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Summary

Analysis of memory-related function in medial temporal lobe using electrocorticographic recordings with chronic subdural electrodes

Takahiro Ota, Kyousuke Kamada, Naoto Kunii, Kensuke Kawai, Nobuhito Saito

Electrocorticography (ECoG) recordings were obtained in 7 patients with refractory epilepsy, in whom chronic subdural electrodes had been placed on both temporal bases, for evaluation of memory-related problems. Averaging and time-frequency analyses were performed for determination of the dominant side in memory function and for the cerebral cortex activity specific to memory function.

In the averaging analysis, a reaction was observed 500 msec after the presentation of a stimulus, and in the time-frequency analysis, activities of synchronization (Syn) followed by desynchronization (Des) were observed in the β band. Both were considered to be memory task-specific activities. In the high γ band, Syn with a latent period of 500–800 msec was observed on the left side. In 5 patients who showed clear laterality in memory function, Syn with a latent period of 500–800 msec was observed in the β region on the dominant side, and Des with a latent period of 800–1000 msec on the non-dominant side. In addition, Syn activity with a latent period of 600-800 msec was observed in the high γ band on the dominant side. Thus, our results showed that analysis of evoked ECoG may allow identification of the dominant hemisphere in memory function as well as the area of memory function.

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FULL-LENGTH ORIGINAL RESEARCH

Cooling of the epileptic focus suppresses seizures with minimal influence on neurologic functions

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Summary

Purpose: Focal brain cooling is effective for suppression of epileptic seizures, but it is unclear if seizures can be suppressed without a substantial influence on normal neurologic function. To address the issue, a thermoelectrically driven cooling system was developed and applied in free-moving rat models of focal seizure and epilepsy.

Methods: Focal seizures limited to the unilateral forelimb were induced by local application of a penicillin G solution or cobalt powder to the unilateral sensorimotor cortex. A proportional integration and differentiation (PID)–controlled, thermoelectrically driven cooling device (weight of 11 g) and bipolar electrodes were chronically implanted on the eloquent area (on the epileptic focus) and the effects of cooling (20, 15, and 10°C) on electrocorticography, seizure frequency, and neurologic changes were investigated.

Key Findings: Cooling was associated with a distinct reduction of the epileptic discharges. In both models, cooling of epileptic foci significantly improved both seizure frequency and neurologic functions from 20°C down to 15°C. Cooling to 10°C also suppressed seizures, but with no further improvement in neurologic function. Subsequent investigation of sensorimotor function revealed significant deterioration in foot-fault tests and the receptive field size at 15°C.

Significance: Despite the beneficial effects in ictal rats, sensorimotor functions deteriorated at 15°C, thereby suggesting a lower limit for the therapeutic temperature. These results provide important evidence of a therapeutic effect of temperatures from 20 to 15°C using an implantable, hypothermal device for focal epilepsy.

KEY WORDS: Epilepsy, Implantable device, Focal brain cooling, Therapeutic temperatures.

Focal or selective brain cooling is a candidate treatment for epilepsy (Stacey & Litt, 2008; Rothman, 2009). The first clinical application was performed almost 50 years ago and demonstrated clear suppression of epileptic seizures in patients with intractable epilepsy (Ommaya & Baldwin, 1963). A number of subsequent studies have confirmed the strong suppressive effect of cooling on epileptic discharges (Vastola et al., 1969; Reynolds et al., 1975; Sartorius & Berger, 1998; Hill et al., 2000; Yang & Rothman, 2001; Karkar et al., 2002, Imoto et al., 2006; Yang et al., 2006; Tanaka et al., 2008) and epileptic seizures (Sourek & Travnicek, 1970; Burton et al., 2005).

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Despite the long history of investigation, the clinical feasibility of focal brain cooling remains unclear. One of the crucial but unresolved issues is to clarify whether "therapeutic temperatures" really exist, since focal brain cooling can suppress epileptic seizures, but is also associated with suppression of synaptic transmission. Indeed, a series of in vivo experiments have shown cooling-induced deterioration of various neurologic functions, including visual function in cats (Lomber et al., 1996; Lomber & Payne, 2004), auditory function in cats (Malhotra et al., 2004), and motor function in monkeys (Sasaki & Gemba, 1984; Brinkman et al., 1985). The cooling temperatures of the cortical surface in these experiments were not explicitly described, but neurologic deterioration was presumably induced by excessive suppression of synaptic transmission. Therefore, to address the issue of clinical feasibility, it is necessary to clarify whether seizure suppression can be achieved with a minimal influence on neurologic function.

This issue was preliminarily investigated by Karkar et al. (2002) wherein bath application of 4°C saline on the cortex in a patient with epilepsy did not influence the amplitudes of motor-evoked potentials. Another study of cooling showed that network synchronization in hippocampal slices was terminated without blocking normal synaptic transmission (Javedan et al., 2002). Although these results are promising, they do not provide direct evidence. Therefore, we addressed the effect of cooling on seizure and neurologic functions in awake, free-moving rats using an implantable cooling system, with a focus on the eloquent cortex.

Methods

Cooling system

A cooling device originally developed in our laboratory (Imoto et al., 2006; Oku et al., 2009; Fujioka et al., 2010) was used in the study. This device includes a cooling component and a heat-processing component. The cooling component (about 11 g in weight) consists of a proportional integration and differentiation (PID)–controlled thermoelectric chip (6.0 × 6.0 mm; maximum current (I max) 1.8A, maxmum voltage (V max) 2.5V, maximum power (Q max) 2.4W; Ferrotec Corp., Tokyo, Japan). The cooling side of the thermoelectric chip is attached to a pure silver plate (thickness of 1 mm) for direct cooling of the cortex. To avoid contact injuries with the brain, a fine thermocouple (Physitemp 23T, Clifton, NJ, U.S.A.) is embedded in the silver plate (Fig. 1A). The thermoelectric chip is controlled by a PID controller (Yamatake Corp., Tokyo, Japan). Each PID value was selected by automatic tuning of the controller to minimize overshooting or undershooting of a target temperature. The temperatures of the brain surface were cooled to 20, 15, and 10°C. Heat from the thermoelectric chip was transferred via a copper-made heat sink (6 × 6 mm with a thickness of 4 mm; see Imoto et al., 2006; Tanaka et al., 2008; Fujioka et al., 2010). The heat sink, with two water channels inside, was connected to the heat processing component via medical catheters (TYGON, R-3603, Saint-Gobain Performance Plastics, Akron, OH, U.S.A.) filled with Ringer's lactate. The

