JOURNAL OF NEUROTRAUMA
Volume 22, Number 12, 2005

Pp. 1411–1418

Changes in Cerebral Blood Flow from the Acute to the Chronic Phase of Severe Head Injury

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ABSTRACT

We studied cerebral blood flow (CBF) in the transition from the acute to the chronic phase of severe head injury in order to determine patterns of change in relation to neurological outcome. We measured CBF with stable xenon-enhanced computed tomography (Xe-CT) in 20 consecutive patients at 1, 2, 3, 4, and 6 weeks after severe head injury, and analyzed the relation between the pattern of change in CBF and neurological outcome at 6 months after injury. CBF values were significantly lower in the brain-injured patients than in 14 healthy volunteers, except at 3 weeks after injury, when CBF increased in the patients to a value that did not differ significantly from that in the normal volunteers. We therefore focused on the change in CBF at 3 weeks after injury. We separated the 20 brain-injured patients into two subgroups, of which the first (subgroup A) consisted of nine patients whose CBF had returned to normal by week 3 post-injury, while the second (subgroup B) consisted of 11 patients whose CBF was subnormal at week 3 post-injury. CBF was significantly higher in subgroup A than in subgroup B at 2 weeks post-injury ($p < 0.05$). CBF in subgroup B remained significantly lower than that in subgroup A throughout the study period. At 6 months post-injury, subgroup A had a significantly better neurological outcome than did subgroup B ($p < 0.05$). We conclude that patients whose CBF returns to normal at 2–3 weeks following severe traumatic brain injury after being abnormally low in the acute phase of injury can be expected to achieve a good neurological outcome.

Key words: cerebral blood flow; neurological outcome; severe head injury; xenon-CT

INTRODUCTION

SEVERAL CLINICAL STUDIES have shown that severe traumatic brain injury often causes disturbances in cerebral blood flow (CBF) that lead to ischemia (Bouma et al., 1991; Enevoldsen et al., 1976) or hyperemia (Obris et al., 1984). Miller et al. (1985) proposed that cerebral ischemia is the single most important cause of brain injury secondary to severe head trauma. Histological evidence indicates that ischemic brain damage is common in most brain-injured patients who die (Miller, 1985). Bouma et al. (1992) reported that early global or regional ischemia after severe head injury was significantly associated with early mortality. Martin et al. (1997) charac-

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terized a cerebral hemodynamic phase during the first 2 weeks after severe head trauma in which reduced CBF is characterized by hypoperfusion, hyporemia, and vasospasm. However, most reports concerned with CBF in patients with severe injury have discussed only abnormalities in CBF in the initial 2 week post-injury period (Corte et al., 1997; Jaggi et al., 1990; Marion et al., 1991; Plougmann et al., 1994; Schröder et al., 1995), and have not made clear whether values reflecting CBF returned to normal in the chronic phases of injury.

The purpose of our study was to determine the pattern of change in CBF from the acute to the chronic phase in patients with severe traumatic brain injury, and to analyze the relation between CBF and neurological outcome. We were also interested in differences in CBF between normal volunteers and patients with severe head injury.

MATERIALS and METHODS

Patient Population

Between October 2000 and September 2002, 49 patients with severe head injury, whose Glasgow Coma Scale (GCS) score was 8 or less on admission, or in whom "talk and deteriorate" syndrome (Lobato et al., 1991) was confirmed, were admitted to the Trauma and Acute Critical Care Center of Osaka University Hospital. Of the 49 patients admitted, 29 did not meet the study criteria and were excluded; this group consisted of 15 patients over age 65 or under age 10 years, seven patients with uncontrollable intracranial hypertension, and seven patients with life-threatening injury to an organ other than the brain. This left 20 patients, consisting of 14 men and 6 women, ranging in age from 19 to 64 years (mean age, 32 years), who were included in the study. In each case, informed consent to participate was obtained from a patient's family member. Control subjects were 14 healthy adult male volunteers ranging in age from 25 to 45 years (mean age, 32 years).

Patient Management

All patients were initially intubated, artificially ventilated with a $PaCO_2$ of 30–35 mm Hg, and resuscitated with lactated Ringer's solution at 1.5–2.0 mL/kg/h. Intracranial pressure (ICP) was monitored with an intraventricular catheter or intraparenchymal sensor (Codman® Micro Sensor Basic Kit; Johnson & Johnson Co, Raynham, USA). In 16 patients, an ICP below 20 mm Hg was maintained with conventional treatments, consisting of cerebrospinal fluid (CSF) drainage, mild hyperventilation ($PaCO_2$ 30–35 mm Hg), and either continuous administration of propofol (4 mg/kg/h) or high-dose barbiturates according to published regimens (Sawada et al., 1982; Shiozaki et al., 1999). In four patients whose ICP remained above 20 mm Hg after high-dose barbiturate therapy, mild hypothermia (34°C) was induced according to our published regimens (Shiozaki et al., 1993, 1998). All treatments for reduction of ICP were completed within 1 week of injury.

Study Protocol

All patients were stabilized hemodynamically during the first week post-injury, and were examined for assessment of CBF at post-injury weeks 1 (7 ± 1 days), 2 (15 ± 1 days), 3 (21 ± 1 days), 4 (28 ± 1 days), and 6 (42 ± 1 days) with a CT scanner (Asteion-Multi TSX-021A; Toshiba, Tokyo, Japan) equipped with a stable xenon gas delivery system (AZ-725; Anzai Medical, Tokyo, Japan), and a matching CBF software package (AZ-7000W; Anzai Medical).

The technical details of CBF measurement with Xe-CT have been described elsewhere (Gur et al., 1982; Plougmann et al., 1994; Segawa et al., 1983; Schröder et al., 1995). Patients inhaled 30% ^{133}Xe gas (Xenon Cold®; Anzai Medical) mixed with 100% oxygen for 3 min, and then inhaled room air for the next 5 min to wash out the ^{133}Xe gas. Scans were obtained in six axial planes, each 5 mm thick and separated from one another by 10 mm, with the lowest plane chosen to include portions of the brain stem and top of the neocortex. Analytic computer software was then used to calculate CBF values. Average blood-flow values for both cerebral hemispheres, including the basal ganglia and excluding the Sylvian sulcus, were determined from tracer activity in regions of interest. End-expiratory ^{133}Xe and CO_2 concentrations, oxygen saturation, and electrocardiographic activity were monitored continuously during scanning. In addition, arterial blood gas levels and hematocrit (Hct) were determined before and after inhalation of ^{133}Xe. The CBF values were corrected to a standard $PaCO_2$ of 34 mm Hg, assuming a 3% increase in CBF for each 1 mm Hg increase in $PaCO_2$ (Bouma et al., 1991). We examined the 14 control subjects with the same stable Xe-CT technique used for the injured patients, and used the resulting data to estimate normal CBF values.

At the time of CBF measurement, we also evaluated clinical data including neurological function, blood pressure (BP), body temperature (BT), blood gas parameters, and Hct. During the 6-week observation period of the study, we evaluated neurological function with the Disability Rating Scale (DRS). The DRS was developed as a single instrument to provide quantative information for charting the progress of patients with severe head injury. The methodological details of the DRS have been described elsewhere (Rappaport et al., 1982).

Patient Outcome

All patients were discharged from the hospital at 6 weeks after injury. Outcome was assessed at 6 months after injury according to the patients' Glasgow Outcome Scale (GOS) scores (1 = death; 2 = vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = mild or no disability) (Teasdale and Jennett, 1974). For statistical comparison, patients with a GOS score of 4 or 5 were classified as having a favorable outcome, and those with a GOS score of 1, 2, or 3 were classified as having an unfavorable outcome. Additionally, a follow-up interview was conducted at 6 months after injury with each patient or a family member, either through a clinic visit or by telephone.

Statistical Analysis

All values are expressed as mean ± standard deviation (SD). Changes in CBF values, DRS score, and other clinical parameters in both subgroups were analyzed by one-way analysis of variance (ANOVA) for repeated measures. When ANOVA indicated differences between the study subgroups, pairwise comparisons were made by calculating Dunnet's q statistic. We used the chi-square test to determine the relation between CBF values at week 3 and neurological outcome. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Clinical characteristics of the 20 patients who met the study criteria are summarized in Table 1. A low ICP was defined as an ICP < 20 mm Hg achieved with conventional treatment, and a high ICP was defined as an ICP ≥ 20 mm Hg despite conventional treatment. Patients with a high ICP required mild hypothermia to control intracranial hypertension. Each of the 4 patients whose GCS score was above 8 at the time of admission showed deterioration in level of consciousness within 24 h after admission.

