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Sequential Assessment of Cerebral Blood Flow in Diffuse Brain Injury by ^{123}I-Iodoamphetamine Single-Photon Emission CT

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PURPOSE: **Our goal was to elucidate the temporal profile of cerebral circulation and its relationship to prognosis in patients with diffuse brain injury by using single-photon emission CT (SPECT) and ^{123}I-iodoamphetamine (IMP).**

METHODS: **A total of 67 assessments were made in 26 patients with diffuse brain injury (Glasgow Coma Scale score ≤ 8). The microsphere method was used for quantifying cerebral blood flow (CBF). The hemispheric CBF was defined as a mean regional CBF (rCBF), and the total cerebral hemispheric CBF (tCBF) as a mean of the bilateral hemispheric CBF. The relationship between patient outcome and tCBF was investigated.**

RESULTS: **The rCBF in patients with diffuse brain injury showed dynamic and global changes with little regional differences. The tCBF values increased in 1 to 3 days, and they were higher in the poor-outcome group than in the good-outcome group. During the period of 14 to 42 days, the tCBF values stayed within normal range in the good-outcome group, whereas they were below normal range in the poor-outcome group.**

CONCLUSION: **Our results revealed a good correlation between patient outcome and CBF values. Quantitative and sequential CBF studies with IMP SPECT are promising for helping to determine the prognosis for patients with diffuse brain injury.**

In 1984, Gennarelli (1) proposed a classification of head injury, consisting of skull injury, focal injury, and diffuse brain injury. Since then, diffuse brain injury has attracted attention, because in many patients who had a poor clinical outcome and normal brain computed tomography (CT) studies, a disturbance in consciousness developed immediately after the injury (2, 3). Although magnetic resonance (MR) imaging enables us to make the diagnosis of diffuse brain injury more easily than with CT (4, 5), many uncertainties remain in regard to the pathophysiology of diffuse brain injury.

Three-dimensional evaluation of cerebral blood flow (CBF) is less difficult with single-photon emission CT (SPECT) than it is with positron emission tomography (6). Results of SPECT studies of cerebral circulation in patients with diffuse brain injury have appeared in the literature. To elucidate the temporal profile of cerebral circulatory status in patients with diffuse brain injury and its relation to prognosis, CBF in these patients was assessed quantitatively with SPECT and *N*-isopropyl-p-[^{123}I]-iodoamphetamine (IMP) (7) and compared with similar assessments in healthy volunteers.

Methods

Patients included 26 persons (13 to 60 years old; mean and SD, 29 ± 15 years) with diffuse brain injury (Glasgow Coma Scale [8] score of 8 or less) who were hospitalized within 6 hours after sustaining their injury. The diagnosis of diffuse brain injury was made when CT scans revealed no intracranial abnormality or only small hemorrhages without space-occupying lesions (9, 10), or when MR studies disclosed shear lesions in the hemispheric white matter, the corpus callosum, the midbrain, the superior cerebellar peduncle, or the brain stem on T1- or T2-weighted images (4, 5). Patients with toxic and metabolic disturbances, a systolic blood pressure below 80 mm Hg, hypoxia with Pao_2 below 70 mm Hg, or who died in the acute stage of trauma were excluded from the study. Patients' outcomes at 3 months after injury were assessed according to the Glasgow Outcome Scale (11). Good outcome was defined as a satisfactory recovery with moderate disability; poor outcome was defined as a persistent vegetative state with severe disability.

