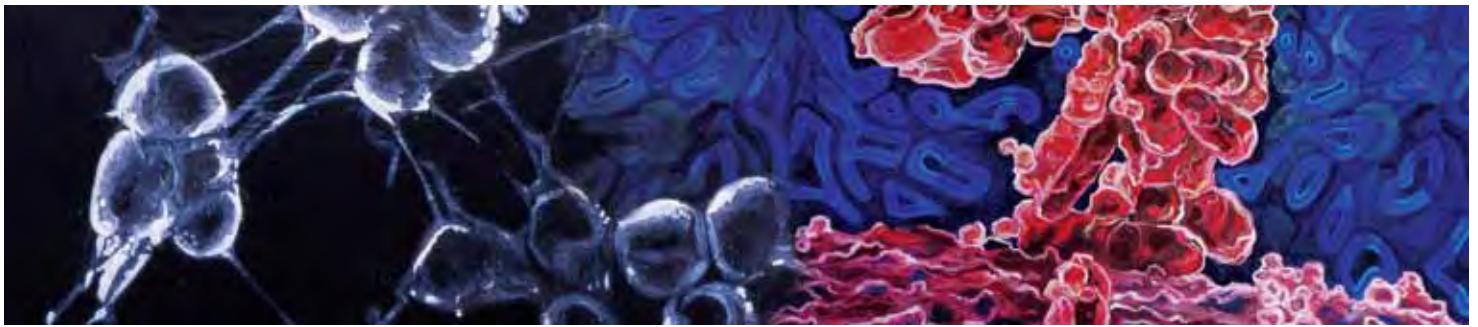


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Rapid and Selective Cerebral Hypothermia Achieved Using a Cooling Helmet

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OBJECT

Hypothermia is by far the most potent neuroprotectant. Nevertheless, timely and safe delivery of hypothermia remains a clinical challenge. To maximize neuroprotection yet minimize systemic complications, ultra-early delivery of selective cerebral hypothermia by Emergency Medical Service (EMS) personnel in the field would be advantageous. The authors (W.E. and H.W.) have developed a cooling helmet by using National Aeronautics and Space Administration spinoff technology. In this study its effectiveness in lowering brain temperature in patients with severe stroke or head injury is examined.

METHODS

Patients were randomly assigned to groups receiving either the cooling helmet or no cooling, and brain temperatures (0.8 cm below the cortical surface) were continuously monitored for a mean of 48 to 72 hours with a Neurotrend sensor and then compared with the patients' core temperatures. There were eight patients in the study group and six in the control group. The mean change in temperature (brain – body temperature) calculated from 277 data hours in the study group was -1.6°C compared with a mean change in temperature of $+0.22^{\circ}\text{C}$ calculated from 309 data hours in the control group. This was statistically significant ($p < 0.0001$). On average, 1.84°C of brain temperature reduction (range $0.9\text{--}2.4^{\circ}\text{C}$) was observed within 1 hour of helmet application. It took a mean of 3.4 hours (range 2–6 hours) to achieve a brain temperature lower than 34°C and 6.67 hours (range 1–12 hours) before systemic hypothermia ($< 36^{\circ}\text{C}$) occurred. Use of the helmet resulted in no significant complications. There was, however, one episode of asymptomatic bradycardia (heart rate < 40) that responded to a 0.5°C body temperature increase.

CONCLUSIONS

This helmet delivers initial rapid and selective brain cooling and maintains a significant temperature gradient between the core and brain temperatures throughout the hypothermic period to provide sufficient regional hypothermia yet minimize systemic complications. It results in delayed systemic hypothermia, creating a safe window for possible ultra-early delivery of regional hypothermia by EMS personnel in the field.

KEY WORDS: STROKE • HEAD INJURY • HYPOTHERMIA • BRAIN COOLING HELMET

To date, hypothermia is by far the most potent method of neuroprotection in animal studies and has the greatest therapeutic potential.^{2,5,17,24,25,42,43,46} Nevertheless, problems remain with timely and safe delivery of this type of therapy.⁹ Although the results of clinical trials have been mixed,^{3,9,31,45} two large pro-

spective randomized clinical trials of resuscitative hypothermia for cardiac arrest have recently shown significant benefit.^{3,31} Preclinical and clinical investigation of hypothermia continues to receive intense attention from the scientific and medical communities. To maximize neuroprotection yet minimize

ABBREVIATIONS USED IN THIS PAPER:

EMS = Emergency
Medical Service

ICP = intracranial
pressure

ICU = intensive
care unit

NASA = National
Aeronautics
and Space
Administration

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systemic complications, ultra-early delivery of selective cerebral hypothermia by EMS personnel in the field would be advantageous. We (W.E. and H.W.) have developed a cooling helmet (Fig. 1) by using NASA spinoff technology. In this study we examine its effectiveness in lowering brain temperature in patients with severe stroke or head injury.