TABLE 1. PATIENT CHARACTERISTICS

Age (years)/ sex	*GCS on admission*	*CT findings*	*Additional injury*	*ICP*	*GOS result*	*Sub-group*
24/M	6	Contusion	—	Low[b]	GR	A
19/M	7	Traumatic SAH	Chest injury, leg fracture,	Low	GR	A
21/M	7	DAI/contusion	—	Low	MD	A
19/M	8	DAI	Arm fracture	Low	GR	A
22/M	8	SDH	—	Low	GR	A
23/M	8	Contusion	Chest injury	Low	GR	A
28/M	8	EDH	Leg fracture	Low	GR	A
30/F	12[a]	SDH EDH	—	High[c]	GR	A
45/M	15[a]	SDH	—	Low	GR	A
21/M	3	Traumatic ICH	—	High	PVS	B
56/F	3	SDH EDH	—	Low	PVS	B
25/M	4	SDH	—	High	MD	B
30/M	4	DAI	Leg fracture	Low	PVS	B
18/M	5	DAI	—	Low	SD	B
39/M	6	Contusion DAI	—	Low	SD	B
60/M	7	DAI	Chest injury	Low	PVS	B
64/F	8	Contusion	Arm fracture	Low	GR	B
64/F	8	SDH	Arm fracture	Low	SD	B
24/F	10[a]	SDH EDH	Pelvic fracture, arm fracture	High	SD	B
62/F	13[a]	SDH	Abdominal injury, arm fracture	Low	SD	B

[a]"Talk and deteriorate" syndrome.

[b]ICP was controlled at 20 mm Hg with conventional treatments.

[c]ICP was > 20 mm Hg, despite conventional treatments and induced mild hypothermia (34°C).

GCS, Glasgow coma scale; ICP, intracranial pressure; GOS, Glasgow Outcome Scale; DAI, diffuse axonal injury; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; EDH, epidural hemorrhage; GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state.

Changes in CBF in Patients and Normal Volunteers

Figure 1 shows the changes in CBF in the 20 patients and the CBF values for the 14 healthy volunteers. A total of 100 CBF studies were done on the 20 patients during the 6-week observation period. Overall, CBF values in the head-injured patients were significantly below those of the healthy volunteers during each of the 6 weeks of the observation period (28.7 ± 10.5 vs. 40.6 ± 6.5 mL/100 g/min; $p < 0.05$), except for week 3 ($p < 0.05$).

Subgroup Analysis

Because CBF in the nine head-injured patients returned to normal by week 3 after injury, we divided them into two subgroups to follow their subsequent course. Subgroup A consisted of nine patients whose CBF was normal or above normal at week 3 after injury, while subgroup B consisted of 11 patients whose CBF was below normal at week 3 after injury. On admission, the two subgroups did not differ significantly with respect to clinical factors including age, GCS score, pupillary abnormalities, CT classification, or ICP (Table 2). DRS score and other clinical parameters such as BT, BP, blood-gas parameters, and Hct at the time of CBF measurement are shown in Table 3. The DRS scores of the two subgroups showed no significant difference during the 3 weeks after injury. However, beyond 4 weeks after injury, the DRS score of subgroup A was significantly lower than that of subgroup B (4 weeks: 8.9 ± 4.5 vs. 21.1 ± 5.9, 6 weeks: 5.1 ± 4.1 vs. 17.0 ± 8.5; $p < 0.05$). Other parameters did not differ for the two subgroups.

As shown in Figure 2, patterns of change in CBF differed significantly in the two subgroups ($p < 0.05$). In subgroup A, CBF values were lower than those of the normal volunteers at week 1 after injury, but had returned to normal by 2 weeks after injury, and at 3 weeks were higher than the values at 1 week post-injury ($p < 0.05$). In subgroup B, CBF values were lower than those of the normal volunteers throughout the 6-week observation pe-

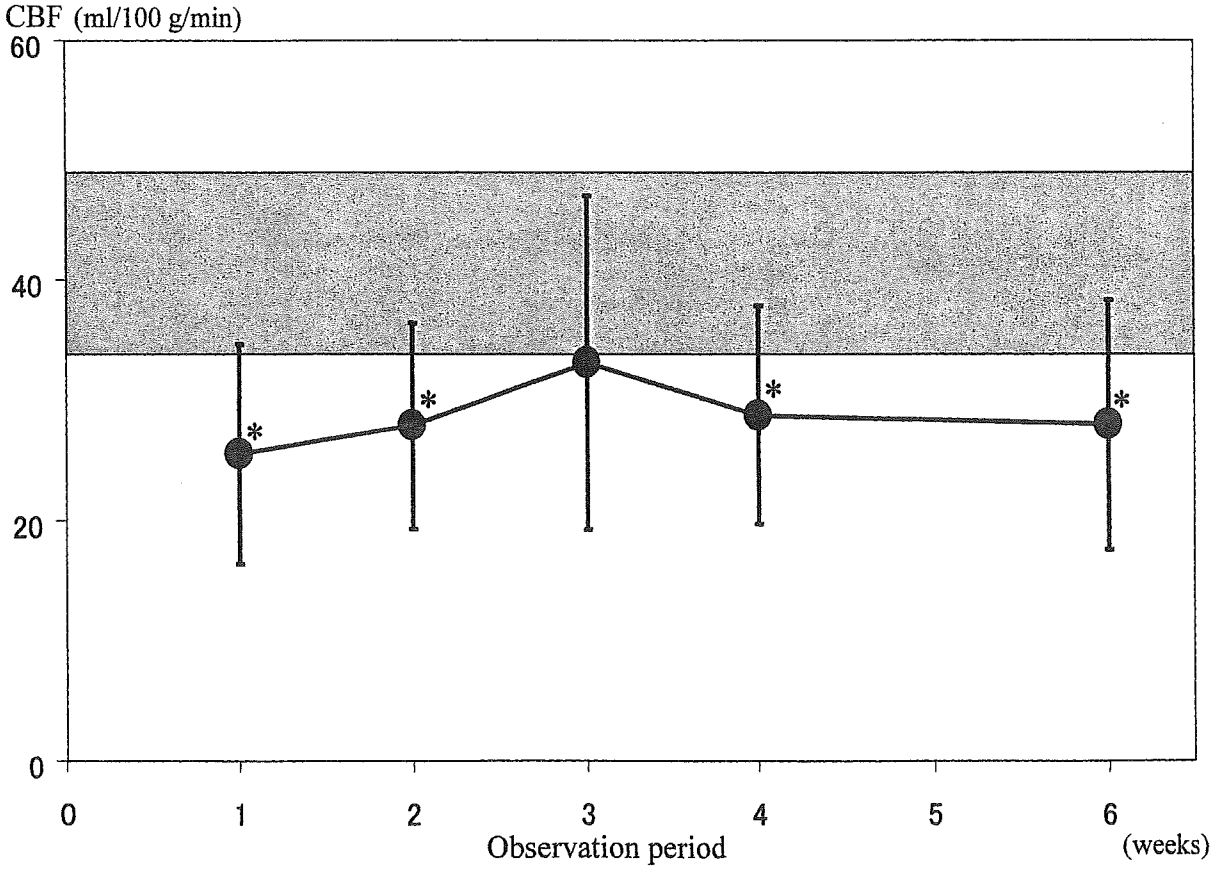

FIG. 1. Cerebral blood flow (CBF) change in the 20 head-injury patients during the 6-week observation period. Data are shown as mean ± SD. The gray zone represents the normal range of CBF, seen in the 14 healthy volunteers. Statistical analysis of each week's CBF value was done with Student's *t*-test. *$p < 0.05$ versus normal volunteers.

TABLE 2. CLINICAL CHARACTERISTICS OF SUBGROUPS A AND B

	Subgroup A, n = *9*	*Subgroup B,* n = *11*
Sex (M/F)	8/1	6/5
Mean age (years)	26 ± 8	42 ± 19
Admission GCS score[a]	9 ± 2	7 ± 3
Pupillary abnormalities on admission	4	6
CT classification[b]		
I	3	1
II	3	3
III	2	2
IV	0	0
Evaculated mass lesion	1	5
Nonevaculated mass lesion	0	0
High ICP	1	3
Outcome		
GR/MD	9	2
SD/V/D	0	9

[a]"Talk and deteriorate" syndrome: two patients in subgroup A and two patients in subgroup B.

[b]Classification of Traumatic Coma Data Bank (Marshall et al., 1992).

GR, good recovery; MD, moderate disability; SD, severe disability; V, vegetative state; D, death.

riod. CBF values in subgroup A were significantly higher than those in subgroup B at week 2 after injury ($p < 0.05$).

Clinical Outcome

In subgroup A, 6-month outcomes after injury consisted of good recovery in eight patients, and moderate disability in one patient. In subgroup B, 6-month outcomes after injury consisted of good recovery in one patient, moderate disability in one patient, severe disability in five patients, and a persistent vegetative state in four patients. The neurological outcome in subgroup A at 6 months after injury was significantly better than that in subgroup B ($p < 0.05$).

