Brain temperature monitoring and modulation in patients with severe MCA infarction

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Article abstract—*Background:* Brain temperature has been measured only occasionally in humans. After head trauma, a temperature gradient in brain temperature compared with body temperature of up to 3 °C degrees higher in the brain has been reported. Elevated temperature facilitates neuronal injury after ischemia. At present, no information concerning changes in brain temperature after acute stroke is available. *Methods:* In 15 patients who had suffered severe ischemic stroke in the MCA territory, intracerebral temperature was recorded with use of two different thermocouples, with intraventricular, epidural, and parenchymatous measurements. Body-core temperature (Foley catheter temperature) and jugular bulb temperature (n = 5) were recorded simultaneously. Measures for reducing brain temperature were compared. *Results:* In all patients, brain temperature exceeded body-core temperature by at least up to 1 °C (range, 1.0 to 2.1 °C). Temperature in the ventricles exceeded epidural temperature by up to 2.0 °C. Brain temperature modulation was independent of single pharmacologic (paracetamol, metamizol) treatments. Only systemic cooling was effective and sustained hypothermic (33 to 34 °C) brain temperatures. *Conclusion:* After MCA stroke, human intracerebral temperature is higher than central body-core temperature. There is also a temperature gradient within the brain, with the ventricle warmer than the surface. Mild hypothermia in the treatment of severe cerebral ischemia with use of cooling blankets is both easy to perform and effective in the therapy of severe hemispheric infarction.

NEUROLOGY 1997;48:762–767

Averting brain damage caused by ischemic injury through therapeutic modulation of brain temperature is a fascinating method of neuroprotection in experimental stroke and other neuronal injuries.[1-3] In several animal models of focal cerebral ischemia, hypothermia reduced infarct volumes up to 90%,[4-7] and an increase in brain temperature has a significantly negative effect on histopathologic findings and outcome after cerebral ischemia.[8-11] Deep hypothermia is used routinely during open heart surgery and occasionally for cerebral protection during neurosurgical operations.[12,13] However, there is surprisingly limited information regarding temperature in the human brain during normal and pathologic conditions.[14]

Experimental data demonstrated that body temperature and brain temperature can differ significantly.[15] In accordance with these findings, some au-

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Received July 1, 1996. Accepted in final form August 29, 1996.

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brain and between body-core and brain in neurosurgical patients.[16-19] For optimal use of hypothermia as a therapeutic tool for neuroprotection, methods both for continuous monitoring of brain temperature and for easy and readily available brain cooling are necessary. In animal models, various measures of controlling brain temperature, including fanning, nasopharyngeal cooling, cardiopulmonary bypass, ice-water immersion, or simply packing the head in ice, have been employed.[20-24] Some of these methods have found clinical application; however, most of them did not provide safe and reliable cooling of the brain.

In a recent multicenter study on hypothermia in severe head trauma patients, Clifton et al.[25] achieved hypothermia with special rotorest beds and a hypothermia blanket wrapped around the patient. To date, there are no reports available on brain temperature monitoring in patients with severe ischemic stroke. Even though hypothermia has a potent cerebroprotective effect after focal ischemia experimentally, clinical studies to modulate brain temperature after middle cerebral artery (MCA) infarction are still lacking.

We report here our experience on brain temperature monitoring and modulation of brain temperature in patients with acute malignant MCA infarction.[26]

Patients and methods. This study is based on 15 consecutive patients, 10 men and 5 women (35 to 54 years of age, with a mean age of 45 ± 12.3 years), who had suffered acute MCA territory stroke and were admitted to the neurocritical care unit (NCCU) for treatment of elevated intracranial pressure (ICP). The study was approved by the local ethics committee. Inclusion criteria were as follows: clinical and computed tomographic (CT) evidence of acute, large MCA infarction (which consisted of early large parenchymal hypodensity and signs of local brain swelling such as effacement of the sulci and compression of the lateral ventricle); follow-up CT examinations within the first 4 days after stroke showing an increased space-occupying effect; further neurologic deterioration compared with the baseline clinical status on admission to the NCCU; no previous disabling neurologic disease; and no terminal illness.