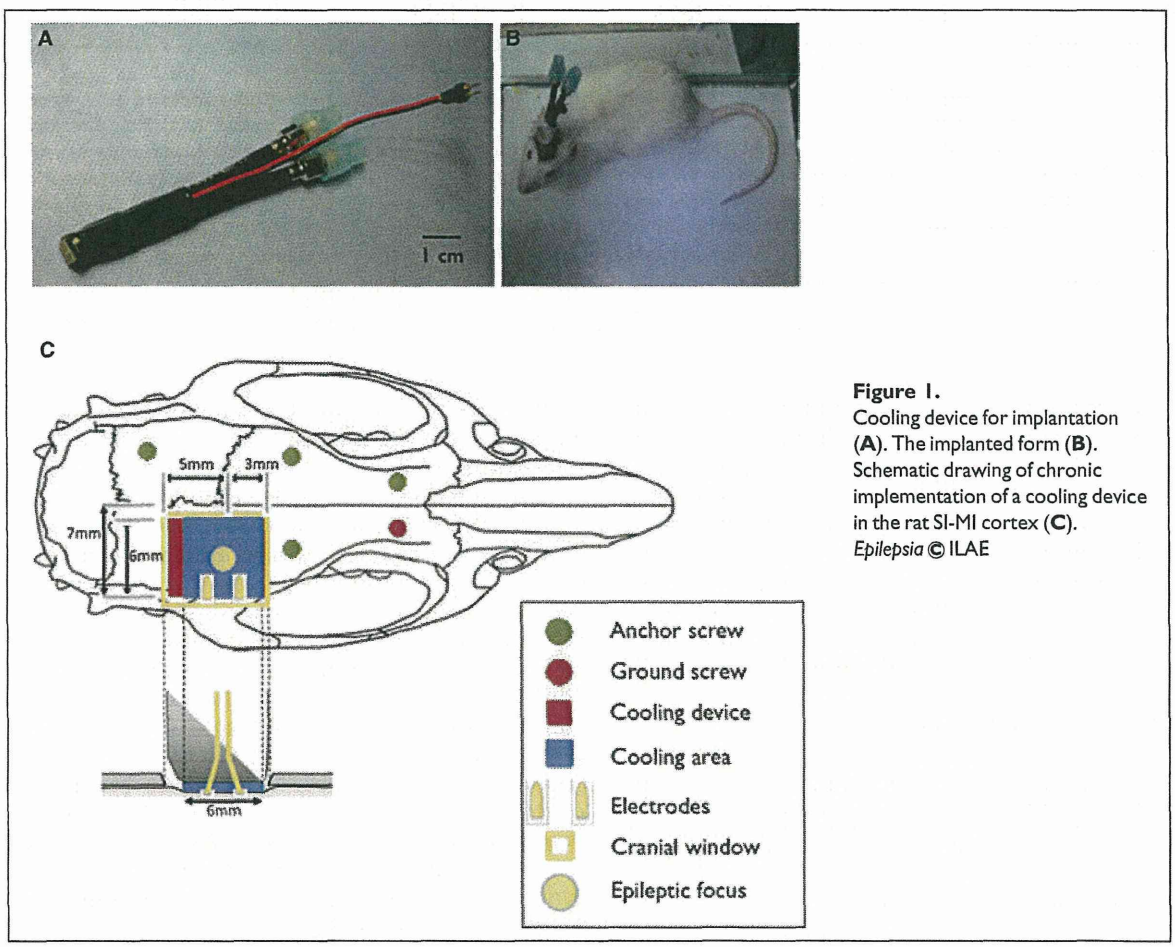

Figure 1.
Cooling device for implantation (**A**). The implanted form (**B**). Schematic drawing of chronic implementation of a cooling device in the rat SI-MI cortex (**C**).
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heat-processing component includes a helium-gas cooler (TwinBird Corp., Tsubame, Japan) and a direct current (DC)-driven pump (flow rate of 200 ml/min), which circulates Ringer's solution at a controlled temperature of 20°C. Cooling was started manually in the current study.

Focal seizure and epilepsy models

Animal experiments were performed using protocols approved by the Yamaguchi University School of Medicine Institutional Animal Care Committee. Male Wistar rats (Chiyoda Kaihatsu Co. Ltd., Tokyo, Japan) (450 ± 50 g) housed in a temperature-controlled room (23.0 ±2.0 °C) were used in the study (n = 29 in total). Following induction of anesthesia by 4% sevoflurane, atropine (0.01 mg/kg) was injected subcutaneously and a mixture of ketamine (40 mg/kg, i.m.) and xylazine (4 mg/kg, i.m.) was administered for maintenance of anesthesia. The rectal temperature was maintained at 37 ±0.2 °C using a heating pad. The skull of the rat was fixed using a stereotactic apparatus (Narishige, Tokyo, Japan) and the skin on the skull was cut following injection of lidocaine (2%). A craniotomy was made with a dental drill over the ipsilateral sensorimotor (SI-MI) area (1.5–7.5 mm lateral, 3.0 mm anterior, and 4.0 mm posterior to the bregma). The cooling device was implanted and fixed in place with medical resin (Unifast II; GC Corp., Tokyo, Japan). The cooling component (6.0 × 6.0 mm) cools the entire somatotopic representation center, except for the tongue and lips, in rats (Fig. 1B,C) (Hall & Lindholm, 1974).

We used a focal seizure model (n = 12) and a focal epilepsy model (n = 6) for induction of focal seizures limited to the unilateral forepaw area. Rats with seizures outside the forepaw area were excluded from the study. Focal seizures were induced by intracortical infusion of a 4% NaCl solution of penicillin G (PG) using a syringe pump (0.3 μl/min at a concentration of 200 IU/μl, up to 1,200 IU) until continuous seizures were stably but minimally induced. Intracortical infusion was performed using a fine needle (28 gauge) with a tip length of 0.8 mm, which was attached to the center of the cooling component. The needle was stereotactically implanted on the eloquent area (i.e., the forepaw area of the sensorimotor [SI-MI] cortex at a depth of 0.8, 1.0 mm anterior, and 3.6 mm lateral to the bregma) using medical resin. Once seizures were induced, experiments were performed within 30 min. The frequency of seizures was stable over this time window. To investigate the effect of cooling when the seizure focus extends out of the forelimb area, >1,200 IU (up to 2,200 IU) of PG solution was also applied (n = 3).

Focal epilepsy was induced by direct application of cobalt powder on the same area of the cortex (Dow et al., 1962). Following a small craniotomy made with a dental drill, cobalt powder (8 mg; Sigma-Aldrich Co. LLC., Tokyo, Japan) was applied on the dura over the eloquent cortex. A sterilized cotton sheet was placed and the skin was sutured. Following a recovery period of 3 days, the rat was reanesthetized and the cooling device was implanted using dental resin at the center of the forepaw area, which became an epileptic focus. Cooling experiments were performed at 9 ± 2 days after implantation.

Neurologic assessments

The effect of cooling on the frequency of seizures before and during cooling was evaluated by the number of involuntary lifts of the forepaw from the floor in 3 min for both the focal seizure and epilepsy models. All tests were recorded by video camera (60 frames/s) and forepaw lifting was evaluated blindly by at least two of four researchers. Comprehensive neurologic functions before and during cooling were assessed on a 21-point neurologic scale, which was originally developed for assessment of a cerebral ischemia model in rodents (Hunter et al., 2000). This scale comprises a battery of 10 items: assessment of paw placement, righting reflex, ability to grip a horizontal bar, time on an inclined platform, rotation, visual forepaw reaching, circling, contralateral reflex, motility, and general condition. This kind of scale is commonly used in behavior assessments of rats (McGill et al., 2005). The assessment was performed three times within 30 min in the current study.

Sensorimotor functions of the limbs were investigated in foot-fault tests and according to the receptive field size in the forepaw area. Foot-fault tests were evaluated using the following formula: (foot faults *per* limb/steps *per* limb) × 100 (Soblosky et al., 1996). The rat was placed gently on an elevated grid and the number of slips into the grid (i.e., foot faults) in 25 paired steps was calculated. The trial was performed three times and mean scores were calculated. Sensory function was evaluated by measuring the receptive field (RF) size of the forepaw area contralateral to the cooling cortex (layer iv; depth 450–800 μm) under the ketamine anesthesia described above (n = 5) (Fujioka et al., 2004). Tactile stimuli were applied on the forepaw areas of the skin (40 points) with von Frey hair-type probes (calculated force of 0.6 g) before and during cooling. The number of reaction fields was counted and defined as the RF size. All behavioral experiments were performed at cooling temperatures of 20, 15, and 10°C. All tests were also recorded by video camera (60 frames/s) and were evaluated blindly by at least two of four researchers.

Electrocorticography

An electrocorticography (ECoG, 1 Ch) over the epileptic focus in all rats was differentially recorded using a pair of needle-type electrodes (impedance 500 kOhm at 500 Hz) attached to the bottom of the cooling device (Fig. 1C). Data were amplified and recorded in Powerlab (ADInstruments, Colorado Springs, CO, U.S.A.) with a sampling rate of 2 kHz (low-cut filter 5 Hz, high-cut filter 100 Hz).

Electrocardiography (ECG)

Before implantation of the device, the skin of the right chest was incised in the supine position and a telemetry system (PhysioTel, DSI, St. Paul, MN, U.S.A.) was implanted in normal rats (n = 4) and in normal sham rats with a cooling device implanted in the brain (n = 4). Two-lead ECG was sampled at 2 kHz with a duration of 1 min and recorded in a PC via a Powerlab instrument (ADInstruments).

Histology

Following the experiments, the rats were sacrificed and hematoxylin and eosin (H&E) staining was performed (5-μm sections).

Statistics

Statistical analyses were performed by paired Student *t*-tests, Dunnett post hoc tests, or Steel-Dwass tests using the R software package (see the homepage; http://www.R-project.org.). $p < 0.05$ was considered to be statistically significant. Analysis of variance (ANOVA) was performed to evaluate the significance of differences between the means of all groups. A Dunnett test or Steel–Dwass post hoc test for multiple comparisons was used to compare groups with parametric or nonparametric data and unequal sample size or sample variance. Data are shown as the mean ±standard deviation (SD) in Student *t*-tests and Dunnett tests, and as the mean ± standard error of the mean (SEM) in the Steel–Dwass test.

Results

Temperature gradient of the cooling area

The temperature gradient under the cooling device was evaluated thermographically on an agar surface warmed to 37°C. This surface was cooled to 20°C with the cooling device (6 × 6 mm). The cooling effect was limited to the contact area and did not reach the perimeter (Fig. 2).

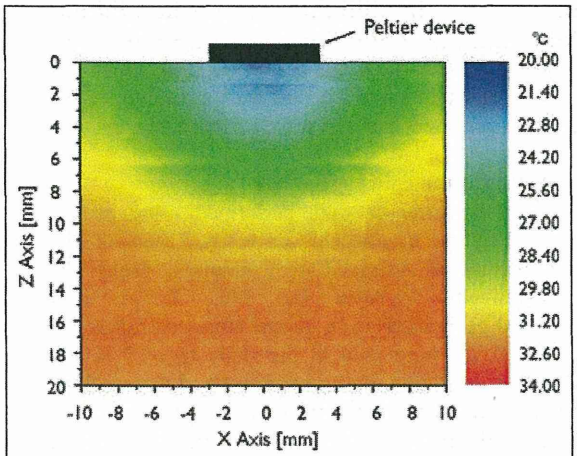

Figure 2.
Temperature gradient under the cooling device. The temperature of the cortical surface was controlled at 20°C. Note that the cooling effect was limited to the contact area and did not reach the perimeter.