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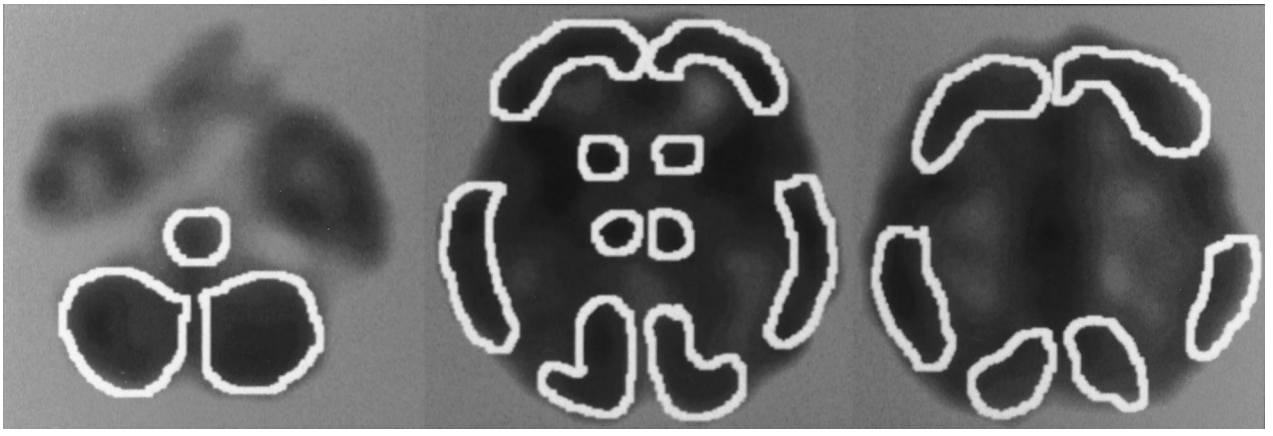

FIG 1. Regions of interest.

Control subjects included 10 healthy volunteers (24 to 41 years old; mean and SD, 31 ± 6 years). Statistical analysis was done with Student's *t* test.

For the SPECT studies, we used a unit equipped with a low-energy high-resolution collimator. IMP is transported from the cyclotron facility 350 km distant from our hospital twice a week. The microsphere method with continuous arterial sampling, as proposed by Kuhl et al (12), Matsuda et al (13), and Murase et al (14), was used for quantifying CBF. In brief, arterial blood was continuously sampled at a constant velocity (1.06 mL/min) for 8 minutes 50 seconds beginning 1 minute after the start of intravenous administration of 222 MBq (6 mCi) of IMP. Scanning was performed for 50 seconds, beginning 7 minutes 35 seconds after the start of the study, followed by repeated 50-second scanning periods 30 to 50 minutes later. The spatial resolution of our system was 6.1 mm at full-width at half-maximum with a section thickness of 12.6 mm parallel to the orbitomeatal line. For image reconstruction, a multiintegration method (15) with Ramp and Butterworth filters was used, and attenuation was corrected by Sorenson's method (16).

Quantitative CBF was calculated by means of the following equation:

$$1) \qquad F = \frac{100 \times R \times H_8 \times S_{40}}{N \times H_{40} \times A \times (TR + D) \times Cf}$$

where F is CBF (mL per 100 g/min), R is continuous blood sampling velocity (mL/min), N is solvent extraction fraction rate, A is radioactivity in 1.0 mL of arterial blood (cpm/mL), T is blood sampling time (minutes), D is dead space (mL), S_{40} is regional resistive index (RI) accumulation at 40 minutes (counts), H_8 is total brain RI accumulation at 8 minutes (counts), H_{40} is total brain RI accumulation at 40 minutes (counts), and Cf is cross calibration factor (counts/cpm).

Regions of interest were set as shown in Figure 1. The hemispheric CBF was defined as a mean regional CBF (rCBF) of regions of interest at the section including the thalamus and the basal ganglia, and the total cerebral hemispheric CBF (tCBF) was defined as a mean of the bilateral hemispheric CBF. Furthermore, CBF correction by $Paco_2$ (= 40 mm Hg) was done according to the equation (1.02 mL/100 g brain per minute per mm Hg $Paco_2$) proposed by Odano et al (17). The study was divided into the following time periods: 0, 1 to 3, 4 to 6, 7 to 13, 14 to 27, and 28 to 42 days. A total of 67 measurements were carried out in 26 patients with diffuse brain injury. In seven patients, only a single study could be performed within the 42-day time frame.

