Comparative Study of Regional Cerebral Blood Flow Images by SPECT Using Xenon-133, Iodine-123 IMP, and Technetium-99m HM-PAO

Shinichi Nakano, Kazuo Kinoshita, Seishi Jinnouchi, Hiroaki Hoshi, and Katsushi Watanabe

Departments of Neurosurgery and Radiology, Miyazaki Medical College, Miyazaki, Japan

Regional cerebral blood flow (rCBF) was measured by single photon emission computed tomography (SPECT) using ^{133}Xe, N-isopropyl-p-[^{123}I]iodamphetamine ([^{123}I]IMP) and [^{99m}Tc] hexamethylpropyleneamine oxime ([^{99m}Tc]HM-PAO) in 24 patients with cerebrovascular diseases. The greatest advantage of ^{133}Xe SPECT was to be able to provide absolute rCBF values without arterial sampling. However, its image quality was very poor. Iodine-123 IMP SPECT provided rCBF images of higher quality and it had good correlation to ^{133}Xe SPECT. Iodine-123 IMP SPECT provided the best images to detect mild ischemic lesions. It could detect obstructive or stenotic changes of large cerebral arteries very well except for a moderate stenosis of internal carotid artery. Technetium-99m HM-PAO SPECT also provided very good rCBF images and it had good correlation to ^{133}Xe SPECT. However, the count-density ratios for the ischemic lesions to the contralateral presumed normal areas of [^{99m}Tc] HM-PAO SPECT were significantly higher than those of [^{123}I]IMP SPECT.

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Regional cerebral blood flow (rCBF) has been measured by dynamic imaging (*1*) and equilibrium flow imaging (*2*) using diffusible or extractable tracers. Xenon-133 (^{133}Xe) has been used most widely in measurement of rCBF with single photon emission computed tomography (SPECT). Recently a number of new radiopharmaceuticals for rCBF imaging have been synthesized in accordance with the development of SPECT technique. The main requirements of these tracers for rCBF imaging with SPECT are high blood-brain barrier (BBB) permeability and retention of a fixed regional distribution for a period sufficient to permit image acquisition. N-isopropyl-p-[^{123}I]iodamphetamine ([^{123}I] IMP) introduced by Winchell et al. (*3,4*) in 1980 meets the two requirements and is used widely to make relative rCBF images with SPECT. However, iodine-123 (^{123}I) is a cyclotron-produced radionuclide and the major disadvantage of [^{123}I]IMP is limited availability. A new lipophilic radiopharmaceutical labeled with technetium-99m (^{99m}Tc) for rCBF imaging, [^{99m}Tc]hexamethylpropyleneamine oxime ([^{99m}Tc]HM-PAO), has been introduced by Holmes et al. (*5*) in 1985. We measured rCBF in patients with cerebrovascular diseases (CVD) by SPECT using ^{133}Xe, [^{123}I]IMP, and [^{99m}Tc]HM-PAO. This study deals with a comparison among these SPECT images.

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For reprints contact: Shinichi Nakano, MD, Dept. of Neurosurgery, Miyazaki Medical College, 5200, Kihara, Kiyotake, Miyazaki 889-16, Japan.

MATERIALS AND METHODS

Patients Selection

This study includes 24 patients with CVD, 19 males and five females, aged 25 to 83 yr (average age 54 yr). All patients underwent three kinds of SPECT studies within 4 days after the onset of CVD. Only two patients (cases 1 and 6) underwent second SPECT studies ~ 1 wk later. All of them underwent neurological examinations, x-ray computed tomographic (CT) scans, and angiographies. Of these 24 patients, 19 had definite low flow lesions and the other five had no low flow lesion.