Effects of cooling on focal seizures

Device implantation

The implanted device (Fig. 1A–C) did not influence ordinary behaviors in sham rats, such as eating, moving, grooming, or sleeping. ECG did not show any cooling-associated changes in rate rhythms (194 ± 6.32 in normal rats vs. 198.5 ± 14.73 in normal sham rats, $p = 0.65$ by Student *t*-test) and did not induce arrhythmia before, during, or after cooling. Although cooling to a target temperature was achieved without overshooting or undershooting, such precise temperature control was generally obtained at the cost of time. The times to reach the target temperatures of 20, 15, and 10°C were 9 ± 0.2, 12 ± 0.4, and 20 ± 0.4 s, respectively (mean ± SD, each n = 4).

Focal seizure model

Intracortical application of a PG solution reliably induced focal seizures limited to the unilateral forelimb area. Cooling of the seizure focus immediately and significantly reduced the frequency of seizures per minute at surface brain temperatures of 20°C (48.7%, $p < 0.0001$), 15°C (11.8%, $p < 0.0001$), and 10°C (0%, $p < 0.0001$), in comparison to the noncooling ictal group (100%, n = 6, Fig. 3A). The reduction of the seizure frequency was coincident with the suppression of epileptic discharges (EDs) in the ECoG (Fig. 4A,D). The effect of cooling-induced seizure suppression was continuous and was not diminished as long as cooling was performed. There was no apparent difference in the extent of suppression between rapid and slow cooling to a target temperature.

The significant reduction of the seizure frequency was also associated with improvement of neurologic scores within the range of 20–15°C. Induction of seizures caused a significant deterioration of neurologic scores (15.6 ±0.43, $p = 0.023$). These scores were improved to 18.33 ± 0.21 at 20°C ($p = 0.027$) and 19.5 ± 0.22 at 15°C ($p = 0.029$), compared to those of the noncooling group (Fig. 3B). These effects disappeared soon after cessation of cooling. Cooling to 10°C also achieved a seizure-free condition, but neurologic scores remained low (15.93 ± 0.21, $p = 0.979$). Additional injection of a PG solution (>1,200 IU) induced seizures outside the forelimb area, which made it impossible to inhibit seizures in the forelimb area, as well as in areas outside the forelimb (Fig. 4B,E).

Implantation of the device for 1 month with 1 h cooling per day did not result in detrimental changes in H&E

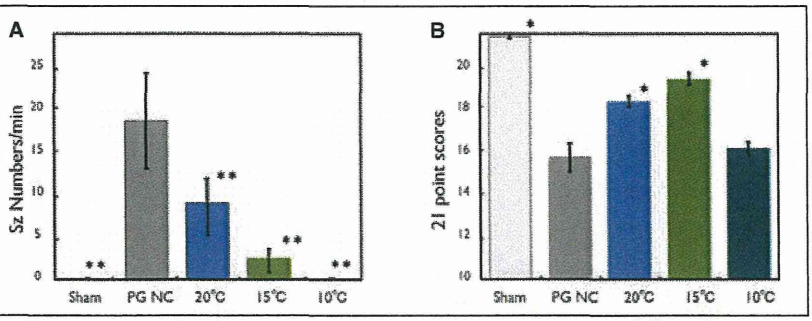

Figure 3.
Frequency of seizures (**A**) and neurologic scores (**B**) as a function of temperature at the seizure foci. PG, penicillin G; NC, noncooling. Error bars: SD in **A**, SEM in **B**. *p < 0.05. **p < 0.01 versus non-cooling groups (n = 6).
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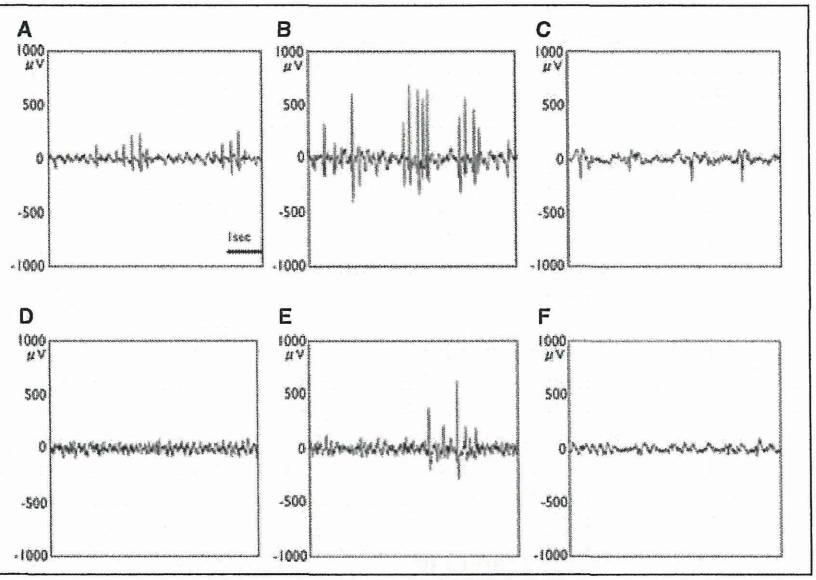

Figure 4.
Epileptic discharges (EDs) before (**A–C**) and during cooling at 15°C (**D–F**) at the seizure focus in penicillin G (PG)–treated (**A,B,D,E**) and cobalt-treated (**C, F**) rats. Suppression of EDs was associated with amelioration of seizure frequency when a seizure focus was in a cooled area—before (**A**) and during (**D**) cooling at 15°C. When the seizure focus extended outside the cooled area due to excess application of PG, EDs were not completely terminated at temperatures down to 15°C (**B, E**). Suppression of EDs also occurred during cooling in a cobalt-treated rat (**C, F**).
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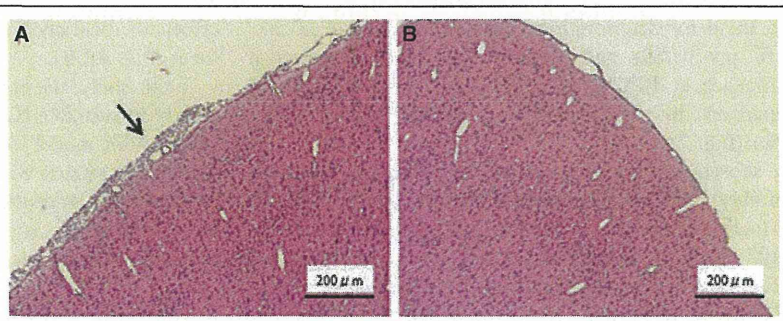

Figure 5.
Following implantation of the device for 1 month, partial fibrosis was observed in the subarachnoid of the cortex, but was limited to the area under the device (shown by an arrow). No histologic changes were observed in the contralateral homologous area.
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staining (n = 5), except for partial fibrosis of the subarachnoid region under the device (Fig. 5).

Focal epilepsy model

Cobalt-induced epileptic seizures limited to the unilateral forelimb area were sufficiently severe and continuous to be suggestive of a state of epilepsia partialis continua. The number of seizures per minute in the cobalt model was double that in the PG model. Seizure frequency was reduced in association with improvement of neurologic scores in a cooling range of 20–15°C and was coincident with suppression of EDs during cooling (Fig. 4C,F). The frequency of seizures per minute was reduced by 54.4% at 20°C ($p < 0.0001$), 3.9% at 15°C ($p < 0.0001$), and 0% at 10°C ($p < 0.0001$) (Fig. 6A). The significantly lower neurologic scores under noncooling, ictal conditions (14.5 ±0.34,

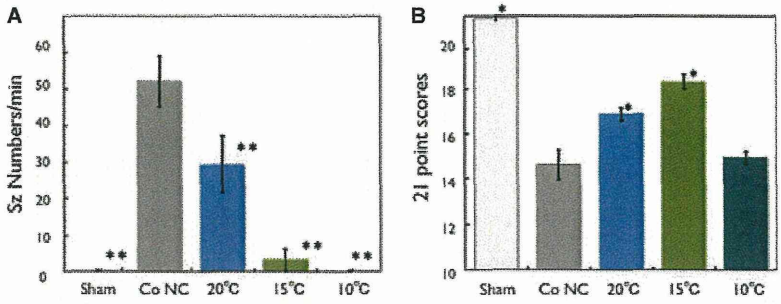

Figure 6.
Frequency of seizures (**A**) and neurologic scores (**B**) as a function of temperatures. Co, cobalt; NC, noncooling. Error bars: SD in **A**, SEM in **B**. *$p < 0.05$. **$p < 0.01$ for ictal rats (n = 6) versus noncooling groups (n = 6).
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p = 0.023) were improved by 16.88 ± 0.28 at 20°C (p = 0.027) and 18.38 ± 0.2 at 15°C (p = 0.029, Fig. 6B), in comparison with the noncooling group (n = 6). As in the PG model, cooling to 10°C did not improve the neurologic scores (14.88 ± 0.41, p = 0.979, Fig. 6B). The therapeutic effect was not diminished as long as cooling was performed.

