Combination of Decompressive Craniectomy and Mild Hypothermia Ameliorates Infarction Volume After Permanent Focal Ischemia in Rats

Arnd Doerfler, MD; Stefan Schwab, MD; Tobias T. Hoffmann, MD; Tobias Engelhorn, MD; Michael Forsting, MD

Background and Purpose—Both hypothermia and decompressive craniectomy (DC) have been shown to reduce ischemic injury in experimental middle cerebral artery (MCA) infarction. This study was designed to evaluate the effect of combined DC and hypothermia on infarction size and neurological outcome in a rat model of MCA occlusion (MCAO).

Methods—MCAO was performed in 72 Wistar rats assigned to groups A through F. In group A, mild hypothermia (32°C) was induced 1 hour after MCAO for 5 hours; normothermia was maintained in group B. After 6 hours of survival, infarction size was calculated for animals of groups A and B. In group C, DC alone was performed 4 hours after MCAO; hypothermia without DC was performed 1 hour after MCAO and maintained for 5 hours in group D. Combined DC and hypothermia were performed in group E. No therapy was performed in group F (control). Infarction size and neurological performance after 24 hours were used as study end points (groups C through F).

Results—Permanent postischemic hypothermia significantly reduced infarction size 6 hours after MCAO compared with controls (group A, 6.6 ± 2.4%; group B, 20.2 ± 2.6%; P < 0.01). Twenty-four hours after MCAO, infarction size was not significantly reduced by hypothermia alone (group D, 21.9 ± 3.6%). Compared with controls (group F, 23.3 ± 3.3%), infarction size was significantly reduced and neurological performance was significantly improved in animals treated by DC (group C, 11.8 ± 3.4; P < 0.001). Combined hypothermia and DC resulted in additional reduction of infarction size (group E, 9.1 ± 2.4%) and improved neurological score (P < 0.01).

Conclusions—Early DC significantly reduces infarction size and improves neurological outcome in MCA infarction in rats. Temporary mild hypothermia delays infarct evolution but does not significantly reduce definite infarction size or improve neurological outcome. Combined hypothermia and DC yield significant additional benefit. (Stroke. 2001;32:2675-2681.)

Key Words: cerebral infarction ■ craniectomy ■ hypothermia ■ middle cerebral artery occlusion ■ rats

Massive unilateral hemispheric infarction occurs in 10% to 15% of stroke patients and can lead to massive cerebral edema, leading to increased intracranial pressure (ICP), clinical deterioration, and death. Because therapeutic prognosis for such patients is poor, with mortality up to 80%, the term malignant middle cerebral artery (MCA) infarction was coined.1 Although the therapeutic window may be particularly short in this setting, these infarcts could potentially benefit from the emergence of aggressive therapies for ischemic stroke, such as thrombolysis, hypothermia, or decompressive hemicraniectomy.

Recently, early thrombolysis proved to be beneficial in acute ischemic stroke, although the risk of intracerebral hemorrhage was significantly increased.2,3 However, approximately 80% of stroke patients currently do not reach medical personnel within the required beneficial 3-hour time window for thrombolysis. Surgical decompression may be an effective therapeutic alternative in selected patients. The few clinical4–7 and experimental results8–10 indicate that decompressive craniectomy for cerebral ischemia not only reduces mortality but also improves outcome and reduces infarction size when performed early after vessel occlusion. The neuroprotective potential of hypothermia during cerebral ischemia has been known for a long time.8,9 Studies on the effect of mild or moderate hypothermia on cerebral ischemia were performed in various models of global or focal cerebral ischemia with and without reperfusion.11–16 Multiple mechanisms for hypothermia-induced neuroprotection have been identified, such as reduced metabolic rate and energy depletion, decreased excitatory transmitter release, decreased generation of free radicals, improvement of ion homeostasis, and reduced vascular permeability, blood-brain barrier disruption,
and edema. By suppression of some of the aforementioned processes, hypothermia could theoretically prolong the survival time of viable tissue to allow endogenous cellular recovery. Experimental studies also suggest that the combination of mild hypothermia with thrombolytic therapy or neuroprotective drugs is more effective than each of these alone. In such cases, hypothermia may be able to increase the therapeutic benefit of other therapies such as reperfusion or craniectomy or expand their time window. Several studies reported beneficial effects of combined treatment such as brief hypothermia and reperfusion or anti-inflammatory and antipyretic drugs. There are no data available in regard to a combined treatment of hypothermia and decompressive craniectomy.

The present study was designed to evaluate the singular and combined effects of decompressive craniectomy and/or mild hypothermia on infarction size and neurological performance in a rat model of MCA occlusion (MCAO).

