Moderate Hypothermia in the Treatment of Patients With Severe Middle Cerebral Artery Infarction

S. Schwab, MD; S. Schwarz, MD; M. Spranger, MD; E. Keller, MD; M. Bertram, MD; W. Hacke, MD

Background and Purpose—Animal research and clinical studies in head trauma patients suggest that moderate hypothermia may improve outcome by attenuating the deleterious metabolic processes in neuronal injury. Clinical studies on moderate hypothermia in the treatment of acute ischemic stroke patients are still lacking.

Methods—Moderate hypothermia was induced in 25 patients with severe ischemic stroke in the middle cerebral artery (MCA) territory for therapy of postischemic brain edema. Hypothermia was induced within 14 ± 7 hours after stroke onset and achieved by external cooling with cooling blankets, cold infusions, and cold washing. Patients were kept at 33°C body-core temperature for 48 to 72 hours, and intracranial pressure (ICP), cerebral perfusion pressure, and brain temperature were monitored continuously. Outcome at 4 weeks and 3 months after the stroke was analyzed with the Scandinavian Stroke Scale (SSS) and Barthel index. The side effects of induced moderate hypothermia were analyzed.

Results—Fourteen patients survived the hemispheric stroke (56%). Neurological outcome according to the SSS score was 29 (range, 25 to 37) 4 weeks after stroke and 38 (range 28 to 48) 3 months after stroke. During hypothermia, elevated ICP values could be significantly reduced. Herniation caused by a secondary rise in ICP after rewarming was the cause of death in all remaining patients. The most frequent complication of moderate hypothermia was pneumonia in 10 of the 25 patients (40%). Other severe side effects of hypothermia could not be detected.

Conclusions—Moderate hypothermia in the treatment of severe cerebral ischemia is not associated with severe side effects. Moderate hypothermia can help to control critically elevated ICP values in severe space-occupying edema after MCA stroke and may improve clinical outcome in these patients. 

Key Words: hypothermia ■ intracranial pressure ■ neuroprotection ■ outcome ■ stroke, ischemic ■ treatment

The neuroprotective effect of profound hypothermia has long been recognized, but use of hypothermia for the therapy of neuronal injuries was abandoned because of management problems and severe side effects, such as cardiac arrhythmia, shivering, infections, and coagulation disorders.1 In the past decade, it has come to be recognized that even mild (34°C to 36°C) or moderate (34°C to 28°C) therapeutic modulation of temperature may substantially avert brain damage caused by ischemia in both experimental stroke and other neuronal injuries.2,3 After focal cerebral ischemia, hypothermia reduced infarct volumes up to 90%,4–6 whereas hyperthermia had a significantly negative effect on histopathological findings and outcome.7–9

The mechanisms by which hypothermia is neuroprotective are not fully understood yet. Hypothermia, however, was found to reduce cerebral metabolism, decrease levels of excitatory amino acids, stabilize the blood-brain barrier, and account for membrane stabilization and the decrease in heat shock proteins after induced brain injury.10–12

Several clinical studies reported the effects of hypothermia in the therapy of traumatic brain injury.13–16 All demonstrated that mild to moderate hypothermia has the potential to limit the extent of secondary brain injury and may be effective in the treatment of patients with severe traumatic head injury.

Even though hypothermia has potent cerebroprotective effects after experimental focal ischemia, clinical studies on hypothermic therapy after middle cerebral artery (MCA) infarction are not available. However, 2 recent clinical studies emphasized the importance of body temperature for stroke prognosis and severity.17,18 Reith et al18 demonstrated lower mortality and better outcome in patients with mild hypothermia (<36.5°C) on admission. Azzimondi et al17 showed that fever in the first 7 days after stroke was an independent predictor of poor outcome.

We performed an open pilot study on the efficacy, feasibility, and safety of induced moderate hypothermia in the therapy of patients with acute, severe MCA infarction and increased intracranial pressure (ICP).

