Hyperemia prior to acute brain swelling during rewarming of patients who have been treated with moderate hypothermia for severe head injuries

KOJI IIDA, M.D., PH.D., KAORU KURISU, M.D., PH.D., KAZUNORI Arita, M.D., PH.D., AND MINAKO OHTANI, M.D., PH.D.

Department of Neurosurgery and Division of Emergency Medicine and Intensive Care Medicine, Hiroshima University School of Medicine, Hiroshima, Japan

Object. The goal of this study was to elucidate the optimal time for rewarming of patients who have been treated with hypothermia for severe head injury.

Methods. Eleven patients with severe head injuries who had been treated by hypothermia underwent transcranial Doppler (TCD) ultrasonography examinations. The patients were divided into two groups: Group A consisted of three patients in whom acute brain swelling occurred during the rewarming period and Group B was composed of eight patients who displayed no significant intracranial hypertension during or after hypothermia therapy. In all patients, the mean flow velocity of the middle cerebral artery (FV MCA ), recorded transcranially and the mean flow velocity of the internal carotid artery (FV ICA ), recorded high in the neck, were monitored at 24-hour intervals after the patient was admitted to the hospital. In Group A, the FV MCA was normal at 48 hours (maintenance state of hypothermia) in each patient, and abnormal increases and peak values (> 100 cm/second) occurred from 96 to 144 hours postinjury (rewarming period). The FV ICA, which was monitored concurrently also varied as the FV MCA increased. The pulsatility indices in the arteries decreased at the time of the peak FV MCA. The enhanced FV MCA was consistent with hyperemia because of the low FV ICA/FV MCA ratios (< 3). Two patients in whom jugular venous oxygen saturation was monitored were found to have high values (> 80%), representing hyperemia. All intracranial pressures (ICPs) that lay within the normal range at 48 hours postinjury elevated acutely after the peak FV MCA. In Group B, both FV MCA and FV ICA values were normal at 48 hours postinjury and remained stable throughout the rewarming period. Values of ICP were also maintained within the normal range until the patients were weaned from hypothermia therapy.

Conclusions. Hyperemia, detectable by TCD ultrasonography, may serve as an index in the prediction of acute brain swelling, and rewarming should be terminated when such a hemodynamic phenomenon is observed.

KEY WORDS • hyperemia • severe head injury • hypothermia • rewarming • transcranial Doppler ultrasonography • acute brain swelling

To improve outcomes of patients with severe head injury, prevention of secondary damage to the already injured brain is essential. Recently clinical investigators have reported that hypothermia has the effect of decreasing ICP and, thus, the potential to limit the extent of secondary brain injury that is caused mainly by ischemia during the acute phase. Although recently negative results of hypothermia for severe head injury have been reported, its clinical application has become widespread. For obtaining the highest efficacy and preventing the many complications of hypothermia, techniques and methods for induction and maintenance of hypothermia now seem to have been established and they include blanket cooling, a safe temperature range (32–34°C), an appropriate time before initiation, and various kinds of systemic and neurological monitoring. Concerning rewarming, however, the optimal time for initiation has not yet been established. During rewarming, which in previous studies has been conducted slowly, the main problem encountered is a repeated increase in ICP, especially that due to acute brain swelling. Therefore, we performed this preliminary study to elucidate the optimal time for rewarming by examining cerebral hemodynamics in patients with acute brain swelling by using TCD ultrasonography.

Clinical Material and Methods

In our hospital to be eligible for hypothermia therapy patients must be younger than 70 years of age and have a postresuscitation GCS score between 4 and 7 after severe head injury. Patients were excluded from therapy if they exhibited hypoxia (O₂ saturation < 95% for > 30 minutes), major multiple injuries requiring laparotomy or thoracotomy, incomplete hemostasis, pulmonary failure, or sustained hypotension (systolic blood pressure < 100 mm Hg). The amount of time before initiation of hypothermia therapy

Abbreviations used in this paper: ANOVA = analysis of variance; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CT = computed tomography; FV = flow velocity; FV MCA/FV ICA = FV of the middle cerebral artery/FV of the internal carotid artery; GCS = Glasgow Coma Scale; ICP = intracranial pressure; JV = jugular vein; PI = pulsatility index; SD = standard deviation; SjvO₂ = saturation of oxygen in the JV; TCD = transcranial Doppler.
was not taken into consideration; however, cooling was initiated within 6 hours after injury if possible.

