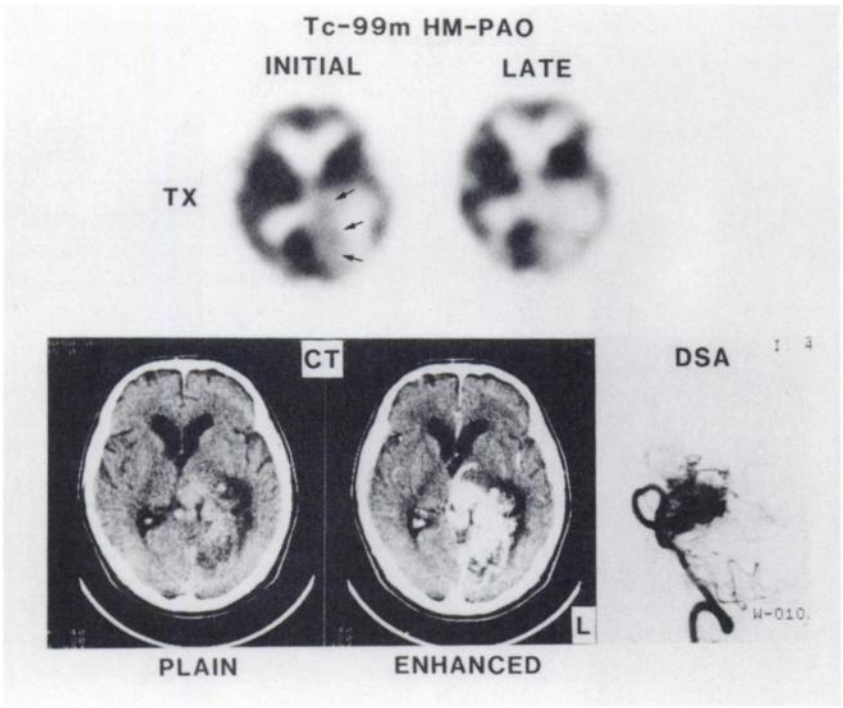

FIGURE 5
Case 23 of arterio-venous malformation: enhanced x-ray CT (lower column; middle) and vertebral angiography in lateral projection with DSA (lower column; right) demonstrated AVM in the left thalamic area. The warm image of AVM (↗) in the initial image with [^{99m}Tc]HM-PAO brain SPECT reduced in activity in the late image (CT = x-ray computed tomography, DSA = Digital subtraction angiography, other abbreviations as in Fig. 2).

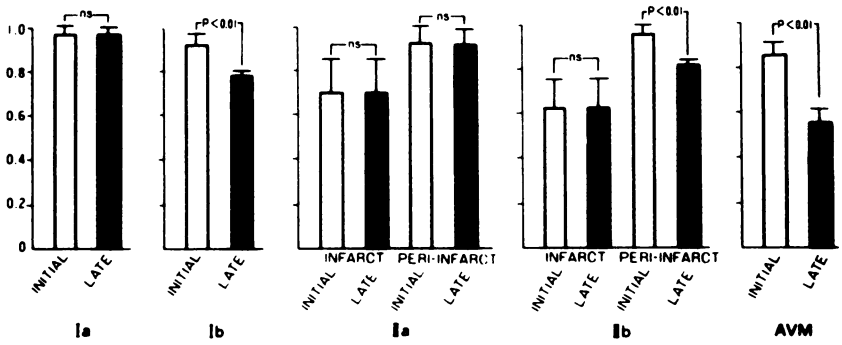

FIGURE 6
Semiquantitative analysis of the D/N ratio in the initial image and the late image with [^{99m}Tc]HM-PAO brain SPECT depending on the classification of temporal distribution.

Filling Out Phenomenon of [^{99m}Tc]HM-PAO

Visual analysis demonstrated the filling out phenomenon of [^{99m}Tc]HM-PAO in the area of Group Ib, in the peri-infarct area of Group IIb, and in the vascular component of AVM including hemangioma. In a semiquantitative analysis, comparing the initial image with the late image, the D/N ratio of the late image in the area of Group Ib and those in the peri-infarct area of Group IIb dropped significantly ($p < 0.01$). The filling out phenomenon of [^{99m}Tc]HM-PAO brain SPECT was also demonstrated visually and semiquantitatively in AVM, as reported previously (*15*).

The regional distribution of [^{99m}Tc]HM-PAO in rat brain is similar to that observed for carbon-14 (^{14}C) labeled iodoantipyrine as a reference for rCBF (*10*). Technetium-99m HM-PAO shows rapid brain uptake and prolonged retention, probably a result of the rapid conversion of the molecule into a less lipophilic form, that is unable to leave the brain within 2–3 min after administering the tracer (*16*). So [^{99m}Tc]HM-PAO brain SPECT could be applied to evaluate rapid changes of rCBF such as occur in the Wada test (*17*). The flow-related distribution without change was in the manner of the distribution of [^{99m}Tc]HM-PAO in the brain. The reason for the filling out phenomenon of [^{99m}Tc]HM-PAO in the brain might remain unsolved.

