Hemicraniectomy and Moderate Hypothermia in Patients With Severe Ischemic Stroke

D. Georgiadis, MD; S. Schwarz, MD; A. Aschoff, MD; S. Schwab, MD

Background and Purpose—We compared the clinical course of 36 consecutive patients with severe acute ischemic stroke (more than two thirds of the middle cerebral artery territory) treated with hemicraniectomy (CE; n = 17) or moderate hypothermia (MH; n = 19) in terms of intracranial pressure control, mortality, and specific treatment parameters.

Methods—Over a period of 18 months, patients with severe ischemic stroke were treated with CE when the nondominant hemisphere was affected and with MH when the dominant hemisphere was affected. MH (33°C) was induced with either cold blankets and fans (n = 11) or endovascular cooling (n = 8). Intracranial pressure was monitored invasively in all cases.

Results—Age, sex, cranial CT findings, level of consciousness, and time to treatment were similar between the 2 groups; significant differences were noted in National Institute of Health Stroke Scale (NIHSS) score (20 [range, 18 to 22] and 17 [range, 16 to 18] for MH and CE, respectively) but were not present when NIHSS score was corrected for aphasia (17 [range, 15 to 19] and 17 [range, 16 to 18] for MH and CE, respectively). Mortality was 12% for CE and 47% for MH; 1 patient treated with MH died as a result of treatment complications (sepsis) and 3 of intracranial pressure crises that occurred during rewarming. Duration of mechanical ventilation and of neurological intensive care unit stay did not significantly differ, but duration of catecholamine application and maximal catecholamine dosage were significantly higher in the MH group.

Conclusions—In patients with severe ischemic stroke, CE results in lower mortality and lower complication rates compared with MH. Both treatment modalities, however, are associated with intensive medical treatment and a prolonged stay in the neurological intensive care unit. (Stroke. 2002;33:1584-1588.)

Key Words: craniectomy ■ hypothermia ■ stroke, acute ■ stroke management

The neuroprotective properties of moderate hypothermia (MH) in acute ischemic stroke were demonstrated in several experimental models.1–3 Furthermore, recent clinical findings suggested that MH may reduce mortality in patients with space-occupying middle cerebral artery (MCA) infarction.4,5 Hemicraniectomy (CE) was also reported to improve outcome. Since 1988, 7 studies including a total of 129 treated patients have been published.6–12 The overall mortality rate was 23.2%, and most patients demonstrated a Barthel index >60. Although both approaches constitute promising treatment modalities for space-occupying cerebral infarction, no study has yet compared their effectiveness in controlling intracranial hypertension and reducing mortality. Furthermore, selection criteria for MH or CE are lacking; thus, in most centers, the decision is based on the availability of neurosurgeons, their willingness to perform CE, and the subjective evaluation of individual patient parameters, mainly age and severity of initial symptoms.

Here, we describe the clinical course of 36 consecutive patients with ischemic infarction involving at least two thirds of the MCA territory who were treated with MH or CE, with particular emphasis on intracranial pressure (ICP) control, treatment parameters, and mortality.

Patients and Methods
From April 2000 until September 2001, 36 patients with severe acute ischemic stroke were treated with CE (n = 17) or MH (n = 19). The decision for aggressive treatment was based on either (1) initial cranial CT (CCT) findings consistent with a large MCA infarction (early large parenchymal hypodensity of more than two thirds of the MCA territory and signs of local brain swelling such as effacement of the sulci and compression of the lateral ventricle) or (2) delineation of an infarction involving more than two thirds of the MCA territory on follow-up CCT, which was routinely performed 12 to 24 hours after admission, according to our institutional protocol, and further deterioration of level of consciousness (LOC). Additionally, the severity of clinical symptoms, as assessed by the National Institute of Health Stroke Scale (NIHSS), should be >15. Patients with any previous disabling neurological disease or terminal illness were excluded from this protocol. Allocation to the MH or CE group was based on the affected hemisphere, with CE being performed for the nondominant and MH for the dominant hemisphere. This is the only currently feasible study option because German law does not allow randomization in patients unable to give informed consent. Thus, patients were offered CE or MH, depending on the affected
hemisphere. Potential risks and benefits of each concept were discussed with patients and/or their families. Consent for CE or MH was obtained in all cases.