DISCUSSION

We noticed two distinct patterns of change in CBF in patients with severe traumatic brain injury during the first 6 weeks after injury. In the first pattern, seen in subgroup A of our brain-injured patients, CBF values returned to normal at week 3 after injury, while in the second pattern, seen in subgroup B, CBF values remained low throughout the 6 weeks after injury. Patients in subgroup A showed significantly better neurological outcomes than those in subgroup B.

Martin et al. (1997) reported time-dependent changes in ^{133}Xe-clearance–determined CBF in patients with severe closed head injury during the first 2 weeks after injury. They described the changes in CBF as occurring in three discrete phases: hypoperfusion in the first 24 h, hyperemia on days 1–3, and vasospasm on days 4–15 post-injury. As far as we know, however, Martin and colleagues did not observe changes in CBF beyond the initial 2 weeks after injury. We therefore measured CBF in our head-injured patients at weeks 1, 2, 3, 4, and 6 after injury, and investigated the relation between change in CBF and neurological outcome. Because CBF was influenced by various interventional procedures during the first week after admission, such as the use of sedative drugs, control of BT, and surgery, we began our study at 1 week after injury, to exclude the influence of these procedures.

Our study clearly showed that CBF in patients with severe head injury was significantly below that of healthy subjects except at week 3 after injury. Martin et al. (1997) hypothesized that CBF recovered gradually beyond 2 weeks after injury as a result of decreased vasospasm. Several other studies have also reported that vasospasm may be an important determinant of outcome in severe head injury (Pasqualin et al., 1984; Martin et al., 1995). However, our study found two characteristic patterns of change in CBF during the initial 6 weeks after injury. The first pattern was that seen in subgroup A, in which CBF was below normal at week 1 after injury, increased at week 2 , reached a peak value at week 3, and remained normal thereafter. In the second pattern, seen in subgroup B, CBF remained subnormal throughout the entire 6-week period of observation after injury. To explain these two patterns of change in CBF, we hypothesize that the low CBF of subgroup B is linked to a reduction in cerebral metabolism despite a decrease in vasospasm. To clarify the relation between cerebral blood supply and cerebral metabolic demand from the acute to the chronic phase of severe head injury, future studies will require the measurement of cerebral oxygen and glucose metabolism with the Xe-CT, together with three-dimensional CT angiography, analysis of SjO_2, and [^{18}F]fluorodeoxyglucose–positron emission tomography (FDG-PET).

A further important point in our study was that subgroup A had a significantly better neurological outcome than did subgroup B. By 2 weeks after injury, almost all of our patients had lost consciousness, and their DRS scores were quite high. However, beyond 4 weeks post-injury, the DRS scores of subgroup A had recovered to a degree that they were significantly lower than those for subgroup B, and patient consciousness in subgroup A re-

TABLE 3. CLINICAL DATA FOR SUBGROUPS A AND B

	Week 1		*Week 2*		*Week 3*		*Week 4*		*Week 6*	
Group	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
DRS	24.2 ± 3.5	26.5 ± 2.6	19.9 ± 2.7	22.8 ± 4.9	17.8 ± 4.1	22.1 ± 5.6	8.9 ± 4.5*	21.2 ± 5.9	5.1 ± 4.1*	17.0 ± 8.5
BT (°C)	37.4 ± 0.6	37.5 ± 0.4	37.4 ± 0.4	37.2 ± 1.2	37.3 ± 0.6	37.4 ± 0.2	37.5 ± 0.7	36.9 ± 0.5	37.3 ± 0.2	37.3 ± 0.2
Bp sys (mm Hg)	135 ± 10	167 ± 15	128 ± 12	139 ± 19	118 ± 4	135 ± 14	122 ± 13	127 ± 13	124 ± 13	122 ± 12
Bp dia (mm Hg)	72 ± 7	87 ± 14	71 ± 12	75 ± 12	68 ± 8	74 ± 10	57 ± 12	71 ± 12	69 ± 15	73 ± 13
PaO_2 (mm Hg)	111 ± 19	113 ± 19	109 ± 12	101 ± 14	87 ± 31	97 ± 17	104 ± 9	92 ± 13	102 ± 11	97 ± 6
$PaCO_2$ (mm Hg)	36 ± 3	36 ± 4	39 ± 3	37 ± 5	38 ± 5	39 ± 3	38 ± 4	38 ± 4	39 ± 4	41 ± 2
pH	7.445 ± 0.21	7.448 ± 0.17	7.458 ± 0.02	7.446 ± 0.31	7.450 ± 0.09	7.441 ± 0.20	7.463 ± 0.180	7.457 ± 0.19	7.472 ± 0.19	7.438 ± 0.09
BE (mEq/L)	0.9 ± 1.2	0.7 ± 2.0	3.3 ± 1.8	1.8 ± 1.6	2.3 ± 3.4	2.5 ± 1.6	3.3 ± 1.7	2.8 ± 1.8	1.5 ± 0.9	2.9 ± 0.7
Hct (%)	31.2 ± 6.9	30.3 ± 4.7	29.8 ± 6.1	29.1 ± 2.4	27.7 ± 1.7	29.9 ± 4.5	34 ± 3	32 ± 2	34.5 ± 1.6	36.3 ± 1.7

*Group A versus group B, $p < 0.05$.

The Disability Rating Scale (DRS) is an ordinal scale that ranges from 0 to 30, with 0 rated as no disability and 30 rated as death.

BT, body temperature; Bp sys, systolic blood pressure; Bp dia, diastolic blood pressure; Hct, hematocrit.

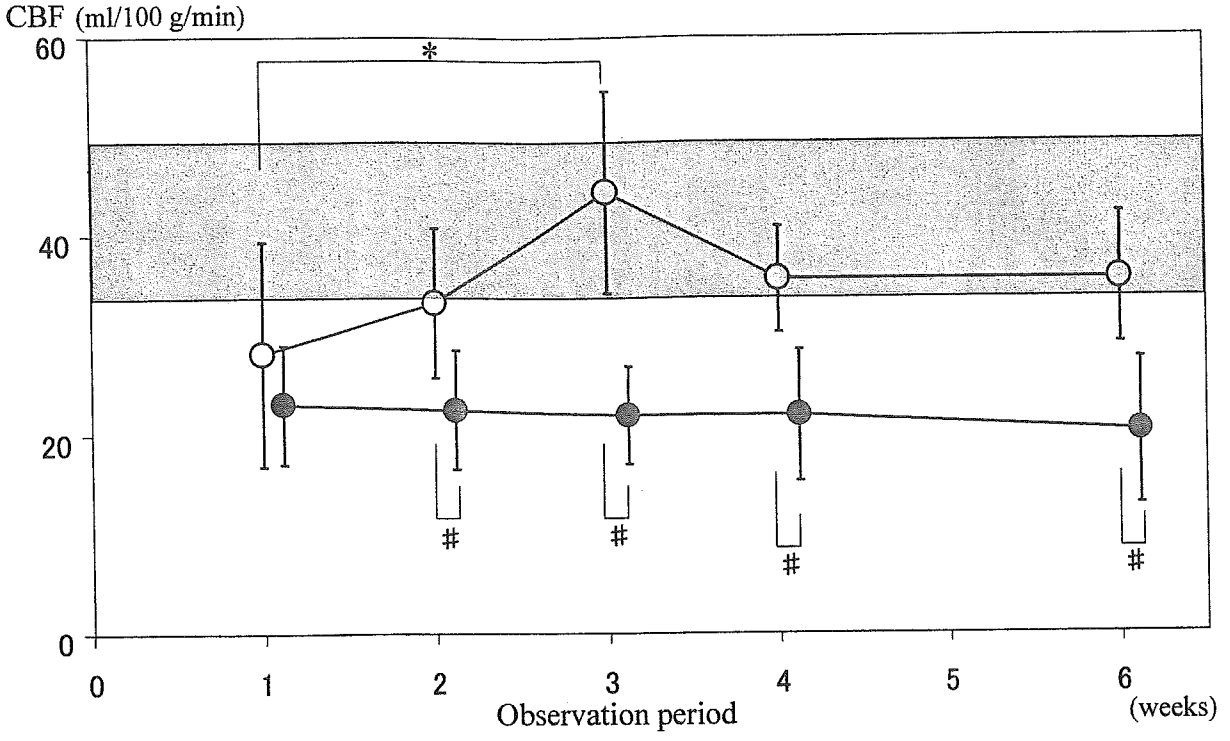

FIG. 2. Cerebral blood flow (CBF) patterns in subgroups A and B during the 6-week observation period. Data are shown as mean ± SD. Open circles, CBF data for subgroup A; closed circles, CBF data for subgroup B. The gray zone represents the normal range of CBF, seen in the 14 healthy volunteers. Statistical analysis was done by calculating Dunnet's q statistic. *$p < 0.05$ for CBF at week 1 versus week 3 after injury; #$p < 0.05$, subgroup A versus subgroup B.

vealed improvement (Table 3). Even at 2 weeks post injury, the CBF in subgroup A was significantly higher than that in subgroup B. Because the two subgroups' neurological states at 2 or 3 weeks after injury were similar, we conclude that patients with severe head injury whose CBF returns to normal within 3 weeks after injury are highly likely to regain consciousness, and hypothesize that CBF at 2 or 3 weeks after injury may be one of the most useful factors for predicting neurological outcome following severe head injury.