In this investigation, we set further strict inclusion criteria: patients had to have completed hypothermia therapy, been monitored with serial TCD ultrasonography during hypothermia, and suffered no complication that might influence cerebral hemodynamics such as pneumonia causing hypercapnia, cardiac dysfunction, or renal failure.

Between 1995 and 2000, 11 consecutive patients who satisfied the inclusion criteria of this study were selected. Three of the 11 patients manifested acute brain swelling during the rewarming period. After nonsurgical resuscitation the GCS scores were 4 in all three patients with acute brain swelling. Initial CT scans obtained in these three cases revealed an evacuated mass lesion in one patient and diffuse injury in two patients. In the other eight patients, the GCS scores were 4 in five patients, 6 in two patients, and 7 in one patient. Initial CT scans in these eight cases revealed evacuated mass lesions in five patients and diffuse injury in three patients.

Immediate treatment consisted of sedation induced by midazolam followed by controlled ventilation and continuous monitoring of arterial blood pressure. After general circulatory stability had been achieved, early CT scans were obtained and craniotomies were performed immediately to evacuate mass lesions.

In all 11 patients, monitoring of ICP and SjvO₂ in the right internal jugular vein was routine. In one patient 2 years of age, SjvO₂ monitoring could not be performed. Hypothermia was induced by use of a cooling blanket and injection of ice water through a nasogastric tube. Thereafter, IV temperatures of 32 to 34°C were maintained with the aid of cooling blankets. Midazolam (0.2 mg/kg/hr) and vecuronium (0.04 mg/kg/hr) were administered continuously. Mannitol

---

**TABLE 1**

*Results of TCD ultrasonography studies performed during hypothermia therapy in Group A*†

<table>
<thead>
<tr>
<th>Temperature (°C) in JV</th>
<th>FV MCA§</th>
<th>PI MCA</th>
<th>FV ICA§</th>
<th>PI ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>32–34</td>
<td>61.7 ± 14.6</td>
<td>0.99 ± 0.30</td>
<td>33.7 ± 7.1</td>
<td>0.75 ± 0.23</td>
</tr>
<tr>
<td>34–36</td>
<td>115.3 ± 14.5</td>
<td>0.74 ± 0.06</td>
<td>55.0 ± 15.6</td>
<td>0.52 ± 0.27</td>
</tr>
<tr>
<td>32–34†</td>
<td>64.3 ± 8.1</td>
<td>1.07 ± 0.27</td>
<td>40.0 ± 4.6</td>
<td>0.91 ± 0.34</td>
</tr>
<tr>
<td>p Value‡</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± SDs. Abbreviations: NS = not significant; PI MCA = PI of the FV MCA; PI ICA = PI of the FV ICA.
† Jugular venous temperature after hypothermia was induced for a second time.
‡ Statistical analysis was performed using repeated-measures ANOVA.
§ Flow velocity is expressed in centimeters per second.

---

**FIG. 1.** Graph showing the results of serial TCD ultrasonography examinations of the mean FV ICA (ICAFV) and its PI in Group A. The peak FV ICA, accompanied by a relatively low PI, occurred during the rewarming period (34–36°C). The asterisk indicates the temperature of the patients after hypothermia was induced for the second time. The probability values indicate statistical significance by repeated measurements (ANOVA). Values are represented as means ± SDs. n.s = not significant.

**FIG. 2.** Graph depicting the results of serial TCD ultrasonography examinations of the mean FV ICA (ICAFV) and its PI in Group A (measured at the same times as data shown in Fig. 1). The asterisk indicates the temperature of the patients after hypothermia was induced for the second time. The probability values indicate statistical significance by repeated measurements (ANOVA). Values are represented as means ± SDs.
was given to patients in whom ICP was greater than 20 mm Hg. Dopamine and/or dobutamine were injected continuously to maintain arterial pressure within the normal range and CPP higher than 70 mm Hg. The patients’ PaO₂ and PaCO₂ were maintained at levels higher than 100 mm Hg and between 30 and 35 mm Hg, respectively. Rewarming was initiated after a 48- to 72-hour maintenance period and patients were warmed at a rate of 0.5 to 1˚C per day.