Materials and Methods
Animal Preparation
Seventy-two male Wistar rats (weight, 280 to 320 g) were allocated to 6 treatment groups (A through F) of 12 animals each. The study was approved by the local animal protection committee; all procedures were in accordance with institutional guidelines. Animals were allowed free access to food and water before the procedure and were anesthetized with ketamine (4 mg/100 g) and xylazine (1.5 mg/100 g) by intramuscular injection. Monitoring of hematocrit, pH, PO2, PCO2, and blood pressure during anesthesia was performed with the use of a femoral artery catheter.

Focal cerebral ischemia was induced in all animals by an endovascular occlusion technique of the MCA first described by Koizumi and colleagues. The right common carotid artery and the right external carotid artery were exposed through a midline neck incision. A 4-0 monofilament nylon suture, whose tip had been coated with silicone, was then inserted through an arteriotomy of the common carotid artery and gently advanced into the internal carotid artery to a point approximately 18 mm distal to the carotid bifurcation. Mild resistance to this advancement indicated that the suture had entered the anterior cerebral artery, thus occluding the origins of the MCA and the posterior communicating artery. The common carotid artery was loosely ligated just distal to the arteriotomy, after which the neck wound was closed.

Study Design
Experiment 1
The effect of permanent mild hypothermia on infarction size was evaluated. Mild hypothermia (32°C) was induced 1 hour after MCAO and maintained for 5 hours (group A); normothermia (37°C) was maintained in group B. After 6 hours of survival, infarction size was calculated by 2,3,5-triphenyltetrazolium chloride (TTC) staining.

Experiment 2
The effect of temporary mild hypothermia on infarction size and neurological performance 24 hours after MCAO was evaluated. Forty-eight animals were randomly allocated to groups C through E. In group C, decompressive craniectomy alone was performed 4 hours after MCAO. Hypothermia without craniectomy was performed 1 hour after MCAO and maintained for 5 hours in group D. Decompressive craniectomy 4 hours after MCAO combined with hypothermia 1 hour after MCAO was performed in group E. No therapy was performed in group F (control) (Table 1). Infarction volume (in percentage of total brain volume) and neurological performance at 24 hours after MCAO were used as study end points (groups C through F).

Contra-lateral temporalis muscle and rectal probes were used to monitor temperature. Measurement of rectal temperature was performed throughout the anesthetic condition (before and during MCAO and hypothermia). Measurement of temporalis muscle temperature was started 30 minutes after endovascular occlusion and monitored throughout the anesthetic condition. We maintained temporalis muscle temperature at the desired level at 37°C or 32°C because contra-lateral temporalis muscle temperature has been reported to approximate closely intraparenchymal brain temperature. In the hypothermic groups (A, D, and E), 1 hour after MCAO whole-body hypothermia was induced with the use of ice packs until a target temperature of 32°C in the temporalis muscle was reached and thereafter was maintained at 32°C until 6 hours after MCAO. Cooling was performed at an average rate of 0.2°C/min; target temperature was obtained in roughly 25 minutes.

After 5 hours of hypothermia while under general anesthesia, re-warming to 37°C was performed gradually within 30 minutes (groups D and E). Total duration of anesthesia was identical for all groups C through F. Animals were then allowed to recover from anesthesia and were housed in a room maintained at 22°C for an additional 18 hours.

Decompressive craniectomy was performed as described recently in animals of group C and E by creating a bone flap 10 × 5 mm in the temporal and parietal bone with the use of a dental drill; additional bone was removed under microscopic control with the use of microscissors (Figure 1). The dura was then opened in a cruciate incision. No cortical resection of infarcted brain was attempted. At the end of the procedure, the temporalis muscle and skin flap were adapted and sutured in place.

Neurological Score and Infarction Size
Twenty-four hours after MCAO, animals (groups C through F) were neurologically examined by an investigator blinded to various

Figure 1. Coronal CT scan illustrating extent and location of craniectomy site.
Described by Lin et al,27 the corrected infarction volume (CIV) is calculated according to the slice thickness of 2 mm per slice. Each area (ischemic brain) was marked, and the infarct volume was quantified with the use of IMAGE View, Brain Power Inc) was used. Infarction volumes were described as percentage of the total brain volume.

For statistical analysis of all results, commercial software (StatView, Brain Power Inc) was used. Infarction volumes were described by ANOVA; for statistical analysis of the neurological score and body weight, the nonparametric Kruskal-Wallis test was used. A probability value of $P<0.05$ for an overall difference between the 3 groups was considered significant. To conclude that 2 given groups were significantly different, Fisher’s least significance difference test was performed; when the overall differences between 4 groups were significant, ANOVA or the Kruskal-Wallis test was performed. A probability value of $P<0.05$ between 2 specified groups was considered significant. All values were expressed as mean±SD.