The ICP was monitored in all patients with one of two different types of intraparenchymatous and epidural sensors and transducers (Spiegelberg pneumatic transducer, Spiegelberg AG, Hamburg, Germany, n = 12; Camino microsensor, Johnson & Johnson, Raynham, MA, n = 3). Indication for ICP monitoring was set because of CT or clinical evidence of large MCA or hemispheric infarction and emerging severe brain edema. ICP devices were inserted ipsilaterally to the affected hemisphere in eight patients and bilaterally in seven patients via a burr hole and was placed in the white matter next to the frontal horn of the lateral ventricle. Medical treatment included osmotherapy and mild hyperventilation.[27] In case of further neurologic deterioration, decompressive surgery was performed according to our own internal treatment protocol in seven patients.[28] Clinical data were obtained daily from all patients using the 6-point Scandinavian Stroke Scale (SSS) and Glasgow Coma Scale (GCS; range 0 to 15).[29,30] Four weeks after stroke, clinical outcome was assessed with the SSS and Rankin scale (RS), and activities of daily living were rated with the Barthel index (BI).[31,32]

Brain temperature was measured with two different temperature sensors. All thermosensors were specified to be used only once. The Spiegelberg intraparenchymatous ICP probe, which also can be used as an intraventricular ICP device, has a thermistor in the tip of the probe. The wires were led through the air-tubing of the catheter. The sensors were negative temperature coefficient (NTC) thermistors, which are inherently accurate and have virtually no drift. Thermistors are semiconductors with an electrical resistance dependent on the temperature. Therefore, the temperature coefficient is negative. As opposed to thermocouple technology, thermistors can be chosen that are suited to the temperature range of interest. The accuracy for the temperature measurements is lower than 0.1 °C. In the epidural probe, the thermistor is situated in the baseplate. The wires are in additional tubing. Temperature reading and ICP values were recorded online on a modified cerebral perfusion pressure (CPP) monitor (manufactured by Spiegelberg AG). The other temperature monitor was a thermocouple that was introduced with the Licox system (GMS, Mielckendorff, Kiel, Germany), a special intracranial bolt with three entries that allow advancement of the ICP device, O_2 probe, and thermocouples via one burr hole. The thermocouple is 0.5 mm in size and 200 mm in length and made of Ni/NiCr. The intraventricular thermocouples were recalibrated after each measurement period and proved to be reliable, with an accuracy within 0.1 °C. A Foley temperature catheter for bladder temperature reading with a temperature resolution of 0.1 °C was used for monitoring body-core temperature (Mon-a-therm, Mallinckrodt, St. Louis, MO). Jugular bulb temperature was monitored in five patients with optimetric jugular bulb catheters (Opticath; Abbott Laboratories, North Chicago, IL) with a thermistor. The catheters were placed for cerebrovenous oxygen saturation monitoring.[33] We attempted to control brain temperature by various means. During all procedures, the patients were sedated (fentanyl infusion 5 to 10 μg/kg/hr and midazolam 1 to 4 mg/kg/hr) and received neuromuscular blockade with atracurium (0.3 to 0.6 mg/kg/hr). Monitoring in the NCCU always consisted of continuous monitoring of ICP, electrocardiograms, and blood pressure. Room temperature was between 18 and 20 °C. In this study, only cooling blankets (Warm Touch, Mallinckrodt, St. Louis, MO) with cool ventilator air fanning the patient's body surface were used for external cooling.

Results. *Patients.* The mean SSS score on admission was 23.6 ± 6.5 (median, 27). Mean GCS on admission was 9 points (range, 4 to 13). All patients presented with severe hemiparesis and forced eye and head deviation. All patients had suffered large MCA territory stroke. The etiology of stroke was cardioembolism in 10 patients, internal carotid artery dissection with secondary MCA embolization in 3 patients, and remained unknown in 2 patients. Three of 15 patients who underwent ICP monitoring for major space-occupying infarction died. All 12 survivors, including 7 patients who were treated with craniectomy, were dis-

