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Early Cerebral Circulation Disturbance in Patients Suffering from Severe Traumatic Brain Injury (TBI): A Xenon CT and Perfusion CT Study

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Abstract

Traumatic brain injury (TBI) is widely known to cause dynamic changes in cerebral blood flow (CBF). Ischemia is a common and deleterious secondary injury following TBI. Detecting early ischemia in TBI patients is important to prevent further advancement and deterioration of the brain tissue. The purpose of this study was to clarify the cerebral circulatory disturbance during the early phase and whether it can be used to predict patient outcome. A total of 90 patients with TBI underwent a xenon-computed tomography (Xe-CT) and subsequently perfusion CT to evaluate the cerebral circulation on days 1–3. We measured CBF using Xe-CT and mean transit time (MTT: the width between two inflection points [maximum upward slope and maximum downward slope from inflow to outflow of the contrast agent]) using perfusion CT and calculated the cerebral blood volume (CBV) using the AZ-7000W98 computer system. The relationships of the hemodynamic parameters CBF, MTT, and CBV to the Glasgow Coma Scale (GCS) score and the Glasgow Outcome Scale (GOS) score were examined. There were no significant differences in CBF, MTT, and CBV among GCS3–4, GCS5–6, and GCS7–8 groups. The patients with a favorable outcome (GR and MD) had significantly higher CBF and lower MTT than those with an unfavorable one (SD, VS, or D). The discriminant analysis of these parameters could predict patient outcome with a probability of 70.6%. During the early phase, CBF reduction and MTT prolongation might influence the clinical outcome of TBI. These parameters are helpful for evaluating the severity of cerebral circulatory disturbance and predicting the outcome of TBI patients.

Key words: severe traumatic brain injury, early cerebral circulation disturbance, a xenon CT, a perfusion CT

Introduction

Traumatic brain injury (TBI) is widely known to cause dynamic changes in cerebral blood flow (CBF). These hemodynamic changes play a key role in the pathophysiology of TBI. In particular, the secondary brain insults, such as hypotension, hypercapnia, and hypoxia, have been reported to cause decreases in CBF. Ischemia is one of the major risk factors contributing to death and disability in TBI patients. In fact, several clinical TBI studies have linked low CBF to poor outcome.[1–8] Several factors can cause a decrease in CBF: intracranial hypertension, systemic arterial hypotension, cerebral edema, focal tissue compression by hematomas, and microvascular circulation disturbance.[9–13] The maintenance of adequate CBF is a critical objective of managing severe TBI patients. Therefore, understanding circulatory disturbance might be helpful for determining its pathogenesis, developing appropriate treatment plans, evaluating treatment results, and predicting outcomes.

Positron emission tomography (PET), single-photon emission computed tomography (SPECT), and xenon-enhanced computed tomography (Xe-CT) are used to

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evaluate the cerebral circulation and metabolism in the early phase of severe TBI.[2,3,14–17] Recently, there has been interest in using CT perfusion imaging to assess the patients with stroke and delayed cerebral vasospasm (CVS) after subarachnoid hemorrhaging.[18–20] A number of hemodynamic parameters are available for CT perfusion imaging. One such parameter, the mean transit time (MTT), is defined as the mean time required for blood to perfuse through a region of tissue and is highly sensitive to hemodynamic disturbances. There have been several investigations of cerebral circulatory disturbance during the delayed CVS phase using the MTT.[19–22] In these studies, the MTT was identified as the most sensitive perfusion parameter for detecting the delayed CVS.[20] However, few investigations have attempted to explain the circulatory disturbances using CBF, MTT, and cerebral blood volume (CBV) during the early phase of severe TBI.[23–25]

The purpose of this study was to determine the relationship between the hemodynamic parameters in the early phase (post-injury days 1–3), neurological grade at the onset of treatment, and patient outcome. We measured the MTT, CBF, and CBV using CT perfusion and Xe-CT and evaluated their utility as predictors of the severity of early circulatory disturbance and outcome.