Patients Preparation

The patients were placed in a supine position in a quiet room with their eyes closed. In ^{133}Xe SPECT the patients breathed ^{133}Xe gas at the concentration of 10 mCi/l for a minute with a nose clamp and a rubber mouthpiece connected to the Ventil-Con spirometer. Then the spirometer was switched to open circuit and measurements continued for further 9 min. Iodine-123 IMP was obtained from Japan Mediphysics on the day of examination. It was free of iodine-124 (^{124}I) and contained at most 4.5% of iodine-125 (^{125}I). While [^{99m}Tc]HM-PAO was prepared from a nonradioactive kit (Amersham International, plc, Buckinghamshire, UK) and its radiochemical purity was supposed to be more than 90% at the time of injection. The dynamic SPECT(D-SPECT) started immediately after intravenous injection of 3 mCi of [^{123}I]IMP or 20–30 mCi of [^{99m}Tc]HM-PAO. The data acquisition time of the D-SPECT was 20 min. And then as the static SPECT (S-SPECT) an early scan and a delayed scan started 30 min and 4 hr after injection of these tracers, respectively. The patients were in the ward at rest between the two scans. There was at least 2 days interval between [^{123}I] IMP and [^{99m}Tc]HM-PAO SPECT studies. Xenon-133 SPECT was performed on the same day on which [^{123}I]IMP or [^{99m}Tc]HM-PAO SPECT was done.

Data Acquisition and Analysis

This study was performed with a ring-type gamma camera (SET 020, Shimadzu Co., Kyoto, Japan) which consists of a gantry assembly with 64 scanning detectors. This system has two rings and simultaneously acquires two parallel slices with a center-to-center interslice distance of 3.5 cm. A high sensitivity (HS) collimator was used in the D-SPECT and ^{133}Xe SPECT and a high-resolution (HR) one was done in the S-SPECT. The raw data were reconstructed by the method of filtered backprojection, using a Ramachandran-Butterworth filter. Reconstruction was performed using a Data General Eclipse S-120 processor for a 64 × 64 matrix image in the [^{123}I]IMP and [^{99m}Tc]HM-PAO SPECT and a 32 × 32 one in the ^{133}Xe SPECT. Slice thickness was 24 mm and 16 mm in the HS and HR collimators, respectively. In ^{133}Xe SPECT the calculation of rCBF was performed by employing the Celsis modification of the Kanno and Lassen algorithm (*6,7*). In the D-SPECT the data acquisition was performed every 2 min for 20 min and serial ten images were obtained. In the S-SPECT the data acquisition lasted until 600,000 counts were collected.

The 19 patients with definite low flow lesions were separated into three groups from the findings of CT scan and neurologic examination. Group 1 contained nine patients with cortical infarctions with irreversible neurological deficits. Group 2 contained five patients with reversible cortical dysfunctions. At the time of examinations the cortical functions were disturbed, whereas they had full recovery later and CT scan revealed no abnormal density area in cerebral cortex. The cortical dysfunction evaluated in this study were only motor asphasia and homonymous hemianopsia. Group 3 contained five patients with lacunar infarctions. These patients had only hemiparesis which was considered to result from lacunar infarctions by CT scan. They had normal cortical functions and CT scan revealed no abnormal density area in cerebral cortex. In each group a circle region of interest (ROI) of 1.75 cm diameter (4 × 4 matrix in the [^{123}I]IMP and [^{99m}Tc] HM-PAO SPECT) was placed over the ischemic lesion. For comparison an equal size region of interest (ROI) was placed over the presumed normal region of the contralateral cerebral hemisphere as symmetrical as possible. Then ^{133}Xe rCBF of the two regions were calculated. In the D-SPECT time-activity curves (TACs) were constructed. The count-density ratio for the lesion to the contralateral presumed normal area (Lesion/Normal ratio, L/N ratio) was calculated in the early image of the S-SPECT.

In the [^{123}I]IMP SPECT study, the redistribution of the tracer in the lesions in the delayed scan were classified into three grades: none, poor, or good redistribution. Data analysis was done without smoothing.

RESULTS

The clinical data of the 19 patients with definite low flow lesions were summarized in Table 1. All of them had occlusive or stenotic changes of large cerebral arteries. Not only [^{123}I]IMP SPECT but also [^{99m}Tc]HM-PAO SPECT had good correlation to ^{133}Xe SPECT (Figs. 1 and 2). All SPECT studies could show severe ischemic lesions very well (Fig. 3). However, in all groups the L/N ratios of [^{99m}Tc]HM-PAO SPECT were significantly higher than those of [^{123}I]IMP SPECT (Group 1,2: $p < 0.01$, Group 3: $p < 0.05$). Thus the ischemic degree evaluated by the [^{99m}Tc]HM-PAO SPECT was milder than that of [^{123}I]IMP SPECT. Xenon-133 SPECT had also disadvantage in detecting mild ischemic lesions due to poor spatial resolution. Iodine-123 IMP SPECT provided the best images to evaluate mild ischemic lesions (Fig. 4).