Histology in cobalt-treated rats shows bowl-shaped necrotic changes (Dow et al., 1962), which were limited to the shallow cortex in our study. There were no other particular cooling-associated changes.

Effects of cooling on neurologic functions

Because neurologic improvement was limited in the cooling ranges of 20–15°C, we hypothesized that cooling below 15°C induced excessive blockage of synaptic transmission. Therefore, we investigated the effects of cooling on normal neurologic functions in sham rats. Apparent neurologic deficits in ordinary behaviors (walking, eating, grooming, and so on) were not observed by cooling to 15°C. Neurologic functions (n = 6) were robust with cooling to 20°C (20.9 ± 0.06, 99.8%, vs. sham group, p = 0.92), but a trend for deterioration began at 15°C (20.6 ±0.20, 98.1%, p = 0.089), and these changes reached statistical significance at 10°C (18.2 ± 0.21, 86.7%, p = 0.012), in comparison to the noncooling group (20.95 ±0.05, 100%) (Fig. 7A).

A subsequent investigation of sensorimotor functions invariably revealed significant deterioration at 15°C. In foot-fault tests (n = 6), cooling to 20°C did not induce substantial changes (% error of 1.1 ± 1.31%, p = 0.957), but the findings reached statistical significance at 15°C (3.34± 0.73%, p = 0.018) and 10°C (18 ± 3.45%, $p < 0.0001$, Fig. 7B). In anesthetized sham rats (n = 5), RFs of the forepaw under the cooling area began to diminish at 20°C (84.1%, p = 0.099) and reached statistical significance at 15°C (30.6%, $p < 0.0001$) and 10°C (1.2%, $p < 0.0001$), in comparison to the noncooling group (100%) (Fig. 7C).

Discussion

This study provided important evidence for a therapeutic effect of low temperature on focal seizure and epilepsy in an animal model. The results build on findings in previous studies (Yang & Rothman, 2001; Rothman et al., 2005; Yang et al., 2006; Rothman, 2009). Temperatures from 20°C down to 15°C significantly suppressed seizures and were associated with improvement of neurologic function. The effect was powerful, instantaneous, and continuous, which suggests advantages over other existing epileptic therapies.

Limitations and feasibility of focal brain cooling for epilepsy treatment

An indication of focal brain cooling for focal epilepsy requires accurate identification of epileptic foci of a size that is well within the cooling area. These conditions were produced in two animal models. The PG model of focal seizure allows adjustment of the size and extent of seizures (Elger & Speckmann, 1983). Therapeutic effects were obtained when the focal seizure was within the cooling area. However, application of PG >1,200 IU caused the focal seizures to no longer be limited to the forelimb, but to extend over the hind limb and body. In such cases, the suppressive effects of focal cooling were limited, even in the epileptic focus (Fig. 4B,E).

In our study, the epileptic focus in the cobalt model was clearly identifiable (Chang et al., 2004). The epileptic seizures in this model were more severe than those in the PG model, but seizure control was as prominent as that in the PG model. Therapeutic temperatures were also identified in the cobalt model, suggesting the feasibility of focal brain cooling as therapy for focal epilepsy.

Factors influencing the therapeutic cooling temperature

The results of the study show that therapeutic temperatures are not uniquely defined, but are changed by factors such as seizure severity and the size of the focus. Other factors that can influence the therapeutic temperatures include antiepileptic drugs (AEDs) and neuroplasticity. We did not use AEDs in the study, but the assumed synergistic effects of AEDs during cooling (Sourek & Travnicek, 1970) may increase the upper limit of the therapeutic temperature. Another important aspect of focal brain cooling is the involvement of functional compensation, presumably due to

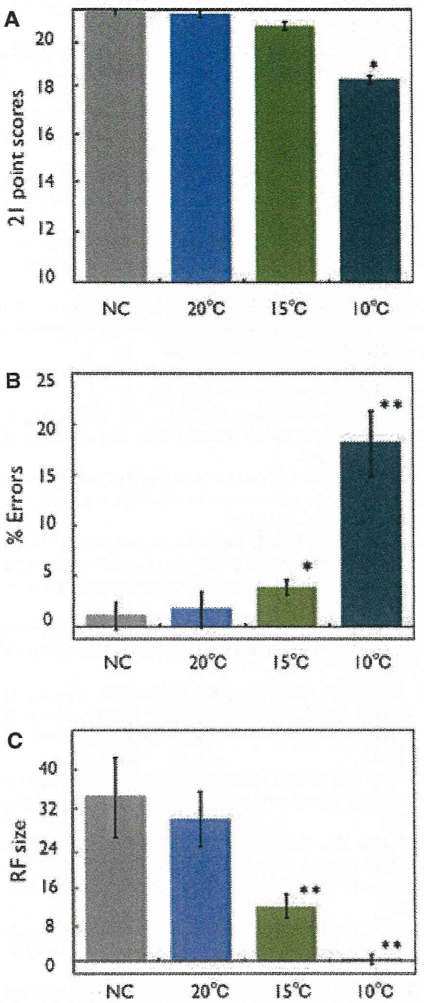

Figure 7.
Temperature-dependent changes in neurologic scores (**A**, n = 7), foot-fault tests (% errors; **B**, n = 6) and sizes of receptive fields (RFs; **C**, n = 5). Error bars: SD. *p < 0.05. **p < 0.01 versus noncooling groups.

behavioral adaptation or neuronal plasticity. This property has been reported in a series of studies in normal monkeys, wherein cooling-induced functional deficits began to be ameliorated over a time course of months (Sasaki & Gemba, 1984; Brinkman et al., 1985). Identification and evaluation of these factors are important issues that remain to be addressed.

Determination of the therapeutic cooling temperature

Our data showed that cooling to 15°C reliably suppressed focal seizures and improved neurologic function (21-point scores), but a detailed investigation of sensorimotor functions (foot-fault tests and receptive field size) in normal sham rats revealed significant deterioration. Clinicians who place an emphasis on seizure suppression may prefer lower therapeutic temperatures at the cost of functional deterioration, whereas those who wish to avoid neurologic dysfunction may prefer higher therapeutic temperatures. Therefore, determining the therapeutic temperature in patients with epilepsy will depend not only on objective criteria but also on subjective criteria that maximize the quality of life.

Mechanism of seizure suppression by focal brain cooling

Focal brain cooling is generally considered to induce reduction of transmitter release (Eilers & Bickler, 1996), kinetic alteration of voltage-gated ion channels (Traynelis & Dingledine, 1988; Hill et al., 2000; Volgushev et al., 2000), and network desynchronization (Javedan et al., 2002). Although the precise antiepileptic mechanisms remain to be determined, it is generally recognized that suppression of synaptic transmission is involved in reduction of seizures. An in vitro study showed that synaptic transmission begins to decrease below 20°C (Volgushev et al., 2000). In a case in which the temperature is <20°C at 1 mm under the cortical surface, but >20°C at a depth of 2 mm, it is reasonable to assume that synaptic transmissions and EDs in the shallow cortex (layer II/III) are selectively suppressed because of the spread through neurons in the shallow layer with horizontal connections to the ipsilateral or contralateral cortex (Nolte, 2009). Selective suppression of synaptic transmission due to a cooling-induced thermogradient in the cortex may contribute to the vulnerability of somatosensory processing, as indicated by the reduction of RFs during cooling. Because the neurons that form a pyramidal tract (layer V) lie deep in the sensorimotor cortex, selective transmission failure may have occurred during surface cooling.

Histologic assessment

Pathologic changes due to cooling were not observed in the PG and cobalt models. Although partial fibrosis under the cooling device did occur, this was probably not caused by cooling, given the histologic tolerance to focal brain cooling even down to 5°C (Yang et al., 2006; Oku et al., 2009). Rather, it is likely that this histologic change was caused by direct contact with the cooling part of the device (i.e., pure silver) because inflammation of the contact area cannot be avoided under free-moving conditions.

Clinical advantages and requirements of the cooling device

Temperature control is of crucial importance in therapeutic applications, given that the range of therapeutic temperatures is narrow and that a small deviation from this range may lead to neurologic dysfunction. Furthermore, varying brain temperatures in the ictal stage may further complicate temperature control. In this regard, thermoelectronic

devices have an advantage over traditional circulatory-cooling devices, since the thermoelectronic devices are small but have sufficient cooling power and precise temperature control. An alternative approach using systemic hypothermia has been used in refractory status epilepticus (Corry et al., 2008), but clinical use of this method is limited by adverse effects and limitations on the cooling temperature (31–35°C) and period.

Clinical demand for an implantable cooling device will not be limited to the epileptic field. Other potential applications include treatment for cerebrovascular diseases, including poststroke rehabilitation (Clark & Colbourne, 2007), neurotrauma (Clark & Colbourne, 2007), and pain (Fujioka et al., 2010), all of which will depend on thermal modulation of neuronal excitability.