Our study had several limitations. Because our study population was small, our study groupings may have produced some biases. For example, the number of patients over 50 years old was 0 (0%) in subgroup A and 5 (45%) in subgroup B; the number of patients with GCS scores under 5 on admission was 1 (11%) in subgroup A and 5 (45%) in subgroup B; the number of patients treated with mild hypothermia for a high ICP was 3 (27%) in subgroup A and 0 (0%) in subgroup B; and the number of patients who underwent evacuation of mass lesions was 1 (11%) in subgroup A and 5 (45%) in subgroup B, although none of these differences was statistically significant. Nevertheless, we cannot rule out the possibility that the low CBF in subgroup B may have been a natural consequence of early intracranial pathology. Obviously, further study of the effects of severe head injury is needed, with an important goal of this research seeking to determine whether therapeutic procedures for increasing CBF can improve neurological outcome in patients whose CBF remains subnormal beyond 3 weeks post-injury.

In sum, we measured CBF with Xe-CT in normal volunteers and patients with severe head injury, and observed two patterns of change in CBF during 6-week period post-injury. The first pattern was a subnormal CBF at 1 week after injury, followed by an increase at 2 weeks, with a peak value at 3 weeks, and a sustained normal level beyond 3 weeks. The second pattern was a low CBF throughout the initial 6 weeks following injury. A good neurological outcome at 6 months after injury was associated with the first of these two CBF patterns.

ACKNOWLEDGMENTS

This study was supported by grant 15131001 for Research on Brain Science from the Ministry of Health and

Welfare of Japan, Grant-in-Aid 15390545 for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and a grant from the Marine and Fire Insurance Association of Japan, Inc.

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Relationship Between Cerebral Circulatory Reserve and Oxygen Extraction Fraction in Patients With Major Cerebral Artery Occlusive Disease

A Positron Emission Tomography Study

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Background and Purpose—The present study examined the relationship between circulatory and metabolic reserve in patients with hemodynamic impairment.

Methods—Positron emission tomography was used to investigate 40 patients with major cerebral artery occlusive disease. The ratio of cerebral blood volume to cerebral blood flow (CBV/CBF) and vasoreactivity in response to hypercapnia ($\%CBF_{hypercapnia}$) and acetazolamide (ACZ) stress ($\%CBF_{ACZ}$) were measured to evaluate circulatory reserve. Oxygen extraction fraction (OEF) was measured to evaluate metabolic reserve. To detect relationships between circulation reserve and OEF, cerebral hemispheres were grouped into 5 or 6 stepwise groups based on reduction of circulation reserve.

Results—OEF was significantly elevated in hemispheres with CBV/CBF $\geq$0.11 minutes and in hemispheres with $\%CBF_{hypercapnia}$ <0%. OEF was significantly increased according to $\%CBF_{ACZ}$ in hemispheres with $\%CBF_{ACZ}$ <15% and plateaued at levels below −15%.

Conclusions—Metabolic reserve consumption began at CBV/CBF $\geq$0.11 minutes, $CBF_{hypercapnia}$ <0%, and CBF_{ACZ} <15%. (***Stroke***. **2006;37:534-536.**)

Key Words: ischemia ■ tomography, emission computed

Decreases in cerebral perfusion pressure attributable to steno-occlusive lesions of the cerebral artery are compensated for via 2 mechanisms.[1–3] The first involves maintaining cerebral blood flow (CBF) by autoregulatory vasodilation of the resistant vessels (circulatory reserve). The second involves maintenance of cerebral metabolic rate of oxygen ($CMRO_2$) by increasing oxygen extraction fraction (OEF) from the blood to the brain (metabolic reserve). The relationship between circulatory and metabolic reserve in various clinical scenarios has remained unclear.[4,5] To clarify the relationship between circulatory and metabolic reserve, the present study investigated correlations between cerebral blood volume/CBF ratio (CBV/CBF) and OEF, between vasoreactivity in response to hypercapnia and OEF, and between vasoreactivity in response to acetazolamide (ACZ) stress and OEF.

Materials and Methods

Subjects

Table 1 shows patient characters and exclusion criteria.

Positron Emission Tomography and Data Analysis

CBF, OEF, CBV, and $CMRO_2$ were measured by positron emission tomography (PET), as reported previously.[6] CBF measurements were performed during the resting state and under hypercapnia and ACZ stress in each subject. Hypercapnia was induced by inhalation of 7% CO_2, beginning at 60 s before and continuing throughout CBF measurement. For ACZ stress, 1 g of ACZ was administered intravenously over 2 minutes, beginning at 10 minutes before the start of scanning. Two transaxial slices were selected, including the corona radiata and centrum semiovale, and regions of interest (20 mm) were drawn on 3 superficial portions covering the cortical territory of the middle cerebral artery (MCA) in each ipsilateral and contralateral hemisphere. Mean CBF, CBV, OEF, and $CMRO_2$ values were calculated in each hemisphere. For each mean value, vascular response to hypercapnia ($\%CBF_{hypercapnia}$) was calculated as the percentage change in resting CBF per absolute change in $PaCO_2$ (mm Hg), and vascular response to ACZ stress ($\%CBF_{ACZ}$) was calculated as the percentage change in resting CBF.

To detect trends between each parameter (CBV/CBF, $\%CBF_{hypercapnia}$, and $\%CBF_{ACZ}$) and OEF, we used the moving average method (7-point simple moving average). Based on these trends, we divided the hemispheres into 5 or 6 groups by reduction of circulation reserve (Figure).

Received October 13, 2005; accepted November 3, 2005.

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Stroke **is available at http://www.strokeaha.org**

DOI: 10.1161/01.STR.0000199085.40000.cf

TABLE 1. Patient Characters and Exclusion Criteria

Age 64±10.5 (range 44–78)
Males 30; females 10
Lesion of artery
Severe stenosis of cervical internal carotid artery 13
Severe stenosis of middle cerebral artery 13
Complete occlusion of cervical internal carotid artery 12
Unilateral cervical internal carotid artery occlusion and contralateral mild stenosis 2
Neurorogical deficit
Mild hemiparesis 32
Transient ischemic attack 8
Exclusion criteria
Severe neurological deficit (not independent of activities of daily living)
Large infarction by evaluating MRI (>4 cm diameter)
$Paco_2$ did not increase by >3 mm Hg during hypercapnia

All data are expressed as means±SD. Data were evaluated statistically using 1-way ANOVA or paired *t* tests. Values of $P<0.05$ were considered statistically significant.

Results

Table 2 and 3 show the physiological changes during the resting state, and under hypercapnia and ACZ stress, as well as the mean values measured by PET of the bilateral MCA territories in all patients.

The Figure a shows the relationship between OEF and CBV/CBF; OEF differed significantly between groups 5 and 6 ($P<0.05$; 1-way ANOVA) but not between any of the other consecutive groups.

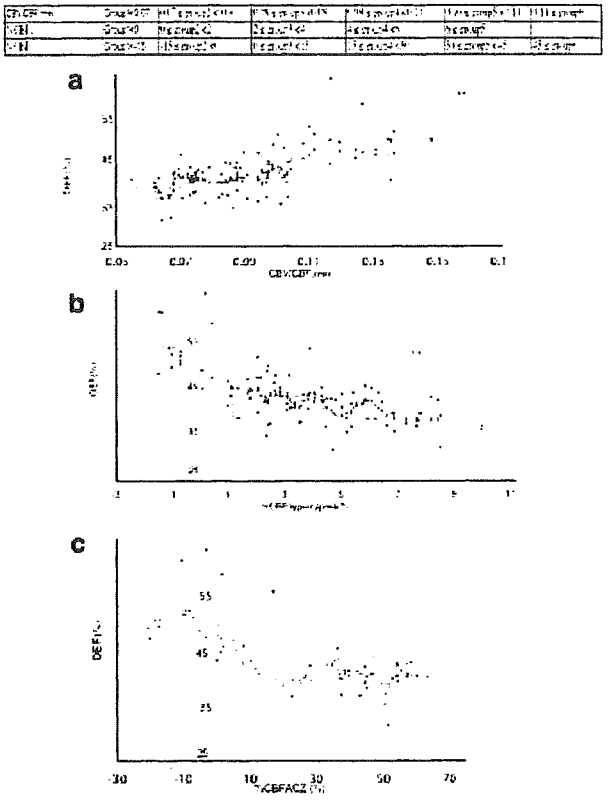
The Figure b shows the relationship between OEF and $\%CBF_{hypercapnia}$; OEF differed significantly between groups 1 and 2 ($P<0.05$; 1-way ANOVA) but not between any of the other consecutive groups.