Of the five patients without any low flow lesion only one patient (Case 20) had ~ 50% of internal carotid artery (ICA) stenosis. Even [^{123}I]IMP SPECT could not detect moderate ICA stenosis. The other four patients had no abnormal findings in angiographies (Table 2).

The TACs derived from [^{99m}Tc]HM-PAO D-SPECT showed rapid saturation and subsequent stable retention of [^{99m}Tc]HM-PAO uptake in brain tissue (Fig. 5). Thus the early and delayed images in ^{99m}Tc-HM-PAO SPECT have little differences. While the TACs derived from ^{123}I-IMP D-SPECT showed gradual increase of ^{123}I-IMP uptake in brain tissue (Fig. 6). Thus the delayed images were quite different from the early ones and could not reflect rCBF. Severe ischemic lesions had no redistribution of the tracer in the delayed images of [^{123}I]IMP SPECT, whereas mild ischemic lesions had good redistribution (Table 1).

DISCUSSION

Xenon-133 SPECT

Since the early work of Mallet and Veall (*8*) and later Orbist et al. (*9,10*) rCBF measurement with ^{133}Xe inhalation method has been developed and used widely with improvement of measurement by the SPECT technique. The advantages of ^{133}Xe SPECT are: (a) it provides absolute rCBF values without arterial sampling, (b) it has the ability of repeat examination, and (c) ^{133}Xe has a lower radiation dose. However, its greatest drawback is poor spatial resolution, and ^{133}Xe SPECT cannot

TABLE 1
Clinical Data of 19 Patients with Definite Low Flow Lesions

Group	Case	Age (yr)	Sex	CT	Angiography	^{133}Xe-rCBF (ml/100g/min)	L/N ratio ^{123}I-IMP	L/N ratio ^{99m}Tc-HM-PAO	Redistribution (^{123}I-IMP)
	1	42	M	C*	ICA§ occlusion	14 (35%)	31%	42%	No
	2	51	M	C	ICA occlusion	16 (40%)	30%	37%	No
	3	56	M	C	MCA¶ occlusion	15 (37%)	27%	33%	No
	4	54	M	C	MCA occlusion	18 (36%)	37%	43%	No
1	5	50	M	C	MCA occlusion	19 (43%)	34%	35%	No
	6	83	M	C	MCA embolism	4 (9%)	24%	27%	No
	7	62	M	C	PCA** occlusion	13 (32%)	22%	30%	No
	8	54	M	C	PCA occlusion	16 (37%)	39%	45%	No
	9	70	M	C	PCA occlusion	18 (25%)	28%	27%	No
						14.8 ± 4.2 (32.7 ± 9.6%)	30.2 ± 5.4%	35.4 ± 6.8%	
	10	42	M	N‡	ICA occlusion	26 (49%)	53%	62%	Poor
	11	56	M	L	MCA occlusion	27 (66%)	52%	65%	Poor
2	12	25	M	L	MCA occlusion	30 (57%)	54%	63%	Poor
	13	60	M	N	PCA occlusion	28 (62%)	64%	70%	Poor
	14	40	F	N	PCA occlusion	33 (57%)	54%	60%	Poor
						28.8 ± 2.8 (58.2 ± 6.4%)	55.4 ± 4.9%	64.0 ± 3.8%	
	15	68	F	L†	MCA occlusion	46 (70%)	81%	89%	Good
	16	26	M	L	MCA occlusion	40 (83%)	78%	85%	Good
3	17	53	M	L	MCA occlusion	36 (73%)	72%	88%	Poor
	18	50	M	L	MCA occlusion	42 (79%)	82%	88%	Good
	19	55	F	L	MCA stenosis	44 (89%)	87%	91%	Good
						41.6 ± 3.8 (78.8 ± 7.6%)	80.0 ± 5.5%	88.2 ± 2.2%	

* Cortical infarction.
† Lacunar infarction.
‡ Normal.
§ Internal carotid artery.
¶ Middle cerebral artery.
** Posterior cerebral artery.

delineate skull base lesions because of ^{133}Xe gas in the paranasal sinuses. Furthermore, ^{133}Xe inhalation requires comprehension of instructions and active patient cooperation, which may be difficult to achieve for patients with cognitive and linguistic deficits.