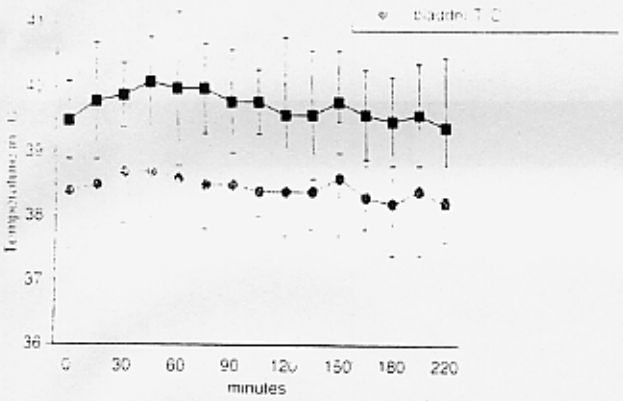

Figure 1. Representative bladder and intraparenchymatous temperatures in 15 patients measured every 15 minutes. Measures were recorded with a mean of 15 hours after stroke onset.

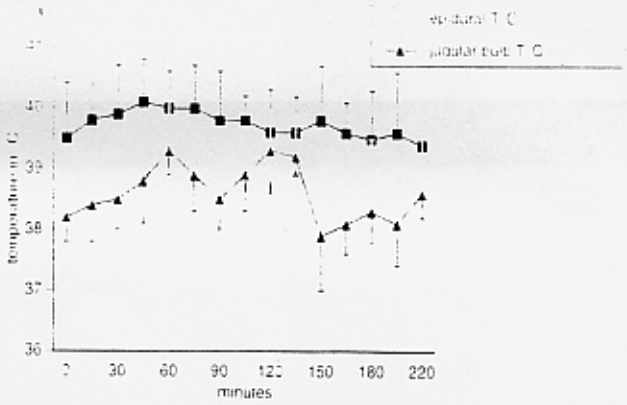

Figure 3. Representative intraparenchymatous, epidural, and jugular bulb temperatures measured every 15 minutes. Measures were recorded with a mean of 15 hours after stroke onset.

charged to rehabilitation programs. Their neurologic outcome according to the SSS score 4 weeks after stroke was 31.3 ± 8.3. The mean BI of the surviving patients was 65 (range, 45 to 70), and the mean RS was 3 points (range, 2 to 4).

The mean interval between onset of symptoms of ischemic stroke and insertion of the monitoring device was 9 hours (range, 4 to 24 hours). The patients were not fluid restricted, and serum sodium levels and osmolarity were normal in all patients prior to ICP device (= thermocouple) insertion. The average monitoring period varied between 3 and 7 days (mean, 4.9 ± 2.5 days). The ICP at time of insertion was normal (<20 mm Hg) in 11 (73%) of the patients. The mean initial ICP was 18.9 ± 10.4 mm Hg (range, 13 to 36 mm Hg). In all patients, ICP values increased continuously during the first 2 days after probe insertion and rose to values above 25 mm Hg during the acute stage of the disease. Most patients (12 of 15) had fever above 39 °C (bladder temperature) during the measurement period. We attempted to keep body temperature below 38.5 °C with either antipyretics or alcohol body washing in all patients.

Brain temperature and bladder temperature. In all patients, intraparenchymatous brain temperature exceeded body-core temperature, with a mean of 1.5 ± 0.3 °C (range, 1.0 to 2.1 °C). The difference between brain temperature and body-core temperature varied individually and over the measurement period (figure 1). Hence, the difference between brain and body-core temperature was independent of the measured ICP or CPP. In three patients who died, brain temperature dropped below bladder temperature hours before bilaterally dilated and fixed pupils and clinical signs of herniation were visible (figure 2).

The temperature in the ventricles exceeded the epidural temperature with a mean of 1.0 °C (range, 0.6 to 2.0 °C) and body temperature by 1.9 °C (range, 1.0 to 2.8 °C). Epidural temperature was always lower than the ventricular temperature. Compared with body-core temperature, epidural readings were almost always higher but demonstrated a higher inter-individual variability. Temperatures as measured in the jugular bulb showed values comparable with the epidural temperatures (figure 3).

