Annals of Nuclear Medicine Vol. 10, No. 3, 293–298, 1996

Cerebral blood flow and vascular response to hypercapnia in hypertensive patients with leukoaraiosis

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Both arteriosclerosis and leukoaraiosis have a close relationship with hypertension, but the relationship between cerebral hemodynamics and leukoaraiosis in hypertensive patients has not been fully examined. To clarify this issue, we measured the regional cerebral blood flow (rCBF) and cerebrovascular response to hypercapnia in hypertensive patients with various degrees of leukoaraiosis. The subjects consisted of 7 normotensive normal controls and 17 hypertensive patients. The hypertensive patients were divided into three groups according to the severity of white matter lesions (leukoaraiosis) on MRI and the presence of dementia, namely, (1) negative or mild leukoaraiosis without dementia, (2) moderate to severe leukoaraiosis without dementia and (3) severe leukoaraiosis with dementia. Both the rCBF and the cerebrovascular response to hypercapnia were measured by the O-15 H_2O bolus-injection method and positron emission tomography. The rCBF in hypertensive patients without dementia did not decrease when compared with the normotensive controls, but the rCBF in hypertensive patients with dementia markedly decreased in the cerebral cortices and white matter. On the other hand, the cerebrovascular response to hypercapnia declined with the severity of leukoaraiosis, and it decreased most severely in patients with severe leukoaraiosis and dementia. Our results indicate that the reduction in the cerebral hemodynamic reserve capacity has a close relationship with the severity of leukoaraiosis in hypertensive patients, although the rCBF is maintained in hypertensive patients without dementia, and suggest that arteriosclerotic change reduces cerebrovascular CO_2 response and causes a leukoaraiosis in hypertensive patients.

Key words: cerebrovascular response, hypercapnia, cerebral blood flow, hypertension, leukoaraiosis, positron emission tomography

INTRODUCTION

HYPERTENSION is a major risk factor for cerebrovascular accidents, and is also the cause of arteriosclerosis.[1] Recent advances in magnetic resonance imaging (MRI) have helped to reveal a high incidence of white matter lesions (leukoaraiosis) in hypertensive patients,[2,3] but not all white matter lesions observed on MRI images are of vascular origin.[4,5] To clarify the significance of leukoaraiosis on the cerebral hemodynamics in hypertensive patients, we therefore measured the regional cerebral blood flow (rCBF) in the resting state and during the inhalation of 5% CO_2 in hypertensive patients with various degrees of leukoaraiosis by using O-15 H_2O PET and then compared the results with those in the normotensive controls.

SUBJECTS AND METHODS

The subjects consisted of 7 normotensive normal controls (3 females and 4 males 40 to 72 years of age, mean ± SD was 60 ± 12) and 17 hypertensive patients (7 females and 10 males, ranging from 41 to 78 years of age). MRI (GE, Signa 1.5 T) was performed on all subjects, and digital subtraction angiography was also performed on all hypertensive patients. All of the normotensive control subjects were volunteers who were social workers, and were carefully selected by neuropsychological tests and

Received February 14, 1996, revision accepted April 1, 1996.

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Table 1 Age, arterial blood pressure on admission, duration of hypertension and the neurological tests in normotensive normal controls and hypertensive patients

group	age (yrs)	blood pressure (mmHg)		duration of hypertension (yrs)	neurological tests	
		systolic	diastolic		HDS	WAIS
normotensive normal control (n = 7)	60 ± 12	120 ± 23	72 ± 12	—	—	—
(1) negative or mild leukoaraiosis (n = 6)	54 ± 7	170 ± 23	99 ± 21	13 ± 11	31.0 ± 1.9	110 ± 6.6
(2) moderate to severe leukoaraiosis (n = 5)	67 ± 9*	174 ± 30	95 ± 17	9 ± 7	28.0 ± 5.8	93.3 ± 15.1
(3) severe leukoaraiosis with dementia (n = 6)	63 ± 14	164 ± 36	108 ± 23	18 ± 16	16.0 ± 7.4	70.2 ± 7.3

HDS: Hasegawa's dementia scale (ranging from 0 to 32.5 points, cut off point below 22 for dementia), WAIS: Wechesler Adult Intelligence Scale, the number in parenthesis is number of cases, and values are mean ± SD, *: $p < 0.02$ significantly higher than group (1)