Application of the cooling device for treatment of epilepsy

Focal brain cooling may be applied therapeutically for patients who have an epileptic focus on the eloquent cortex (i.e., motor or language area) or those who cannot be treated with AEDs. Cooling may also be used as a diagnostic tool in intracranial ECoG monitoring of patients with potential neurosurgical indications, but in whom the focus cannot be clearly defined. In such cases, the final surgical indication would be decided by preliminary application of cooling to the focus. There are several physiologic and technical issues to be solved before the device can be applied in intractable epilepsy. However, this study is an important step toward medical use of an implantable hypothermal device for treatment of focal epilepsy and other neurologic disorders.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Significance of Differences Between Brain Temperature and Core Temperature (Delta T) During Mild Hypothermia in Patients With Diffuse Axonal Injury

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Abstract

The differences between brain and bladder temperature (delta T), and the relationship of delta T to cerebral perfusion pressure (CPP) and jugular venous oxygen saturation (SjO_2) were studied during hypothermia in 11 patients with severe traumatic brain injury, of whom 5 underwent conservative treatment for diffuse axonal injury (DAI) (DAI group) and 6 who underwent decompressive craniectomy for hematoma (SDH group). All patients underwent hypothermia treatment. Brain temperature was monitored via an intraparenchymal catheter. Bladder temperature was used as the core temperature. SjO_2 was measured continuously. The outcome of all patients was evaluated at discharge using the Glasgow Outcome Scale. Delta T in the SDH group was significantly lower than that in the DAI group. No relationship was found between delta T and CPP during the investigation period. A significant correlation between delta T and SjO_2 was seen in the DAI group, but not in the SDH group. Decompressive craniectomy affects the brain temperature through external environmental factors. Measurement of brain temperature may be a reliable indicator of cerebral blood flow and brain metabolism in patients with DAI and closed cranium during hypothermia. Further experience is required to test this proposal.

Key words: brain temperature, cerebral perfusion pressure, decompressive craniectomy, jugular venous oxygen saturation, traumatic brain injury

Introduction

Hypothermia is known to provide neuroprotection after traumatic brain injury (TBI).[4,10,15] Therapeutic cooling of the brain prevents the release/diffusion of excitatory amino acids,[2,19] nitric oxide synthesis,[14] and disruption of the blood-brain barrier.[16] However, only body temperature measurement is not sufficient to infer the actual temperature of the brain under clinical conditions.[11] The brain temperature fluctuates under physiological and pathophysiological conditions, providing an indicator of changes in brain metabolism, cerebral blood flow (CBF), external environment, neuronal damage, and brain function.[1,9] Recently, technologies have been developed for measuring brain temperature directly, leading to a better understanding of the intracranial physiological state. Adequate brain temperature monitoring is also important for achieving efficient hypothermia. At present, jugular bulb temperature is used frequently for brain temperature monitoring, because of the ease of access. However, the various sites commonly used for temperature monitoring, such as the bladder, tympanic membrane, esophagus, pulmonary artery blood, and jugular bulb, may show discrepancies.[7,18] Recently, the significance of differences between brain temperature and core temperature (delta T) has attracted attention. The brain temperature of patients with TBI can differ significantly from body temperature,[20] suggesting that this temperature difference might provide useful prognostic information. Furthermore, the difference between brain and rectal temperature is correlated with CBF and outcome.[17] Decompressive craniectomy is frequently performed for relief of medically refractory intracranial pressure (ICP) caused by severe brain edema, and has large effects on regional blood flow, metabolism, and heat ex-

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change.[21] Therefore, the effect of decompressive craniectomy must be considered in monitoring brain temperature.

The present study examined the difference between brain and bladder temperature, and the relationship to cerebral perfusion pressure (CPP) and jugular venous oxygen saturation (SjO_2) in patients undergoing hypothermic therapy with or without decompressive craniectomy.

Materials and Methods

Brain temperature monitoring was performed in 11 patients after severe TBI with a Glasgow Coma Scale (GCS) score of 8 or less on admission. The 10 male patients and one female patient were aged 15 to 73 years (mean 44.5 years). Five patients underwent conservative treatment for diffuse axonal injury (DAI). Six patients underwent decompressive craniectomy for evacuation of subdural hematoma (SDH) or contusional hematoma. The outcome of all patients was evaluated at discharge using the Glasgow Outcome Scale. All patients or family gave informed consent to the procedures.

Anesthesia was induced using midazolam (0.2 mg/kg). Muscle relaxation was achieved with vecuronium bromide (0.1 mg/kg). Anesthesia was maintained with midazolam (0.2–0.4 mg/kg/hr), butorphanol tartrate infusion (0.02–0.04 mg/kg/hr), and vecuronium bromide infusion (0.05 mg/kg/hr) during hypothermia. After intubation, ventilation was mechanically controlled to maintain the $PaCO_2$ within the range 30–35 mmHg. All patients received medical management to maintain the ICP below 20 mmHg, and the mean CPP above 70 mmHg. If necessary, vasopressor agents such as dopamine were used to support blood pressure, or glycerol was used to reduce ICP.

All patients underwent hypothermia using water-cooling blankets. The brain temperature was reduced to 33°C or 35°C, then maintained at this level for at least 3 days, depending on the individual patient's ICP. After hypothermia, the patients were rewarmed slowly at a rate not exceeding 0.5°C/day.

An ICP sensor (Camino Laboratories, San Diego, California, USA) was carefully inserted into the brain tissue (right frontal lobe) to measure ICP and brain temperature. The probe was placed 2–2.5 cm from the brain surface, and the ICP and brain temperature were measured continuously. The accuracy of the temperature measurement was ±0.3°C. Using a retrograde internal jugular vein approach, a 5.5 Fr Opticath (Dainabot, Tokyo) was inserted into the internal jugular vein via a 6 Fr introducer sheath. The catheter was then advanced to the jugular bulb. The correct position of the catheter tip was checked radiologically. The SjO_2 and the internal jugular vein blood temperature were measured continuously. SjO_2 was corrected by measurement of blood sampled from the internal jugular vein at least once per day. Bladder temperature was measured continuously with a commercially available thermocouple (Terumo®, Tokyo) for core temperature. The accuracy of the temperature measurement was ±0.3°C (32–40°C). Water at 32°C or 35°C measured with a mercury thermometer was also found to be at the same temperature using the ICP sensor and the thermocouple for bladder temperature. The hemodynamic monitoring included continuous measurements of arterial blood pressure, heart rate, and peripheral oxygen saturation.

All clinical parameters, including arterial blood pressure, ICP, SjO_2, brain temperature, and bladder temperature, were recorded every hour from all patients. These data were used as parameters every 8 hours during the hypothermic period when the brain temperature was below 36.0°C. The patients were classified into two groups based on the therapeutic treatment given: DAI group, 5 patients with conservative treatment; SDH group, 6 patients with decompressive craniectomy.

In the first analysis, the temperature difference (delta T) between the brain and bladder was used. Differences between the mean delta T in the DAI and SDH groups were examined with the unpaired *t* test. In the second analysis, CPP was calculated with the mean arterial blood pressure and ICP. The correlation between delta T and CPP or SjO_2 was studied with Pearson's linear regression method. Differences were considered statistically significant at $p < 0.05$.

Results

The mean delta T of all patients was −0.17 ± 0.02 °C (mean ± standard error of the mean). The mean delta T in the SDH group (−0.23 ± 0.03) was significantly lower than that in the DAI group (−0.08 ± 0.04) ($p = 0.0021$). No relationship was found between delta T and CPP during the investigation period (Fig. 1). Figure 2 illustrates the relationship of delta T to SjO_2. A significant correlation between delta T and SjO_2 was seen in the DAI group ($R = 0.438$, $p = 0.0004$). However, no such correlation was found in the SDH group. The clinical outcomes of patients in the DAI group were good recovery in 1 case, moderate disability in 2, and persistent vegetative state in 2. The outcomes in the SDH group were moderate disability in 1 case, severe disability in 3, and persistent vegetative state in 2.

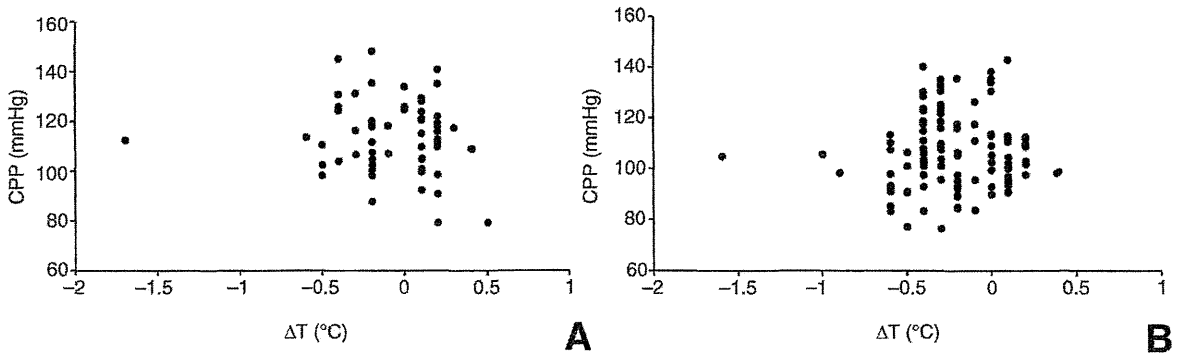

Fig. 1 Relationships between brain and bladder temperature difference (delta T) and cerebral perfusion pressure (CPP) in 5 patients who underwent conservative treatment for diffuse axonal injury (DAI group, A) and 6 patients who underwent decompressive craniectomy for evacuation of subdural hematoma (SDH group, B).