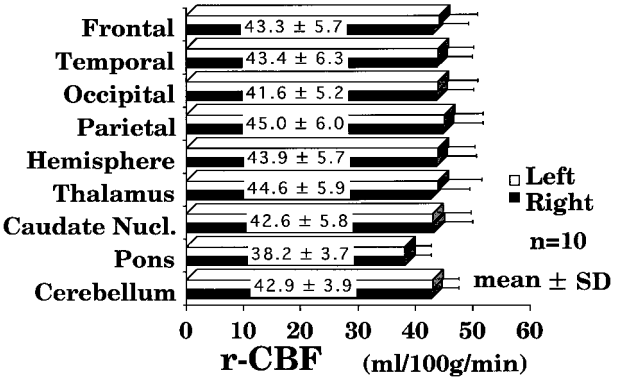

FIG 2. The rCBF in healthy volunteers showed only a little difference and the tCBF was 43.9 ± 5.7 mL per 100 g/min. *Hemisphere* indicates the mean rCBF for the regions of interest (frontal, temporal, occipital, thalamus, caudate nucleus).

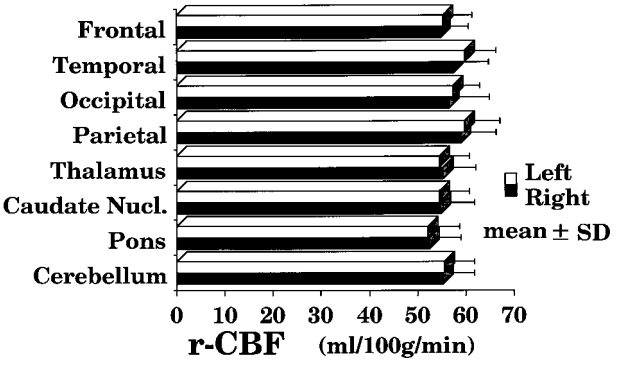

FIG 3. The rCBF in patients with diffuse brain injury at 1 to 3 days showed little difference.

Results

In the 10 healthy volunteers, rCBF showed only small regional differences, and tCBF was 43.9 ± 5.7 mL per 100 g/min (Fig 2). In the patients with diffuse brain injury, rCBF showed a global change with small regional differences (Fig 3).

A comparison of tCBF in the patients with diffuse brain injury with that in the volunteers disclosed an increase at 1 to 3 days (54.0 ± 6.1 mL per 100 g/min; $P < .05$; Student's *t* test) (Fig 4). The value of tCBF

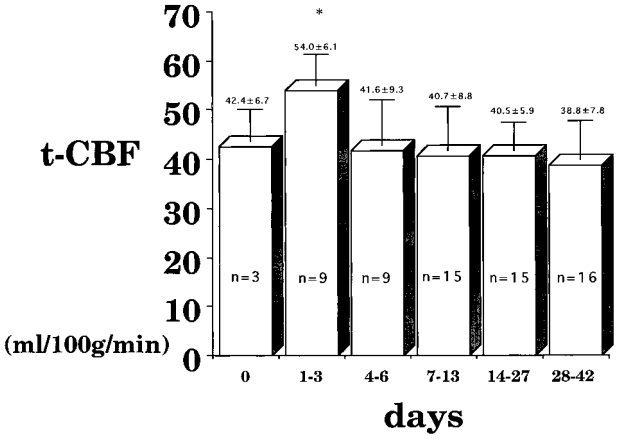

FIG 4. Sequential changes in tCBF in patients with diffuse brain injury. Significant differences in tCBF relative to normal values were observed at 1 to 3 days ($^{*}P < .05$; Student's *t* test).

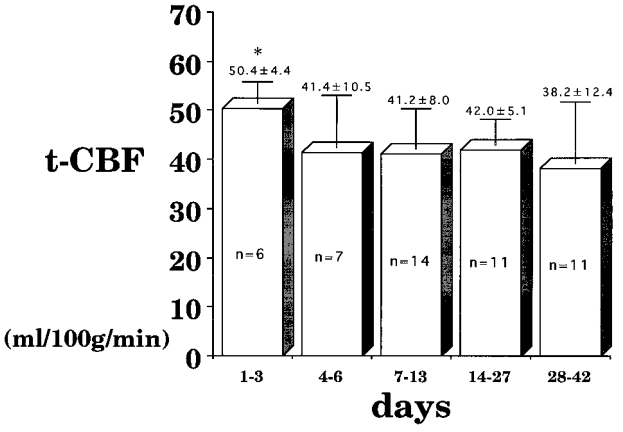

FIG 5. Sequential changes in tCBF in the good- and poor-outcome groups. Significant differences in tCBF relative to normal values were observed at 1 to 3 days ($^{*}P < .05$; Student's *t* test).

