Feasibility and Safety of Moderate Hypothermia After Massive Hemispheric Infarction

Stefan Schwab, MD; Dimitrios Georgiadis, MD; Jörg Berrouschot, MD; Peter D. Schellinger, MD; Carmelo Graffagnino, MD, FRCP(C); Stephan A. Mayer, MD

Background and Purpose—Moderate hypothermia decreases ischemic damage in experimental stroke models. This multicenter study was performed to evaluate (1) the safety and feasibility of moderate hypothermia and (2) its potential to reduce intracranial hypertension in acute stroke patients.

Methods—Fifty prospective patients with cerebral infarction involving at least the complete middle cerebral artery territory treated with moderate hypothermia were evaluated. Hypothermia was induced with the use of cooling blankets as well as alcohol and ice bags within 22±9 hours after stroke onset and maintained for 24 to 72 hours; subsequently, patients passively rewarmed over a mean duration of 17 hours. Outcome was assessed at 4 weeks and at 3 months.

Results—Time required for cooling to <33°C varied from 3.5 to 11 hours. The most frequent complications of hypothermic therapy were thrombocytopenia (70%), bradycardia (62%), and pneumonia (48%). Four patients (8%) died during hypothermia as a result of severe coagulopathy, cardiac failure, or uncontrollable intracranial hypertension. An additional 15 patients (30%) died during or after rewarming because of rebound increase in intracranial pressure (ICP) and fatal herniation. A shorter (<16 hours) rewarming period was associated with a more pronounced rise of ICP. Elevated ICP values were significantly reduced under hypothermia. Neurological outcome according to the National Institutes of Health Stroke Scale score 4 weeks after stroke was 29, and Rankin Scale score 3 months after stroke was 2.9.

Conclusions—Moderate hypothermia is feasible in patients with acute stroke, although it is associated with several side effects. Most deaths occur during rewarming as a result of excessive ICP rise. Our preliminary observation that a longer duration of the rewarming period limits the ICP increase remains to be confirmed in future studies. (Stroke. 2001;32:2033-2035.)

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

The potential of hypothermia in reducing neuronal damage was demonstrated in several animal models of focal cerebral ischemia.1,2 The feasibility and safety of this technique for acute stroke were only examined in 1 study, describing a total of 25 patients.3 We analyzed data from 50 consecutive patients with acute stroke, treated with moderate hypothermia in the neurocritical care units of 4 university clinics, to evaluate the feasibility and safety of moderate hypothermia. The efficacy of moderate hypothermia in reducing intracranial pressure (ICP) was also examined.

Subjects and Methods

Data from 50 consecutive patients (35 men and 15 women; mean age, 57±8 years; range, 30 to 75 years) treated with moderate hypothermia are presented in this study. The indication for moderate hypothermia was acute ischemic cerebral infarction, involving at least the complete territory of the middle cerebral artery (MCA). Patients with history of disabling neurological disease, terminal illness, or severe cardiac failure (New York Heart Association class III or IV) were excluded from this protocol. None of the 50 patients received thrombolytic therapy, mostly because of late arrival in the hospital. Because no data on the ideal timing for initiation of moderate hypothermia are currently available, this time point was based on individual decision making; some patients were treated immediately after initial cranial CT scan; others were treated only after clinical or radiological signs of midline shift became evident. Standard management of all patients entailed arterial catheters, central venous line, intubation, and invasive monitoring of the ICP. This was performed with the use of 3 different types of intraparenchymatous sensors and transducers (Spiegelberg pneumatic transducer, Spiegelberg AG; Codman microsensor, Johnson & Johnson; Camino monitoring system, Camino Laboratories). ICP devices were always inserted ipsilaterally to the affected hemisphere. ICP values were recorded hourly during the patient’s stay in the intensive care unit.

Initial patient status and patient status at 4 weeks were assessed with the National Institutes of Health Stroke Scale (NIHSS). Clinical outcome was assessed with the Rankin Scale and the 100-point Barthel Index 3 months after stroke.
The body-core temperature was kept between 32°C and 33°C for 24 to 72 hours. The exact duration of moderate hypothermia was decided at the discretion of the treating physicians; its maximum duration was set at 72 hours. After this time period, passive rewarming of the patients over 24 hours to normal temperatures was allowed. Again, the pace of rewarming was decided by the local physician.