Subjects and Methods

Patients

A total of 90 patients who were admitted to our hospital with severe TBI from 2002 to 2011 were prospectively enrolled. The TBI of all patients was verified by CT on admission. The patients who were admitted to the intensive care unit (ICU) with TBI that was sufficiently severe to justify mechanical ventilation and a Glasgow Coma Scale (GCS) score of 8 or less within 8 h after trauma were included in this study. The exclusion criteria for this study were (1) patients with major organ damage or functional failure complications, (2) patients with hypotension (systolic pressure <90 mmHg), hypoxia (O_2 saturation <95% for >30 min), (3) patients who suffered from brain herniation prior to the cerebral circulation examination, (4) patients who were in a state of cardiopulmonary arrest on arrival, and (5) patients with early postinjury instability owing to severe multiple injuries. The neurological conditions of all the patients were recorded by the attending neurosurgeons throughout their hospital stay. The clinical statuses of the patients according to the GCS were recorded on admission. The written informed consent for the study was obtained from the patients' family members, and the study protocol was approved by the ethics committee of our institute.

Management protocol

All patients were admitted to the ICU from the emergency room after initial stabilization and brain CT, as well as surgery for those who required craniotomy to evacuate an intracranial mass. We classified focal injury and diffuse injury largely on the basis of initial CT according to the TCDB classification.[26] Extracerebral hematomas and intracerebral contusions or hematomas causing significant mass effects were the indications for urgent surgery.[27] All patients were treated based on the guidelines for management of severe TBI of the Japan Society of Neurotraumatology.[27] The management protocol included mechanical ventilation, sedation induced by the continuous infusion of sedative agents, and the administration of analgesic agents as clinically required for ventilation purposes and intracranial pressure (ICP) control according to the clinical situation. The therapeutic end point was defined as the maintenance of an ICP of <20 mmHg when ICP monitoring was employed. To achieve this, mild hyperventilation (reduction in $PaCO_2$ to 35–40 mmHg), mild hypothermia (reduction of body temperature to 35–36°C), and the administration of boluses of 20% mannitol and/or vasopressors were implemented according to the patient's clinical condition. When ICP exceeded 25 mmHg, the mean systemic blood pressure was increased to 95–100 mmHg to maintain the cerebral perfusion pressure (CPP) at 50–70 mmHg wherever possible.

The outcome was assessed at 3 months after onset according to the Glasgow Outcome Scale (GOS).[28] For statistical purposes, a simplified GOS scoring system was used, with a favorable outcome being indicated by a GOS score of higher than 3 and a poor outcome being indicated by a GOS score of 3 or below. Each survivor participated in a personal interview either by clinic visit or telephone.

Imaging technique

After standard CT study, the Xe-CT and perfusion CT were performed subsequently using an X Vigor scanner (Toshiba, Tokyo, Japan). As measuring CBF using perfusion CT is not a quantitative method, we measured CBF using Xe-CT. We measured MTT by perfusion CT and calculated the CBV using the AZ-7000W98 computer system (Anzai Medical, Tokyo, Japan). CBV maps were produced by multiplying CBF and MTT according to the central volume principle: CBV = CBF × MTT.[29] The CBF, MTT, and CBV maps were created at the level of the basal ganglia.

During Xe-CT, the patients inhaled 30% of stable xenon for 4 min (wash-in), followed by 5 min of desaturation (wash-out), using a xenon gas inhalation system (AZ-725; Anzai Medical).[30] The CT scans were performed at 1-min intervals, and in each scan, 3 levels of the brain (centered on the basal ganglia) were imaged by moving the CT table. A 512 × 512 matrix and a 10-mm slice thickness were used. The exposure factors were 120 kV (p) and 200 mA, and the scan time was 2 s. The pixel size was 0.469 mm × 0.469 mm. The CBF maps were created using the resultant CT images and end-tidal xenon data. The unweighted filtering over a 9 × 9 area was performed on the original CT images prior to computation. A λ-guided calculation method[31] was applied using end-tidal xenon as a substitute for arterial xenon. On a pixel-by-pixel basis, the CBF (ml/100 g/min) and λ, the xenon brain–blood partition coefficient, were calculated according to the Gauss–Newton method using the Kety autoradiographic equation.