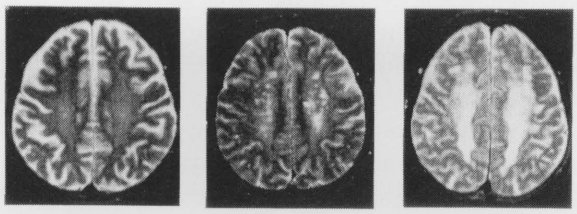

Fig. 1 Typical MR images in each group. (1) negative to mild white matter lesions (left), (2) moderate white matter lesions (center), (3) severe white matter lesions (right).

neuroimaging including CT and MRI. Five of them were negative on MRI. A 70-year-old male and a 72-year-old male showed only mild white matter lesions on MRI. The hypertensive patients were diagnosed according to the criteria of the mean scoring points.[6] Both the patients with occlusive lesions of cerebral arteries on the angiograms and the patients with a major stroke were excluded from this study. Among 17 hypertensive patients, 8 patients were untreated for hypertension. All 9 treated patients were examined while receiving anti-hypertensive drugs. Twelve out of 17 patients had a history of transient ischemic symptoms such as weakness in the limbs. Dementia was diagnosed by the DSM-III-R criteria[7] while referring to other neuropsychological tests such as Hasegawa's dementia scale (HDS) or Wechesler Adult Intelligence Scale (WAIS). The hypertensive patients were divided into three groups according to the severity of the leukoaraiosis on MRI and the presence of dementia, namely, group 1, negative or mild leukoaraiosis without dementia, group 2, moderate to severe leukoaraiosis without dementia, and group 3, severe leukoaraiosis with dementia. The typical MRI images in each group are shown in Figure 1. Four out of 6 patients in group 1, 2 out of 5 patients in group 2, and 2 out of 6 patients in group 3 were untreated for hypertension. Two out of 6 patients in group 1, 3 out of 5 patients in group 2, and 5 out of 6 patients in group 3 had a history of transient ischemic symptoms. The ages, arterial blood pressure on admission, duration of hypertension (years), HDS and WAIS are all shown in Table 1. There was no significant difference in age between the normotensive controls and the hypertensive groups, although the age of the patients with moderate to severe leukoaraiosis was significantly higher than that of the patients with negative or mild leukoaraiosis. The dementia rating scores decreased with the severity of leukoaraiosis.

PET was performed with a HEADTOME-III device which had a spatial resolution of 8.2 mm in full-width at half maximum, and simultaneously obtained 5 contiguous slices 15 mm apart. The subjects were placed in the supine position on a bed in a semidark room. A small canula was placed in the femoral artery for arterial blood sampling. A transmission scan with a $^{68}Ge/^{68}Ga$ ring source was obtained for each patient for attenuation correction. The rCBF was measured by the O-15 H_2O bolus-injection method[8,9] in the resting state and during the inhalation of 5% CO_2 at an interval of 15 min. In the O-15 H_2O PET study, 740 MBq of O-15 H_2O was infused as a bolus and the scan was started when the radioactivity appeared on a monitor for the head. The data were collected for 75 sec in each scan. The arterial blood was continuously drawn at a rate of 15 m*l*/min for 2 min, and radioactivity was recorded with a beta-ray detector system using a plastic scintillator (1.1 cm thick and 5.1 cm in diameter). Dispersion and time delay of the input function were corrected according to Iida's method.[10] The fixed time constant (10 s) was used for dispersion correction.

The regions of interest (ROI) over an area of 14 × 14 mm or 18 × 14 mm were established on the PET images referring to the MR images, as shown in Figure 2. The response to CO_2 was expressed as the percent change in rCBF per 1 mmHg change in $PaCO_2$. The values on both sides were averaged into a single value. A statistical analysis was performed by Student's t-test or Welch's t-test with unequal variance.