All patients were sedated with midazolam or propofol; morphine or fentanyl was used for analgesia. Additionally, all patients received neuromuscular blockade (vecuronium or atracurium) before the initiation of moderate hypothermia; this regimen was continued until rewarming at 36°C was achieved. No anticoagulants were used in any patient. Patients’ heads were elevated at 30°C. Increased ICP was treated with intermittent boluses of mannitol (0.5 g/kg), glycerine (10 g/d), or hypertonic saline (50 mL, 20%) at the discretion of the treating physicians. This treatment did not constitute part of the moderate hypothermia protocol and was not recorded for later evaluation. Hyperventilation or barbiturates were not part of our treatment regimen.

Normal distributed values were expressed as mean±SD and compared by Wilcoxon’s test. Significance was declared at the $P<0.05$ level.

### Results

The mean NIHSS score on admission was 25 (range, 15 to 32); Glasgow Coma Scale score was 9 points (range, 4 to 12). All patients had complete MCA territory stroke; 5 patients had an additional anterior or posterior artery territory infarction. The etiology of stroke was cardioembolism in 34 patients, atherothrombotic disease at the carotid bifurcation in 3 patients, and unknown in 5 patients. No signs of infection were evident in any patient. The etiology of stroke was cardioembolism in 34 patients, atherothrombotic disease at the carotid bifurcation in 3 patients, and unknown in 5 patients. No signs of infection were evident in any patient before initiation of hypothermia.

The mean interval between onset of symptoms of ischemic stroke and initiation of hypothermia was 22±9 hours (range, 4 to 75 hours). The time required for cooling to $<33°C$ bladder temperature varied from 3.5 to 11 hours (mean, 6.5 hours). Moderate hypothermia was sustained for 24 to 72 hours (mean, 55 hours). During this time, temperature values remained stable (maximal increase observed, 0.7°C; maximal decrease observed, 0.8°C). Passive rewarming lasted between 11 and 24 hours (mean, 17 hours). The ICP monitoring device was inserted at a mean of 21 hours after stroke onset (range, 6 to 32 hours), and the ICP monitoring period varied between 3 and 7 days.

The mean ICP before the initiation of moderate hypothermia was 19.8±14.2 mm Hg (range, 4 to 36 mm Hg). When the steady state of hypothermia was reached, ICP values were reduced to 12.4±5.3 mm Hg ($P<0.05$). ICP values were sustained at constant levels in 37 of 50 patients during moderate hypothermia; a moderate increase (maximum increase observed was $+25\%$ of the initial value) was noted in remaining cases. A rise of ICP values was observed in all patients during rewarming; as the patient’s temperature reached 36°C ICP, values rose to measured mean values of 23.4±8.7 mm Hg (range, 17 to 71 mm Hg). A shorter (<16 hours) rewarming period was associated with a more pronounced rise of ICP ($15\%$ to $26\%$; $P>0.05$, 2-sample t test) (Figure).

Cardiac arrhythmia (with prolongation of the PR and QT intervals) and sinus bradycardia occurred in 31 patients (62%); arterial hypotension as a result of arrhythmia only occurred in 2 patients who therefore required antiarrhythmic therapy (Table). Arterial hypotension was observed in all patients; maintenance of cerebral perfusion pressure $>70$ mm Hg was thus only feasible under use of crystalloid fluids ($n=50$) and vasopressor agents ($n=47$). Severe arterial hypotension ($<50$ mm Hg) was observed in 3 patients and was refractory under high doses of vasopressor agents in 1 case, while the remaining 2 patients finally died of cardiac failure. The most frequent complication of moderate hypothermia was pneumonia, encountered in 48% of patients. Serum potassium concentrations were markedly decreased in all patients during cooling and in the steady state of hypothermia. Potassium was only substituted if its serum level dropped to $<3.0$ mmol/L, which was the case in 5 patients in this study, and only to levels of approximately 3.5 mmol/L. Potassium levels spontaneously increased between 1 and 1.5 mmol/L after termination of hypothermia. Sodium, creatinine, hematocrit, and hemoglobin levels remained essentially unchanged during the observation period. No relation between prevalence of complications and duration of hypothermia was noted in this study, with the exception of pneumonia, the prevalence of which increased with longer duration of hypothermia.