The perfusion CT was performed just after the plain CT and Xe-CT. Twenty dynamic conventional scans were obtained in a 50 mm plane above the orbitomeatal orientation, which included the basal ganglia; the thalamus; and parts of the anterior, middle, and posterior cerebral arterial territories. Thirty milliliters of nonionic contrast material (Iomeron 300; Eisai Co., Ltd., Tokyo, Japan) was injected into the central vein through a 16-gauge cannula with a power injector (Auto Enhance A-60; Nemoto Kyourindo, Tokyo, Japan) at an infusion rate of 9 ml/s. The CT scanning began 5 s after starting the injection. The CT scans were performed at the intervals of 2 s for 30 s, and subsequently, at 6 s intervals for 30 s. The resultant CT images were used to calculate MTT.[30] On a pixel-by-pixel basis, the time-course of the changes in CT enhancement (time–density curve) was fitted to the gamma variant using the Gauss–Newton method, while the width between the two inflection points (maximum upward slope and maximum downward slope) (Fig. 1) was calculated as the MTT value.[32] The regions of interests (ROIs) were right and left hemispheres at the level of the basal ganglia (Fig. 2). The right and left hemispheric CBF/MTT were calculated excluding the ventricle regions and massive hematomas and contusions with <5 ml/100 g/min CBF in CBF mapping. Then, we averaged the right and left CBF/MTT values, and used the average value in this study. The CBV maps were created by multiplying the CBF and MTT according to the central volume principle: CBV = CBF × MTT.[29]

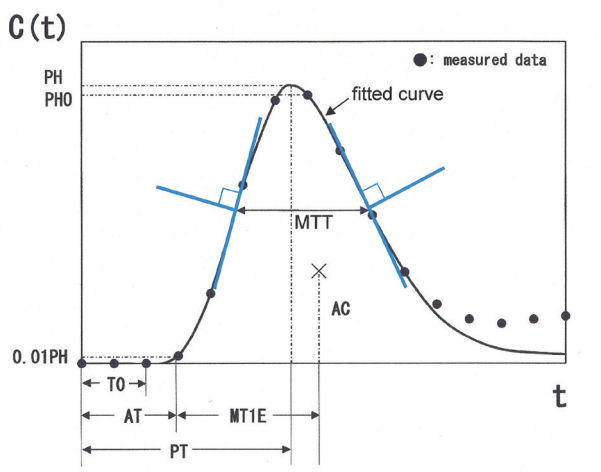

Fig. 1 Time density curve and time parameters. Some time parameters were obtained from perfusion CT. We employed the mean transit time (MTT) in this study. AT: time to the appearance of the contrast agent, PT: time to the peak height, MT1E: time from AT to the gravity center of the fitting time–density curve, MTT: time between the first inflection and second inflection.

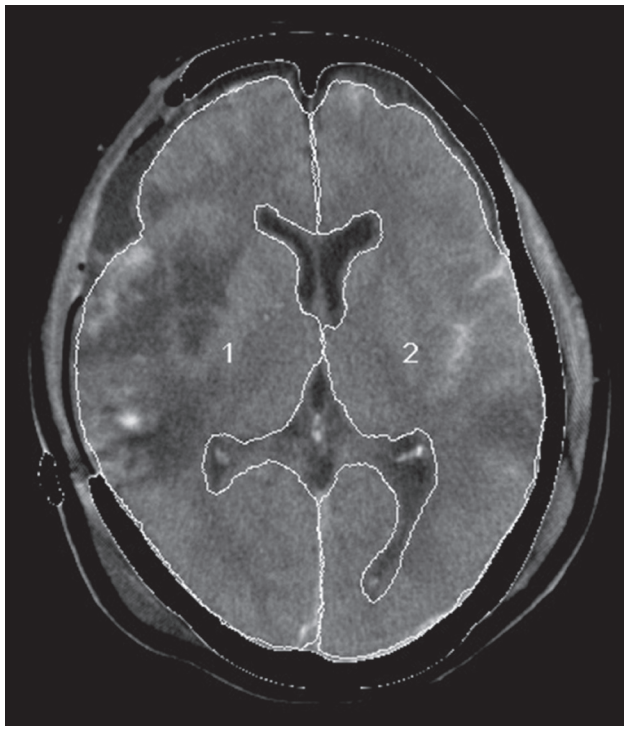

Fig. 2 The regions of interests (ROIs) in the brain. The ROIs were right and left hemispheres at the level of the basal ganglia.