Subjects and Methods
This study is based on 25 patients, 18 men and 7 women (age, 35 to 72 years; mean, 49±14 years), who had suffered acute severe MCA-territory stroke and were admitted to the neurocritical care unit for treatment of elevated ICP. The study was approved by the local ethics committee. Inclusion criteria were clinical and computed

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tomographic evidence of acute, large, complete MCA infarction (which consisted of early large parenchymal hypodensity and signs of local brain swelling, such as sulci effacement and lateral ventricle compression); further neurological deterioration compared with the baseline clinical status on admission to the neurocritical care unit; and control computed tomography at that time showing complete MCA infarction with an increased space-occupying effect with compression of the lateral ventricle beginning midline shift and compression of the basal cisterns. Patients with any previous disabling neurological diseases or terminal illnesses were excluded from this protocol.

The ICP was monitored in all patients with 2 different types of intraparenchymatous sensors and transducers (Spiegelberg pneumatic transducer, Spiegelberg AG, n=16; Codman microsensor, Johnson & Johnson, n=9). ICP devices were inserted ipsilaterally to the affected hemisphere in 18 patients and bilaterally in 7 patients. Clinical data were obtained daily from all patients and assessed with the Scandinavian Stroke Scale (SSS) and Glasgow Coma Scale (GCS). Clinical outcome was assessed 4 weeks and 3 months after stroke with the 58-point SSS and the Rankin scale. Daily living activities were rated with the 100-point Barthel index (BI).

General Critical Care
The focus of critical care for all patients was to maintain cerebral perfusion pressure (CPP) above 70 mm Hg. CPP was calculated as the difference between mean arterial blood pressure and ICP. To reach mean arterial blood levels >90 mm Hg, vasopressors (norepinephrine 0.2 µg·kg⁻¹·min⁻¹) were used. Hemoglobin concentration was maintained at >90 g/L. Patients with increased ICP (>20 mm Hg) were treated with intermittent boluses of mannitol (0.5 to 1 g/kg) before initiation of hypothermia. Hyperventilation or end-expiratory pressure or Fi O₂ were treated with intermittent boluses of mannitol (20 mm Hg) were treated with intermittent boluses of mannitol.

Temperature Protocol
Brain temperature was measured with the Spiegelberg intraparenchymatous ICP probe, which has a thermistor in its tip. Accuracy for temperature measurements is <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 (Moni- therm, Mallinckrodt). All patients were sedated with fentanyl and propofol and received neuromuscular blockade with continuous infusion of atracurium (0.3 to 0.6 mg/kg IV).

Room temperature in the intensive care unit was between 18°C and 20°C. In this study, a cooling blanket (Polar Bair, Augustine Medical) with cool ventilator air fanning the patient’s body surface was used for external cooling. Acid-base management was guided by blood-gas analysis not corrected for temperature to maintain auto-regulation (α-stat management). Once the body-core temperature reached 33°C, it was kept between 33°C and 34°C for 48 to 72 hours. During the next 24 hours, the patient was passively rewarmed to a normal temperature.

Evaluation of Side Effects
Side effects known to be related to hypothermia, such as infections, coagulation disorders, and decreased cardiac performance with bradycardia, cardiac arrhythmia, and hypotension, were documented and analyzed. Sepsis as a systemic response to infection was suspected, according to the criteria of the American College of Chest Physicians, when ≥2 of the following conditions became manifest: heart rate >90 bpm, white blood cell count >12,000 or <4000 cells/mm³, respiratory rate >20 breaths per minute, or PaCO₂ <32 mm Hg. Body temperature as 1 further point was not analyzed. Pneumonia was suspected if the following criteria were met: new infiltrates on chest x-ray, purulent tracheobronchial secretions, and impairment of pulmonary gas exchange. Renal function was evaluated by urine output and creatinine clearance. Activated prothrombin and partial thromboplastin times were measured every 6 hours to evaluate intrinsic and extrinsic coagulation pathways. Platelet counts, serum enzymes, and electrolytes were determined every 12 hours.

Statistics
All values are expressed as mean±SD. Median is also given for ordinal data, such as SSS and BI. Physiological measurements within groups were analyzed by nonparametric tests as appropriate (Wilcoxon signed-rank test). Significance was assigned at P<0.05.