The extent of infarction was evaluated on the basis of the findings of the follow-up CCT scan and graded from 1 to 3 (1 = MCA infarction involving at least two thirds of the MCA territory [subtotal MCA infarction], n = 16; 2 = MCA infarction involving the complete MCA territory, n = 11; 3 = subtotal or total MCA infarction with additional involvement of other vascular territories, n = 9). Infarcts affecting additional territories were not caused by brain swelling that compressed the anterior or posterior cerebral artery but were already delineated on initial CCT scan. The patient with bilateral MCA infarction was initially diagnosed with a right MCA infarction and therefore treated with CE. Early signs of left hemispheric infarction were later noted on the initial CCT scan.

Clinical assessment was based on the NIHSS, which was performed within the first hour after admission to the neurological intensive care unit (NICU). To enhance comparability of the 2 patient groups, we also used a modified NIHSS, which did not include language-relevant subscores (omitting subitems 1.b, LOC questions; 1c, LOC commands; and 9, best language). Additionally, LOC was assessed for each patient by use of a scale ranging from 1 to 4 (awake, drowsy, stupor, coma).

Diagnostic workup of patients enrolled in this study entailed (1) ultrasound examination of the extracranial and intracranial vessels by means of Duplex sonography (Acuson 128, Acuson) and transcranial Doppler (Multi-Dop X-4, DWL); (2) transthoracic and, when appropriate, transesophageal echocardiography; and (3) extensive hematology testing, including serum hematocrit level, platelet count, fibrinogen, proteins C and S, antithrombin III, antiphospholipid antibodies, and activated protein C resistance.

ICP was invasively monitored with parenchymal catheters (Spiegelberg pneumatic transducer, Spiegelberg AG; Codman Microsensor, Johnson & Johnson) that were inserted into the affected hemisphere in all cases. ICP catheters were inserted during surgery in patients who underwent CE and 1 to 2 hours before initiation of hypothermia in the MH group. Arterial blood pressure was also monitored invasively with a catheter inserted into the radial artery. Body temperature was measured with a Foley temperature catheter inserted into the bladder (Mon-a-therm, Mallinckrodt). Patients were nursed in the 30° head elevation position.

Crystallloid or colloid fluids were applied when appropriate to maintain cerebral perfusion pressure >70 mm Hg. If this treatment remained ineffective, vasopressors were introduced. Fluid homeostasis was maintained by exact evaluation of fluid intake and output, aiming at a central venous pressure between 8 and 12 cm H₂O. Parenteral nutrition or enteral feeding was begun as soon as possible. All patients were sedated with midazolam at the time of the study; fentanyl was used for analgesia and atracurium (0.3 to 0.6 mg/kg body weight) for neuromuscular blockade during MH. ICP crises were initially treated with bolus infusions of mannitol (0.5 to 1 g/kg body weight) or hypertonic (10%) solution of sodium chloride (80 mL/15 minutes); TRIS buffer (initially 1 mmol/kg body weight followed by continuous infusion aiming at a pH ranging from 7.5 to 7.55) and barbiturates (initially 200 mg bolus infusion of thiopental followed by 2 to 5 mg/kg body weight per hour) constituted further alternatives. Forced hyperventilation was not used in any case. Patients were ventilated with a volume-controlled, pressure-regulated mode and an inspiratory-expiratory ratio of 1:2 (Servo 300, Siemens).

MH was induced in the first 12 patients by external cooling with blankets (Hico Varitherm 550, Hirtz & Co. Hospitalwerk) and with cool ventilator air fanning the patient’s body surface. The remaining 7 patients were treated with endovascular cooling; technical details of this method and data on its feasibility are presented elsewhere. In brief, an 8.5F × 35-cm catheter central line (ICY, Alsius Corporation) was inserted into the femoral vein and advanced to the inferior vena cava in all 7 patients. In addition to a single infusion lumen, the catheter consisted of 1 lumen ending in 3 balloons, which were perfused with a sterile normal saline solution via a closed-loop tubing system. This was connected to a mobile temperature manage-
observed between patients treated with MH and those treated with CE (Table). Time to treatment was similar for both groups (Table). Duration of MH was 71 ± 21 hours (minimum, 24 hours; maximum, 116 hours), whereas duration of rewarming varied between 25 and 34 hours. Prolongation of hypothermia (>72 hours) was always related to ICP increases during rewarming attempts.

A total of 8 patients were initially admitted to other hospitals and transferred to our department as a result of neurological deterioration or signs of extensive cerebral infarction on follow-up CCT scan. Five patients had undergone systemic thrombolyis and 1 had local thrombolyis before admission to the NICU. Four of these patients were subsequently treated with MH and 2 with CE. Of these patients, 5 survived and 1 died.