Statistical analysis

All parameters are presented as the mean ± standard deviation. The value of each parameter

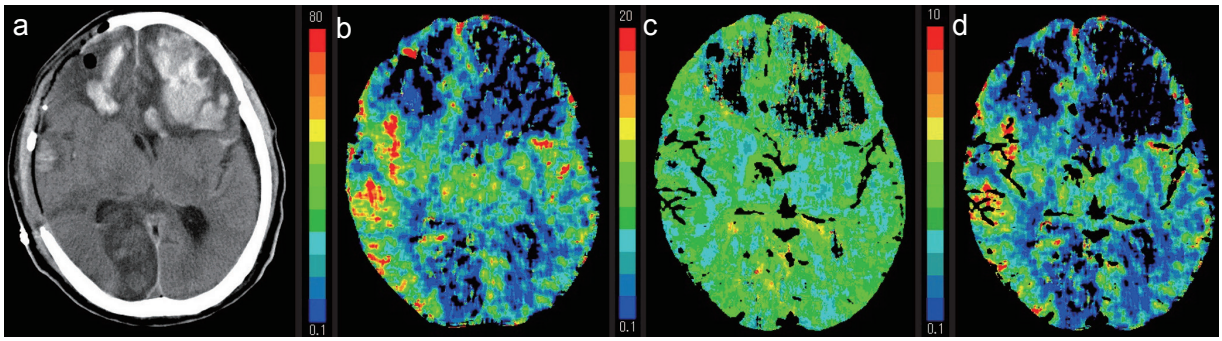

Fig. 3 Computed tomography scan (a), cerebral blood flow map (b), mean transit time map (c), and cerebral blood volume map (d).

was averaged using ROIs in both the hemispheres at the basal ganglia level (Fig. 3). The *t*-test, analysis of variance, and multiple comparison analysis were used to assess the differences between groups. The statistical significance was set at $P < 0.05$ for differences between patient groups. All statistical calculations were performed with a personal computer using a statistical software package (SPSS, version 21.0; SPSS Japan, Tokyo, Japan).

Results

We recruited 90 patients (15 women) who were ranged from 14 to 85 years (mean: 45.5 years). The demographic and clinical characteristics of the patients selected for analysis are summarized in Table 1.

Out of the 90 patients, 36 (40%) did not undergo treatment for a mass lesion or decompression. The remaining patients underwent surgical craniotomy for a mass lesion or decompression. We measured the CBF using Xe-CT and the mean transit time using perfusion CT and calculated the CBV using the AZ-7000W98 computer system in the early phase (post-injury days 1–3 [mean day 1.7]; so-called hyperemia phase).[33]

Table 1 Patient characteristics

Characteristic	Number of patients (%) (Total = 90)
Male %	75 (83)
Mean age in years (range)	45.5 (range 14–85)
GCS at the onset of treatment (number of patients)	
3–4	30 (33)
5–6	26 (29)
7–8	34 (38)
GOS	
GR	11 (12)
MD	13 (14)
SD	22 (24)
VS	17 (19)
D	27 (30)
Type of TBI (Marshall classsification on initial CT)	
Evacuated mass and no evacuated mass	59 (66)
Diffuse injury II	23 (24)
Diffuse injury III + IV	8 (9)

GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, TCDB: Traumatic Coma Data Bank.

1. The relationship between GCS and the hemodynamic parameters CBF, MTT, and CBV

The CBF increased with the neurological grade at the onset of treatment, although there were no significant differences: 26.7 ± 12.0, 28.5 ± 8.8, and 33.6 ± 13.8 ml/100 g/min in the GCS 3–4, 5–6, and 7–8 patients, respectively, indicating no significant grade dependence ($P > 0.05$; ($P = 0.065$), analysis of variance) (Fig. 4a). The MTT decreased with the neurological grade at the onset of treatment, although there were no significant differences: 7.2 ± 1.7, 6.9 ± 1.4, and 6.5 ± 1.8 s in the GCS 3–4, 5–6, and 7–8 patients, respectively, indicating no significant grade dependence ($P > 0.05$, analysis of variance) (Fig. 4b). CBV did not increase with the neurological grade at the onset of treatment: 3.0 ± 1.0, 2.9 ± 0.6, and 3.1 ± 0.9 ml/100 g in the GCS 3–4, 5–6, and 7–8 patients, respectively, indicating no significant grade dependence ($P > 0.05$, analysis of variance) (Fig. 4c).