Pharmacokinetics of [^{99m}Tc]HM-PAO in the Blood

A high proportion of the radioactivity of [^{99m}Tc]HM-PAO remaining in the blood is a result of the entrapment of [^{99m}Tc]HM-PAO within red blood cells and plasma protein, the trapping mechanism of which is similar to that of brain retention. Our results showed that the percent dose of activity of [^{99m}Tc]HM-PAO in the plasma fraction was 1.66%/l at 30 min and 0.89%/l at 4 hr reflecting loss of activity in the whole blood (3.54%/l at 30 min and 2.59%/l at 4 hr). The result of percent dose in the whole blood is in agreement with

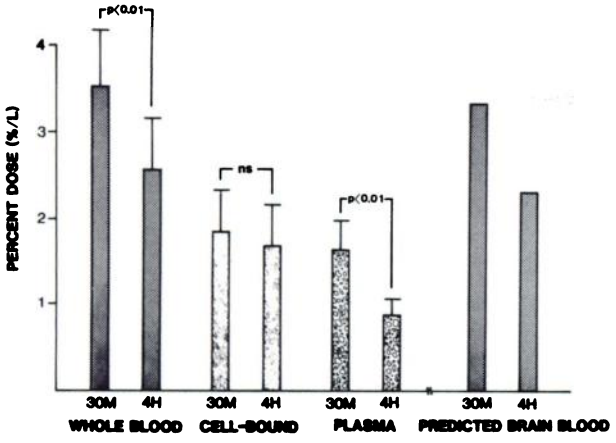

FIGURE 7
Temporal change of activity of [^{99m}Tc]HM-PAO in the whole blood, cell-bound, plasma and predicted brain blood.

the value reported previously (*2*). The cause of the reduction of activity in the plasma is thought to be derived from metabolism of plasma protein in the liver or from excretion of plasma protein by the bile and urinary system. With a case of AVM, if the original count of vascular component in the initial image was cut by 30% as blood clearance of [^{99m}Tc]HM-PAO during 3.5 hr, the estimated D/N ratio was in accord with the actual value of D/N ratio in the late image. These findings might explain that the filling out phenomenon was attributed to a clearance of plasma activity and not to washing out of [^{99m}Tc]HM-PAO from brain parenchyma.

Technetium-99m HM-PAO Washout from the Brain

If the uptake rate of [^{99m}Tc]HM-PAO in the brain was reported as 4.1% in the 1,400 ml (*2*), activity as expressed by percentage dose in the brain was 2.93%/l. Since the predicted activity in brain blood was 3.36%/l at 30 min and 2.35%/l at 4 hr, activity ratio of whole blood to brain parenchyma resulted in 1.15 at 30 min and 0.80 at 4 hr. In an equilibrium state, the brain count in the brain SPECT consists of the brain parenchymal count and the circulating blood count. If cerebral blood volume (CBV) was 70 ml, CBV based on a count equivalent to brain parenchyma was 80.5 ml at 30 min and 56.0 ml at 4 hr. That is, the apparent washout volume of brain blood was 24.5 ml per 1,400 ml of the whole brain during 3.5 hr and the clearance rate contributed by the reduction of plasma activity resulted in 0.5% per hour. From the results of temporal measurements of the regional distribution of [^{99m}Tc]HM-PAO, the clearance of [^{99m}Tc]HM-PAO from the brain was reported to be 0.5% per hour in animals (*10*) and in man (*5*). Therefore, [^{99m}Tc]HM-PAO should be hardly washed out from the brain within at least 3.5 hr. We conclude that washout of [^{99m}Tc]HM-PAO from blood played a major role in the regional change of activity with [^{99m}Tc]HM-PAO brain SPECT.

Clinical Significance of Filling Out Phenomenon

The activity contribution of cerebral blood to cerebral parenchyma would be small (*18*). This speculation might apply to normal brain tissue, but not pathologic brain tissue where rCBF was decreased accompanying the increment of rCBV. In cerebral ischemia, a decrease of cerebral perfusion pressure may be compensated by the cerebral blood reserve. Autoregulation maintains sufficient oxygen supply to cerebral tissue. Experience of positron work with ^{15}O showed that the state of cerebral vascular resistance may thus be assessed by the flow-to-volume ratio (*19,20*). This idea was adapted to SPECT by employing [^{123}I]IMP and [^{99m}Tc]RBC (*21*).

In Group Ib, the initial image probably masked the area of decreased rCBF with increased rCBV which was reflected by increased activity of [^{99m}Tc]HM-PAO in the plasma. Since those who were in Group Ib became free of neurologic deficit when they were discharged, the area showing filling out phenomenon was thought to be mild cerebral ischemia. In addition, filling out phenomenon in Group IIb was observed where autoregulation might be still maintained in the peri-infarct area, but not infarcted area, as shown in Figure 4. As the blood pool of [^{99m}Tc]HM-PAO might interfere in detecting a truly rCBF image in the initial image, the late image of [^{99m}Tc]HM-PAO brain SPECT was mandatory to evaluate rCBF accurately. The filling out phenomenon in [^{99m}Tc]HM-PAO brain SPECT would be useful for detecting the area of increased CBV where mild cerebral ischemia accompanying cerebral vascular reserve at just the same slice of rCBF image, since it was explained by rather high activity in the plasma in the initial image and then by cleared activity from vessels in the late image. This finding, also, gives rise to the assumption that [^{99m}Tc]HM-PAO brain SPECT allows us not only to detect the truly cerebral blood flow, but also to evaluate the potential of cerebral vascular reserve.

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