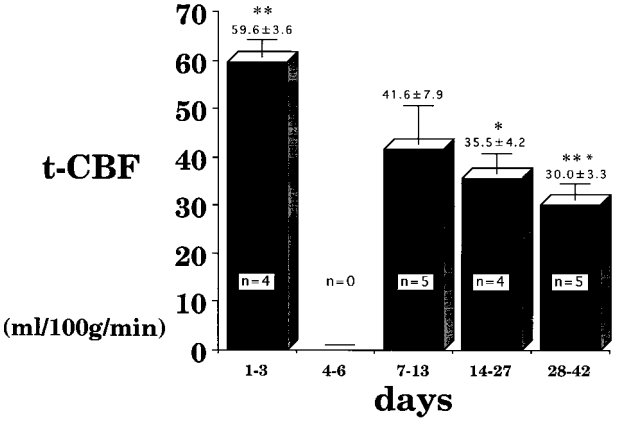

FIG 6. Sequential changes in tCBF in the poor-outcome group. Significant differences in tCBF relative to normal values were observed at 1 to 3 days ($^{**}P < .01$), at 14 to 27 days ($^{*}P < .05$), and at 28 to 42 days ($^{***}P < .01$) (Student's *t* test).

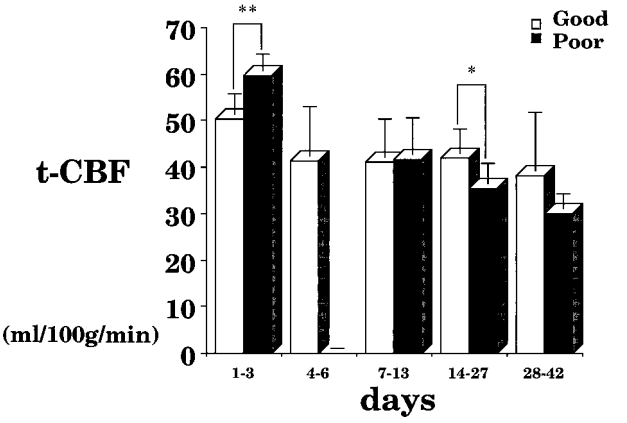

FIG 7. Sequential changes in tCBF in the good- and poor-outcome groups. Significant differences in tCBF relative to normal values were observed at 1 to 3 days ($^{**}P < .01$) and at 14 to 27 days ($^{*}P < .05$) (Student's *t* test).

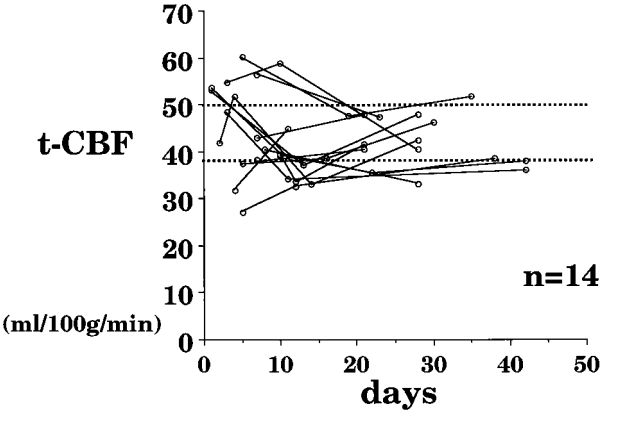

FIG 8. Sequential changes in tCBF in the good- and poor-outcome groups. The tCBF at 14 to 42 days stayed within an almost normal range.