CLINICAL MATERIAL AND METHODS

Study Design

This study was designed as a randomized, controlled trial. The protocol and consent procedures were approved by the local institutional review board. Treatment assignments (cooling helmet or no cooling)

Figure 1.

Photograph showing the helmet worn by William Elkins, a NASA scientist, who invented this technology. The cooling helmet has an outer pneumatic liner pressurized to allow close contact with the cranium and neck. The device also is adjustable to fit a significant range of head sizes.



were generated from a randomization table. Patients consecutively admitted to our neurological ICU with either severe stroke or head injury were eligible for the study. Patients with overwhelming systemic diseases, cervical spine injuries, and/or significant forehead and facial lacerations were excluded from the study. There were eight patients in the study group and six in the control group.

Description of the System

The brain hypothermia device consists of two components, the head/neck liner and the conditioning unit.

Head/Neck Liner. Figure 1 shows the helmet, in which the liner is constructed of a lightweight, thin, flexible, urethanelaminated nylon fabric. There are two integrated layers consisting of a conformal liquid cooling heat exchanger and a pressurizable air bladder. The liner, with its uniform flow of conditioned cold liquid, is only approximately 1/16 in thick. The outer pneumatic liner is pressurized to allow close contact with the cranium and neck. The head/neck liner has bilateral frontal openings (approximating the Kocher points) and an anterior midline neck opening for access if required. It is also adjustable and allows a close fit over a significant range of head sizes.

Conditioning Unit. The conditioning unit consists of an insulated ice reservoir and a control system, both contained in a portable unit weighing approximately 22 lb when fully loaded with ice and water. There is approximately 3.25 ft² of heat-exchanger area in the unit. The conditioning unit can be operated with a direct-current power supply or D-cell batteries. The control system provides the following: 1) temperature control; 2) liquid pump and pressure control; and 3) air pump (air pressure control is integrated into the liner).

The study protocol was initiated within 24 hours after admission. Standard treatment for severe stroke and head injury was administered and brain temperatures (acquired 0.8 cm below the cortical surface) were continuously monitored for a mean of 48 to 72 hours with a Neurotrend sensor (Codman & Shurtleff, Inc., Raynham, MA) and compared with the patients' bladder (core) temperatures. In the study group, all patients' heads were shaved before application of the cooling helmet in the ICU, and warming blankets were used to maintain a core temperature above 35°C if the patient was older than 45 years of age and 33°C if they were younger.

RESULTS

The mean change in temperature (brain – bladder temperature) calculated from 277 data hours in the study group was -1.6°C compared with a mean change in temperature of $+0.22^{\circ}\text{C}$ calculated from 309 data hours in the control group; this was statistically significant ($p < 0.0001$). On average, 1.84°C of brain temperature reduction (range $0.9\text{--}2.4^{\circ}\text{C}$) was observed within 1 hour of helmet application. It took a mean of 3.4 hours (range 2–6 hours) to achieve a brain temperature lower than 34°C and 6.67 hours (range 1–12 hours) before systemic hypothermia ($< 36^{\circ}\text{C}$) occurred. A mean $0.63^{\circ}\text{C}/\text{hour}$ (range $0.15\text{--}1.45^{\circ}\text{C}/\text{hour}$) passive rewarming rate was observed. Use of the helmet resulted in no significant complications. There was, however, one episode of asymptomatic bradycardia (heart rate < 40) that responded to a 0.5°C body temperature increase. No rebound hyperthermia or ICP elevation was observed.