Iodine-123 IMP SPECT

Iodine-123 IMP crosses the BBB easily and is extracted almost completely during a single passage through cerebral circulation. Kuhl et al. (*11*) have shown good correlation between [^{123}I]IMP deposition at 5 min after i.v. injection and rCBF measured by microsphere extraction in dogs. Since then the [^{123}I] IMP SPECT for the measurement of rCBF has been validated by many investigators (*12–14*).

Early Images

The initial pattern of [^{123}I]IMP distribution is slightly modified with time with a decreased gray-to-white matter ratio. In rats Rapin et al. (*14*) showed that the gray-to-white matter ratio was ~ 10 in the first 3 min and then dropped to 4.4 1 hr later. The TACs derived from the D-SPECT in our study also showed gradual increase of [^{123}I]IMP uptake in brain tissue. Therefore, Lassen et al. (*13*) have stressed that the [^{123}I]IMP tomograms should be taken within the first 10 min in order to map rCBF. Yet, the images obtained within the first hour were said to be qualitatively acceptable because the redistribution effects were slight. Though the early scan of our study started 30 min after injection of [^{123}I]IMP, the images were very satisfactory compared to ^{133}Xe rCBF images. L/N ratios in the [^{123}I]IMP SPECT had very good correlation to the ^{133}Xe rCBF ratios. Thus, the early images in our study were thought to be good relative rCBF maps.

The early images of [^{123}I]IMP SPECT had high spatial resolution and they provided a good distinction between gray and white matters. Therefore, they showed the differential diagnosis between the cortical and perforator infarctions before abnormal low-density areas appeared on x-ray CT examinations. If rCBF in the non-affected cerebral hemisphere were almost normal, quantitative analysis would be made by L/N ratios and [^{123}I]IMP SPECT would be more useful than ^{133}Xe SPECT. However, the major drawback of [^{123}I]IMP

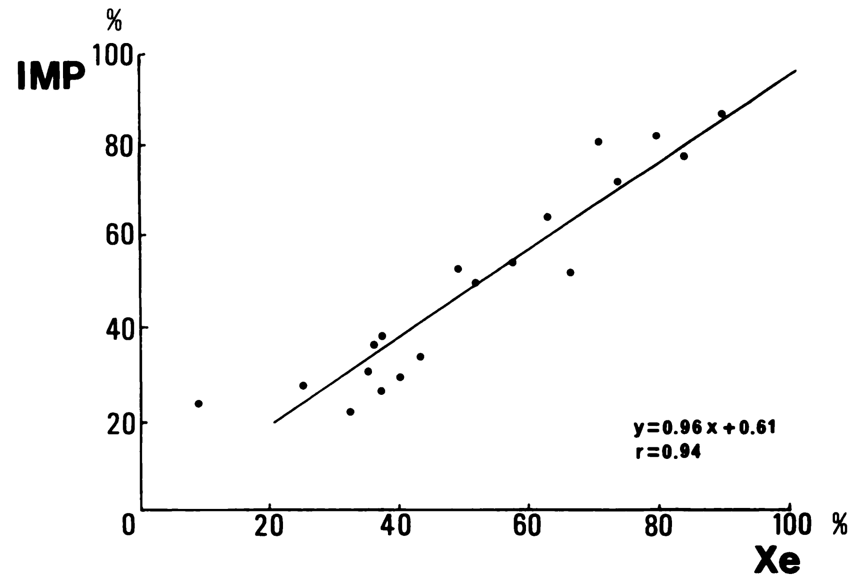

FIGURE 1
Correlation between L/N ratios of the [^{123}I]IMP SPECT and those of ^{133}Xe rCBF values ($p < 0.001$).

SPECT is inability to detect the decrease of rCBF in the nonaffected cerebral hemisphere.

In cases with perforator infarctions it is very important for our making a therapeutic plan to assess the coexistence of occlusive or stenotic changes of large cerebral arteries. The slice thickness of [^{123}I]IMP SPECT is 16 mm and pure small perforator infarctions could not be detected because of the partial volume effect. However, the coexistence of MCA occlusion, even MCA stenosis, could be detected as mild to moderate low perfusion in MCA territory. Of course the coexistence of ICA occlusion also could be detected, whereas that of ICA stenosis may fail to be detected (Case 20). In these cases with arterial occlusive or stenotic changes not only anticoagulant therapy but also angiographies and indication of EC-IC bypass surgery should be considered.

Although [^{123}I]IMP SPECT cannot provide absolute rCBF values, it revealed very good relative rCBF images and was clinically the most useful method of the three SPECT studies in the diagnosis of CVD.