All patients underwent TCD ultrasonography examinations at approximately 24-hour intervals after admission to the hospital. The mean FVMCA and the mean FVIC were measured using transcranial and cervical insonation, respectively. The PI (peak systolic velocity/mean velocity) for each measurement was also calculated. We compared the TCD ultrasonography findings in the three patients with acute brain swelling (Group A) with those in the other eight patients (Group B).

Results
Changes in the Mean FV and PI in Group A

According to the TCD ultrasonography data for the three patients in Group A (Table 1 and Figs. 1 and 2), the FVMCA and FVIC values were normal, and the corresponding PI was relatively high in the MCA at 48 hours postinjury, during the maintenance period of hypothermia (32–34˚C in the JV). Normal mean FVs ± SDs in these two arteries are 60 ± 7 and 36.3 ± 8.6 cm/second, respectively. The FVMCA began to increase during the rewarming period and peaked between 96 and 144 hours postinjury (34–36˚C in the JV). When the FVMCA peaked, the probe in the JV indicated temperatures of 34.2, 34.8, and 35.2˚C in these three patients, respectively. Concurrently, the PI decreased relatively between 96 and 144 hours. Because these patients displayed signs of acute brain swelling after the peak FVMCA, hypothermia was again induced and the FVMCA recovered to its normal value. Over the same period, the change in the FVIC coincided well with that in the FVMCA. Between 96 and 144 hours postinjury (34–36˚C in the JV), the mean FVIC increased to approximately 170% of its value during the maintenance period, and the PI tended to decrease. The peak FVIC exceeded 100 cm/second, indicating abnormal increases in all three patients. In two of the three patients the SjvO₂, which was measured simultaneously with the peak FVMCA, was significantly increased (82.7 and 85.6%). During the maintenance period (48 hours postinjury) the SjvO₂ values were both normal, that is, 74.5 and 75.3%.

In all three patients, the FVMCA/FVIC ratios, which were calculated simultaneously with the peak FVMCA value, were less than 3 (1.81, 2.35, and 2.3).

Correlation Between FVs and ICP and Clinical Course After Acute Brain Swelling in Group A

The initial ICPs measured before induction of hypothermia in each patient in Group A were 19, 33, and 43 mm Hg. One patient in whom the initial ICP was 19 mm Hg had undergone emergency external decompression because of a subdural hematoma and ICP monitoring was started after the decompression. A review of the results of ICP monitoring in Group A (Fig. 3), shows that ICP recovered to the normal range 48 hours postinjury (maintenance state of hypothermia of 32–34˚C in the JV) and remained low (normal range 6–18 mm Hg).
Nevertheless, the ICP tended to increase at the peak of the FV MCA. An abnormal increase (> 100 cm/sec- second) in FV MCA was observed in one patient 24 hours before the FV MCA peaked. Throughout the time period during which there was an abnormal increase in FV MCA, the ICP was unstable and often greater than 20 mm Hg in two patients. At that time, the ICP responded to conventional osmotherapy (that is, mannitol treatment) by which we managed to prevent the ICP from further increasing. The rewarming speed was greatly reduced because of the unstable ICP. Afterward, in all three patients, an additional significant acute increase in ICP was observed between 12 and 36 hours after the abnormal increase in FVMCA had been detected, and CT scans performed immediately after these ICP increases revealed diffuse brain swelling without any evidence of another lesion that might cause an increase in ICP, such as deteriorations in the intracranial hematomas. While hyperventilation was applied, hypothermia (32–33˚C in the JV) was again induced in all three patients and this therapy continued for 5 to 12 more days until their ICPs stabilized. In two of the three patients, reintroduction of hypothermia therapy was accompanied by barbiturate therapy. The outcomes in the three patients were good recovery, severe disability, and persistent vegetative state.