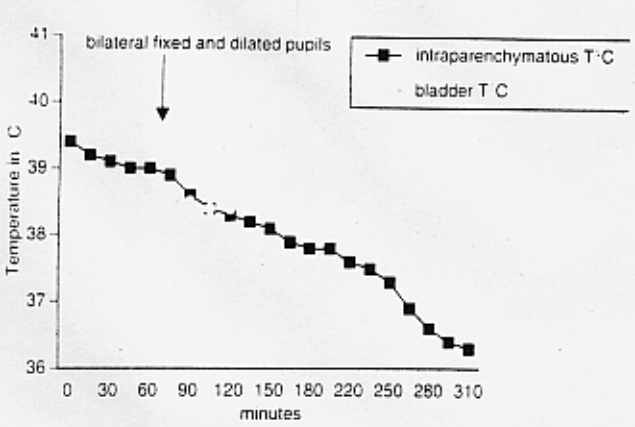

Figure 2. Representative temperature measurements in a patient after the clinical diagnosis of brain death with bilaterally fixed and dilated pupils (arrow). Measures were recorded 74 hours after stroke onset.

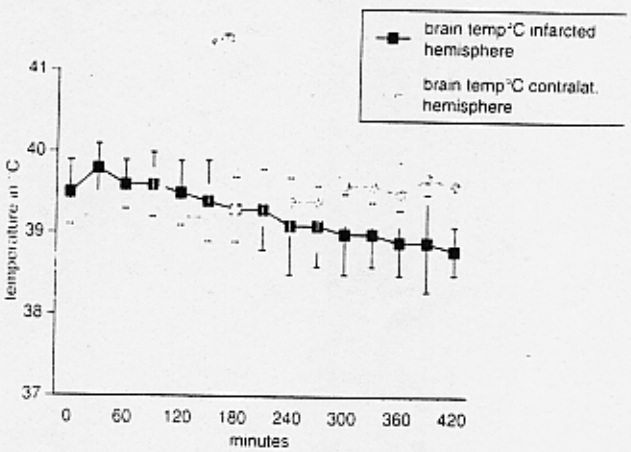

Figure 4. Bilateral intraparenchymatous temperature monitoring in patients showing higher temperatures in the infarcted hemispere within the first hours after stroke. Monitoring began within six hours after onset of symptoms. Measurements were taken every 30 minutes.

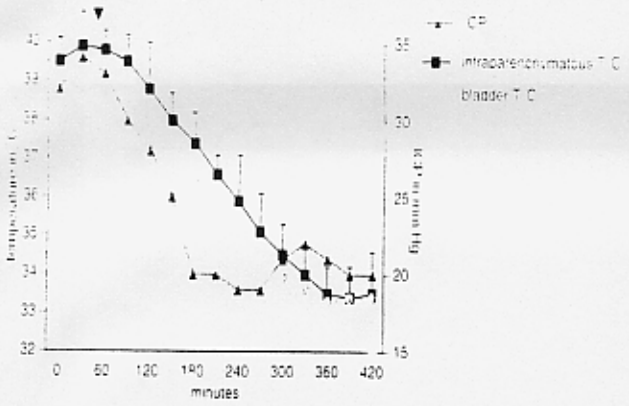

Figure 5. Temperature measures and ICP course after induction of cooling with cooling blankets and alcohol washing.

In those seven patients in whom bilateral intraparenchymatous temperature was measured, a significant temperature gradient between the infarcted and contralateral hemispheres was observed. In three patients, in whom bilateral ICP and temperature monitoring were started within the first 6 hours after the MCA infarction, brain temperatures were up to 0.6 °C higher in the infarcted hemisphere than in the contralateral hemisphere. After 12 hours, lower temperatures were found in the infarcted hemisphere. In the further course, a gradient of 0.6 to 0.9 °C was noted (figure 4).