The Figure c shows the relationship between OEF and $\%CBF_{ACZ}$; OEF differed significantly between groups 2 and 3 ($P<0.05$; 1-way ANOVA) and between groups 3 and 4 ($P<0.05$; 1-way ANOVA) but not between any of the other consecutive groups.

Discussion

Cerebral circulatory reserve has been estimated by measuring CBV, the ratio of CBV to CBF (CBV/CBF), and vascular response to vasodilatory agents.[1–5] However, whether these methods allow direct evaluation of circulation reserve remains unclear.[3,7–10] Metabolic reserve has only been estimated by measuring OEF on PET, but PET facilities are insufficient for widespread clinical use.

To date, the precise relationship between circulatory and metabolic reserve has been unclear.[4,5] In this study, we investigated the relationship between 3 parameters (CBV, CBV/CBF, and vascular response to vasodilatory agents) and metabolic reserve. We identified the point at which consumption of the metabolic reserve begins for each parameter. These points may be the most important factors for evaluating hemodynamics, and reconstructive surgery may prove to be more useful in patients with hemodynamics below these thresholds.



Group division and relationships between 3 parameters, circulation reserve, and OEF. Black dots indicate absolute values for each hemisphere. Blue dots indicate moving average values. Red dots indicate average values within each group. a, Relationship between CBV/CBF and OEF. OEF consumption began at CBV/CBF >0.11 minutes. b, Relationship between $\%CBF_{hypercapnia}$ and OEF. OEF consumption began at $CBF_{hypercapnia}$ <0%. c, Relationship between $\%CBF_{ACZ}$ and OEF. OEF consumption began at CBF_{ACZ} <15%, plateauing at CBF_{ACZ} <−15%.

Conclusion

The present study confirmed relationships between circulatory and metabolic reserve, with consumption of the metabolic reserve beginning when CBV/CBF increased to ≥0.11 minutes, $\%CBF_{hypercapnia}$ decreased to <0%, and $\%CBF_{ACZ}$ decreased to <15%.

TABLE 2. Physiological Change During Resting State, Hypercapnia, and ACZ Stress

	Resting State	Hypercapnia	ACZ Stress
Mean blood pressure mm Hg	99.9±15.7	101.6±16.8	101.1±14.9
$Paco_2$ mm Hg	37.9±2.9	43.9±3.7*	36.8±2.8
Pao_2 mm Hg	94.8±11.0	102.3±8.1	95.79±11.8
pH	7.44±0.02	7.398±0.02*	7.44±0.02

Values are given as mean±SD (*$P<0.01$; paired *t* test).

TABLE 3. Mean Values Measured by PET

	Ipsilateral	Contralateral
r-CBF (mL/min/100 g)	32.1±6.4*	37.6±7.6
C-CBF (mL/min/100 g)	38.2±11.1*	48.4±13.3
ΔC-CBF (%)	3±2.61*	4.9±2.4
D-CBF (mL/min/100 g)	38.3±12.8*	54.7±14.1
ΔD-CBF (%)	17.7±25.61*	44.6±16
CBV (mL/100 g)	3.26±0.53*	3±0.35
$CMRO_2$ (mL/min/100 g)	2.44±0.55*	2.67±0.45
OEF (%)	43.7±6.2*	41.1±4.8

Values are given as mean±SD (*$P<0.01$; paired t test).

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Original Article

Hemodynamic Influences of Losartan on the Brain in Hypertensive Patients

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The effects of angiotensin II receptor blockers on cerebral hemodynamics in humans have not been well elucidated. The present study evaluated the effects of losartan on cerebral hemodynamics in hypertensive patients using positron emission tomography. Ten patients with essential hypertension (mean age, 60.8 years) were examined. In each patient, regional cerebral blood flow was measured by [O-15] labeled water positron emission tomography before and after the oral administration of losartan for 8 to 23 weeks. In 8 patients, the baseline regional cerebral blood flow measurement was followed by 1,000 mg of acetazolamide challenge to measure the cerebral perfusion reserve. Systemic blood pressures before and after treatment were 153.8±10.8/96.0±6.5 mmHg (systolic mean±SD/diastolic mean±SD) and 133.4±11.2/83.6±6.5 mmHg, respectively; this difference was significant. The baseline global cerebral blood flow values before and after treatment were 38.4±6.9 ml/min/100 g and 38.2±8.2 ml/min/100 g, respectively; this difference was not significant. The results of the global cerebral blood flow response to the acetazolamide challenges were not statistically different before and after treatment. A regional analysis showed no statistical difference in regional cerebral blood flow or cerebral perfusion reserve throughout the brain before and after treatment. Losartan's effect on reducing the blood pressure did not affect either the baseline regional cerebral blood flow or the cerebral perfusion reserve in patients with mild to moderate hypertension. The inclusion of losartan in anti-hypertensive regimens could be advantageous for cerebral circulation in patients with essential hypertension. (*Hypertens Res* 2005; 28: 43–49)

***Key Words*: cerebral blood flow, hypertension, losartan, positron emission tomography, cerebrovascular reactivity**

Introduction

Angiotensin II receptor blockers are the latest generation of anti-hypertensive drugs. Losartan, an angiotensin II receptor blocker, has been reported to have protective effects against hypertensive organ damage as well as on systemic blood pressure. The LIFE study (*1*) was a prospective, double-blinded and randomized clinical trial in which losartan was shown to be more effective at preventing cardiovascular morbidity and death than atenolol. In the LIFE study, interest was focused on the preventive effects of losartan on primary fatal or non-fatal strokes. Losartan appeared to have beneficial effects on cerebral vessels beyond a reduction in blood pressure.

The effect of angiotensin II receptor blockers on cerebral hemodynamics is still controversial. Previous studies have suggested that angiotensin II receptor blockers do not influence cerebral blood flow under baseline conditions.

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Recieved June 16, 2004; Accepted in revised form September 29, 2004.

Table 1. Characteristics of the Subjects

Patient No.	Age (years old)	Gender	Losartan dose (mg/day)	Duration (weeks)	Brain MRI	Coexisting disease
1	61	M	50	23	asym WMI	hyperchol
2*	60	F	100	20	ns	ns
3	60	M	50	19	ns	ns
4*	64	M	50	9	lacunar inf	ns
5	62	F	100	22	asym WMI	hyperchol
6	52	M	50	12	ns	ns
7	59	M	50	12	asym WMI	ns
8	62	M	100	11	asym WMI	ns
9	65	M	100	8	ns	ns
10	63	F	100	18	ns	hyperchol

M, male; F, female; MRI, magnetic resonance imaging; asym WMI, asymptomatic white matter ischemic lesion; lacunar inf, lacunar infarction; hyperchol, hypercholesterolemia; ns, not specific. *Patient refused to undergo acetazolamide challenge. Duration means the therapy period from the start of losartan administration to the second cerebral blood flow measurement.

Vraamark *et al.* (*2*) reported that candesartan shifted the autoregulation curve towards the left in hypertensive rats. Strömberg *et al.* (*3*) reported that losartan shifted the upper limit of the autoregulation curve towards the right in rats with experimental hypertension induced by angiotensin II. Finally, in an experiment by Näveri *et al.* (*4*), losartan increased cerebrovascular resistance in rats with acute hypotension induced by hemorrhage.

However, these previous results were based on animal models and some observed acute effects of angiotensin II receptor blockers on cerebral blood flow. Few reports have evaluated the chronic effects of losartan on cerebral hemodynamics in hypertensive patients. The purpose of this paper was to elucidate the hemodynamic status before and after losartan administration using positron emission tomography and an acetazolamide challenge.

Methods

Subjects

Subjects were selected from patients with essential hypertension, defined according to the criteria of the VIth Joint National Committee (*5*). We excluded patients who met any of the following conditions: age under 40 years; severe hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg) or uncontrolled diabetes (HbA1c >8%); a history of stroke within the previous 3 months; angina pectoris or myocardial infarction; heart failure; renal failure (serum creatinine >2 mg/dl); severe stenosis (>50%) of the carotid artery and/or middle cerebral artery (assessed by ultrasonography and magnetic resonance angiography); currently taking anti-hypertensive drugs; atherosclerosis obliterans; any type of dementia; or currently taking tranquilizers, histamine blockers, analgesics, or diuretics.