Delayed Images

The delayed images obtained 4 hr after injection of [^{123}I]IMP could not delineate the distinction between the gray and white matter well because of redistribution of the tracer. Thus they are not suitable to assess rCBF. Our results showed that the irreversible ischemic lesions were well delineated even in the delayed images, whereas the mild ischemic lesions became less distinct

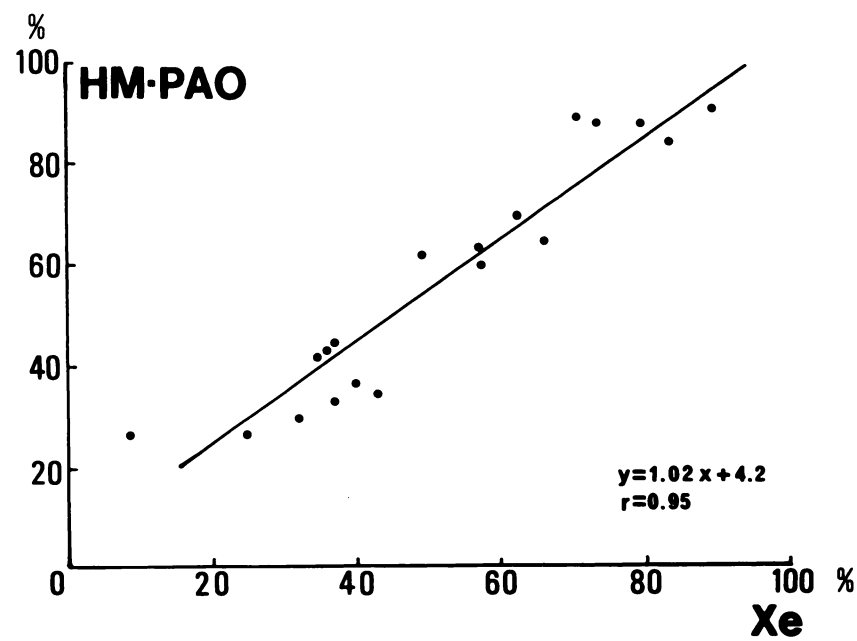

FIGURE 2
Correlation between L/N ratios of the [^{99m}Tc]HM-PAO SPECT and those of ^{133}Xe rCBF values ($p < 0.001$).