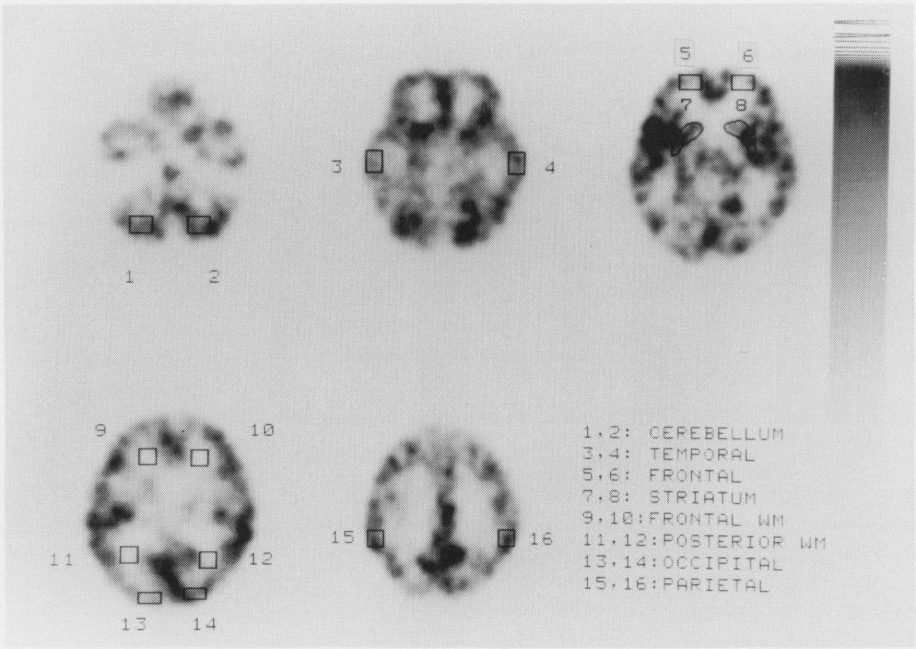

Fig. 2 Regions of interest in the brain regions.

Table 2 Hemoglobin, arterial PCO_2, blood pressure on the PET study in normotensive normal controls and hypertensive patients

group	hemoglobin (g/dl)	$PaCO_2$ (mmHg)		blood pressure (mmHg)			
		at rest	CO_2 load	at rest		CO_2 load	
				systolic	diastolic	systolic	diastolic
normotensive normal control (n = 7)	12.9 ± 1.2	40.7 ± 4.0	46.6 ± 5.1	135 ± 22	74 ± 14	151 ± 23	79 ± 12
(1) negative or mild leukoaraiosis (n = 6)	12.3 ± 0.5	39.2 ± 1.7	47.5 ± 2.9	176 ± 27*	97 ± 13*	197 ± 25#	102 ± 12#
(2) moderate to severe leukoaraiosis (n = 5)	12.5 ± 1.6	40.9 ± 1.7	46.5 ± 2.4	186 ± 33*	92 ± 12*	216 ± 35#,§	104 ± 13#
(3) severe leukoaraiosis with dementia (n = 6)	14.5 ± 2.0+	37.9 ± 5.3	44.0 ± 5.2	150 ± 37	100 ± 14#	154 ± 44	102 ± 22

(mean ± SD)

#: $p < 0.01$ significantly higher than controls, *: $p < 0.02$ significantly higher than controls,
+: $p < 0.05$ significantly higher than group (1), §: $p < 0.05$ significantly higher than group (3)

RESULTS

The hemoglobin, arterial blood gas, and the blood pressure in a PET study are shown in Table 2. There was no significant difference in the hemoglobin level between control subjects and hypertensive patients, but it was significantly higher in patients with severe leukoaraiosis and dementia than in patients with negative or mild leukoaraiosis. $PaCO_2$ increased by 5 to 7 mmHg during the inhalation of 5% CO_2. The blood pressure increased slightly during the inhalation of 5% CO_2 compared with that in the resting state, but without any significant difference between them. Both systolic and diastolic arterial blood pressure levels in the PET study were significantly higher in hypertensive patients without dementia than those in control subjects, but the systolic arterial blood pressure in patients with severe leukoaraiosis and dementia was not significantly higher than in control subjects either in the resting state or during the inhalation of 5% CO_2.

The mean values for rCBF in cerebral cortices and subcortical white matters in each group of patients are shown in Figure 3. There was no significant difference in the rCBF values between the hypertensive patients without dementia and the normotensive normal controls, despite the presence of leukoaraiosis. Nevertheless, the rCBF values decreased significantly in the cerebral cortices as well as in the frontal and posterior periventricular white matter in patients with severe leukoaraiosis and dementia compared with the normotensive controls. The cerebrovascular responses to hypercapnia in each group