Eighteen patients were nominated for the study. Of these 18 patients, 10 patients agreed to participate in the study and provided their written informed consent after receiving a detailed explanation of the study, including the irradiation dosage used in the positron emission tomography procedure. The profiles of these patients are shown in Table 1. The mean age of the patients was 60.8±3.4 (mean±SD) years. Of the 10 patients, one had a non-disabling pure motor hemiparesis due to lacunar infarction and four had mild asymptomatic white matter ischemic lesions (Fazekas (*6*) grade 1, minimal patchy white matter foci), as revealed by brain magnetic resonance imaging. Three patients had hypercholesterolemia, and none had diabetes. All portions of the study were performed in agreement with the ethical guidelines of the hospital.

Drug Control

On enrollment in the study, the clinical history of the patients was thoroughly checked. The administration of drugs that might influence the baseline cerebral blood flow was prohibited during the study period. Prescriptions for chronic diseases such as hypercholesterolemia were continued unchanged throughout the study period. Patients underwent an initial cerebral blood flow measurement using positron emission tomography with [O-15] labeled water. Subsequently, the patients received a daily oral dose of losartan (NU-LOTAN™; Banyu Pharmaceutical Co., Ltd., Tokyo, Japan) titrated to 50 mg. Follow-up examinations were performed every 2 to 4 weeks, and the drug dosage was increased up to 100 mg a day unless the patient reached a target sitting blood pressure of less than 140/90 mmHg. When the sitting blood pressure reached the target range and stabilized with losartan administration, the patient underwent a second cerebral blood flow measurement.

Table 2. Syetemic Blood Pressure, Pulse Rate, and Arterial Gas Tension during Cerebral Blood Flow Measurement

	Before losartan			After losartan		
	Baseline (n=10)	ACZ_{10} (n=8)	ACZ_{20} (n=8)	Baseline (n=10)	ACZ_{10} (n=8)	ACZ_{20} (n=8)
SBP (mmHg)	153.8±10.8	159.2±15.5	159.5±16.6	133.4±11.2*	138.0±15.8*	138.8±17.5*
DBP (mmHg)	96.0±6.5	95.9±6.3	97.6±7.2	83.6±6.5*	82.8±7.7*	84.5±6.5*
Pulse (bpm)	64.4±7.9	64.3±6.7	64.9±5.0	61.0±7.0	61.3±7.2	63.4±7.2
pH	7.409±0.021	7.426±0.023	7.423±0.033	7.406±0.014	7.416±0.010	7.412±0.019
$PaCO_2$ (mmHg)	38.7±2.8	37.2±2.9	36.7±4.3	39.5±2.1	37.9±2.2	37.6±1.8
PaO_2 (mmHg)	81.6±8.7	87.9±13.8	91.0±15.6	80.5±6.6	85.8±9.5	87.3±9.9

SBP and DBP, systolic and diastolic blood pressure, respectively; $PaCO_2$ and PaO_2, arterial gas tension for carbon dioxide and oxygen, respectively; ACZ_{10} and ACZ_{20}, 10 and 20 min after acetazolamide injection, respectively; bpm, beats per minute. Data are listed in mean±SD. *$p<0.01$ *vs.* baseline in before losartan.

Cerebral Blood Flow Measurement

All patients underwent two cerebral blood flow measurements. As described above, the first and second measurements were performed before and after the administration of losartan, respectively. We used a high-performance positron emission tomography scanner (SET-2400W; Shimadzu Co., Kyoto, Japan) that uses 63 slices (slice thickness of 3.1 mm) and a spatial resolution of 3.7 mm full width at half maximum. Regional cerebral blood flow was quantitatively measured using positron emission tomography, an [O-15] labeled water injection, and an autoradiographic method (*7*). During each session, the patient was asked to lie on the scanner bed in a supine position in a quiet, dimly lit room. One session consisted of four scans. First, two consecutive scans were performed for the baseline condition. Then, after the intravenous administration of acetazolamide titrated to 1,000 mg, two additional scans were performed at an interval of 10 min. At the end of every scan, the patient's blood pressure, pulse rate, and arterial blood gas tension were measured. The data obtained for the baseline condition were averaged using the two measurements.

Blood Pressure Measurements

Blood pressure was measured using a mercury sphygmomanometer and a 6-inch cuff, with the patient lying supine on the scanner bed. Systolic and diastolic blood pressure (Korotkoff phase I and phase V, respectively) were averaged using two readings obtained 3 min apart.

Cerebral Blood Flow Image Analysis

The regional cerebral blood flow image data set obtained by the positron emission tomography scanner was transformed stereotaxically into an identical normal brain template using statistical parametric mapping-99 software (*8*) (SPM99; Wellcome Department of Cognitive Neurology, University College London, London, UK) running in a MATLAB™ (The MathWorks Inc., Natic, USA) environment. Identical regions of interest (the whole cerebrum, whole cerebellum, bilateral upper and lower frontal lobes, bilateral temporal lobes, bilateral occipital lobes, bilateral parietal lobes, bilateral basal ganglia areas, and bilateral thalami) were drawn on standardized cerebral blood flow images. Except for the whole cerebrum and whole cerebellum, the regions of interest were drawn on the gray matter of each region and consisted of multiple small circular regions of interest (20 mm in diameter) linked together.

Statistical Analysis

Blood pressure, pulse rate, arterial blood gas tensions, and baseline cerebral blood flow measurements obtained before and after treatment were compared using paired *t*-tests. The effects of acetazolamide on systemic conditions and an increased cerebral blood flow were analyzed using a one-way repeated-measure analysis of variance (ANOVA) followed by Bonferroni's multiple comparison. These analyses were performed using statistical analysis software (SPSS 11.5J; SPSS Japan Inc., Tokyo, Japan) on a personal computer running Windows™. Differences were considered to be significant when the statistical p value was less than 0.05.

Results

Losartan was well tolerated by all the patients and no complications or adverse effects occurred. The period of losartan therapy ranged from 8 to 23 weeks, and the final losartan dosages required to control the patients' blood pressures were 50 mg/day in 5 patients and 100 mg/day in 5 (Table 1). Of the 10 patients in the study, 8 patients safely underwent two acetazolamide challenges; the examination was well tolerated in these patients. Two patients (Nos. 2 and 4 in Table 1) refused to undergo the acetazolamide challenge. Thus, the physiological parameters and baseline regional cerebral blood flow were assessed in 10 patients, while the changes in these parameters after an acetazolamide challenge were assessed in

Table 3. Changes of Individual Cerebral Blood Flow, Response to Acetazolamide, and Systemic Parameters before and after Losartan Administration

PtNo	Baseline gCBF (ml/min/100 g)		INC%max (%)		Mean BP (mmHg)		P_{CO_2} (mmHg)	
	Before	After	Before	After	Before	After	Before	After
1	31.7	32.3	29	42	114.3	111.7	41.2	41.4
2	39.0	41.1			111.1	98.2	37.8	36.2
3	34.7	35.4	42	39	116.5	94.2	37.1	38.5
4	48.0	50.3			130.7	105.3	35.0	42.0
5	48.6	39.9	65	58	113.5	109.8	44.6	40.5
6	31.6	38.8	29	41	112.8	104.3	38.8	37.4
7	28.1	28.2	23	28	109.7	87.5	39.0	38.4
8	40.4	29.6	34	50	110.3	93.2	37.7	40.3
9	40.4	33.7	68	47	107.2	94.3	39.8	38.1
10	41.1	52.6	49	39	126.3	103.5	35.9	42.6

gCBF, global cerebral blood flow; INC%max, maximum percent increase of gCBF from baseline after acetazolamide injection; BP, systemic blood pressure; P_{CO_2}, arterial partial pressure of carbon dioxide; PtNo, patient number.

8 patients.

Table 2 shows the physiological data for the patients. The baseline systemic blood pressures before and after losartan administration were 153.8±10.8/96.0±6.5 (systolic mean±SD/diastolic mean±SD) mmHg and 133.4±11.2/83.6±6.5 mmHg, respectively. Both the systolic and diastolic blood pressures decreased significantly after losartan administration. Arterial blood gas tensions, arterial pH, and the pulse rate measured before and after losartan administration did not change significantly. Although a slight elevation in blood pressure was observed during the acetazolamide challenges, both before and after losartan administration, the effect of the acetazolamide challenge on the baseline blood pressure values was not significant.

None of the regional cerebral blood flow images obtained during the positron emission tomography examinations showed major abnormalities, and all of the images were successfully transformed into standardized normal brain images using the SPM99 software.