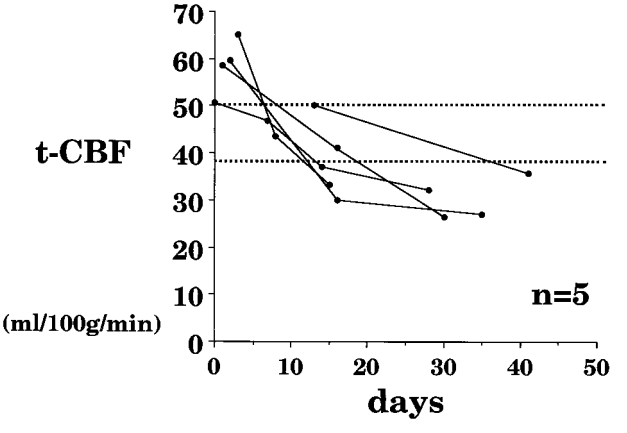

FIG 9. Sequential changes in tCBF in the good- and poor-outcome groups. The tCBF at 14 to 42 days was below the normal value.

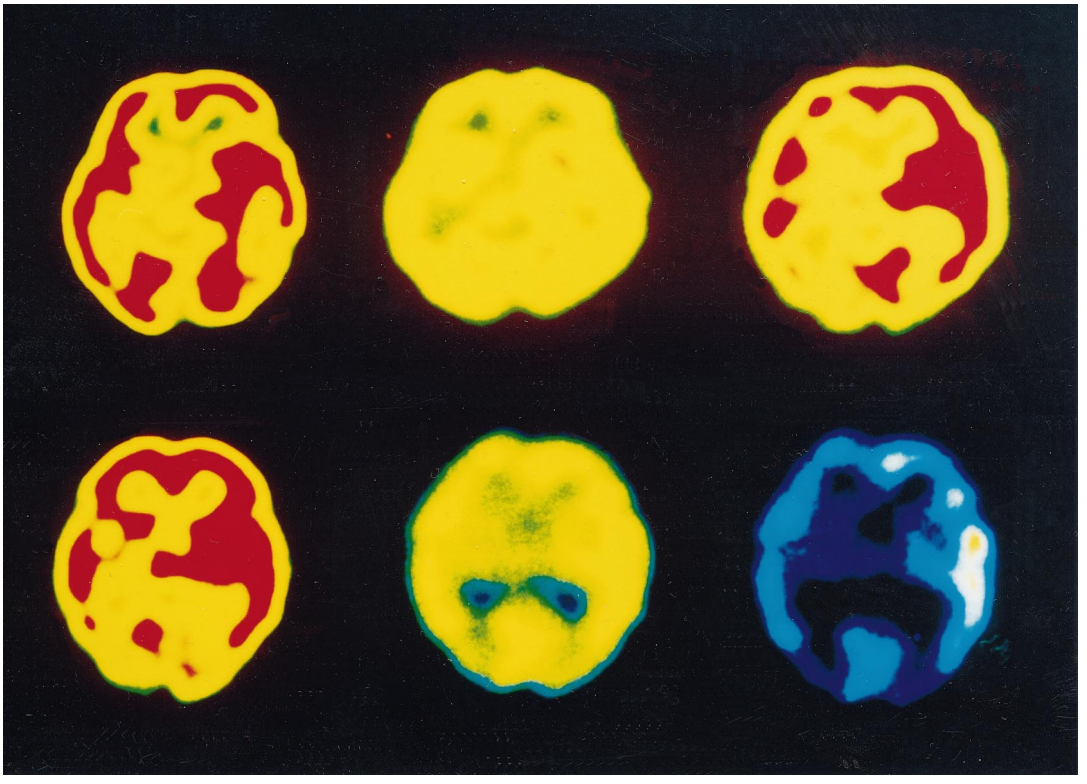

FIG 10. Sequential CBF images with ^{123}I-IMP SPECT in patients with a good outcome (*top row*) and with a poor outcome (*bottom row*). (*Top row, left to right*: day 1, day 13, day 28; *bottom row, left to right:* day 1, day 16, day 30.)

at 1 to 3 days and at 14 to 42 days correlated well with outcome. At 1 to 3 days, tCBF in both the good- and poor-outcome groups was higher than in the control subjects; however, the increase was more marked in the poor-outcome group ($P < .01$) (Figs 5 and 6). There was a significant difference between the two groups at 14 to 27 days (Fig 7). In the sequential CBF study (60 measurements in 19 cases), tCBF in the good-outcome group remained within an almost normal range, but it was significantly lower in the poor-outcome group at 14 to 42 days (Figs 8–10).

