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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-

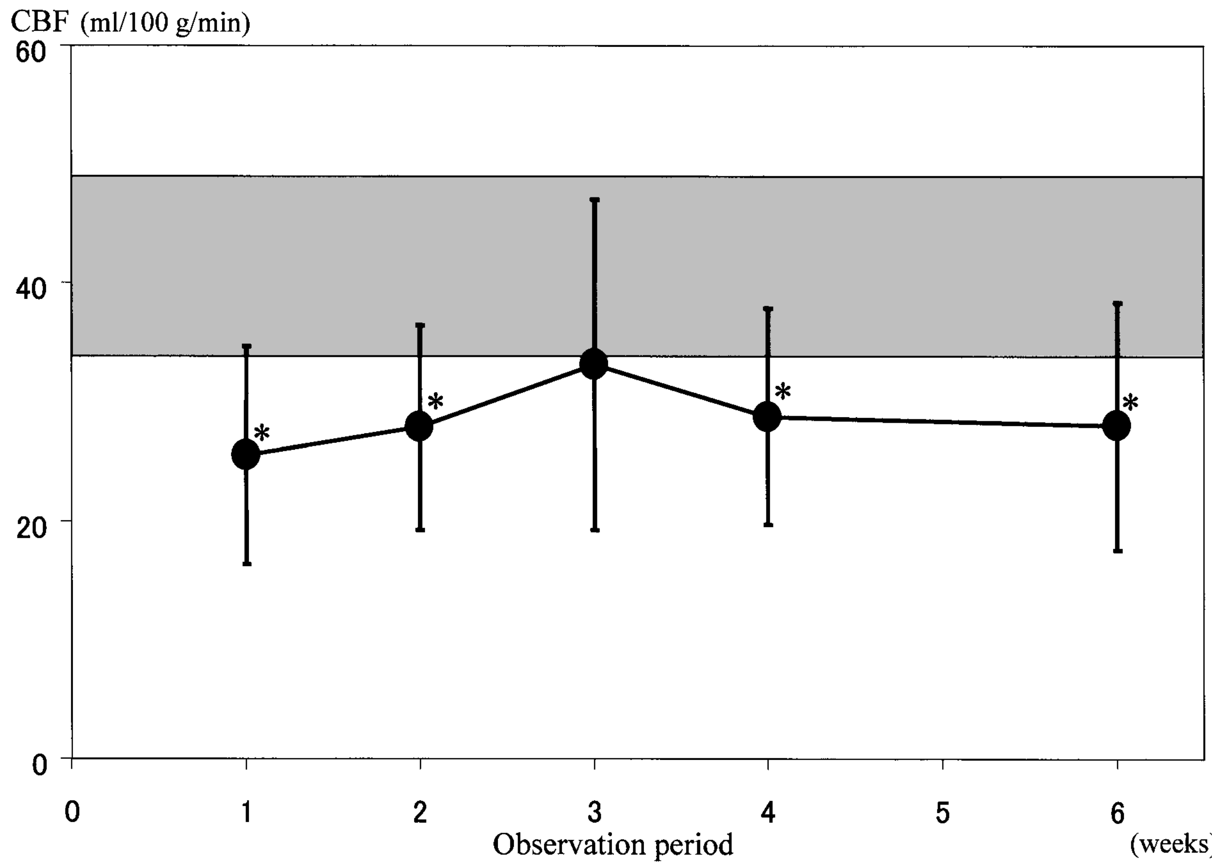

FIG. 1. Cerebral blood flow (CBF) change in the 20 head-injury patients during the 6-week observation period. Data are shown as mean ± SD. The gray zone represents the normal range of CBF, seen in the 14 healthy volunteers. Statistical analysis of each week's CBF value was done with Student's *t*-test.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

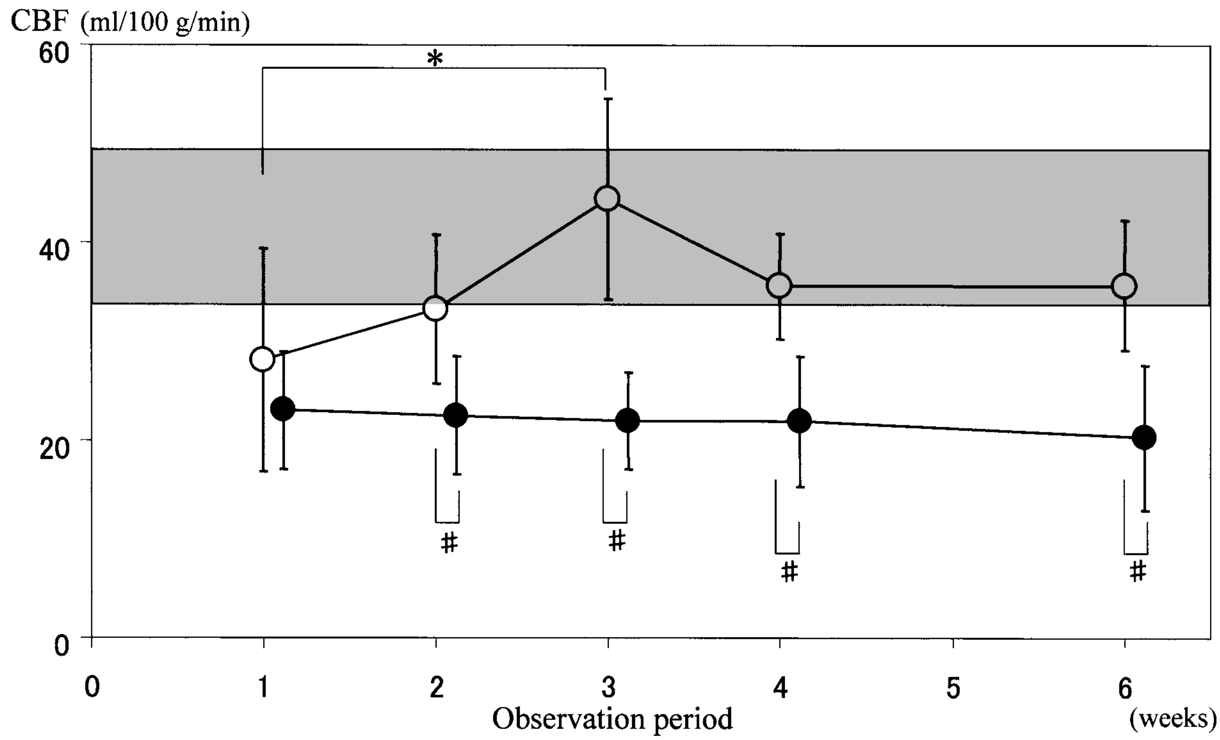

FIG. 2. Cerebral blood flow (CBF) patterns in subgroups A and B during the 6-week observation period. Data are shown as mean ± SD. Open circles, CBF data for subgroup A; closed circles, CBF data for subgroup B. The gray zone represents the normal range of CBF, seen in the 14 healthy volunteers. Statistical 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.

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