Results
Patients
On admission, the median SSS score was 24 (range, 18 to 28); the mean GCS was 9 (range, 4 to 13). All patients presented with severe dense hemiparesis and forced eye and head deviations. All patients had suffered large MCA-territory stroke. Twenty patients had complete MCA-territory stroke; 5 patients had additional anterior or posterior artery territory infarctions. The cause of stroke was cardioembolism in 18 patients, internal carotid artery dissection with secondary MCA embolization in 3 patients, atherothrombotic disease at the carotid bifurcation in 1 patient, and unknown in 3 patients. Of 25 patients, 11 (44%) who underwent moderate hypothermic therapy for major space-occupying infarction died (Table 1).

Mean interval between onset of symptoms of ischemic stroke and initiation of hypothermia was 14 hours (range, 4 to 24 hours). Time required for cooling to 33°C bladder temperature was from 3.5 to 6.2 hours. Moderate hypothermia was sustained for 48 to 72 hours (median, 65 hours). Passive rewarming took between 17 and 24 hours (median, 18 hours). The monitoring device was inserted at a mean of 10 hours after stroke onset (range, 6 to 32 hours), and the average ICP monitoring period varied between 3 and 7 days (mean, 4.9±2.5 days). Mean initial ICP was 20.9±12.4 mm Hg (range, 13 to 36 mm Hg). In all patients, ICP values de-
Side Effects
Before initiation of hypothermia, a systemic response to infection was absent in all 25 patients, whereas after rewarming, 7 patients had a septic syndrome according to the above-mentioned criteria. The most frequent complication of moderate hypothermia was pneumonia, which was encountered in 10 of the 25 patients (40%). In 6 patients, pneumonia was diagnosed during rewarming. Activated prothrombin and partial thromboplastin times remained unchanged during hypothermia. However, platelet count decreased significantly during hypothermia and was lower than initial values. This effect lasted up to 3 days after rewarming. The observed thrombopenia was asymptomatic and did not cause any bleeding complications. Urine output and creatinine clearance did not demonstrate a statistically significant difference before, during, or after induction of hypothermia. A significant increase in serum amylase and lipase in 7 of the 25 patients (28%) with maximal lipase levels of 1200 U/L (normal value, <150 U/L) occurred under hypothermic therapy. However, there were no clinical signs and symptoms of acute pancreatitis in any patient. Analysis of serum sodium concentrations remained unchanged during hypothermia, but serum potassium concentrations were markedly decreased during cooling and in the steady state of hypothermia. Cardiac arrhythmias (with prolongation of the PR and QT intervals) and sinus bradycardia were seen in 15 patients, whereas no patient developed severe hypotension or required further antiarrhythmic therapy (Table 3).

Discussion
Conventional treatment of elevated ICP after ischemic stroke consists of artificial ventilation, osmotherapy, and barbiturate administration. The value and duration of these measures have come under scrutiny. Prolonged hyperventilation has been discouraged because the potential decrease in cerebral arterial blood flow resulting from additional hypocarbia might exacerbate tissue ischemia. Early use of such agents as glycerol or mannitol may, at least in theory, actually hasten tissue shifts and therefore lead to an aggravation of brain edema. Barbiturate therapy has as yet failed to be of therapeutic benefit in the treatment of postischemic brain edema. Because of the potential adverse effects of “conventional therapy,” new therapeutic concepts for the treatment of brain edema have to be used.

In animal models with both focal and global ischemia, moderate hypothermia reduced secondary brain injury and infarction size and improved neurological outcome. However, most of these studies used a narrow time window, with

### TABLE 2. Effects of Moderate Hypothermia on Intracranial and Systemic Physiological Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normothermia</th>
<th>Hypothermia</th>
<th>After Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP, mm Hg</td>
<td>20.9±12.4</td>
<td>13.4±8.3*</td>
<td>19.4±8.7</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>68±14</td>
<td>78±21*</td>
<td>70±21</td>
</tr>
<tr>
<td>Brain temperature, °C</td>
<td>38.4±1.3</td>
<td>33.3±0.7</td>
<td>37.4±0.9</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>37.5±0.9</td>
<td>33.0±0.2</td>
<td>36.8±0.9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>84±6</td>
<td>62±10*</td>
<td>80±12</td>
</tr>
</tbody>
</table>

*P<0.05 vs baseline.

