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Hemodynamic and metabolic state of hyperfixation with ^{99m}Tc-HMPAO brain SPECT in subacute stroke

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By means of positron emission tomography (PET), we investigated the hemodynamic and metabolic state of the hyperfixation identified as the increased accumulation with ^{99m}Tc-*d,l*-hexamethylpropyleneamine oxime (HMPAO) by single photon emission computed tomography (SPECT) in patients with subacute stroke. We studied four patients with subacute stroke having hyperfixed areas evaluated with CBF, $CMRO_2$, OEF and CBV by PET. The hyperfixation rate with ^{99m}Tc-HMPAO was obtained by comparing the surplus rate with standardized CBF. The OEF and $CMRO_2$ values in the hyperfixed areas of 4 patients were significantly lower than those in normal 5 controls ($p < 0.01$), but CBF and CBV were almost the same in patients and normal controls, but the hyperfixation rate of 0.30 ± 0.15 in 4 patients correlated well with CBV ($r = 0.97$, $y = 11.75x + 0.42$; $p < 0.05$).

Hyperfixation with ^{99m}Tc-HMPAO in the infarct area revealing a mismatch between $CMRO_2$ and CBF meant relative luxury perfusion. The hyperfixation rate determined by ^{99m}Tc-HMPAO brain SPECT correlated with CBV in the PET study. We can conclude that one of the main factors which caused hyperfixation was vasodilatation as well as the blood brain barrier disruption and the neovascularization.

Key words: hyperfixation, cerebral infarction, Tc-99m HMPAO, brain SPECT, PET

INTRODUCTION

THE DISTRIBUTION of ^{99m}Tc-*d,l*-hexamethylpropyleneamine oxime (HMPAO) with single photon emission computed tomography (SPECT) was proportional to that of the regional cerebral blood flow (CBF),[1] and the increased activity with ^{99m}Tc-HMPAO brain SPECT in subacute stroke was understandable as hyperemia.[2] Nevertheless, it has been reported that this increased activity in subacute stroke might be due to hyperfixation with ^{99m}Tc-HMPAO manifested as a higher count rate over the infarct area than that of the opposite side.[3] The asymmetry index of the hyperfixation in part of the infarct region in patients with subacute stroke showed excess of 9% to 30% with ^{133}Xe.[3,4]

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We measured CBF, the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and the oxygen extraction fraction (OEF) in four patients with subacute stroke by means of ^{15}O gas steady-state positron emission tomography (PET) and compared it with that of the hyperfixed areas in ^{99m}Tc-HMPAO brain SPECT.

MATERIALS AND METHODS

Patients and Controls

We studied 4 patients (3 males, 1 female; mean age, 63 ± 18 years; range, 36–78 yr) who showed increased accumulation in the infarct region on ^{99m}Tc-HMPAO brain SPECT images. Two patients had atrial fibrillation due to cardiac embolism. The other two were diagnosed as having artery-to-artery embolic stroke with intraluminal angiographical filling defects suggesting emboli. The clinical and neuroradiological features of the patient are summarized in Table 1.

Five healthy volunteers (3 males, 2 females; mean age, 48 ± 16 years; range, 28–73 yr) underwent PET studies to

Table 1 Patient profile and MRI findings

Patient no.	Age (yr)	Sex	Neurological deficits	MRI findings	
				Site	Gd-DTPA enhancement
1	77	M	aphasia	Left MCA territory	+++
2	56	M	right hemiparesis aphasia	Left MCA territory	++++
3	36	F	left hemiparesis	Right basal ganglia and corona radiata	+++
4	78	M	left hemiparesis aphasia	Right MCA territory	++

MCA: middle cerebral artery, Enhancement Intensity: mild; ++, moderate; +++, marked; ++++

Table 2 Comparison of the parameters with PET in the hyperfixed area with those with ^{99m}Tc-HMPAO brain SPECT

Patient no.	Time from onset of stroke (days)	PET parameters				Hyperfixation rate
		CBF (ml/100 g/min)	$CMRO_2$ (ml/100 g/min)	OEF	CBV (ml/100 g)	
1	7	40.23	1.36	0.19	3.27	0.22
2	9	27.18	0.74	0.15	6.23	0.46
3	13	38.45	0.91	0.22	4.32	0.39
4	28	30.23	0.99	0.23	2.00	0.14
mean ± SD	14 ± 10	34.02 ± 6.3	0.99 ± 0.26*	0.20 ± 0.05*	3.96 ± 1.79	0.30 ± 0.15
normal control (mean ± SD)		40.44 ± 5.01	3.28 ± 0.59	0.48 ± 0.09	2.66 ± 0.71	

*$p < 0.01$ vs. normal controls

determine normal values. The volunteers were free of cerebrovascular risk factors and neurologic symptoms or signs. No focal brain lesions were detected by CT and Magnetic Resonance Imaging (MRI). The ethics committee of our hospital approved this study and written informed consent to participate was given by all subjects.