ILLUSTRATIVE CASE

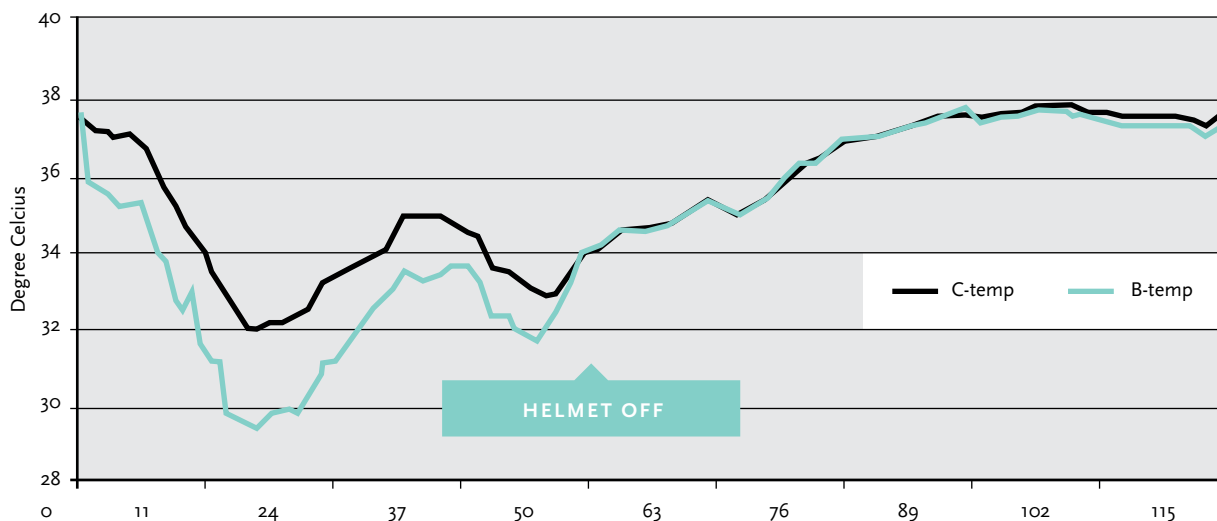
This 17-year-old woman presented with severe head injury (Glasgow Coma Scale Score 7). Computerized

tomography scans of her head demonstrated traumatic subarachnoid hemorrhage, a small subdural hematoma, and diffuse petechial intraparenchymal hemorrhages consistent with shear injury. Her initial ICP reading was approximately 35 mm Hg. The cooling helmet was applied after her admission to the hospital. The patient was also intubated, paralyzed, and sedated. A Neurotrend sensor, an ICP microsensor (both obtained from Codman & Shurtleff, Inc.), and a pulmonary artery catheter (Abbott Laboratories, North Chicago, IL) were placed to monitor intraparenchymal brain temperature, ICP, cardiac output, and core temperature, in addition to other vital signs that are routinely and continuously monitored in the ICU.

Brain temperature was slightly higher than core temperature at baseline. Within 15 minutes after application of the cooling helmet, the brain temperature dropped by approximately 2°C , whereas the core temperature did not drop below 37°C until 4 to 5 hours later (Fig. 2). The cooling helmet maintained brain temperature at approximately 1.5 to 2.5°C below core temperature throughout the 48-hour cooling period. When the core temperature dropped to 32°C and brain temperature dropped to 29.4°C , active body warming was initiated to minimize the risk of cardiac arrhythmia. After the cooling helmet was removed at Hour 48, the brain temperature approached the core temperature within 1 to 2 hours, and then both rose gradually to 37°C over a 30-hour period. B-temp = brain temperature; C-temp = core temperature.

Figure 2. Core Temperature vs Brain Temperature

Graph showing that, within 15 minutes after application of the cooling helmet, the brain temperature dropped by approximately 2°C , whereas the core temperature did not drop below 37°C until 4 to 5 hours later. The cooling helmet maintained brain temperature at approximately 1.5 to 2.5°C below core temperature throughout the 48-hour cooling period. When the core temperature dropped to 32°C and brain temperature dropped to 29.4°C , active body warming was initiated to minimize the risk of cardiac arrhythmia. After the cooling helmet was removed at Hour 48, the brain temperature approached the core temperature within 1 to 2 hours, and then both rose gradually to 37°C over a 30-hour period. B-temp = brain temperature; C-temp = core temperature.



When the core temperature dropped to 32°C and the brain temperature dropped to 29.4°C, active body warming was initiated to minimize the risk of cardiac arrhythmia. The core temperature, as illustrated by the graph in Fig. 2, was maintained thereafter at 33 to 35°C with external warming blankets. After the cooling helmet was removed at Hour 48, the brain temperature approached the core temperature within 1 to 2 hours and then together both rose gradually to 37°C over a 30-hour period. No deleterious effects, such as arrhythmia, infection, clinically significant coagulopathy, and so on, were observed. At her 6-month follow-up visit, the patient had gone back to school and had resumed cheerleading activities, although she had minor right-sided tremors.