As the peak response time (*i.e.*, 10 or 20 min after acetazolamide injection) to acetazolamide differed by patient, we selected individual maximum cerebral blood flow value for the analysis. Table 3 shows the individual changes in global cerebral blood flow, the maximum percent increase in cerebral blood flow (INC%max) induced by acetazolamide, mean systemic blood pressure, and arterial partial pressure of carbon dioxide. In 3 patients (Nos. 5, 8, and 9), there was a considerable decrease in global cerebral blood flow after losartan administration. In contrast, the other 2 patients (Nos. 6 and 10), showed considerable increases in global cerebral blood flow after losartan administration. Table 4 shows the mean global and regional baseline cerebral blood flow values and the INC%max for the two conditions. The mean baseline global cerebral blood flow values obtained before and after losartan administration were 38.4±6.9 ml/min/100 g and 38.2±8.2 ml/min/100 g, respectively; these values were not significantly different. The mean global INC%max before and after losartan administration were 42.4±17.0% and 43.0±8.9%, respectively. No significant differences among the mean global INC%max values were observed. The same relationships were seen for every brain region examined, *i.e.*, there were no significant differences in the baseline cerebral blood flow and INC%max values obtained before and after losartan administration.

Discussion

In the present study, losartan was shown to reduce blood pressure without deteriorating baseline cerebral blood flow or the cerebral blood flow response to acetazolamide in patients with essential hypertension. No regional differences in this effect were observed in the brain. Only a few previous studies have evaluated the effect of losartan on the brain in hypertensive patients. Matulla *et al.* (*9*) indirectly suggested that losartan did not change the resting global cerebral blood flow in normal individuals, based on ultrasonography findings. This previous study measured blood flow velocities in the middle cerebral artery, not the cerebral blood flow, and only evaluated the acute effects of losartan. The present clinical study evaluated the chronic effects of losartan on regional cerebral blood flow. In this study, three patients (Nos. 5, 8, and 9) out of 10 showed considerable decrease in baseline cerebral blood flow after losartan administration. In one patient (No. 5), the decrease might be explained by the change in arterial carbon dioxide gas tension. In the rest 2, although it was possible that losartan affected the baseline cerebral blood flow, it was also possible that the drift in cerebral blood flow measurement by positron emission tomography partially influenced the result. The reproducibility of the method has been reported to have a SD of almost 10% (*10*).

Positron emission tomography, [O-15] labeled water, and SPM99 software were used in this study. These methods offer

Table 4. Regional Cerebral Blood Flow at Baseline and Cerebral Perfusion Reserve

Region	Before losartan		After losartan	
	Baseline CBF (ml/min/100 g) (n=10)	INC%max (%) (n=8)	Baseline CBF (ml/min/100 g) (n=10)	INC%max (%) (n=8)
Cerebrum global	38.4±6.9	42.4±17.0	38.2±8.2	43.0±8.9
Cerebellum global	44.0±8.7	45.9±11.4	42.8±8.7	51.0±16.6
Frontal Base Rt	41.9±8.9	44.3±17.6	40.9±8.1	45.4±7.8
Top Rt	43.5±9.2	42.3±11.3	41.2±8.4	43.0±7.3
Base Lt	42.0±8.4	47.5±20.8	41.7±8.8	49.9±13.4
Top Lt	43.2±9.2	46.0±16.0	41.7±9.1	46.5±10.8
Temporal Rt	39.0±6.1	43.1±19.0	39.4±7.2	47.1±9.3
Lt	39.1±6.8	42.3±19.7	39.2±9.2	52.1±14.0
Parietal Rt	42.2±8.5	39.0±13.7	41.0±8.2	45.3±7.0
Lt	42.5±7.2	39.9±16.4	41.6±8.7	45.9±8.4
Occipital Rt	41.4±5.5	39.8±23.5	42.9±9.1	38.8±10.9
Lt	43.0±5.6	35.0±19.7	44.3±11.0	41.5±10.6
Basal ganglea Rt	50.8±9.9	51.4±18.6	50.8±11.5	52.9±11.7
Lt	49.4±9.9	53.5±26.1	49.7±13.1	62.3±19.4
Thalamus Rt	54.4±14.0	50.8±18.1	50.4±13.0	53.8±17.1
Lt	52.9±9.6	56.3±20.9	51.5±15.2	58.1±15.9

INC%max, maximum percent increase of regional cerebral blood flow from baseline after acetazolamide injection; Rt, right; Lt, left.

some advantages for this type of study. Regional cerebral blood flow measurement using positron emission tomography and [O-15] labeled water is a reliable and quantitative method. A single measurement requires only 2 min to perform, and measurements can be repeated every 10 min because the half-life of [O-15] is as short as 2 min. This characteristic enabled us to measure both the baseline cerebral blood flow and the cerebral blood flow after an acetazolamide challenge within about 1 h. To quantify the regional cerebral blood flow, we used a region of interest-based analysis. This type of analysis using native cerebral blood flow images is limited by positional changes of the head from session-to-session and by inter-subject differences in the shape of the brain. SPM99 have been developed as an analysis tool for detecting areas with statistically significant signal changes among images obtained under different scanning conditions and for different individuals. Using the SPM99 module enabled us to correct for inter-scan head motion and to minimize inter-individual structural differences in the head. Using these techniques, corresponding regions of interest were obtained in all of the patients.

Theoretically, organ blood flow is determined by blood pressure and vascular resistance. Our data indicated that losartan reduced the cerebral vascular resistance whereas the blood pressure reduced. Unlike in the present study, Näveri *et al.* (*4*) reported that the administration of losartan in a hemorrhagic hypotensive animal model increased cerebrovascular resistance. These conflicting results may be explained by the fact that Näveri *et al.* examined the acute effects of losartan in an experimental animal model, whereas our data were focused on the chronic effects of losartan in humans in a clinical environment.

Under physiological conditions, global cerebral blood flow is controlled by autoregulation, irrespective of changes in systemic blood pressure. The vascular responses of large arteries and the resistance of small cerebral vessels play pivotal roles in this mechanism. Furthermore, the renin-angiotensin system is known to have a large effect on the regulation of vascular tonus (*2–4, 11*). It is thus of concern that losartan administration may have shifted the cerebral autoregulation curve to the left or right. However, elucidating the upper and lower limits of the cerebral autoregulation curve is difficult in real patients. In the present study, patients were categorized as having mild or moderate hypertension, and thus the average right shift of the autoregulation curve was likely to be small. It remains unclear whether or not losartan affects the cerebral hemodynamics in patients with severely impaired autoregulation.

Instead of elucidating the autoregulation range, we applied an acetazolamide challenge to test cerebral vasomotor reactivity. The intravenous administration of acetazolamide titrated to 1,000 mg causes a dramatic dilatation in the cerebral resistant vessels as a result of extracellular acidosis (*12*), which in turn causes the regional cerebral blood flow to increase to its maximum possible value. This effect has been used to evaluate cerebral vasomotor reactivity and the cerebral perfusion reserve (*13*). The cerebral perfusion reserve is considered a safety margin against a drift in cerebral perfusion pressure. This idea has been supported by several previous studies (*14–16*) which concluded that compromised

cerebral perfusion reserve was associated with an increased risk of cerebral ischemic events. Our data suggested that losartan did not affect the cerebral perfusion reserve. This property is thought to be beneficial to patients with cerebral ischemic lesions, such as those seen in the present study.

Stroke prevention is a major goal in the treatment of hypertension. Inada *et al.* (*17*) reported that candesartan treatment reduced the incidence of stroke in stroke-prone spontaneously hypertensive rats. In the LIFE (*1*) losartan was more effective at preventing fatal and non-fatal stroke events than atenorol (adjusted risk reduction, 24.9%) and resulted in fewer adverse events. The results raise the question of whether angiotensin II receptor blockers are superior to angiotensin-converting enzyme inhibitors. In patients with symptomatic heart failure (*18*) or acute myocardial infarction (*19*), losartan was equally beneficial but not superior to captopril. Which of these drugs is superior for stroke management remains uncertain, but both drugs owe their protective effects to the inhibition of the renin-angiotensin system. Many experimental studies have proved that the inhibition of the renin-angiotensin system modulates vascular tonus (*2–4*, *10*), prevents (*20*) or improves (*21*, *22*) vascular wall remodeling or improves endothelial functions (*23*, *24*). In a human study, candesartan reduced oxidative stress and inflammation (*25*), which were related to organ damage. Angiotensin II receptor blockers as well as angiotensin converting enzyme inhibitors seem to be promising for the prevention of stroke.

In conclusion, losartan has been accepted as an effective anti-hypertensive drug with good tolerability. Our results showed that losartan effectively lowered the blood pressure without affecting the baseline cerebral blood flow or cerebral perfusion reserve in patients with mild to moderate hypertension. This characteristic protects the brain from unexpected episodes of hypotension during treatment with losartan. The effect of this drug on the brain in patients with stroke or in those with severe hypertension awaits further study.