2. The relationship between the outcome and the hemodynamic parameters CBF, MTT, and CBV

The outcome worsened as CBF was decreased: 36.8 ± 13.1, 30.4 ± 11.4, 27.9 ± 9.1, 27.4 ± 10.5, and 19.1 ± 8.9 ml/100 g/min in the GR, MD, SD, VS, and D groups, respectively, indicating a significant CBF dependence ($P < 0.05$, analysis of variance).

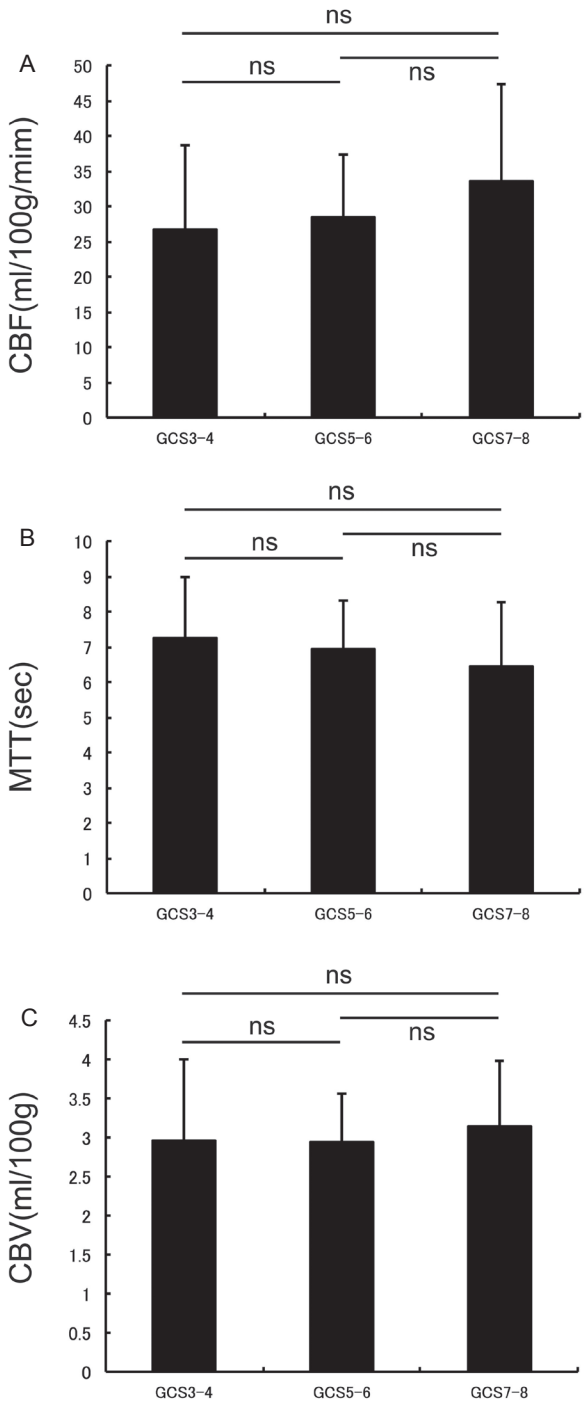

Fig. 4 A: Cerebral blood flow (CBF) was compared in patients with Glasgow Coma Scale (GCS) 3–4, 5–6, and 7–8. The analysis of variance showed no significant differences in CBF ($P > 0.05$, $P = 0.065$). B: Mean transit time (MTT) was compared in patients with Glasgow Coma Scale (GCS) 3–4, 5–6, and 7–8. The analysis of variance showed no significant differences in MTT ($P > 0.05$). C: Cerebral blood volume (CBV) was compared in patients with Glasgow Coma Scale (GCS) 3–4, 5–6, and 7–8. The analysis of variance showed no significant differences in CBV ($P > 0.05$).

The CBF was significantly higher in the GR + MD group (34.0 ± 12.4 ml/100 g/min) than in the SD + VS + D group (26.1 ± 10.7 ml/100 g/min) ($P < 0.05$) (Fig. 5a). The multiple comparisons revealed a significant difference between the GR and D groups ($P < 0.05$).