### TABLE 3. Side Effects of Moderate Hypothermia on Various Organ Systems

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normothermia</th>
<th>Hypothermia</th>
<th>After Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count, count/mL</td>
<td>183 (145–310)</td>
<td>110 (20–180)*</td>
<td>160 (50–210)</td>
</tr>
<tr>
<td>aPTT, s</td>
<td>27 (20–45)</td>
<td>34 (25–50)</td>
<td>30 (20–55)</td>
</tr>
<tr>
<td>Serum lipase, U/L</td>
<td>140 (60–190)</td>
<td>250 (140–1200)*</td>
<td>200 (135–1000)</td>
</tr>
<tr>
<td>Serum potassium, mmol/L</td>
<td>4.1 (3.5–4.7)</td>
<td>3.4 (3.1–3.9)*</td>
<td>4.4 (4.0–5.2)</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>139 (134–145)</td>
<td>140 (138–150)</td>
<td>145 (139–155)</td>
</tr>
<tr>
<td>Creatinine clearance, mL·min⁻¹·min⁻²</td>
<td>81 (60–100)</td>
<td>65 (45–90)</td>
<td>70 (45–95)</td>
</tr>
<tr>
<td>Norepinephrine, μg·kg⁻¹·min⁻¹</td>
<td>0</td>
<td>0.32 (0.0–0.45)*</td>
<td>0.08 (0.0–0.24)</td>
</tr>
</tbody>
</table>

aPTT indicates activated partial thromboplastin time. Values in parentheses are ranges.

*P<0.05 vs baseline.
hypothermia initiated within 60 to 90 minutes after induction of experimental ischemia. Markarian et al.²⁸ demonstrated the best results in a focal ischemia model when hypothermia was applied within the first 30 minutes and lasted 3 hours. Applying these data to clinical practice would suggest that induced hypothermia is beneficial only in the very first few hours after stroke onset.

Several neurosurgical studies showed a positive effect of mild hypothermia on uncontrollable intracranial hypertension after severe head trauma.¹³–¹⁶ Head-injured patients treated with mild hypothermia between 32°C and 34°C core temperature had a significant reduction in ICP and cerebral blood flow compared with the normothermia-treated control group. All studies indicated better outcome with hypothermia and a beneficial effect in limiting secondary brain injury. In most of these studies, hypothermia was delivered within the first 6 to 16 hours after head injury. Duration of hypothermia varied from 24 to 48 hours, whereas neither the optimal duration of hypothermia nor the optimal time after the trauma for therapy in these patients could be identified.

Similar to these clinical studies, hypothermia was induced in this study a mean of 14 hours after the ischemic injury. Obviously, this time delay has to be reduced in further trials because according to experimental data, hypothermia has the most positive effect when applied very early after cerebral ischemia. We chose a relatively long duration of hypothermia to overcome maximum brain swelling, which is known to occur between days 2 and 5 after ischemia.²⁹–³²

In space-occupying MCA infarction, outcome is fatal in most patients, with a mortality rate of about 80% with standard treatment.³¹,³² Clinically, the patients have a severe hemispheric syndrome with head turning and eye deviation. They usually show a rapid decline in consciousness and develop the signs of herniation 2 to 4 days after onset of symptoms.³¹,³² All patients in this study fulfilled the criteria for diagnosis of a “malignant” MCA infarction.³³ However, the mortality rate was only 44%, and survivors reached a favorable outcome with a mean BI of 70 (Figure 1 and Table 4). It is known from animal models with global ischemia and traumatic brain injury that moderate hypothermia attenuates secondary brain damage by reducing cerebral ischemia and postischemic brain edema and preserving the blood-brain barrier. Hypothermia significantly reduced the ICP, which is similar to the results of Marion et al.¹⁴ and Shiozaki et al.,¹⁶ who used hypothermic therapy in traumatic brain injuries. With a merely unaffected mean arterial blood pressure and increased CPP, hypothermic therapy appears to benefit stroke patients because uncontrolled intracranial hypertension is the main cause of death in the first week after stroke.²⁹–³² However, rewarming the patients constantly led to a secondary increase in ICP, which required additional ICP therapy with mannitol. In some cases, it even exaggerated initial ICP levels. It is known that the rewarming period is a high-risk time for brain injury because metabolic needs may outstrip oxygen delivery at various temperatures.³³ Of the 11 patients who died, 5 had untreated elevation of ICP during rewarming, whereas in 6 patients, signs of transtentorial herniation occurred with a body temperature of 33°C. The rebound increase in ICP after rewarming might suggest that hypothermia only delays the deleterious effects caused by ischemic injury and thus does not result in any substantial improvement. The fact that most patients had lower ICP levels than before induction of hypothermia speaks clearly against this hypothesis (Figure 2). However, rewarming has to be considered the “critical phase” of hypothermic therapy. This rebound after rewarming might be due to a proposed hypermetabolic response after induced hypothermia, as it was described after cardiopulmonary bypass surgery.³⁴