Brain temperature modulation. In eight patients, pharmacologic agents were used to decrease body-core and brain temperatures. All patients had bladder temperatures greater than 39 °C. All patients repeatedly received paracetamol (1 g) or metamizol infusion (500 mg). Both drugs decreased core temperatures by a mean of 1.1 °C (range, 0.6 to 1.3 °C). However, brain temperature decreased only slightly, by a mean of 0.6 °C (range, 0.3 to 1.0 °C). Moreover, this effect was not sustained, and brain temperatures returned to previous values within 3 hours, compared with 5 hours for core temperatures. Because of incipient transtentorial herniation, two patients received high-dose thiopental infusion. In both patients, a marked decrease in core temperatures (−1.6 °C), but only a mild drop in brain temperatures (−0.6 °C), was seen. In five patients, whole-body cooling with cooling blankets and alcohol washing was effective and hypothermic (33 to 34 °C) brain temperatures sustained. With immediate neuromuscular blockade and opioid (fentanyl 10 μg/kg) administration, core temperatures and brain temperatures decreased rapidly. Within 3 hours, a mean decrease in both core and brain temperatures of 2.8 °C (range, 1.9 to 3.9 °C) could be achieved (figure 5). ICP values, which were recorded simultaneously, showed a mean decrease of 15 mm Hg compared with baseline measures before induction of hypothermia. Moreover, CT performed 12 hours after induction of hypothermia regularly demonstrated a decrease of midline shift and mass effect of brain edema. Mean decrease in midline shift was 3.4 mm (range, 2 to 4.5 mm) (figure 6).

Discussion. Interest in brain temperature monitoring has gained further with the emerging therapeutic potential of hypothermia as a neuroprotective measure. However, all previous studies performed brain temperature monitoring in neurosurgical patients with head trauma, brain tumor, or large intracerebral hematoma. Busto et al.[3] addressed the importance of brain temperature in experimental cerebral ischemic injury. He was able to show a reduction in ischemic injury depending on the level of intra-ischemic brain temperatures. In our study, brain temperatures in stroke patients were consistently higher than body-core temperatures. These results confirm the findings of others, who all showed a significant gradient between body-core and brain temperatures in head trauma patients.[14,17] The explanation for this may lie in the high metabolic activity of cerebral tissue with a considerable production of heat.[35,36] Nurse and Corbett[37] postulated an acute phase of locomotor hyperactivity to be the cause of

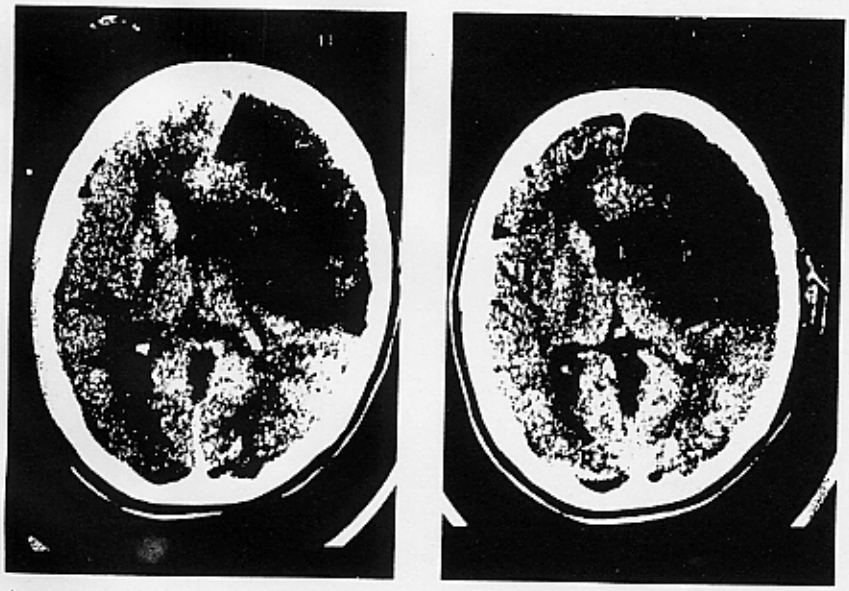

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Figure 6. (A) CT at the septum pellucidum level in a 35-year-old woman with left-hemispheric MCA infarction. Note compression of the lateral ventricle and severe midline shift (5 mm). (B) After 12 hours of hypothermic therapy, there was a reduction of mass effect and only slight midline shift (2 mm).