The outcome worsened as MTT was prolonged: 6.0 ± 1.1, 6.1 ± 1.0, 7.1 ± 1.4, 8.0 ± 2.3, and 8.6 ± 1.1 s in the GR, MD, SD, VS, and D groups, respectively, indicating a significant MTT dependence ($P < 0.05$, analysis of variance). The MTT was significantly longer in the GR + MD group (6.1 ± 1.1 s) than in the SD + VS + D group (7.6 ± 1.8 s) (Fig. 5b). The multiple comparisons revealed significant differences between the GR and VS groups and between the GR and D groups ($P < 0.05$). The outcome did not worsen as CBV decreased: 3.3 ± 0.8, 2.8 ± 0.8, 2.9 ± 0.8, 3.3 ± 1.0, and 2.5 ± 0.9 ml/100 g in the GR, MD, SD, VS, and D groups, respectively, indicating that the outcome was not dependent on CBV ($P > 0.05$; ($P = 0.067$), analysis of variance). The CBV was not significantly higher in the GR + MD group (3.1 ± 0.8 ml/100 g) than in the SD + VS + D group (3.0 ± 0.9 ml/100 g/min) ($P = 0.47$) (Fig. 5c).

3. Parameters significantly influencing outcome

The discriminant analysis of the above three parameters was performed. As a result, the MTT was found to be an effective discriminant parameter, whereas, the CBF and CBV were not. We obtained the discriminant equation, $y = 0.671\text{MTT} - 4.595$ from the discriminant analysis. Using a cutoff value (6.85 s) of MTT for prediction of outcome, we were able to predict the outcomes with a probability of 70.6% (Fig. 6). If the MTT value was <6.85, then the patient's outcome was favorable.

Discussion

As it is important to understand the cerebral circulation dynamics induced in the early phase of TBI to determine its pathogenesis, develop appropriate treatment plans, evaluate treatment results, and predict outcomes. The changes in CBF following TBI in patients have been described as having a triphasic pattern: I, hypoperfusion, which occurs during the first 24 h (post-injury day 0); II, hyperemia, which occurs in post-injury days 1–3; and III, vasospasm, which occurs in post-injury days 4–14.[33] Obrist et al.,[5] Overgaad et al,[7] and others[1,2] have described a similar time course for the post-traumatic hemodynamic phase. The ischemia in TBI patients regardless of when detected has been shown to be correlated with poor outcome.[2,6] Although we found decreased CBF in the poor outcome group, a diagnosis of ischemia cannot be made based solely on it.