Acknowledgements

We are grateful to the cycrotron staffs of Osaka University Hospital for their technical support. We would also like to thank Ms. M. Ikuzawa, Ms. A. Kanzawa, Ms. K. Tsunoda, and Ms. M. Sudo for their secretarial assistance.

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Metabolic Penumbra of Acute Brain Infarction: A Correlation with Infarct Growth

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Volume expansion associated with brain infarction occurs in perfusion–diffusion mismatch of magnetic resonance imaging. We aimed at elucidating the metabolic impairment of this phenomenon with ^{15}O positron emission tomography and perfusion and diffusion magnetic resonance imaging. Eleven patients with acute unilateral embolic occlusion of the internal carotid or middle cerebral artery were studied within 6 hours of onset. Regional cerebral blood flow and cerebral metabolic rate of oxygen ($CMRO_2$) were compared with those in the contralateral cerebral hemisphere. The relative apparent diffusion coefficient of water was estimated as a marker of cytotoxic edema. Relative cerebral blood flow and relative $CMRO_2$ in an evolving infarct (normal diffusion initially, but abnormal on day 3) were significantly ($p < 0.05$) less than those in the periinfarct area (normal diffusion initially and on day 3). The relative apparent diffusion coefficient between the evolving infarct and periinfarct showed no significant difference. These findings indicated that the initial 3-day volume expansion of an embolic brain infarction was associated with disturbed $CMRD_2$ but not with cytotoxic edema as early as 6 hours after onset. The "metabolic penumbra" defined as normal water diffusion with depressed $CMRO_2$ is a target to reduce the volume expansion of brain infarction.

Ann Neurol 2005;57:495–504

The volume expansion of an embolic brain infarction occurs within several days after stroke onset.[1–4] It is preferentially found in the perfusion–diffusion mismatch of magnetic resonance imaging (MRI) where the cerebral perfusion appears abnormal but the diffusion of water is normal. The larger volume of perfusion–diffusion mismatch has resulted in more infarct growth during the first week.[5] The patients with severe perfusion deficits in the MRI were at high risk for lesion enlargement.[6] Cerebral blood flow (CBF) was less in the lesions that progressed to infarction than in those that did not.[7,8] Although these previous studies suggest that severe ischemia in the perfusion–diffusion mismatch increased the probability of expanding the infarct, the magnitude of the metabolic impairments has not yet been precisely investigated.

Quantitative CBF, cerebral blood volume (CBV), cerebral oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen ($CMRO_2$) can be measured by means of positron emission tomography (PET) with $H_2{}^{15}O$, $C^{15}O$, and $^{15}O_2$.[9–11] However, it requires more than 1.5 hours to complete the measurements, and thus was not applicable in acute stroke patients. Instead, relative CBF (relCBF), relative $CMRO_2$ (relCMRO$_2$), and relative OEF (relOEF) were attained through count-based PET in patients with acute stroke[12,13] or stenoocclusive arterial disease.[14,15] With this method, relative changes in CBF, OEF, and $CMRO_2$ to the reference region could be estimated.

In this study, we prospectively investigated the relCBF, relCMRO$_2$, and relOEF in the perfusion–diffusion mismatch of MRI in patients with acute ischemic stroke within 6 hours of onset. These parameters and the apparent diffusion coefficient (ADC) of water were correlated with the volume expansion of the infarction, which may occur during the first 3 days of onset.

Patients and Methods

Patients

Eleven patients with acute embolic infarction caused by the unilateral occlusion of the internal carotid or intracranial main artery were enrolled in this study (4 men and 7 women; aged 63–80 years; mean age ± SD, 70.6 ± 5.4 years). Nine of 11 patients had 1 or more risk factors for stroke.

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Received Oct 19, 2004, and in revised form Jan 10, 2005. Accepted for publication Jan 11, 2005.

Published online Mar 28, 2005, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20427

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Published by Wiley-Liss, Inc., through Wiley Subscription Services

The remaining two patients (Patients 8 and 11) had no risk factors. On admission, 5 of 11 patients demonstrated total aphasia with conjugate deviation or loss of consciousness. The remaining six patients showed hemiparesis with the cortical sign (disorientation, conjugate deviation, hemispatial neglect, or aphasia). The time of onset was determined by reliable information obtained from the patients or their relatives. In all patients, computed tomography (CT) confirmed no intracranial or intracerebral hematoma. The occlusion site of the artery was examined by conventional angiography in 8 of 11 patients or by three-dimensional time-of-flight magnetic resonance angiography (MRA; see later for information about the pulse sequence used) in the other 3 patients. The location of the occlusion was the unilateral internal carotid artery in three patients, the unilateral middle cerebral artery (MCA) M1 in four patients, and the unilateral MCA M2 or distal in four patients. Two patients were nominated for a double-blind trial of thrombolytic therapy, and they underwent an intravenous infusion of tissue-plasminogen activator or placebo after the initial MRI and PET study. The remaining nine patients were treated conservatively because the use of thrombolytic agents was not available. Informed consent was received from all patients or an appropriate relative before the study. Our institutional review committee approved this study. Table 1 summarizes the patient data regarding age and sex, neurological deficits, risk factors for stroke, National Institutes of Health Stroke Scale on admission, the time of MRI and PET examination after onset, the occlusion site on the initial cerebral angiography or MRA, and the presence or absence of recanalization of the occluded artery studied with MRA 3 days after onset.

Magnetic Resonance Imaging

The MRI studies were performed with a 1.5T whole-body superconductive scanner (Magnetom Vision; Siemens Medical Systems, South Iselin, NJ) on admission and on day 3 after onset. Each study began with a conventional T2-weighted turbo spin-echo sequence (TR, 3,600 milliseconds; TE, 96 milliseconds; excitations, n = 1). Nineteen T2-weighted imaging slices were obtained parallel to the anterior commissure–posterior commissure (AC-PC) line with a 6mm slice interval. The T2-weighted imaging was followed by three-dimensional time-of-flight MRA (TR, 39 milliseconds; TE, 6.5 milliseconds; flip angle, 20 degrees; field of view, 20cm; slice thickness, 1mm; excitations, n = 1; slab thickness, 60mm; partition 60; matrix size, 128 × 128 pixels), and the diffusion-weighted image (DWI) was performed by a single-shot, spin-echo, echo planar pulse sequence (repetition time, 4,000 milliseconds; TE, 100 milliseconds). Nineteen DWI slices were obtained (slice thickness, 5mm; interslice gap, 1mm; field of view, 23cm; matrix, 256 × 256 pixels; flip angle, 90 degrees). Gradients with two different b values (b = 0 and 1,000sec/mm^2) in the orthogonal x, y, and

Table 1. Summary of Patient Data

Patient No.	Age (yr)/ Sex	Main Neurological Deficit on Admission	Risk Factors for Stroke	NIHSS on Admission	Interval of Examination after Onset (min)		Occlusion Site on Initial Cerebral Angiography	Recanalization on Follow-up MRA
					MRI	PET		
1	68/F	Hemiparesis, disorientation	HT	10	90	225	MCA proximal	−
2	70/M	Total aphasia, conjugate deviation	Af	21	180	225	MCA proximal	+
3	80/F	Total aphasia, conjugate deviation	HT, HL, Af	20	70	100	MCA proximal	+
4	65/F	Hemiparesis, conjugate deviation anosognosia	HT, HL	18	80	110	MCA proximal	+
5	74/M	Hemiparesis, conjugate deviation hemispatial neglect	HT, Af	19	240	180	ICA[a]	−
6	63/M	Total aphasia, loss of consciousness	Af	27	150	180	ICA[a]	+
7	74/F	Hemiparesis, sensory aphasia	HT, DM	14	35	75	MCA distal	+
8	69/F	Hemiparesis, total aphasia	None	6	115	90	MCA distal	−
9	64/F	Hemiparesis, anosognosia hemispatial neglect	HT, HL	3	310	275	MCA distal[a]	+
10	75/M	Total aphasia, loss of consciousness	HT	27	75	120	ICA	−
11	75/F	Total aphasia, loss of consciousness	None	21	60	90	MCA distal	+
Mean ± SD	70.6 ± 5.4			16.9 ± 7.9	127.7 ± 85.0	151.8 ± 68.2		

[a]MRA finding on admission.

NIHSS = National Institutes of Health Stroke Scale; MRI = magnetic resonance imaging; PET = positron emission tomography; MRA = magnetic resonance angiography; HT = hypertension; HL = hyperlipidemia; DM = diabetes mellitus; MCA = middle cerebral artery; Af = atrial fibrillation; ICA = internal cerebral artery; DWI = diffusion-weighted magnetic resonance imaging; T_2WI = T_2-weighted magnetic resonance imaging.