Changes in the Mean FV and the PI in Group B

In Group B (Table 2 and Figs. 4 and 5) the TCD ultrasonography data demonstrated that FV MCA and FV ICA values were normal in all eight patients at 48 hours postinjury, during the hypothermia maintenance period (32–34˚C in the JV). There were no significant differences in these values between Groups A and B. In contrast with changes in FV MCA in Group A, the mean FV MCA values ± SDs in Group B remained almost stable during the rewarming period; that is,

**TABLE 2**

Results of TCD ultrasonography studies performed during hypothermia therapy in Group B

<table>
<thead>
<tr>
<th>Temperature (˚C) in JV</th>
<th></th>
<th></th>
<th></th>
<th>p Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>32–34</td>
<td>34–35</td>
<td>35–36</td>
<td></td>
</tr>
<tr>
<td>FV MCA †</td>
<td>46.3 ± 11.8</td>
<td>61.3 ± 12.1</td>
<td>50.0 ± 17.8</td>
<td>NS</td>
</tr>
<tr>
<td>PI MCA †</td>
<td>0.98 ± 0.18</td>
<td>0.93 ± 0.26</td>
<td>0.92 ± 0.16</td>
<td>NS</td>
</tr>
<tr>
<td>FV ICA †</td>
<td>30.0 ± 9.0</td>
<td>37.3 ± 7.6</td>
<td>32.2 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>PI ICA †</td>
<td>0.94 ± 0.21</td>
<td>0.87 ± 0.12</td>
<td>1.01 ± 0.29</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Statistical analysis was performed using repeated-measures ANOVA.
† Flow velocity is expressed in centimeters per second.
Hyperemia during rewarming from hypothermia in severe head injury

61.3 ± 12.1 and 50 ± 17.8 cm/second at JV temperatures of 34 to 35˚C and 35 to 36˚C, respectively. In Group B, there was no patient in whom the FVMCA displayed a significantly high value (> 100 cm/second) during the entire course of hypothermia therapy. In addition, the FVICA remained stable during the rewarming period as well. In both arteries the PI values remained relatively high at 48 hours postsurgery, and exhibited no significant changes with respect to the SjvO₂ in this group. The SjvO₂ at 48 hours postsurgery was normal (67.5 ± 7.2% [SD]), and remained stable during the rewarming period; that is, 69.3 ± 7.2 and 67.8 ± 6.6% (mean ± SD) at JV temperatures of 34 to 35˚C and 35 to 36˚C, respectively.

Correlation Between FVs and ICP ± SD in Group B

The mean initial ICP ± SD in Group B was 31.8 ± 19.5 mm Hg (range 7–56 mm Hg). The initial ICP values in two patients in whom ICP monitoring was started after external decompression were 7 and 8 mm Hg. In the other six patients, the initial ICP was remarkably high, greater than 30 mm Hg. There was no significant difference in initial ICP values between Groups A and B. The results of ICP monitoring in Group B (Fig. 6) revealed that ICP was controlled within the normal range during hypothermia. A slight elevation in ICP was observed at JV temperatures of 35 to 36˚C. In two patients, the ICP increased to greater than 20 mm Hg at 35 to 36˚C; however, no further increase in ICP was induced by conventional osmotherapy (that is, mannitol treatment). No specific changes in FVICA were observed in these two patients compared with the values in the other six patients. The outcomes in Group B were good recovery in two patients, moderate disability in two patients, severe disability in one patient, and persistent vegetative state in three patients.

Blood Gases and CPP in Groups A and B

Values of arterial blood gas and CPP in both groups during the TCD ultrasonography examinations are shown in Tables 3 and 4. There were no significant differences among these parameters, and the values of PaCO₂ and CPP were optimal during the TCD ultrasonography examinations.

### Table 3

<table>
<thead>
<tr>
<th>Factor</th>
<th>Temperature (˚C) in JV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32–34</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>35.4 ± 0.9</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>180.0 ± 28.1</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>83.7 ± 9.3</td>
</tr>
</tbody>
</table>

* Statistical analysis was performed using repeated-measures ANOVA. There were no statistically significant differences between time periods.
† Jugular venous temperature after hypothermia was introduced for the second time.

### Table 4

<table>
<thead>
<tr>
<th>Factor</th>
<th>Temperature (˚C) in JV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32–34</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>35.5 ± 4.0</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>168.9 ± 41.7</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>82.2 ± 12.3</td>
</tr>
</tbody>
</table>

* Statistical analysis was performed using repeated-measures ANOVA. There were no statistically significant differences between time periods.