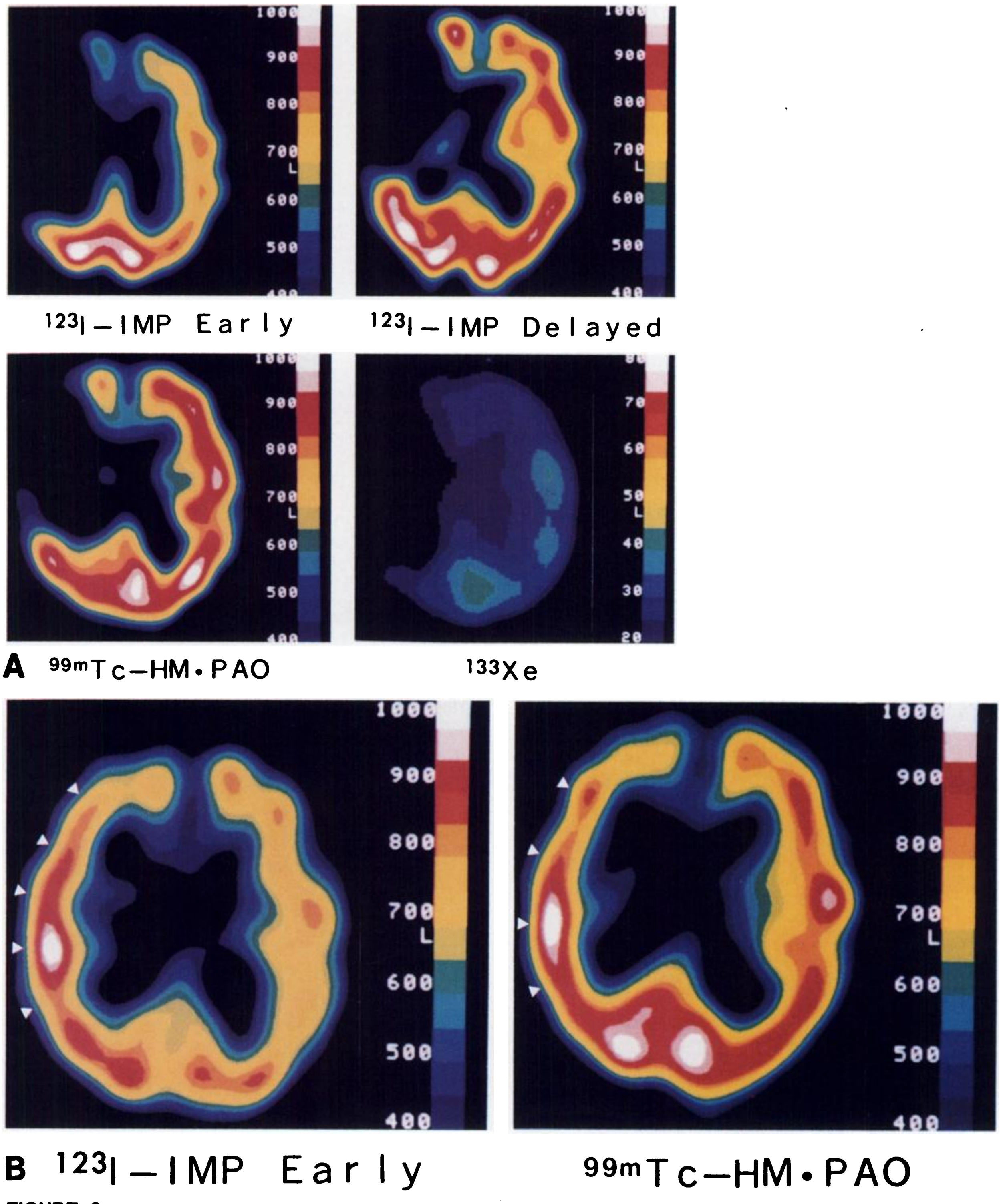

FIGURE 3
Cerebral embolism in a 83-yr-old man. He suddenly developed left hemiplegia, whereas CT scan on that day revealed no abnormal density area. A: ^{113}Xe and [^{99m}Tc]HM-PAO SPECT studies on that day revealed extremely low blood flow in the entire territory of right middle cerebral artery (MCA). Iodine-123 IMP SPECT on the fourth day also showed extremely low uptake in the right MCA territory and there was no redistribution of the tracer in the lesion in the delayed scan. Only ^{133}Xe SPECT could show low blood flow even in the left cerebral hemisphere, which suggested to be diaschisis via corpus callosum. The [^{123}I]IMP and [^{99m}Tc]HM-PAO SPECT studies could not detect the diaschisis because they could not provide absolute rCBF values. B: About 1 wk later, [^{123}I]IMP and [^{99m}Tc]HM-PAO SPECT studies revealed a high radioactivity area corresponding to the infarct area, which seemed to be luxury perfusion due to recanalization (arrow heads).