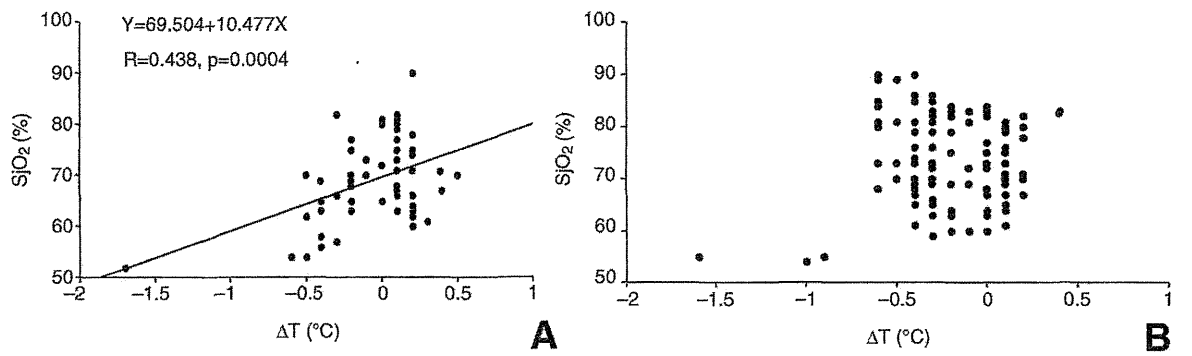

Fig. 2 Relationships between brain and bladder temperature difference (delta T) and jugular venous oxygen saturation (SjO_2) in 5 patients who underwent conservative treatment for diffuse axonal injury (DAI group, A) and 6 patients who underwent decompressive craniectomy for evacuation of subdural hematoma (SDH group, B).

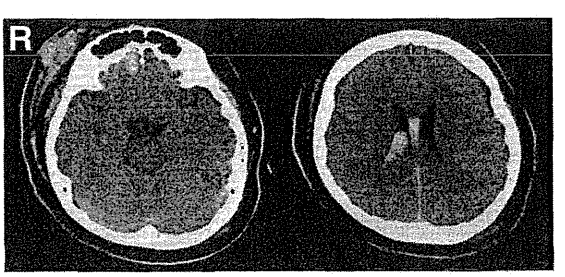

Fig. 3 Representative case. Computed tomography scans on admission showing intraventricular hemorrhage and contusion in the right frontal lobe.

Representative Case

A 17-year-old male was involved in a motor vehicle accident and was admitted to our hospital with disturbed consciousness of GCS score 6 (E1, V1, M4). Computed tomography showed intraventricular hemorrhage and a small contusion in the right frontal lobe (Fig. 3). He underwent conservative treatment with hypothermia therapy with neuromonitoring. On Day 4, ICP suddenly elevated and SjO_2 decreased. At the same time, delta T gradually decreased (Fig. 4). After appropriate ICP treatment, SjO_2 recovered. Correspondingly, delta T also increased (Fig. 4).

Discussion

Increasing amounts of evidence indicate that brain temperature is higher than core temperature in patients with acute neurological injuries. However, brain temperature was lower than bladder temperature in most of our patients. This study measured brain temperature with intraparenchymal catheters

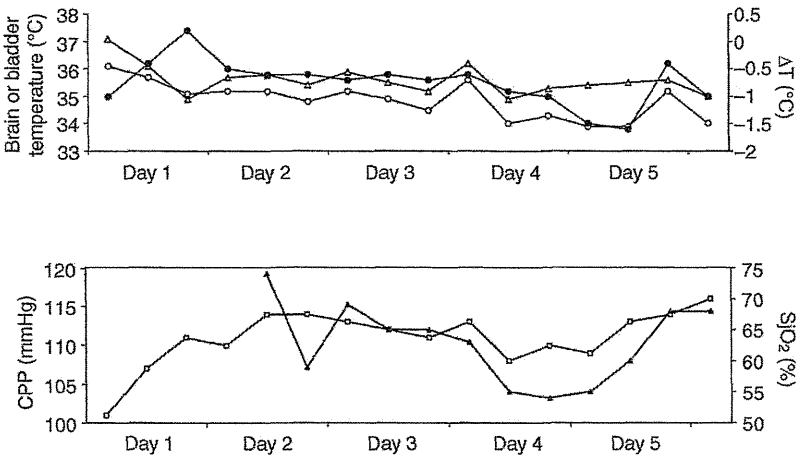

Fig. 4 Representative case. Graph showing changes in neuromonitoring during hypothermia therapy. ○: brain temperature, △: bladder temperature, ●: brain and bladder temperature difference (delta T), □: cerebral perfusion pressure (CPP), ▲: jugular venous oxygen saturation (SjO_2).

at a depth of 2–3 cm from the brain surface. Many clinical studies have used intraventricular catheters for brain temperature measurement. Brain temperature is known to increase gradually, with a significant correlation with depth.[6] The highest temperature is found in the lateral ventricle, which is 1.2°C higher than the intraparenchymal temperature. This difference between intraventricular and intraparenchymal temperatures may have caused the inverse findings for the temperatures of the brain and bladder in this study. Alternatively, this inversion of the brain and bladder temperatures may have resulted from ischemia induced by low CBF, decreased cerebral metabolic demand, or changes in hypothalamic regulation due to pharmacological treatment (sedation, paracetamol) during hypothermia.[17]

This study found that the difference between brain and bladder temperatures in the SDH group was significantly lower than that in the DAI group, possibly because the brain temperature in the DAI group was increased by the higher cerebral metabolism and CBF induced by DAI. In addition, the brain temperature in the SDH group may have been influenced by environmental factors. Only intraparenchymal temperature fluctuated greatly after opening of the dura and during active cooling, whereas all other temperatures (jugular bulb, tympanic membrane, esophagus, bladder, pulmonary artery) remained at similar levels.[5] However, intraparenchymal brain temperature in a closed cranium remains constant, with no cooling effect from the environment.[8] Thus, brain temperature in an opened cranium may be influenced by environmental factors, and only brain temperature in a closed cranium will accurately reflect global brain temperature without environmental influences.

An animal study has shown that cerebral blood temperature changes are closely related to CPP.[3] A decrease in cerebrovenous temperature would be induced by decreased CBF via reduced exchange of thermal energy from arterial blood to the cerebral component. Therefore, brain temperature is influenced by CBF. Some studies have looked at the differences between brain temperature and core temperature in a clinical setting, since the introduction of technology for direct measurement of brain temperature.[5,12,17,20] Brain temperature was much higher than rectal temperature if CPP was reduced to between 50 and 20 mmHg, indicating impaired CBF.[13] Furthermore, this difference decreased significantly as CPP was reduced to below 20 mmHg, indicating irreversible impairment of CBF. These findings may show that decreased arterial blood flow reduced "wash out" of the heat generated by brain metabolism with CPP between 50 and 20 mmHg. With CPP under 20 mmHg, misery perfusion induced a decreased temperature gradient. However, our results indicated no relationship between delta T and CPP. In our study, CPP was kept above 70 mmHg by therapeutic management. CBF will be influenced by factors other than CPP, so the changes in brain temperature observed in this study were not related to CPP.

Our SjO_2 findings in patients with closed cranium showed a close relationship with delta T. SjO_2 is an indicator of the balance between CBF and cerebral metabolism. As CBF exceeds the cerebral metabolic rate for oxygen, SjO_2 also increases. Although we were unable to measure CBF in this study, the brain temperature and the difference between brain and core temperature are both largely dependent on CBF.[17] Therefore, the increased temperature difference reflects the higher SjO_2 resulting from increased CBF. These findings suggest that measurement of brain temperature is a good indicator of

CBF and cerebral metabolism, and can be used easily at the bedside. However, this relationship was not found in patients with decompressive craniectomy, since the brain temperature will be influenced by the environment in these patients. Furthermore, the physiological and pathophysiological conditions in SDH or contusional hematoma are not uniform spatially or chronologically. In contrast, since the conditions in DAI are uniform, both the brain temperature and SjO_2 are good indicators of the condition of the whole brain.

The present study demonstrated that the mean delta T in the SDH group was significantly lower than that in the DAI group. Therefore, decompressive craniectomy influences the brain temperature through environmental factors. Furthermore, we found a close relationship between delta T and SjO_2 in DAI patients with closed cranium. Measurement of brain temperature may be a reliable indicator of CBF and brain metabolism in DAI patients with closed cranium during hypothermia. However, only a small number of cases were examined in this study, and further experience is required to confirm these findings.