Duration of mechanical ventilation was 211 hours (range, 168 to 254 hours) for all patients and 234 hours (range, 186 to 300 hours) for survivors. No significant differences in the duration of mechanical ventilation were evident between patients treated with MH and those treated with CE (Table). Catecholamine application was necessary for 126 hours (range, 108 to 146 hours; minimum, 6 hours; maximum, 316 hours). Significant differences were evident between the 2 groups, with significantly longer use in the MH group. This difference became more pronounced when only data from survivors were analyzed (Table).

Maximal dose of epinephrine was 1 mg/h (range, 0.7 to 1.4 mg/h). Significant differences were evident between the 2 groups (Table). ICP increased >20 mm Hg during the first 10 days after stroke onset in 16 patients (44%). Of these patients, 5 had suffered subtotal and 7 had experienced total MCA infarction, whereas the remaining 4 patients had suffered an infract extending over the MCA territory. Of these 16 patients, 6 had undergone CE, and 10 had undergone MH (Table). A total of 28 episodes of increased ICP were observed in these 6 CE patients compared with 110 episodes in 9 MH patients. Of these 110 episodes, 50 occurred during the rewarming period. The maximal ICP values recorded in the 2 groups were similar [21 mm Hg (range, 17 to 30 mm Hg) and 22 mm Hg (range, 20 to 29 mm Hg) for CE and MH, respectively]. Length of stay in the NICU was 14 ± 7 days for all patients and 17 ± 7 days for survivors. No significant differences were evident when survivors treated with MH were compared with those treated with CE (Table).

Eleven of the 36 patients died (overall mortality, 30.6%); mortality was significantly higher in the MH (9 of 19 patients, 47%) compared with the CE (2 of 17 patients, 12%; P < 0.02, χ² test) group. Also, significant differences in NIHSS (17 [range, 16 to 18] versus 21 [range, 19 to 24]; P < 0.002, Mann-Whitney U test) were evident between survivors and nonsurvivors (survivors and nonsurvivors, respectively; CE: 55% versus 0%; P < 0.03, Mann-Whitney U test), and CCT findings (14 subtotal MCA infarcts, 8 total MCA infarcts, and 3 infarcts involving additional territories versus 2 subtotal MCA infarcts, 3 total MCA infarcts, and 6 infarcts involving additional territories; χ² test) were evident between survivors and nonsurvivors. Mortality increased from 2 of 16 patients (13%) with subtotal MCA infarcts to 3 of 11 patients (27%) with total MCA infarcts and 6 of 9 patients (67%) with infarcts involving additional vascular territories. No significant age differences were observed between survivors and nonsurvivors in the whole patient population (survivors: 54 ± 10 years; minimum, 35 years; maximum, 73 years; nonsurvivors: 54 ± 11 years; minimum, 39 years; maximum, 73 years; P = 0.9) or in any of the 2 treatment groups (MH: 58 ± 12 versus 53 ± 11 years, P = 0.4, survivors and nonsurvivors, respectively; CE: 55 ± 6 years for survivors; 2 nonsurvivors were 51 and 59 years of age). Uncontrollable intracranial hypertension was the cause of death in both patients treated with CE. A massive hemorrhage occurred in the infarct area on the 10th day after