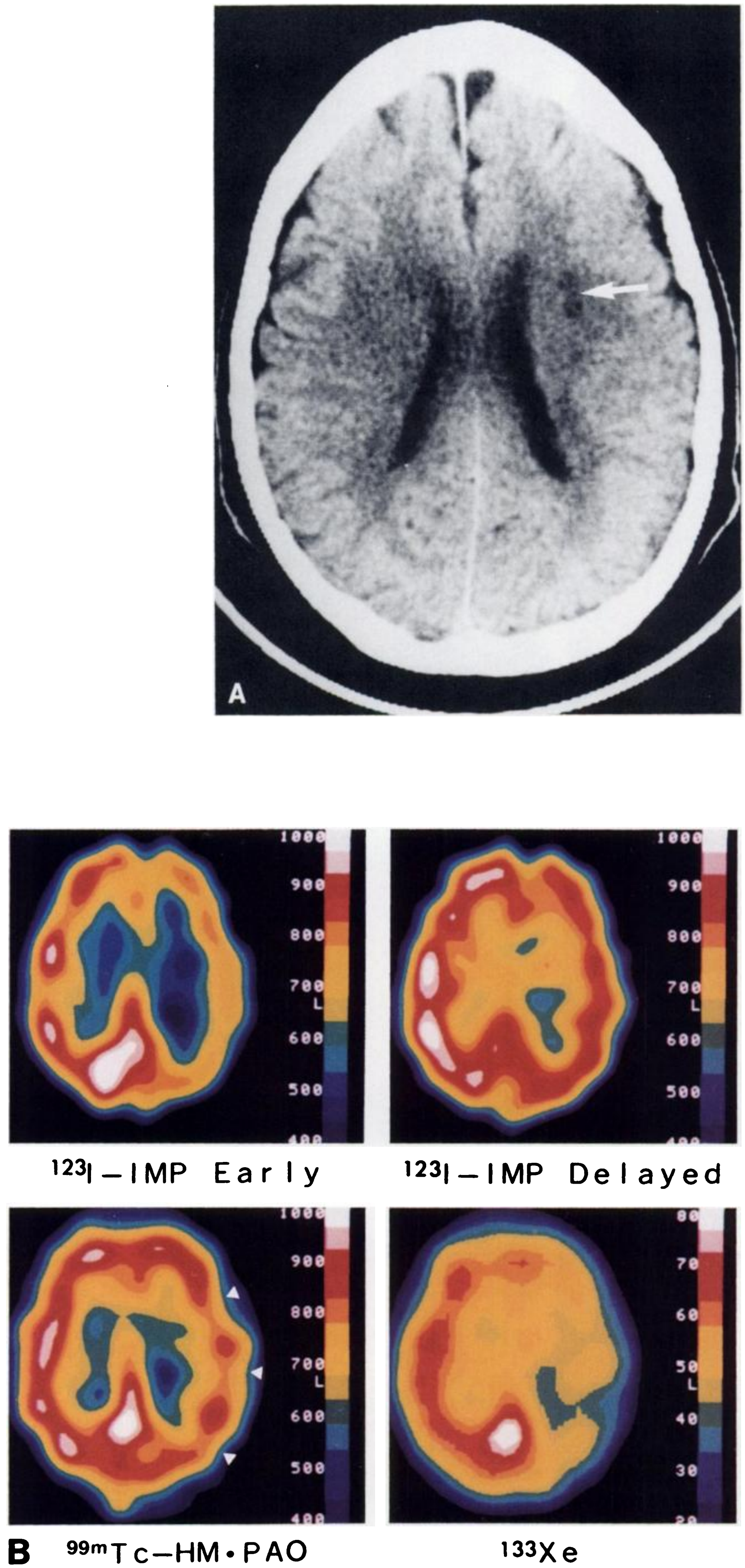

FIGURE 4
Lacunar infarction in a 68-yr-old woman. She suddenly developed right hemiparesis. A: CT scan on that day revealed no abnormal density area but a spotty low density area was observed in the white matter of the left frontal lobe on the next day (arrow). B: The left MCA territory was delineated as a minimal low uptake area in the [^{99m}Tc]HM-PAO SPECT on that day (arrow heads). However, ^{133}Xe and [^{123}I]IMP SPECT studies on the third day showed apparently low flow in the entire territory of left MCA, which suggested the coexistence of MCA stenosis or occlusion. As might have been expected, angiography disclosed left MCA occlusion. The delayed scan of the [^{123}I] IMP SPECT showed good redistribution of the tracer in the lesion.

TABLE 2
Clinical Data of Five Patients Without Any Low Flow Lesions

Case No.	Age	Sex	CT	Angiography
20	47	M	L	50% ICA stenosis
21	51	M	L	N
22	58	M	N	N
23	81	F	N	N
24	54	F	N	N

in them. This "lessening distinction" finding in the delayed images may suggest tissue viability to some extent.

Technetium-99m HM-PAO SPECT

Recent experimental studies (*5,15–19*) have demonstrated that [^{99m}Tc]HM-PAO crosses the BBB freely and is retained in the brain tissue for several hours in a similar way to [^{123}I]IMP. The brain uptake of [^{99m}Tc]HM-PAO is very fast and it reaches its maximum within 10 min after i.v. injection. The initial distribution remains constant for several hours without appreciable change in the gray-to-white matter ratio. The TACs derived from the D-SPECT in our study also demonstrated rapid saturation and subsequent stable retention of ^{99m}Tc-HM-PAO uptake in the brain tissue. Thus the early and delayed images of [^{99m}Tc]HM-PAO SPECT have little differences, which suggests that [^{99m}Tc]HM-PAO seems to be well-suited for SPECT imaging of rCBF.