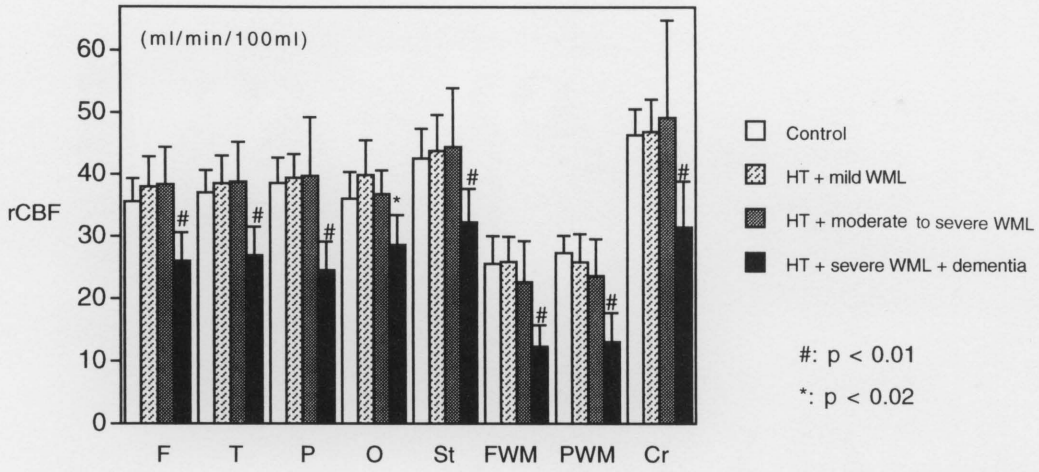

Fig. 3 The rCBF in each group of patients. There was no significant difference in the rCBF between hypertensive patients without dementia and the normotensive normal controls, despite leukoaraiosis. However, rCBF markedly decreased in the cerebral cortices (F: frontal, T: temporal, P: parietal, O: occipital, St: striatum, Cr: cerebellum), frontal (FWM) and posterior (PWM) periventricular white matter regions in patients with severe leukoaraiosis and dementia.

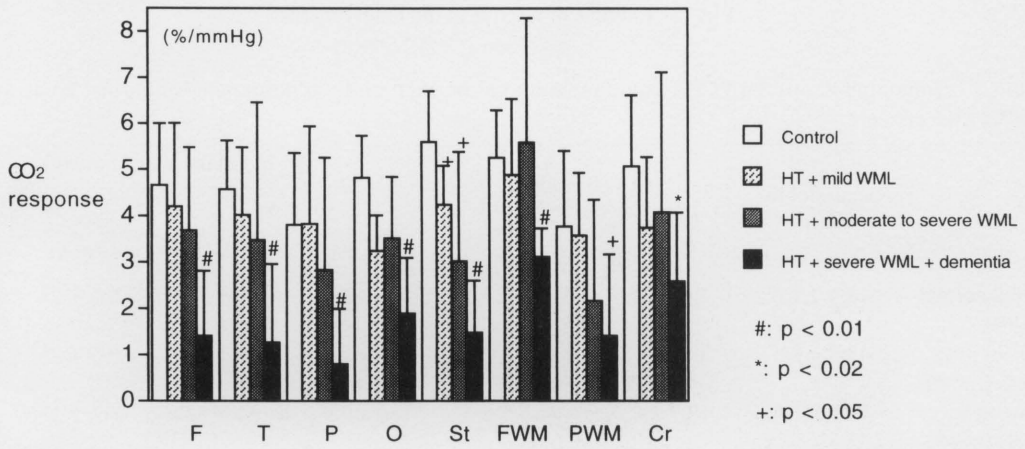

Fig. 4 The cerebrovascular response to hypercapnia in each group of patients. The cerebrovascular response to hypercapnia declined with the severity of leukoaraiosis, especially in the striatum, although there was no significant reduction in either cortical or white matter regions in hypertensive patients without dementia, while it was most severely impaired in patients with severe leukoaraiosis and dementia.

of patients are shown in Figure 4. The cerebrovascular response to hypercapnia decreased with the severity of leukoaraiosis in the cortical and subcortical regions, especially in the striatum, while the CO_2 response was almost the same in the hypertensive patients without dementia and the normotensive controls in all regions except for the striatum. The patients with severe leukoaraiosis and dementia showed a marked decline in the cerebrovascular response to hypercapnia in the cerebral cortices as well as the periventricular white matter.

DISCUSSION

Hypertension causes sclerosis of the perforating medullary arteries which may thus result in ischemic damage to the brain. The sclerotic rate of the medullary arteries correlated well with the degree of ischemic white matter lesions and blood pressure.[11] The cerebral hemodynamics of hypertensive patients has been studied mainly by means of the Xe-133 inhalation method by several authors. According to a report by Tominaga et al.,[12] the resting CBF values and cerebrovascular CO_2 reactivity were similar in the normotensive and the hypertensive patients. Griffith et al.[13] reported normal CBF and a decrease in vasoreactivity in hypertensive patients. In contrast, Rodriguez et al.[14] and Nobili et al.[15] reported that the CBF decreased in the hypertensive patients without any neurological symptoms, but there was no description of white matter lesions in these studies, and it was difficult to evaluate the hemodynamics in deep white matter due to

methodological problems. We therefore measured rCBF and cerebrovascular response to hypercapnia by O-15 H_2O PET.