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特集 頭部外傷 update

頭部外傷に対する低体温療法の適応と限界

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Application and Limitations of Hypothermia Therapy for Traumatic Brain Injury

by

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No treatment method for severe traumatic brain injury (TBI) has proven effective to replace hypothermia therapy, emphasizing the major role of this therapy for patients with TBI. To improve the effectiveness of hypothermia therapy, earlier hypothermia induction is necessary, and management of brain temperature should be based on individual pathophysiology through neuromonitoring during the maintenance and rewarming periods of this therapy. Recently, the protective effects of hypothermia therapy have been confirmed for patients with severe TBI after craniotomy. The outcome of TBI patients with hypothermia therapy is expected to improve with the use of the brain temperature management method and selection of appropriate pathophysiology.

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Key words: traumatic brain injury, hypothermia, neuromonitoring, brain temperature

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はじめに

頭部外傷後早期には，血腫などの占拠性病変のみならず，呼吸・循環障害など全身性要素による脳血流代謝異常が二次性脳損傷の進展へと関与し，転帰に大きく寄与する[1)28)]．頭部外傷治療の主な目的は，この二次性脳損傷をできるだけ抑制し，頭部外傷患者の転帰改善につなげることである．しかし，近年の本邦における傾向としては，一次性脳損傷が大きい重症例に対して治療成績も良好とは言えないため，二次性脳損傷に対する治療法の選択やゴールを熟慮せず容易に治療を断念してしまう傾向がある．低体温療法の目的は，まさにこの二次性脳損傷を抑制することに他ならない．

本法の歴史を振り返ると，1993年に頭部外傷に対する脳保護効果に関する臨床研究が相次いで報告されて[6)25)37)]世界的に注目を浴びたが，2001年には多施設無作為対照臨床研究（NABIS：H）において有意な効果が認められず[7)]，現在は積極的に起用される治療法とは言い難い．しかし，その後も重症頭部外傷治療において低体温療法に代わる有効な治療法は出現せず，手詰まり感

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が強いのが現状である．そのためわれわれは，重症頭部外傷の治療成績を改善させるべく，低体温療法の適応や管理方法を試行錯誤している．本稿では，低体温療法の歴史的背景を振り返りながら基礎研究・臨床研究をreviewし，低体温療法の適応や管理法についての現状と今後の展望について考察する．

低体温療法の歴史的背景

低体温療法の歴史は，ギリシア時代にHippocratesが皮膚切開の前に局所表面冷却を行い麻酔として使用したのが始めとされている[12]．また，1938年にはTemple Fay (1895-1963)[11]が初めて全身冷却という手法で悪性腫瘍の増悪の抑制と除痛を目的に低体温療法を行った．第二次世界大戦後，心臓手術の分野で低体温の導入が模索されるようになり，この頃から低体温と脳損傷の関係について論議されるようになった．1956年，イヌの中大脳動脈結紮モデルを用いて，25℃以下にて脳梗塞巣の体積が有意に減少することを示した[35]のが，低体温療法の脳保護効果についての初めての報告と思われる．1960～1970年代にかけて，凍った川や池に溺水した後の蘇生例において転帰良好例が報告され[23][40]，低体温の脳保護作用が次第に注目されるようになった．しかし，現在ほど全身管理の技術や知識が豊富でない当時は，循環障害や感染症など臨床的な合併症が前面に立ち，いったんは低体温療法は影を潜めてしまった．その後1987年には，32℃の軽微低体温療法によって脳虚血モデルでの脳保護効果を示す報告があり[2]，全身合併症を最小限にとどめる管理が可能な体温であったことから，低体温療法が再び注目を集めるターニングポイントとなった．同時期，重症急性硬膜下血腫の偶発的低体温例における転帰良好例が報告され[42]，頭部外傷でも低体温療法が注目されるようになった．1991年には，実験的頭部外傷モデルにて低体温療法の脳保護効果が報告され[5]，世界各国に頭部外傷に対する低体温療法の臨床的応用が広がることとなった．1993年には米国ならびに日本から相次いで，頭部外傷に対する低体温療法の良好な結果を示した臨床研究が報告されて[6][25][37]脚光を浴びた．以降，頭部外傷に対する低体温療法に関して，基礎的ならびに臨床的研究が数多く報告された[4][7][10][13][14][22][24][27][32][41][45][50]．低体温療法の作用機序として，グルタミン酸放出の抑制のみならず，さまざまな機序が報告された．いずれの作用機序も受傷後早期から低体温療法の導入が必要とされるものである．受傷後治療導入が遅れた例でも，低体温時間の延長や緩やかな復温にて脳保護効果を拡大する報告[4][13][14][26][43]もみられ，以後の臨床応用に大きなヒントを与えている．その後，低体温療法の頭部外傷治療におけるevidenceを求めて大規模臨床研究が1994年から開始された．良好な結果が期待されたが，2001年のCliftonら[7]の報告では，頭部外傷に対して低体温療法の有効性が認められず，再び衰退の一途をたどることとなった．

低体温療法の作用機序と合併症

低体温療法の作用機序には，多くの二次性脳損傷抑制に関与した機序が含まれる．グルタミン酸放出の抑制[3]やカルシウム依存性カスケード反応の抑制[29]，脳代謝の抑制[52]，活性酸素やNO産生の抑制[18][19]，アポトーシスの抑制[51]，血液脳関門破綻の抑制[41]などが報告されている．重症頭部外傷治療に低体温療法を導入する際は，これらの機序を念頭に置いて適切な管理を行う必要がある．

また，低体温療法の導入による多くの合併症が報告されている．感染症（免疫能低下）や電解質異常（低カリウム血症），血小板減少などの他に，体温低下に伴い不整脈の出現や心拍出量の低下，それに伴う代謝性アシドーシスなど，循環器領域に関連した合併症も多い．さらには，肝機能障害や腎機能障害，消化管機能障害，高血糖などである．冷却温度が低いほど，維持時間が長いほど合併症の頻度は高いとされている．Tokutomiら[48]は，33℃と35℃の低体温療法を比較し，35℃では合併症の発現率が有意に減少し，低体温療法による効果は33℃と変わりないと報告した．それ以降，低体温療法では34℃あるいは35℃で管理する施設が多い．この温度であれば，肺理学療法や口腔ケアなどの肺炎予防策と厳重な全身管理を行えば，深刻な合併症に陥ることは少ない．

低体温療法の脳温管理

1 導入時間

低体温療法への導入時間は，より早期が望まれる．低体温療法の作用機序は，当初損傷により誘発されるグルタミン酸放出の抑制が主であると考えられ，受傷前からのpre-treatmentでのみ効果を有すると考えられていた．しかし，受傷後からのpost-treatmentでも脳保護効果が認められるようになった[4][5][10][24]ため臨床応用へと発展した．しかし，大多数の実験モデルでは，受傷直後あるいは受傷後10分程度にて低体温療法が導入されており，この点で実験モデルと臨床応用との間に乖離がある．臨床的にはCliftonら[7]によるNABIS：Hにおいて，

低体温療法は有意な脳保護効果を認めることができなかった．彼らはその二次解析の中で，低体温の導入時期の観点から搬入時に偶発的低体温であった患者群に注目した[8]．45歳以下の搬入時から偶発的低体温であった患者群においては，平温療法群での予後不良率が76%であったのに対し，低体温療法群では52%と有意に低下していた[8]．つまり，早期の導入こそが低体温療法の脳保護効果を引き出す要素であると考えた．このデータを根拠に，Clifton ら[9]は2005年より新しい臨床研究を開始した（NABIS：HII）．患者の選択基準を16〜45歳の若年者とし，受傷後2.5時間以内に臨床研究登録可能な症例とした[9]．その結果，平均4.4時間で33℃まで冷却完了が成されていた[9]．しかし，最終的な転帰では，平温療法群で予後不良率が56%，低体温療法群で60%と有意な脳保護効果を認めることができなかった[9]．基礎研究では，低体温療法の脳保護効果に関して多くの肯定的データが報告されているのに対して，臨床研究で evidence が得られないのは，受傷後超早期の低体温導入が困難である可能性がある．現在の臨床現場では NABIS：HII で示された受傷後4時間前後の低体温療法への導入が限界値ではないかと考えられる．日本では病院前救急診療として，早期医療介入による救命率の向上と転帰改善を目的として，ドクターヘリの運行が開始された．2010年10月現在，19道府県23カ所に配置され[21]，さらなる運行規模の拡大をみせている．重症頭部外傷患者においても，頭部外傷の二次性脳損傷の要因である低酸素血症や低血圧へ早期に対応し，転帰良好例が有意に多いと報告されている[36]．今後，このような病院前救急医療の改善により，治療開始時間の短縮と早期の低体温療法への導入が期待される．