PET and SPECT examinations

The PET study was followed by SPECT within 24 hours, then by MRI within 6 days. The CBF, OEF, $CMRO_2$ and CBV values were measured with a Headtome IV PET scanner (Shimadzu, Kyoto, Japan) at a spatial resolution of 4.5 mm at FWHM and under ^{15}O-labeled gas inhalation.[5] Emission scans were corrected for the effect of tissue attenuation by comparison with corresponding transmission scans with an external ^{68}Ge-^{68}Ga ring source. Separate scans were obtained during continuous inhalation of ^{15}O-labeled carbon dioxide and ^{15}O-oxygen to measure CBF and OEF, respectively. A third scan measured CBV after the inhalation of ^{15}O-labeled carbon monoxide. During the scans, serial blood samples were obtained through a fine gauge brachial artery catheter to measure arterial isotope activity and arterial oxygen content (O_2con). The $CMRO_2$ value was calculated as CBF × OEF × O_2con.

Transaxial slices were 6 mm thick. SPECT studies were performed by means of a ring-type gamma camera (Headtome SET-070; Shimadzu, Kyoto, Japan) with a 7.2-mm FWHM. Patients were intravenously injected with 740 MBq of ^{99m}Tc-HMPAO while resting in the supine position with their eyes covered in a dimly lit room. The post-injection interval was 10 min. Image data from 30-min acquisitions were collected into a 128 × 128 matrix with a high resolution collimator.

All data were corrected for attenuation of 0.11 cm^{-1}, and tomographic data were reconstructed with a filtered backprojection algorithm so that 5-mm thick transaxial slices were obtained.

MRI were obtained with a 1.5 Tesla superconducting magnet (Siemens, Magnetom H15). The intensity of contrast enhancement in the infarcted areas after the administration of Gd-DTPA was graded as: none, faint, mild, moderate and marked.[6]

Tc-99m HMPAO brain SPECT and PET images were analyzed with MRI images for anatomical guidance. The regions of interest (ROIs) were placed manually over areas of increased accumulation in the infarct area and the contralateral cerebellum in ^{99m}Tc-HMPAO brain SPECT images. We also drew ROIs at the areas of PET images corresponding to the same areas in the SPECT images to obtain CBF, $CMRO_2$, OEF and CBV values. The hyperfixation rate (HFR) was calculated as the surplus rate compared with CBF after standardization with the cerebellum shown as follows.

$$HFR = \left(\frac{Chf}{Ccb} - \frac{CBFhf}{CBFcb}\right)$$

(Where, Chf = mean counts in the hyperfixed area with ^{99m}Tc-HMPAO brain SPECT, Ccb = mean counts in the cerebellum with ^{99m}Tc-HMPAO brain SPECT, CBFhf = CBF in the hyperfixed area with PET, CBFcb = CBF in the