**Discussion**

Secondary brain insults arise through systemic or intracranial mechanisms. Ischemia, particularly that consisting of a reduction in CBF due to compromised CPP and uncoupling between the CBF and an increased cerebral metabolic rate, is the major cause of secondary brain injury. In previous reports, two main goals of hypothermia therapy have been described: 1) reduction of ICP and improvement in ischemia during the acute phase in the treatment for severe head injury, and 2) protection of the brain by preventing ischemia, in which case hypothermia is induced as soon as possible after injury. Therefore, major attention has been focused on the normalization of ICP and improvement in ischemia during the rewarming period or the optimal timing for initiation of rewarming has not been established, however. In previous studies, cooling periods were selected according to their potential for increasing the incidence of complications. Marion, et al., found no increase in the incidence of complications. Shiozaki and associates and Clifton, et al., reported on patients who were cooled for 48 hours and, although there was no statistical significance in their findings, both showed a trend toward increased incidences of pneumonia and sepsis.
These reports focused on the cooling period without taking into consideration the patient’s cerebral condition or addressing the question of whether the injured brain could tolerate rewarming. Shiozaki and associates reported that the death of one of their patients was due to uncontrollable intracranial hypertension after accidental warming to 37°C. Despite very slow rewarming, some patients exhibited repeated increases in ICP after ICP and SjvO2 were normalized during the cooling period. In particular, acute brain swelling directly leads to fatality. Therefore, for cerebral monitoring to have prognostic value, some relevant modalities would be necessary during rewarming.

Transcranial Doppler ultrasonography has been well used for its convenience and safety as a noninvasive method of indirect measurement of CBF in many brain disorders. In the treatment of severe head injury, major hemodynamic complications detectable by TCD ultrasonography include vasospasm, hyperemia, and hypoperfusion due to intracranial hypertension. Both vasospasm and hyperemia are associated with an abnormally increased FV MCA (>100 cm/second). The increased FV MCA caused by hyperemia can be diagnosed by simultaneous measurement of the ipsilateral FV ICA. In other words, an increased FV MCA with an FV MCA/FV ICA ratio less than 3 is consistent with hyperemia. The simultaneous increases of FV MCA and FV ICA can be explained by increased blood flow volume due to a loss of autoregulation and cerebral vasodilatation. Therefore, in this study, three patients suffering from acute brain swelling with abnormally increased FV MCA were thought to demonstrate hyperemia, based on the calculation of their FV MCA/FV ICA ratios. Significant elevation of SjvO2 values at a peak during the rewarming period. Hyperemia has been found to be associated with intracranial hypertension in various brain disorders, and an increase in ICP is a common and frequent complication detectable by TCD ultrasonography examinations in this study, we were unable to determine the precise threshold value of FV MCA that would indicate the ICP elevations that respond to mannitol and those that do not, or the precise relationship between Jv temperature and the appearance of hyperemia, and subsequent acute brain swelling. At any rate, the possibility of an acute increase in ICP should be taken into consideration when an abnormal increase in FV MCA is encountered during the rewarming period.

After acute brain swelling occurred, we again induced hypothermia and administered barbiturate therapy in two of three patients. Barbiturate medications reduce brain metabolism to approximately 50% of the normal rate by silencing electrical activity and attenuate CBF by almost 50%. Hypothermia may also have the effect of causing cerebral vasospasm. Although we do not know the mechanism by which hypothermia and barbiturates influence hyperemia, the increased ICP could be normalized and stabilized by a prolonged period of hypothermia.

Conclusions

From the findings of this preliminary report, it may be necessary to reevaluate the length of the hypothermia maintenance period, the length of ICP or SjvO2 monitoring, and other parameters to determine the appropriate time to initiate rewarming. When performing rewarming, TCD ultrasonography, a rapid and noninvasive diagnostic method, is useful for repeated evaluation of cerebral hemodynamics. Hyperemia, detectable by TCD ultrasonography, may serve as an index in the prediction of acute brain swelling, and rewarming should be terminated when such a hemodynamic phenomenon is observed.

References


K. Iida, et al.
Hyperemia during rewarming from hypothermia in severe head injury


Manuscript received April 8, 2002. Accepted in final form December 20, 2002.

Address reprint requests to: Kazunori Arita, M.D., Ph.D., Department of Neurosurgery, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. email: karita@hiroshima-u.ac.jp.