2 維持時間

実験的頭部外傷モデルで低体温療法の有効性を示した報告では，その維持時間は1時間であった[5]．その後の報告では，低体温療法の維持時間は3〜6時間と長期化してきた[4)10)13)14)32)42)49]．これは，低体温維持時間の長い条件が脳保護効果に優れていた解析結果のためと思われる．臨床的には，それまで低体温療法の維持時間は，多くの報告で24時間あるいは48時間であった[7)27]．しかし，Jiang ら[16]は最大で14日間の long-term hypothermia を施行し，良好な治療成績を報告した．受傷後1年時の予後良好率は，平温療法群27.27%に対して低体温療法群では46.51%まで有意に改善した[16]．また彼らは，低体温療法の維持時間が2日間の short-term hypothermia と5日間の long-term hypothermia の受傷後6カ月時の転帰を比較し[17]，予後良好群は short-term hypothermia で29.0%に対して long-term hypothermia では43.5%と有意な改善を報告した[17]．これらより，低体温療法は長時間低体温を維持するほど脳保護効果は期待できると思われるが，合併症の増加が危惧される．脳保護効果と合併症抑制をにらんだ適正な維持時間が最重要課題であり，頭蓋内圧（ICP）センサーなどの頭蓋内環境のモニタリングが必須である．Cochrane review では，成人の頭部外傷に対する低体温療法の8つの大規模臨床研究が検討されている[46]．モニタリングなしでプロトコールどおりに1〜2日低体温療法を実施し，そのまま復温を開始した臨床研究は3つ，ICP をモニタリングして正常化された後に復温し，結果的に3〜5日間の低体温療法となった臨床研究が5つあった．この review 中，低体温療法の有効性は前者では皆無であったが，後者5つ中4つで改善が示された[9]．また，Murakami ら[30]は，搬入時 Glasgow Coma Scale（GCS）3で両側瞳孔散大した最重症例に対して，ICP モニタリング下に ICP が正常化する28日後まで低体温療法を継続し，会話や歩行可能なまでに改善した例を報告している．すなわち，低体温療法の維持時間には至適時間はなく，モニタリング下に個々の症例の病態に応じて個別化されるべきである．現時点では ICP のモニタリングが適当かと思われるが，今後さまざまなモニタリング下で検討する余地がある．また，維持時間が長期化する場合，合併症の低減がもう一つの課題となる．

3 復 温

1997年の Marion ら[27]の臨床研究において，入院時偶発的低体温であった患者群中平温療法群に割り付けられた患者群の転帰不良は66%と高率であった（2001年の Clifton らの臨床研究では同じ条件にて52%）[7]．本研究では偶発的低体温例に対して積極的に復温したことが理由の1つとして考察されている[7]．この考察をきっかけに低体温療法の復温法が重要視されるようになった．その後，実験的頭部外傷モデルにおいても，急速な復温により脳損傷や微小脳循環を増悪させるデータが示された[33)43)44]．また，臨床的にも入院時偶発的低体温であった頭部外傷患者についての復温は慎重に行うべきである，あるいは急速な復温によって転帰を増悪させるとの報告が相次いだ[20)47]．その機序として，復温中の脳血流と脳代謝の不均衡や脳血管反応性の傷害による微小脳循環障害が基礎実験では認められている[31)44]．臨床的にも復温中に hyperemia，続いて急性脳腫脹を認めた報告がある[15]．つまり復温中は脳循環代謝が不安定であり，こ

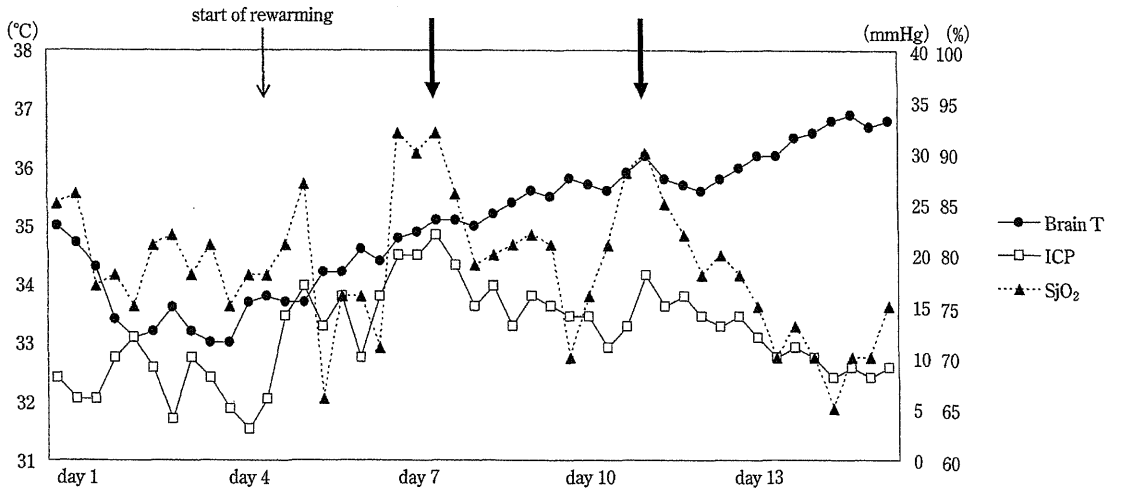

Fig. 1 Graph showing changes in neuromonitoring of our case during hypothermia therapy. The rapid rises of intracranial pressure (ICP) following the rises of jugular venous oxygen saturation (SjO_2) happened twice during rewarming period of hypothermia therapy (arrow).

のステージでも頭蓋内環境のモニタリングが重要である．われわれの施設では，低体温療法導入から復温が完了するまで，全例でICPならびに内頸静脈球酸素飽和度(SjO_2)をモニターしている．61歳女性の低体温療法導入から復温完了までのチャートを示す（Fig. 1）．34℃で72時間の低体温療法を施行し，0.5℃/日の割合でゆっくりと復温した．しかし，復温中にSjO_2が上昇し，続いてICPが上昇する現象が2回発生した．その際，復温をいったん中止する，あるいは0.5℃脳温を下げることにより，ICPは正常範囲へ戻り復温を再開することができた．緩徐な復温は転帰改善のために重要な要素であるが，盲目的に行うのではなく，モニタリング下に脳循環代謝を同時に把握することが必須である．

頭部外傷の病態別にみた低体温療法の適応

頭部外傷に対する低体温療法の適応基準は，多くの臨床研究でGCS score 8以下の重症頭部外傷となっている．しかし，重症頭部外傷の病態は多様で，ICP亢進の有無，びまん性軸索損傷，急性硬膜下血腫，脳挫傷など，さまざまな病態が含まれる．低体温療法の導入は，それぞれの病態に対して異なった治療効果がある．そのため評価の際には，その多様な群を一括して行うことは困難であり，病態別に解析する必要がある．Shiozakiら[38]によれば，ICP亢進を伴う重症頭部外傷に対して低体温療法を導入し，外傷性脳出血/脳挫傷では85%，硬膜下(外)血腫では88.9%の症例でICPの制御が可能であった．しかし，びまん性脳腫脹の症例では全例でICPの制御が不可能であった[38]．また，逆にICP亢進を伴わない重症頭部外傷については，低体温療法の治療効果を認めることができなかった[39]．

近年急性硬膜下血腫や脳挫傷など，開頭術を要する頭部外傷に対し，低体温療法が注目されている．Qiuら[34]の開頭術施行例の検討において，受傷後72時間後のICPが平温療法群では24.57±3.95 mmHgであるのに対して，低体温療法群では22.51±2.44 mmHgと有意に低下していた．また，受傷後1年時の転帰良好率は，平温療法群の47.5%に対して，低体温療法群では70.0%と有意に高かった[34]．同様の結果がNABIS：HIIでも示されている[9]．Diffuse brain injury群では，予後不良率が平温療法群で50%，低体温療法群で70%と有意差は認められていないが，surgically removed haematoma群では，予後不良率が平温療法群で69%に対して低体温療法群では33%と，有意差をもって低下している[9]．日本における頭部外傷への低体温療法に関する多施設無作為対照臨床研究（BHYPO）においても，同様の結果が示されているようである（personal communication）．これらの患者は，開頭時にはすでに低体温療法が導入されているため，減圧時に発生する反応（再灌流によるフリーラジカルの発生など）が高率に抑制されるのではないかと推測される．今後focal injuryにおける低体温療法の有効性に関する作用機序についての検討が必要である．

おわりに

本稿では，頭部外傷に対する低体温療法の管理法や適応症例についてreviewした．これまで，頭部外傷に対する低体温療法に関して，数多くの基礎的・臨床的研究が報告されているが，頭部外傷ではさまざまな病態が存在するため，実際に臨床応用する際には基礎的研究の病態とは異なる条件となることが多い．そのため，各施設が低体温療法の温度管理法をそれぞれ工夫している．結果的に各施設間で低体温療法の温度管理法や治療成績に差が生じている．この問題を解消するためには，モニタリングを指標とした個々の症例の病態に対応した脳温管理が必要と考える．そのためには，最適なモニタリングと目標値の設定などを，さらに検証し標準的な脳温管理法を確立することが必要である．

昨今，頭部外傷の病態別に治療効果が異なっていることが明らかになってきた．今後も臨床研究を通して頭部外傷の病態別治療成績を継続評価し，適応症例の詳細を解明していかなければならない．

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