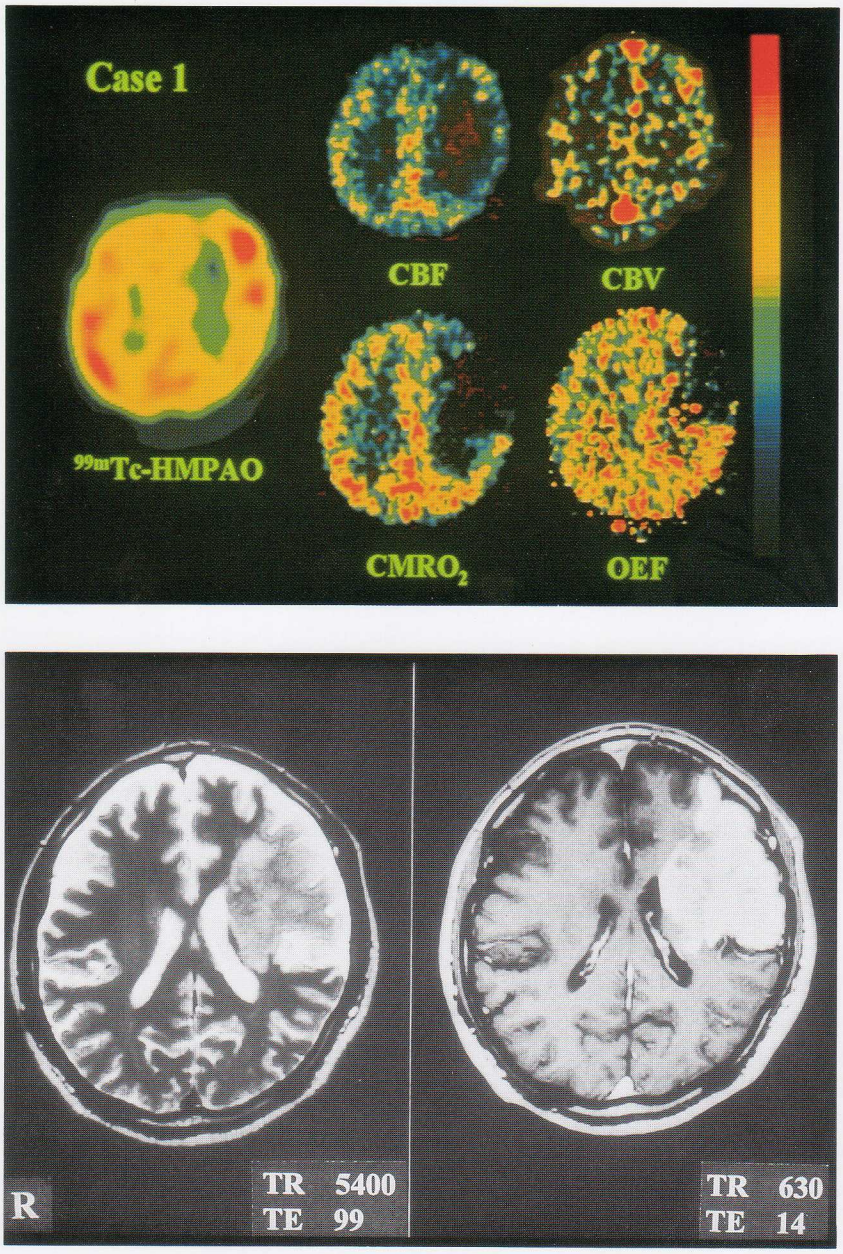

Fig. 1 Case presentation of Case 1 (77 yrs male). (A) Comparison of ^{99m}Tc-HMPAO brain SPECT image (^{99m}Tc-HMPAO) with PET images. ^{99m}Tc-HMPAO brain SPECT image shows the increased accumulation in the left frontal cortical area, while CBF and CBV are increased but $CMRO_2$ and OEF are reduced. (B) T2-weighted MR image (left) (repetition time, 5400 msec; echo time, 99 msec) shows an irregular high intensity area in the left middle cerebral artery territory and T1-weighted MR image (right) (repetition time, 630 msec; echo time, 14 msec) with Gd-DTPA shows marked enhancement in that area.

cerebellum with PET.)

All data are expressed as means ± SD. We compared all of the PET parameters for the patients and normal controls by the unpaired t-test and determined the relationships between the hyperfixation rate and the PET parameters by means of linear-regression analysis and the Pearson correlation coefficient. A two-tailed probability of < 0.05 was considered statistically significant.

RESULTS

The CBF, CBV, OEF and $CMRO_2$ values obtained from the hyperfixed area of infarcts in four patients were 34.02 ± 6.30 ml/100 g/min, 3.95 ± 1.76 ml/100 g, 0.20 ± 0.03 and 0.99 ± 0.26 ml/100 g/min, respectively, and the values obtained from 5 controls were 40.44 ± 5.01 ml/100 g/min, 2.66 ± 0.71 ml/100 g, 0.48 ± 0.09 and 3.28 ± 0.59 ml/100