### Clinical Data, LOC, NIHSS, CCT Findings, Mortality, and Treatment Parameters in 36 Patients Treated With MH or CE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hemicraniection</th>
<th>Hypothermia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age (range), y</td>
<td>52 (47–57)</td>
<td>56 (50–63)</td>
<td>0.2</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>9/8</td>
<td>14/5</td>
<td>0.1</td>
</tr>
<tr>
<td>LOC (awake/drowsy/stupor), n</td>
<td>6/10/1</td>
<td>8/8/3</td>
<td>0.5</td>
</tr>
<tr>
<td>NIHSS (range)</td>
<td>17 (16–18)</td>
<td>20 (18–22)</td>
<td>0.002</td>
</tr>
<tr>
<td>Modified NIHSS (range)</td>
<td>17 (16–18)</td>
<td>17 (15–19)</td>
<td>0.9</td>
</tr>
<tr>
<td>CCT findings (subtotal/total/Add Terr), n</td>
<td>7/6/4</td>
<td>9/5/5</td>
<td>0.8</td>
</tr>
<tr>
<td>Time to treatment (range), h</td>
<td>30 (23–54)</td>
<td>24 (18–24)</td>
<td>0.1</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>2/17 (12)</td>
<td>9/19 (47)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mechanical ventilation (range), h</td>
<td>216 (156–276)</td>
<td>214 (151–285)</td>
<td>0.8</td>
</tr>
<tr>
<td>ICP increase &gt;20 mm Hg, n (%)</td>
<td>6 (35)</td>
<td>10 (53)</td>
<td>0.3</td>
</tr>
<tr>
<td>Norepinephrine duration: all patients (range), h</td>
<td>108 (76–126)</td>
<td>147 (122–176)</td>
<td>0.02</td>
</tr>
<tr>
<td>Norepinephrine duration: survivors (range), h</td>
<td>110 (85–132)</td>
<td>168 (132–242)</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum norepinephrine dosage (range), mg/h</td>
<td>0.7 (0.4–1.1)</td>
<td>1.4 (0.8–2.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stay in NICU: all patients (range), d</td>
<td>14 (11–18)</td>
<td>13 (9–17)</td>
<td>0.6</td>
</tr>
<tr>
<td>Stay in NICU: survivors (range), d</td>
<td>14 (11–20)</td>
<td>18 (13–24)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Modified NIHSS indicates language-relevant subscores excluded; Add Terr, additional territories.
ischemic stroke in the first patient from the CE group who died. Bilateral MCA infarction was noted in the second on follow-up CCT 24 hours after CE. Early signs of left hemispheric infarction were missed on the first CCT scan, so this patient was initially diagnosed as having had right MCA stroke and therefore assigned to the CE group. Uncontrollable intracranial hypertension was the cause of death in 8 of 9 patients treated with MH and occurred during hypothermia in 5 and during rewarming in 3 patients. One other patient from the MH group died of sepsis leading to multiorgan failure.

The most common side effects of MH were pneumonia (15 of 19 patients, 78%), arrhythmia (8 of 19 patients, 42%), bradycardia (11 of 19 patients, 58%; <30 beats/min in 2 of 19 patients, 10%), thrombocytopenia (7 of 19 patients, 37%), and hypokalemia (5 of 19 patients, 26%). Singultus was observed in all patients who underwent endovascular hypothermia. Although serum levels of amylase were moderately elevated in 5 of 19 patients (26%) during MH, no pancreatitis occurred. Finally, severe coagulopathy occurred in 1 patient. This patient died as a result of cerebral herniation 6 hours after coagulopathy was diagnosed. Because the ICP was already markedly elevated 12 hours before the diagnosis of coagulopathy, this condition most probably did not influence the clinical outcome in this case.

A subdural hematoma was observed in 1 patient after CE but required no further treatment. Another patient developed syndrome of the trephined 3 weeks after CE. Therefore, early replacement of the bone flap was planned. The patient suffered anaphylactic shock (probably caused by Gelatipynrosuccinate infusion) followed by cardiac arrest during anesthesia induction. This resulted in a marked deterioration of his neurological status, although no hypoxic injury could be demonstrated on MRI, which was performed 6 hours later. Because this patient was transformed to a peripheral hospital 2 days later, no further neuroradiological examinations were performed. No bradycardia or hypokalemia occurred in the CE group, but 8 patients (47%) developed pneumonia during their stay in NICU.

### Discussion

This article represents the first comparison of MH and CE in the acute treatment of severe ischemic stroke. The fact that predefined criteria were used for treatment allocation allows meaningful comparison of the 2 treatment techniques. The 2 patient groups were indeed comparable in terms of age, sex, extent of cerebral infarction on CCT, LOC, and time elapsed between onset of symptoms and specific treatment. Still, significant differences in the severity of clinical presentation as assessed by the NIHSS were evident. These differences were no longer observed when a modified NIHSS score, corrected for language function, was used. This observation highlights the fact that NIHSS underestimates the severity of nondominant infarction. Similar findings were reported by Woo et al., who observed significantly greater volumes of cerebral infarction for right compared with left hemispheric stroke after adjustment for baseline NIHSS, and by Krieger et al., who examined the value of NIHSS within 6 hours of symptom onset as a predictor of fatal brain swelling and found significant differences, depending on the affected hemisphere (NIHSS of 20 for the left hemisphere and of 15 for the right hemisphere).

The observed differences in mortality between the 2 treatment groups constitute a major finding of the present study. Furthermore, our results highlighted 2 major drawbacks of MH, namely the occurrence of uncontrollable hypertension during rewarming and potentially fatal side effects. These 2 factors accounted for 4 deaths in the study population, corresponding to 21% of MH patients. The 47% mortality rate in patients treated with MH was comparable to earlier results from our department (44%) and slightly higher than the recently published results of a multicenter observational study (38%). In agreement with previous studies, our results demonstrate that treatment with MH is associated with a number of specific complications such as arrhythmia, bradycardia, thrombocytopenia, and hypokalemia, which, although not fatal, require intensive monitoring and treatment, thus further complicating patient management. Although it was not the purpose of this study, we did not observe any differences in the incidence of complications in patients undergoing MH between those who underwent external and those who underwent endovascular cooling. The sole exception was singultus, which occurred only in patients undergoing endovascular cooling and was probably due to diaphragm irritation. Still, it must be stressed that the sample size of this study prohibits definitive statements on this issue.