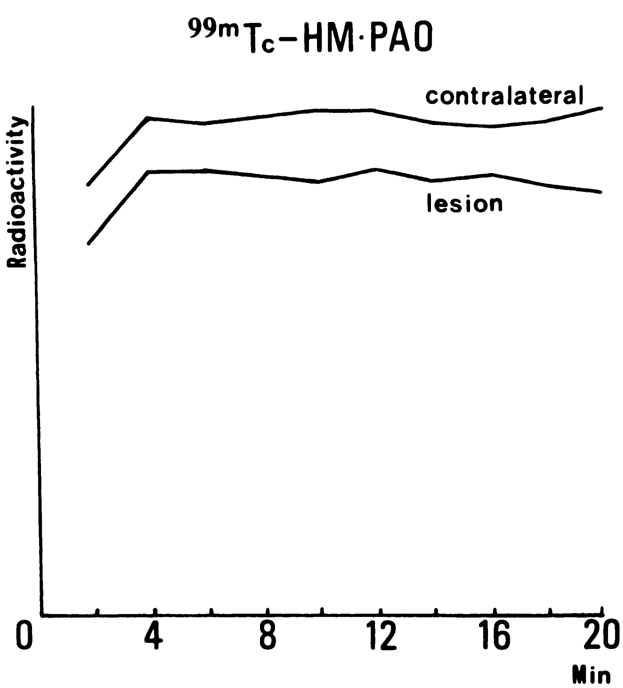

FIGURE 5
TACs derived from [^{99m}Tc]HM-PAO D-SPECT showed rapid saturation and subsequent stable retention of [^{99m}Tc]HM-PAO uptake in brain tissue.

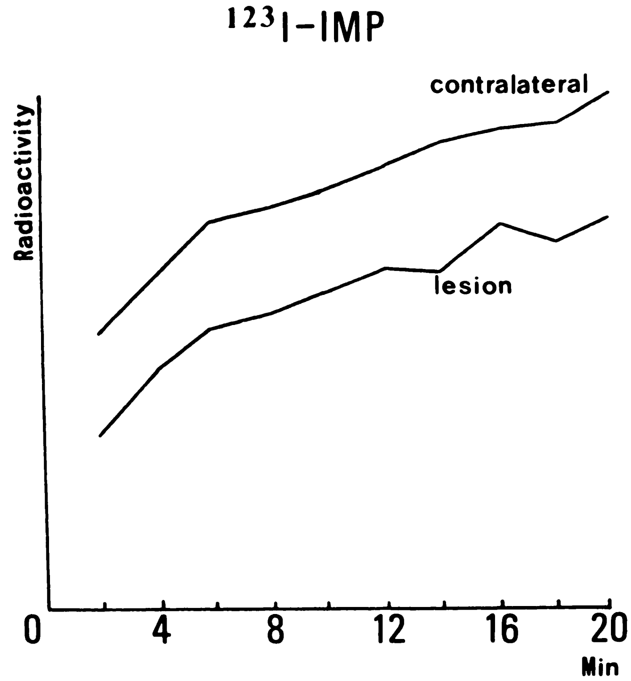

FIGURE 6
TACs derived from [^{123}I]IMP D-SPECT showed gradual increase of [^{123}I]IMP uptake in brain tissue.

However, our study showed that the ischemic degree evaluated by L/N ratios of [^{99m}Tc]HM-PAO SPECT was significantly higher than that of [^{123}I]IMP SPECT. In comparative study of [^{123}I]HIPDM and [^{99m}Tc]HM-PAO Leonard et al. (*20*) also reported that diseased-to-non diseased ratio was a little more marked on the HIPDM images than on the HM-PAO ones. Holm et al. (*21*) supposed that this might be due to incomplete extraction with subsequent recirculation partly due to association of [^{99m}Tc]HM-PAO with RBCs or plasma proteins. Bok et al. (*22*) have demonstrated that the blood clearance of [^{99m}Tc]HM-PAO was quite slow and ~ 10% of the injected activity still remains in blood after 30 min. From these experimental studies, [^{99m}Tc]HM-PAO SPECT images may superimpose the distribution in the brain and intravascular component of [^{99m}Tc]HM-PAO. Therefore, [^{99m}Tc]HM-PAO SPECT can be used as a screening examination in case of emergency, whereas in an accurate evaluation of rCBF ^{133}Xe or [^{123}I]IMP SPECT should be performed.

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