Discussion

Since the introduction of CBF measurement methods, much effort has been made to study cerebral circulation in the aftermath of head injury (18–26). It is evident that severe head injury often causes CBF derangement. In previous investigations, the interval between CBF measurement and head injury has not been consistent, and many reports have described only a single CBF measurement (18, 21, 22) or a nonquantified cerebral circulation image (19, 20, 23–26). Moreover, the majority of studies have dealt with both focal and diffuse brain injury together (18, 19). Our study attempted to address a more detailed analysis of sequential CBF change and was restricted to patients with diffuse brain injury.

In recent years, several CBF tracers such as IMP (7, 26), ^{99m}Tc-d,1-hexamethylpropylenamine oxime (HMPAO) (27), and ^{99m}Tc-ethylcysteinate dimer (ECD) (28) have become available for SPECT studies. IMP is difficult to use in emergency examinations because of its relatively short half-life (13 hours), the high energy of the tracer and the need for a nearby cyclotron facility. Therefore, many current SPECT studies of head injury are done with HMPAO (19, 20, 23–26), for which a CBF quantification method has not yet been established. In our investigation, IMP was chosen in order to assess sequential CBF changes that follow head injury and to compare them with normal values.

Physiological factors affecting CBF are known to include $Paco_2$ (17, 26), Pao_2 (29), arterial blood pressure (30), and age (31). Therefore, children, older persons, and patients with hypotension or hypoxia subsequent to head injury were excluded from our study. Also, for the purpose of comparing individual CBF values measured at different time intervals, CBF was corrected with $Paco_2$ (17, 26). The tCBF value in the healthy volunteers was 43.9 ± 5.7 mL per 100 g/min in our study and was in agreement with the normal values of 47.3 ± 7.4 mL per 100 g/min reported by Greenberg et al (26), and of 47.2 ± 5.4 mL per 100 g/min reported by Kuhl et al (12).

The tCBF values in the patients with diffuse brain injury showed dynamic, chronological changes without large regional differences: they increased in 1 to 3 days after injury and then recovered to within normal range (Fig 4). These dynamic CBF changes have not

been described in previous SPECT studies. We probably were able to do so because we carefully excluded focal brain injury on the basis of findings on acute-stage CT and MR studies. It is of interest that CBF changes were observed globally, without regional differences, because in patients with diffuse brain injury, damage to the axons is a diffuse process.

The CBF value obtained after 24 hours is not always indicative of prognosis (18, 19, 29). In our study, however, we found a significant correlation between outcome and tCBF at 1 to 3 days and at 14 to 42 days after injury. The tCBF of the poor-outcome group was higher 1 to 3 days after injury and lower 14 to 27 days after injury than that of the good-outcome group. Several possibilities have been postulated to explain this early CBF increase, including vasodilatation due to high tissue CO_2 and lactic acidosis after ischemia (29), and dysautoregulation (32). Previous investigators have pointed out that postischemic hyperperfusion was related to the grade of ischemic insult (18, 19, 29, 33–37). In our sequential CBF study, tCBF in the good-outcome group stayed within normal range during the period of 14 to 42 days after injury. In the late stage, however, it is assumed that residual brain function begins to regulate the CBF, which seems to be highly related to outcome.

Conclusion

Our study produced several important findings regarding CBF in patients with diffuse brain injury: CBF showed dynamic and global changes with little regional differences in the course of time, and a good correlation was found between outcome and CBF values. The CBF of the poor-outcome group was higher 1 to 3 days after injury and lower 14 to 27 days after injury than that of the good-outcome group. In the good-outcome group, CBF stayed within a normal range and was higher than in the poor-outcome group 14 to 42 days after injury. Quantitative and sequential CBF studies with IMP SPECT hold promise for helping to determine the prognosis for patients with diffuse brain injury.

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