DISCUSSION

Resuscitative hypothermic neuroprotection has been conclusively established in animal models of both global/focal (permanent and transient) ischemic and traumatic brain injuries.^{2,5,17,24,25,42,43,46} The efficacy of resuscitative hypothermia likely relates to a multitude of factors, such as the delay of initiation (treatment window), the severity, type, region, and duration of injury, the rate of induction, and the depth and duration of cerebral hypothermia. These factors also intertwine and confound each other's effects. Although the critical duration of cerebral hypothermia required for significant neuronal rescue has not been established, in several laboratory studies this has been systematically examined and the investigators have suggested the need for prolonged cooling (48–72 hours).^{6,10,11,62} It is relatively well accepted that interventions after longer delays are less efficacious.^{6,10,12} Prolonged cooling, however, seems to compensate for some delay in initiation of therapy. Studies of brief cooling (a few hours) demonstrated that hypothermia only delayed rather than prevented neuronal degeneration.¹⁶ Nevertheless, when the duration of hypothermia is prolonged (12–48 hours), permanent benefits (28 days–12 months) were documented even after an induction delay of several hours (≤ 6 hours).^{11–14} Whether a critical depth of hypothermia is required for effective neuronal protection remains to be determined. An extradural temperature of 34°C or less has been suggested to be necessary for substantial neuronal rescue.^{26,65} Also, reduction of brain temperature within the mild-to-moderate range diminished histologically confirmed injury in a dose-dependent manner.⁶⁸ On the other hand, hypothermia beyond the mild-to-moderate range may be poorly tolerated and less effective.^{30,40}

The results of clinical trials in which resuscitative hypothermia was used have been mixed.^{3,9,31,45} In the National Acute Brain Injury Study: Hypothermia⁹ although hypothermia treatment significantly reduced elevated ICP, no functionally protective effect was demonstrated at 6 months. Two large prospective randomized clinical trials of resuscitative hypothermia for cardiac arrest, however, have recently shown significant improvement in overall survival and neurological outcome.^{3,31} From studies of head injuries and cardiac arrests in humans, it is generally accepted that hypothermia should be initiated as soon as possible.^{19,56} Therefore, ultra-early delivery of hypothermia by EMS personnel in the field would be advantageous. A target core temperature of 33°C and hypothermia duration of 12 to 48 hours are considered safe and feasible.^{3,9,31,45} Clinical studies of hypothermia induction for acute stroke have a relatively short history in comparison with hypothermia for head injuries and cardiac arrests, and have primarily involved only ischemic types. Two concurrent multicenter studies are in progress^{33,41} in which endovascular cooling is being used in patients with acute ischemic stroke. Both studies are enrolling patients within 12 hours of onset of stroke and have a target core temperature of 33°C; hypothermia is maintained for 12 to 24 hours. Preliminary results indicate that this treatment is feasible and safe.

Systemic hypothermia can cause a variety of cardiac, pulmonary, renal, electrolytic, infectious, and other complications.^{8,9,20,34,37,57} Prolonging hypothermia may improve neuroprotection;^{6,10,11,62} however, it may also lead to an increase in adverse effects.⁴⁴ Although the National Acute Brain Injury Study: Hypothermia⁹ demonstrated only a slight overall increase in complications in the hypothermia group (core temperature 33°C) in patients older than 45 years of age, there were substantially higher rates of complications, including bleeding, sepsis, and pneumonia, in the hypothermia group. Many brain-injured patients are older than 45 years of age and have multiple systemic comorbidities. Careful monitoring and prompt response to systemic hypothermia-associated complications are especially warranted.

Core temperature is often an inaccurate and unreliable guide to brain temperature; thus, the latter must be monitored directly during temperature modulation therapies such as hypothermia.^{28,48,55,63} The cerebral temperature gradient may be different under normothermic, hypothermic, or hyperthermic

conditions.^{28,59,63} Furthermore, this gradient would most likely differ with various methods of hypothermic induction (for example, systemic compared with local).³⁹ Therefore, it is essential to standardize the location of the intracerebral temperature sensor to make comparisons possible and meaningful among brain temperature modulation studies. Through theoretical modeling and calculation, it has been suggested that the mean brain temperature should be measured at 7.5 mm below the cortical surface in adults.⁷¹