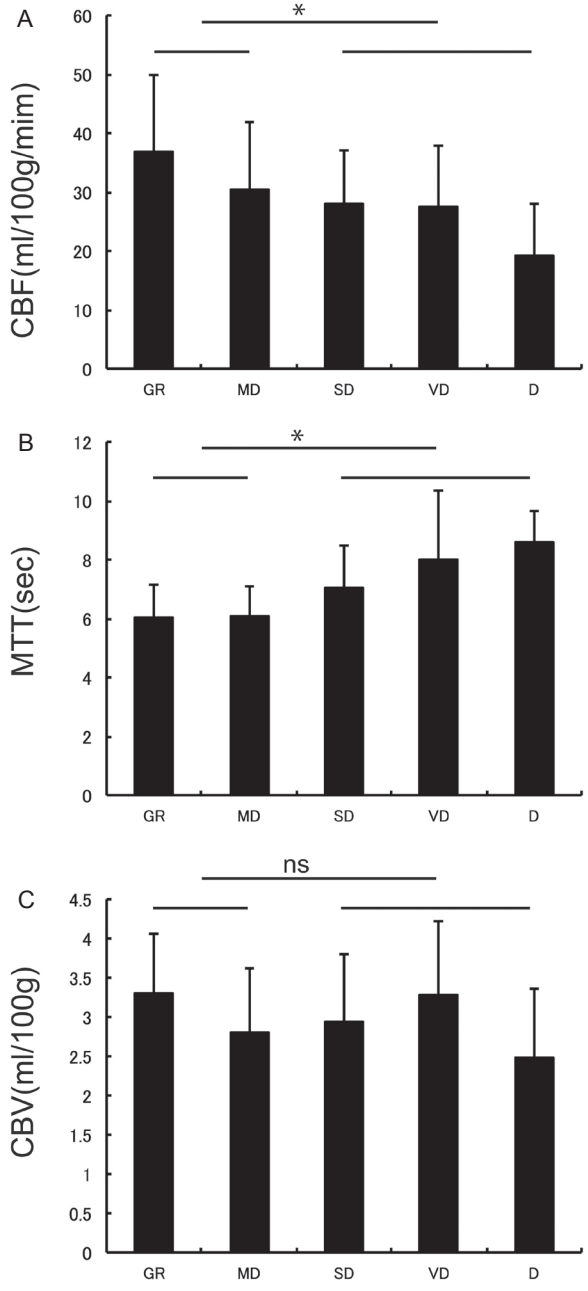

Fig. 5 A: Analysis of variance for cerebral blood flow (CBF) showed significant differences in Glasgow Outcome Scale (GOS). CBF was compared between patients with GOS good recovery (GR) + moderate disability (MD) and severe disability (SD) + vegetative state (VS) + death (D). There was a significant difference between these two groups (*$P < 0.05$). B: Analysis of variance for mean transit time (MTT) showed significant differences in GOS. MTT was compared between patients with GOS GR + MD and SD + VS + D. There was a significant difference between these two groups (*$P < 0.05$). C: Analysis of variance for cerebral blood flow (CBV) showed no significant differences in GOS ($P = 0.067$). CBV was compared between patients with GOS GR + MD and SD + VS + D. There was a significant difference between these two groups ($P > 0.05$).

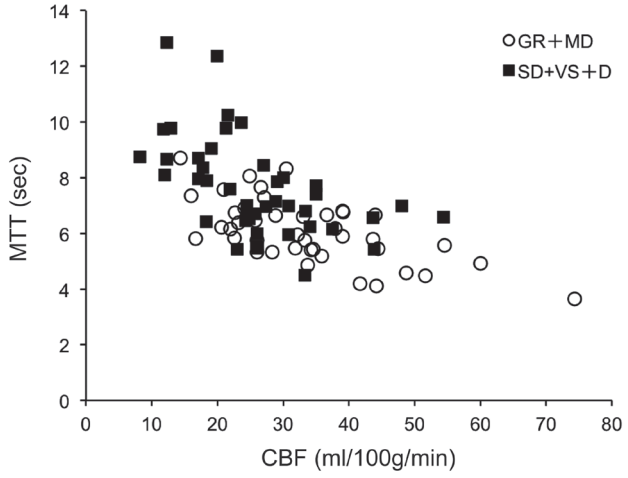

Fig. 6 *Scatter plot* showing the relationship between cerebral blood flow (CBF) and mean transit time (MTT). The favorable outcome group tended to display increased CBF and decreased MTT. The unfavorable outcome group tended to display decreased CBF and increased MTT. Using the discriminant equation $y = 0.671\text{MTT} - 4.595$, we were able to predict outcomes with a probability of 70.6%.

The ischemia should be associated with uncoupling of CBF from cerebral oxidative metabolism. The CBF is markedly influenced by the cerebral metabolic rate of oxygen consumption ($CMRO_2$), body temperature, $PaCO_2$, and ICP, among others. Therefore, in this study, we used both Xe-CT and perfusion CT to evaluate the cerebral circulation using not only CBF, but also the other parameters. The recent studies have reported the utility of perfusion CT for subarachnoid hemorrhaging and stroke.[20,34,35] However, the CBF values obtained from perfusion CT are not quantitative, although they correlate with those obtained from Xe-CT.[30] On the basis of these reports, we performed Xe-CT and perfusion CT simultaneously and evaluated the cerebral circulation of TBI patients using the CBF, CBV, and MTT values obtained with these methods.

In this study, we showed a significant reduction in CBF and significant MTT prolongation in the unfavorable group. It has been reported that the finding of MTT prolongation on perfusion CT is suggestive of a disturbance in the cerebral circulation.[36,37] This finding was also observed in the acute phase of cerebral infarction and cerebral vascular vasospasm after SAH, which are considered to suggest cerebral circulatory disturbance. We measured the MTT (which was calculated as the distance between two inflection points, not from CBF and CBV as in the deconvolution method). It should be noted that the contrast medium injection site, catheter thickness, and the

infusion rate remained constant. Along with the CBF values, the MTT values obtained under these constant conditions were shown to be quantitative and useful for the evaluation of cerebral circulatory disturbance. In this study, the decreased CBF, prolonged MTT, and increased CBV were observed as the GCS at the onset of treatment decreased. These phenomena were considered to be compensatory reactions to cerebral ischemia, although there was no significant difference in these parameters, because severe TBI induced heterogeneous hemodynamic changes, and different types of TBI induce different hemodynamic changes. In fact, there were significant cerebral circulation differences in different types of TBI.[38]