Mortality in patients treated with CE was significantly lower than in our initial report (12% compared with 27%) or the studies by Carter et al. (21%) and Jourdan et al. (28%); only the recent publication by Mori et al. on 19 patients with massive embolic cerebral infarction who underwent CE after displaying signs of clinical deterioration described similar findings (16% mortality). This is probably due to the acquired surgical expertise and the fact that patients with subtotal MCA infarctions were also treated with CE. The results from the CE group are even more impressive when we take into account the facts that 1 patient died on intracranial hypertension caused by hemorrhagic transformation that occurred 10 days after the initial event and that the second patient had bilateral MCA infarcts and thus a particularly poor prognosis. The elapsed time between onset of neurological symptoms and surgical treatment was longer than our target of <24 hours because 4 patients in this group were initially admitted to other hospitals and only later transferred to our department.

Most patients in this study were treated on the basis of initial clinical and neuroradiological findings instead of awaiting manifest signs of cerebral herniation. This suggests that some patients would potentially have experienced a similar outcome even without aggressive therapy. On the other hand, early CCT signs like the ones used in this study are known to have a high predictive value for adverse outcome after acute stroke. Additionally, it must be noted that ICP increases were observed in 5 patients with subtotal MCA infarction even after MH or CE. Because it is currently not possible to identify patients bound to develop intracranial hypertension, our approach of treating all patients meeting predefined criteria appears to be justified.
Nine of 36 patients (25%) described in this study had suffered ischemic infarcts involving multiple vascular territories. Mortality in these patients was significantly higher compared with remaining cases (67% versus 19%), suggesting that this subgroup is less likely to profit from aggressive therapy. This observation remains to be evaluated in a larger patient population.

Our results demonstrated that survival rate is independent of patient age. This implicates that aggressive treatment should not be withheld on the basis of age alone if the therapy is targeted at reducing mortality. Still, it must be noted that we only evaluated the influence of MH and CE on patient mortality. Functional outcome of the survivors represents an equally important parameter, which was not assessed in this study. The findings of Holtkamp et al. who described an improved survival with a poor functional outcome in patients >55 years of age treated with CE, highlight this important issue.

Although duration of mechanical ventilation was similar in the 2 groups, MH was associated with the application of significantly higher doses of catecholamines over a significantly longer period of time compared with CE. This is an obvious finding because hypotensive episodes are a well-documented complication of MH caused by arrhythmia, bradycardia, or the direct negative inotropic effects of MH. Our results demonstrated that CE and MH in patients with severe acute ischemic stroke are associated with the application of norepinephrine for a median of 5 days, mechanical ventilation for a median of 10 days, and a stay in the NICU of ∼15 days. This article provides the first report on these parameters, outlining the extensive requirements of both approaches.

No guidelines concerning choice of treatment in patients with large hemispheric stroke are currently available. Thus, the decision on treatment allocation is met mostly on an individual basis. The present observational study provides the first information on this issue: According to our results, MH is associated with a higher mortality rate and a higher rate of nonfatal complications compared with CE. Thus, our findings suggest that CE should be the treatment of choice, even in patients with ischemic stroke affecting the dominant hemisphere. This result, however, remains to be evaluated in a randomized trial. Because this study did not include a control group, it does not warrant definitive statements regarding the efficacy of either CE or MH in reducing mortality. Still, it must be noted that the overall mortality rate of 31% in the present study is markedly lower than the 78% and 79% rates reported by Hacke et al. and Berrouschot et al. respectively, under medical treatment.

In conclusion, our results suggest that CE is the treatment of choice for severe ischemic stroke because it is associated with lower mortality and lower complication rates compared with MH. Both treatment modalities are associated with intensive medical treatment and a prolonged stay in the NICU.

References
Hemicraniectomy and Moderate Hypothermia in Patients With Severe Ischemic Stroke
D. Georgiadis, S. Schwarz, A. Aschoff and S. Schwab

Stroke. 2002;33:1584-1588
doi: 10.1161/01.STR.0000016970.51004.D9
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/33/6/1584

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/