Systemic cooling is clinically effective in achieving sustained core and brain hypothermia to a similar depth.^{27,58} Nevertheless, it would theoretically be ideal if the brain could be cooled more than the body to maximize hypothermia's neuroprotection yet minimize its systemic complications. In the course of many studies to reduce hyperthermic stress in Air Force operations, the head and neck area has long been identified as the most efficient body region for heat removal.^{32,51,61,70} These regions have the highest skin temperature (thus the largest change in temperature) and a large, constant blood flow volume with little vasoconstriction in response to cold (in contrast with the torso, which has considerable vasoconstriction in response to cold and requires additional "cold power" to overcome the thickening insulation). Potent neuroprotection, a benign complication profile, and successful selectivity of cerebral hypothermia through surface cooling have been well documented in animal models.^{23,26,30,35,36,64,66} Selective brain cooling has also been attempted previously by using localized cerebral ventricular perfusion,^{17,50,54} fans,⁴ cold forced air,⁶⁷ nasal lavage,⁴⁹ perfusion of the brain with cold solutions or blood,^{7,60} and direct application of a cold substance or cooling device onto the head.^{29,47} Rapid and successful selective cerebral hypothermia can be accomplished with a highly invasive extracorporeal system.^{34,53}

To date, it has not been shown in humans that it is possible to cool the brain more than the body through surface cooling, even in very superficial regions.^{15,47} Some researchers have suggested that, unlike small brains, human brains are too large to be cooled by conductive heat exchange.³⁸ In addition, some studies on selective cerebral hypothermia were conducted in animals (for example, piglets) that have a rete caroticum.^{23,66} The rete is a multichannel version of the human internal carotid artery and is surrounded by the cavernous sinus; together these serve as an effective heat exchange mechanism for the brain,¹⁸ whereas humans lack such

a structure for effective heat exchange. Furthermore, in animal models the cooling device may cover 100% of all available head surface area.⁶⁶ This is not practical for clinical use. In our study, however, we clearly demonstrate that, using NASA spinoff technology, this specially designed cooling helmet allows initial rapid and selective brain cooling and results in delayed systemic hypothermia, creating a safe window for ultra-early delivery of regional hypothermia by EMS personnel in the field. In addition, it maintains a significant gradient between the core and brain temperatures (brain temperature < core temperature) throughout the entire hypothermic period (2–3 days) to maximize the neuroprotective effects while minimizing possible systemic complications.

By the mechanism of surface cooling,^{23,34,39} this helmet provides more preferential cooling of the superficial areas of the brain than the deep regions. It is therefore theoretically plausible that injuries in the cortex or nearby may be more responsive to selective cerebral hypothermia through surface cooling, whereas deep injuries may receive better neuroprotection from systemic hypothermia. Nevertheless, at least two additional confounding factors must be taken into consideration: the difference in regional temperature sensitivity^{25,34,69} and the rate at which neuronal death occurs.^{21,22,52} For example, neuronal necrosis in the caudoputamen is particularly sensitive to temperature.²⁵ Cortical tissue may be more amenable to therapies instituted in the postinjury period because cortical cell death occurs more slowly than in the striatum.^{21,22,52} These two factors would be of great importance for assessing the amount of temperature dependent brain protection from injuries. Although an increase in the cerebral temperature gradient could potentially be harmful because of theoretical imbalances between blood flow and metabolism,¹ this is not supported by the majority of the animal data.^{23,26,30,35,36,64,66}

CONCLUSIONS

Using NASA spinoff technology, this specially designed cooling helmet allows initial rapid and selective brain cooling and results in delayed systemic hypothermia, creating a safe window for ultra-early delivery of regional hypothermia by EMS personnel in the field. It maintains a significant gradient between the core and brain temperatures (brain temperature < core temperature) to maximize the neuroprotective effects while minimizing possible systemic complications. Further

studies are needed in which this helmet is used in patients with head trauma and stroke; these studies are required to characterize the temperature of the skin in direct contact with the innermost lining of the helmet, to estimate heat transfer, to ascertain intracerebral temperature profiles with the head unshaved, and so on. Better technologies to control the rate of hypothermia delivery and rewarming will need to be engineered into the second generation of cooling helmets. Also, cooling helmets with modifications to suit prehospital needs better (for example, cervical spine precautions) will make it possible to study the feasibility of ultra-early initiation of selective cerebral hypothermia by EMS personnel.

DISCLAIMER

None of the authors has any affiliation with Coolsystems, Inc.

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