The several factors may result in post-traumatic cerebral circulation disturbance: increased intracranial pressure (ICP), systemic arterial hypotension, cerebral edema, traumatic vasospasm, and microcirculation disturbance. In this study, we measured these parameters in the early phase (days 1–3) before the vasospasm phase while maintaining systemic arterial pressure and arterial partial pressure of carbon dioxide ($PaCO_2$) at 35–40 mmHg. With regard to increased ICP, an animal experiment reported that MTT prolongation in the hyperacute phase (day 0) of SAH was associated with a high mortality rate, and it was found that this was due to the ICP elevation in the acute phase.[39] The prolongation of the cerebral circulation time (CCT) on digital subtraction arteriograms (DSA) has also been reported to reflect increased ICP and to be related to prognosis.[40] These findings demonstrated that reduction in CBF and MTT prolongation could be attributed to increased ICP. In addition, the impaired brain microcirculation contributed to the decreased CBF and the prolonged MTT, as well as the increased ICP. As we did not detect any circulatory disturbance that was consistent with the flow territories of the major vessels, these changes were not thought to be attributable to vasospasm in the major arteries, but rather to represent increased small vessel resistance or the narrowing of small vessels. The cause of the narrowing in the microcirculation may be multifactorial. It has been reported that the extrinsic microvascular compression by damaged and edematous tissue,[10,13] active muscular constriction of the resistance arterioles,[41–43] intravascular thrombosis,[10] and hemoglobin,[44] released as a consequence of post-traumatic SAH, may play a role in trauma-induced microvascular disturbance.

In this study, we demonstrated that there was no significant difference in the CBV value between the favorable outcome group and the unfavorable outcome group. According to the normal scheme of autoregulation, in occlusive cerebrovascular disease, the reduced CBF is thought to trigger vasodilation with subsequent elevation of CBV and extraction of oxygen from blood[45] so as to maintain adequate tissue perfusion. Thus, in the presence of cerebral circulation disturbance, the reduction in CBF, increase in CBV, and prolongation of MTT should be observed. However, in the acute phase after TBI, it is assumed that the increased CBV did not arise due to ICP elevation and autoregulation disturbance. Indeed, in this study, the CBV values of the patients in the unfavorable outcome group were not increased compared with those of the patients in the favorable outcome group. Instead, the reduced CBV in the presence of ischemia would indicate that autoregulation is impaired, a condition that has been proved to be associated with a poorer neurological outcome in patients with TBI.[46,47]

The CBF was significantly lower in patients with a poor outcome than in those with a favorable one, and the MTT was significantly longer in the former than in the latter. The reduction in CBF and MTT prolongation during the early stage of TBI are considered to represent cerebral circulatory disturbance and to be predictors of poor final outcome. However, the discriminant analysis of CBF, MTT, and CBV identified only MTT as a predictor of outcome. Using the discriminant equation $y = 0.671\mathrm{MTT} - 4.595$, we were able to predict outcomes with a probability of 70.6%. To our knowledge, this is the first demonstration of predict of outcome by using the cerebral circulation parameters. The CBF values markedly depend on $CMRO_2$, $PaCO_2$, body temperature, sedative agents, head position, arterial blood pressure, and ICP, among others. Furthermore, the severe TBI induces heterogeneous hemodynamic changes, and different types of TBI induce different hemodynamic changes. Therefore, only MTT could be selected as a useful variable.

The limitation appears to be a direct consequence of the limited spatial coverage provided by perfusion CT and Xe-CT that was limited to a width of 10 mm at the time of the study. Because the severe TBI induces heterogeneous hemodynamic changes and the different types of TBI induce different hemodynamic changes, we could not encompass all the traumatic lesions. Therefore, we could not evaluate the difference between a unilateral lesions and bilateral lesions. Despite this limitation, our findings suggested that the cerebral circulatory disturbance following severe TBI occurs and can be evaluated using the cerebral circulation parameters by these devices. We hope to explore cerebral circulatory parameters of a wider brain area in future research by using multislice CT.

Conclusion

The results of this study show that the cerebral circulatory disturbance following severe TBI occurs

and can be evaluated using the cerebral circulation parameters, CBF and MTT. In addition, we found that it was possible to predict the outcomes with reasonable accuracy based on the circulatory disturbance at this time point, indicating the usefulness of such evaluation.

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