Leukoaraiosis has a close relationship with hypertension. Recent advances in MRI have made it easy to detect white matter lesions. Inzitari et al.[2] and Fukuda et al.[3] reported a high incidence of leukoaraiosis on MRI in hypertensive patients, but the relationship between leukoaraiosis and cerebral hemodynamics has not yet been fully examined. Kobayashi et al.[16] reported that CBF decreased in patients with lacunae while it did not decrease in those with apparent periventricular hyperintensity. Ujike et al.[17] reported that, when using PET, both rCBF and $rCMRO_2$ decreased predominantly in the frontal region in patients with leukoaraiosis and dementia (multi-infarct dementia). Our previous study[18] with PET and the O-15 steady state method revealed an increase in the oxygen extraction fraction (OEF) in the white matter region of patients with leukoaraiosis but without dementia, which therefore implied an insufficient blood flow compared with oxygen consumption, although the rCBF did not decrease significantly, while the rCBF and $rCMRO_2$ did decrease significantly in the cortical regions as well as the white matter in patients with leukoaraiosis and dementia.

In this study, the rCBF in hypertensive patients without dementia (groups 1 and 2) did not differ from those in the normotensive controls. These findings are in good accord with the reports by Tominaga et al.[12] and Griffith et al.,[11] although there was no description of leukoaraiosis in their reports. On the other hand, the rCBF decreased noticeably in hypertensive patients with severe leukoaraiosis and dementia (group 3). This finding closely correlated with our previous report on the O-15 steady-state method.[18] The patients in group 2 showed moderate to severe leukoaraiosis on MRI, but did not show a reduction in rCBF in the cerebral cortices or subcortical regions. These findings indicate that rCBF reflects the brain function better than the structural alternation. Histological studies revealed variation in underlining pathogenesis such as infarcts, demyelination or dilated perivascular spaces in the area with leukoaraiosis.[3] The rCBF may therefore not necessarily decrease in the area with leukoaraiosis on MRI, although the volume of the area may be still correlated with the reduction in rCBF, since we could not individually evaluate rCBF in patients with moderate and severe leukoaraiosis but without dementia due to the limited number of patients in group 2. The mechanism of the reduction in the rCBF in patients with severe leukoaraiosis and dementia is not clear, but it was thought to be caused by both the small-vessel disease and the functional deterioration of the brain due to the disruption of the neural network.

On the other hand, the cerebrovascular response to hypercapnia decreased with the severity of leukoaraiosis, especially in the striatum, and it was most severely impaired in patients with severe leukoaraiosis and dementia. As mentioned above, hypertension causes sclerosis of the perforating medullary arteries, and the sclerotic change also correlates well with the degree of ischemic white matter lesions and blood pressure.[11] The striatum as well as the deep white matter is supplied by the perforating arteries. In addition, the incidence of lacuna is also higher in hypertensive patients.[19] Sclerosis of the small vessels is therefore considered to reduce the vasodilatory capacity. This finding means a decrease in cerebral hemodynamic reserve capacity, which may therefore be an important pathogenesis of leukoaraiosis in hypertensive patients. In hypertensive patients, it is well known that the lower limit of the autoregulation of the cerebral circulation shifts toward higher perfusion pressure,[20] and this upward shift of the autoregulation increases the susceptibility of hemodynamic deterioration under lower blood pressure conditions. When a severe reduction in the perfusion pressure occurs, the rCBF decreases to a lower level than a critical point, resulting in ischemic damage to the brain, and subsequently decreases the rCBF. This process may be accelerated in hypertensive patients with severe leukoaraiosis and dementia, since the vasodilatory capacity was severely impaired in this group of patients. As shown in Tables 1 and 2, the systolic pressure was higher in hypertensive patients without dementia than in hypertensive patients with dementia, although the diastolic pressure was higher in the latter. The rCBF may be maintained by the increased arterial pressure in hypertensive patients without dementia (groups 1 and 2).

In conclusion, the present results indicate that rCBF is maintained at the normal level in hypertensive patients if they do not have dementia, but the hemodynamic reserve capacity evaluated by rCBF response to hypercapnia reduced with accompanying leukoaraiosis. Both rCBF and cerebrovascular CO_2 response are noticeably decreased in hypertensive patients with leukoaraiosis and dementia. These findings suggest that arteriosclerotic change reduces cerebrovascular CO_2 response and causes leukoaraiosis in hypertensive patients.

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