Platelet count decreased in 35 patients (70%) during hypothermia (mostly to values between 50 and 100 000; values between 30 and 50 000 were only observed in 3 cases). This effect lasted up to 3 days after rewarming. Severe coagulopathy, requiring substitution, occurred in 3 patients and was lethal in 1 case. Finally, acute pancreatitis was

### Incidence of Complications in 50 Patients With Acute Stroke Undergoing Moderate Hypothermia

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients (Incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count $&lt;100$ 000/mL</td>
<td>35 (70%)</td>
</tr>
<tr>
<td>Cardiac arrhythmia/bradycardia</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Severe hypotension (MAP $&lt;50$ mm Hg)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Severe coagulopathy</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure.
diagnosed in 3 patients but subsided on conservative management.

Nineteen of 50 patients (38%) who underwent moderate hypothermic therapy for major space-occupying infarction died. With the exception of the 3 aforementioned patients, and 1 additional patient who died of hemorrhage on day 3 while still under moderate hypothermia, all deaths occurred after termination of moderate hypothermia and were due to an extensive increase in ICP. Severe midline shift (3 to 5 mm) was observed in the 11 of 15 patients who underwent cranial CT scan between termination of hypothermia and death. All remaining patients were discharged to rehabilitation programs. Their neurological outcomes according to the NIHSS score 4 weeks after stroke was 29. After 3 months, the mean Barthel Index was 65 (range, 10 to 85), and the mean Rankin Scale score was 2.9 points (range, 2 to 5); 3 patients were lost to follow-up.

**Discussion**

Initiation of moderate hypothermia in patients with acute stroke appears to be feasible with an acceptable temporary delay: all patients in this study reached the target temperature within 12 hours, while merely 6 hours were required in approximately 50% of cases. Moderate hypothermia was shown to be a potent treatment for intracranial hypertension, inducing a significant ICP reduction in all cases. This finding is in agreement with previous reports in patients with acute stroke or severe head injury.

Our results demonstrate that moderate hypothermia represents a treatment option associated with considerable side effects: 4 patients (8%) died of hypothermia-related complications (cardiac failure or coagulopathy); hypotension was observed in 100%, cardiac arrhythmia and bradycardia in 62%, and pneumonia in 48% of our patients. The incidence of pneumonia was thus markedly higher than the 15.8% reported by Chevret et al for patients after a 7-day stay in the intensive care unit. It must be noted that both arrhythmia and pneumonia were successfully treated and did not constitute severe problems; on the other hand, a potential negative influence of these complications in the evolution of acute stroke cannot be ruled out. Alternative techniques for induction of hypothermia are urgently needed for better control of the cooling process. Kammersgaard et al recently reported application of modest hypothermia in patients with acute stroke. This technique appears to be safer than moderate hypothermia and could potentially present an attractive treatment option, provided that its efficacy is established.

Rewarming the patients constantly led to a secondary rise of ICP. 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. Studies on jugular bulb oximetry in patients with cardiopulmonary bypass revealed a major alteration in the balance of the cerebral oxygen supply and demand in response to rewarming. An inadequate increase in cerebral blood flow to meet the cerebral metabolic demand is suggested. A “rewarming shock” with sudden vasodilatation may be due to this proposed hypermetabolic response after induced hypothermia, as described after cardiopulmonary bypass surgery. There may also be a direct effect of hypothermia on the cerebral vessels. In animal experiments hypothermia can enhance contractility of cerebral arteries. At the same time, hypercontractility of isolated cerebral human arteries was observed during rewarming after hypothermia. We noted a significantly lower mortality in association with longer rewarming periods (>16 hours) compared with patients rewarmed within 16 hours. While our study design prohibits any definitive conclusions regarding this intriguing issue, the suggested influence of the duration of the rewarming period on outcome merits further examination.

This study was not designed to assess the efficacy of moderate hypothermia. Still, it must be noted that the mortality observed was merely 38%, which is considerably lower than the 78% mortality described by Hacke et al or the 79% described by Berrouschot et al. Additionally, survivors reached a relatively favorable outcome, with a mean Barthel Index score of 65. These observations should encourage a controlled trial of the effects of hypothermia in acute stroke patients.

In conclusion, moderate hypothermia is feasible in patients with acute stroke. Several side effects were encountered, suggesting that application of this treatment should be limited to specialized units. The incidence of side effects was not influenced by the duration of hypothermia. Still, excessive ICP rise, which was associated with most deaths observed, appeared to depend on the duration of rewarming. This issue remains to be examined in future studies.

**References**

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