The brain temperatures of all 25 patients were consistently higher than body-core temperatures, confirming previous data that showed a significant gradient between body-core and brain temperatures in neurotrauma patients.³⁵,³⁶ This may be explained by the high metabolic activity of cerebral tissue with considerable production of heat.³⁷ 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.

![Figure 1. Survival curve of all patients treated with moderate hypothermia compared with patients treated with conventional therapy.³¹](image)

| TABLE 4. Comparison Between Patients Treated With Hypothermia and Natural History Data |
|--------------------------------|----------------|----------------|
| Characteristics              | Hypothermia    | Natural History* |
| Age, y                      | 49±14          | 56.0±9.4        |
| Infarction of               |                |                |
| MCA                         | 20             | 43             |
| MCA/ACA                     | 5              | 7              |
| MCA/PCA                     | –              | 5              |
| Cause of stroke             |                |                |
| Embolic                     | 18             | 51             |
| Dissection                  | 3              | 4              |
| Other                       | 4              | –              |
| Hemisphere                  |                |                |
| Right                       | 8              | 21             |
| Left                        | 17             | 34             |
| SSS on admission            | 20.5±9.2       | 19.5±7.6       |
| Mortality rate, % (total)   | 44 (11/25)     | 78 (43/55)     |
| Mean BI                     | 70             | 60             |

ACA indicates anterior cerebral artery; PCA, posterior cerebral artery. *Obtained from Hacke et al.³¹
In animal studies, it was reported that toxicity from moderate hypothermia increases as the temperature is further decreased and as the duration of hypothermia is increased.\(^1\) In this study, we could not observe a significant increase in the occurrence of side effects between patients cooled for 48 hours and those treated for 72 hours. Hypothermia affects virtually every organ system. The extent of hypothermia is limited by ventricular ectopy and fibrillation, but this is known to occur only at temperatures <30°C.\(^1\) In the present study, pneumonia was the only severe side effect of moderate, induced hypothermia. However, impairment of pulmonary gas exchange, caused by atelectasis, is a common problem in patients who are ventilated longer. The reported incidence of pneumonia in these patients ranges from 10% to 40%.\(^4\) The risk of developing pneumonia increases when coma, trauma, or impaired airway reflexes are present at admission to the critical care unit.\(^4\) In our study, the incidence of pneumonia of 40% is comparable to these reported data and similar to the findings of Metz and colleagues,\(^5\) who observed pneumonia in 50% of their hypothermically treated patients within the first week in the intensive care unit. Other side effects of hypothermia shown in animal studies are clotting abnormalities and coagulopathy.\(^4\) In baboons, systemic hypothermia led to increased bleeding times.\(^4\) In humans, the enzymatic reactions of the coagulation cascade were shown to be strongly inhibited by hypothermia.\(^4\) However, we could not observe any severe clotting abnormalities in the hypothermia-treated patients. On the other hand, a decrease in platelet counts during the cooling period was regularly seen, with recovery only after rewarming. Also pancreatitis with high serum amylase and lipase levels was observed after hypothermic therapy. The association between hypothermia and pancreatitis is poorly understood yet.\(^4\) In our study, the pathological signs of pancreatitis with elevated levels of amylase and lipase were completely reversible after rewarming.

In conclusion, induced, moderate hypothermia can decrease ICP and may improve mortality in patients with severe postischemic brain edema. Important side effects are reduction in platelet count, increased rate of pneumonia, and elevation of serum amylase and lipase levels. Our own preliminary results suggest a beneficial effect of moderate hypothermia in the treatment of severe space-occupying MCA infarction. However, our data call for a randomized trial of hypothermia in the therapy of malignant MCA infarction. Whether early hypothermic therapy within the first 6 hours after onset of symptoms can reduce infarct size has to be clarified in further clinical trials.

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References


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