ischemia in a rat model. A similar explanation is possible for the finding of initially increased temperatures in the infarcted hemisphere compared with the contralateral hemisphere in the first hours after ischemia. We can only speculate that this finding is due to a release of excitatory neurotransmitters and increased energy (ATP) depletion and lactate accumulation during ischemia.[38-40] Another possibility is that in the early stages of infarct formation, a decrease in cerebral blood flow may result in a decreased capacity for the blood to carry off heat generated by local cerebral metabolism. Some animal models describe the detrimental effects of hyperthermia. Hyperthermia increases lactic acidosis and leads to an acceleration of neuronal death.[41]

In this study, body temperature measurement did not adequately reflect brain temperature with normothermic core temperatures, brain temperatures of 38 °C and more were measured. A better characterization of human brain temperature is necessary if hypothermia is to be implemented as a therapeutic tool.[24] In our study, brain temperature monitoring was safe and carried no additional risk compared with the ICP devices that are routinely used in patients with intracranial hypertension.

Two recent clinical studies emphasized the importance of body temperature for stroke prognosis and severity.[42,43] Reith et al.[42] demonstrated lower mortality and better outcome in patients with mild hypothermia on admission. With hyperthermia, outcome was worse. In another study, Azzimondi et al.[43] showed that fever in the first 7 days after stroke was an independent predictor of poor outcome.

Several neurosurgical studies showed a positive effect of mild hypothermia on uncontrollable intracranial hypertension after severe head traumas.[25,44,45] Head-injured patients treated with mild hypothermia between 32 and 34 °C core temperature had a significant reduction of ICP and cerebral blood flow compared with the normothermic, treated control group. All studies indicated better outcome with hypothermia and a beneficial effect in limiting secondary brain injury. Here, hypothermia was induced either through surface cooling with water-circulating blankets above and below the patient[45] or with cold saline gastric lavage and cooling blankets.[44] In our study, mild hypothermia could be easily and rapidly achieved with cooling blankets and alcohol washing. There were no obvious side effects of this therapy, such as arrhythmias, predisposition for bacterial infection, and hemodynamic instability with profound arterial hypotension. Hypothermia led to a significant decrease in ICP and mass effect of postischemic brain edema.

Conventional therapy of raised ICP after ischemic stroke consists of artificial ventilation, osmotherapy, and barbiturate administration. However, the value and duration of these measures is disputable. For a long time, hyperventilation with a target Pco_2 of 25 to 30 mmHg was considered an effective strategy for [illegible] after intubation and initiation of mechanical ventilation. Recently, vigorous hyperventilation has been discouraged since the potential decrease in cerebral arterial blood flow resulting from additional hypocarbia could exacerbate tissue ischemia.[46] Early use of agents, such as glycerol or mannitol, may actually hasten tissue shifts due to compartment ligation and aggravation of brain edema.[47] Even barbiturate therapy has failed to prove its therapeutic benefit in the treatment of severe brain injury.[48,49] Because of the objections raised against all types of conventional, nonsurgical therapy on the grounds of their potential adverse effects, new therapeutic concepts for the treatment of brain edema must be employed. Hypothermia might be a potent neuroprotective tool in the therapy of acute cerebral ischemia, especially if body and brain temperatures can be reduced rapidly and easily without major risks or complications. However, until now, this therapy is limited to patients treated in an intensive care unit because of emergent brain edema. Anesthesia with opioids and neuromuscular blockers is mandatory but impedes rapid treatment.

In conclusion, brain temperature monitoring is safe and provides reliable data. Body-core temperature does not reflect actual brain temperatures in stroke patients, a finding that is of great importance for further therapeutic trials on hypothermia as a neuroprotective tool in acute cerebral ischemia. Our own preliminary results suggest a beneficial effect of mild hypothermia in the treatment of severe space-occupying MCA infarction by lowering critically elevated ICP. Whether early hypothermic therapy within the first 6 hours after onset of symptoms has a neuroprotective effect, and can reduce infarct size, needs to be clarified in clinical trials that are currently under way.

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