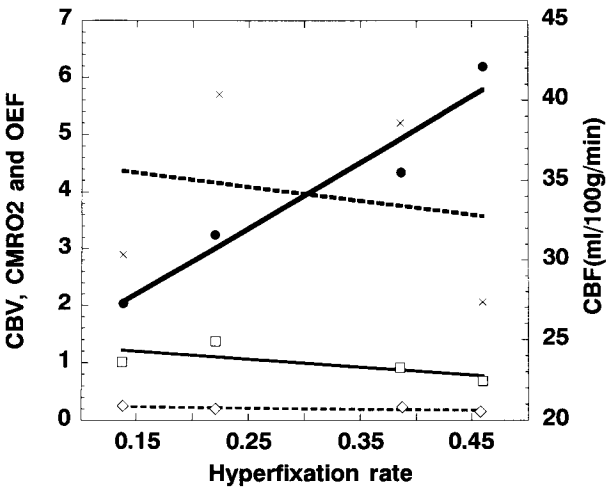

Fig. 2 Correlation between hyperfixation rate and PET parameters; CBV (ml/100 g), CBF (ml/100 g/min), $CMRO_2$ (ml/100 g/min) and OEF. ●: CBV vs. hyperfixation rate where $y = 11.75x + 0.42$, $r = 0.966$ ($p < 0.05$). ×: CBF vs. hyperfixation rate where $y = -8.99x + 36.72$, $r = 0.210$ (ns). □: $CMRO_2$ vs. hyperfixation rate where $y = -1.17x + 1.35$, $r = 0.665$ (ns). ◇: OEF vs. hyperfixation rate where $y = -0.143x + 0.24$, $r = 0.611$ (ns).

g/min, respectively. The OEF and $CMRO_2$ in the hyperfixed area of infarcts in four patients were significantly lower than those of normal controls ($p < 0.01$), whereas CBF and CBV values did not significantly differ from those of controls (Table 2 and Fig. 1). The CBF and $CMRO_2$ ratios of the hyperfixed area of infarct to the normal brain were 0.84 ± 0.16 and 0.30 ± 0.08, respectively. MRI revealed moderate or marked Gd-DTPA enhancement at all hyperfixed areas of infarcts. The hyperfixation rate in four patients was 0.30 ± 0.15, which significantly correlated with CBV ($r = 0.97$, $y = 11.75x + 0.42$; $p < 0.05$), but not with CBF ($r = 0.21$), OEF ($r = 0.61$) or $CMRO_2$ ($r = 0.66$, Fig. 2).

DISCUSSION

The hyperfixation in our 4 patients at the site of the infarct during the subacute phase from 7 to 28 days showed the findings of relative luxury perfusion and its surplus rate correlated well with CBV. We proposed comparing the surplus rate with CBF after standardization with the cerebellum, which might be a more accurate means of quantification in patients with a hyperfixed area. During the subacute phase, ^{99m}Tc-HMPAO hyperfixation appeared in regions of infarct due to reperfusion hyperemia, increased retention possibly related to increased blood brain barrier permeability, or retention in macrophages and leukocytes.[3,4] Forty-eight percent of patients with subacute stroke had the hyperfixation by ^{99m}Tc-HMPAO of which the count exceeded that of the opposite side.[3] The CBF in focal hyperfixation of the infarct was about 80% of that of healthy brain tissue.[4] The hyperfixation by ^{99m}Tc-HMPAO in subacute infarct was reported as an almost equivalent to or increased in terms of CBF compared with unaffected areas where $CMRO_2$ was decreased.[7] The values of $CMRO_2$ in our study were more depressed than those of CBF in areas of subacute infarct with focal hyperfixation, indicating relative luxury perfusion.[8,9] We could suggested that one of the main factors which caused hyperfixation was vasodilatation in addition to the blood brain barrier disruption and the neovascularization as previously reported.

During tracer transport, the unidirectional extraction fraction (E), which is the proportion of tracer extracted from the blood into tissue, depends on the capillary surface area (S) and the capillary permeability for the tracer (P), which is called the capillary permeability-surface product (PS). E increases with increasing S and P.[10] The CBV displayed the grade of vasodilation, vascular space and capillary surface area and disruption of the blood brain barrier caused high capillary permeability of the tracer. The vasodilation indicated by the high CBV value and the disruption of the blood brain barrier that was proven by Gd-DTPA enhancement on MRI caused high PS. The high unidirectional extraction fraction caused by high PS in the hyperfixed area might therefore be the cause of the high retention fraction of ^{99m}Tc-HMPAO, and it was not correlated with CBF. The grade of hyperfixation in the present study was related to the vascular surface area, which was depicted with CBV, and which was proven by the significant correlation between the hyperfixation rate and CBV in the hyperfixed area. Shintai et al. also considered that hyperfixation is related to the increased HMPAO extraction caused by hyperpermeability across the blood-brain barrier.[11] The present study revealed relative luxury perfusion and disruption of the blood brain barrier in hyperfixed areas of ^{99m}Tc-HMPAO brain SPECT images.

In conclusion, the present study showed the hyperfixation by ^{99m}Tc-HMPAO between 7 and 28 days from the onset of stroke in the infarct area indicated relative luxury perfusion the rate of which closely correlated well with CBV. Proposed that one of the main factors which caused hyperfixation was vasodilatation as well as the blood brain barrier disruption and the neovascularization.

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