### Results

No statistically significant differences were noted among the different groups for any of the intraoperative physiological parameters (Table 3). In general, temporalis muscle temperature was approximately $0.3±0.2°C$ higher than rectal temperature in all groups.

### Mortality

Four of 72 animals died. None of the animals of groups A and B died. Two animals of the control group (group F) died.

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None of the animals in the craniectomy group (C) died. One animal each died in groups D and E.

Neurological Performance

The neurological score 24 hours after MCAO is shown in Figure 2. Animals that died were scored 5. The average neurological score of controls was 3.71±0.82. Animals treated by craniectomy alone had a significantly better (P<0.05) neurological score than controls (2.83±0.83). Neurological performance of the animals treated by hypothermia was 3.61±0.76. Animals treated with combined hypothermia and craniectomy had a significantly better neurological score (2.38±0.87) than controls (P<0.01) and animals treated by craniectomy alone (P<0.05).

Infarction Volume

Infarction volumes were calculated from TTC-stained brain sections for animals of experiment 1 (groups A and B) 6 hours after MCAO and for the 44 animals of experiment 2 (groups C through E) that survived until 24 hours after MCAO. Since TTC staining is not sufficient a few hours after death, quantification of infarction size was not possible in those animals of the control group who died before the study end point. Relative infarction volumes in the different treatment groups are shown in Figure 3. Permanent hypothermia (group A) significantly reduced infarction size 6 hours after MCAO compared with controls (group A, 6.59±2.44%; group B, 20.21±2.62%; P<0.01). Twenty-four hours after MCAO, there was no significant reduction of infarction size by hypothermia alone (group D, 21.94±3.55%). Compared with controls (group F, 23.32±3.28%), infarction size was significantly reduced in animals treated by craniectomy (group C, 11.81±3.37%; P<0.001). Combined hypothermia and craniectomy resulted in an additional reduction of infarction size (group E, 9.10±2.41%) compared with control (P<0.01) and craniectomy alone (P<0.05). Regardless of treatment, all animals suffered an infarction in the basal ganglia, supplied by the lenticulostriate arteries. Morphological protection measured 6 hours and 24 hours after MCAO occurred mainly in the cortex and was not significant in the basal ganglia. There was no significant difference between infarction size of control animals calculated 6 hours (group B) or 24 hours (group F) after MCAO.

Discussion

In the present study we examined the singular and combined effects of decompressive craniectomy and mild hypothermia on permanent focal ischemia.

A recently published prospective study in 63 patients with malignant hemispheric infarction revealed the beneficial effects of early decompressive hemicraniectomy on mortality and morbidity. Few experimental data on the usefulness of decompressive craniectomy in acute stroke are available. Two recently published experimental studies in rats showed decompressive craniectomy not only to be lifesaving but also to reduce infarction size and improve functional outcome in a time-dependent fashion. In hemispheric infarction, extensive cerebral edema and marked elevation of ICP may cause ischemia of neighboring brain tissue and thus lead to further progression of infarction. Early decompressive craniectomy may interrupt this vicious cycle by decreasing ICP. This may increase cortical cerebral perfusion pressure; functionally compromised but viable brain may thus be able to survive.

Our results confirm the experimental data available. Compared with controls, early craniectomy 4 hours after MCAO resulted in significantly reduced infarction size and significantly improved neurological score. It is debatable whether an improved neurological score might be accepted as valid in view of a short observation period. Outcome measured at a more distant time point would have been more valuable, since a 24-hour end point does not represent maximal edema formation in this model. However, the improved neurological score reflects the reduced infarction volume in the craniectomy groups. Because of the known high mortality of this type of hemispheric MCA infarction within the first 3 days because of massive brain swelling and subsequent herniation, we confined our experimental protocol to 24 hours after vessel occlusion and did not attempt longer survival periods. However, this relatively short survival period may not assess final infarction volume. It could be argued that we simply postponed development of ischemic brain damage with post-ischemic hypothermia. Indeed, postischemic hypothermia 3 hours after global ischemia has shown to be effective in

Figure 2. Neurological score 24 hours after MCAO. Animals treated with a combination of hypothermia and craniectomy had a significantly better neurological score. Means and SDs are presented for all groups. *P<0.05.

Figure 3. TTC-derived relative infarction volume (percentage of the total brain volume) 24 hours after MCAO. Means and SDs are presented for all groups. *P<0.05.
reducing neuronal damage 3 days after ischemia, but the neuroprotective effect was less evident at 7 days, and no effect was documented at 2 months. On the other hand, several experimental studies in rats demonstrated that infarction size in hypothermic and normothermic animals did not change significantly when the animals were killed 24 or 72 hours after MCAO, demonstrating that hypothermia was not merely slowing the evolution of the infarct but permanently preventing a greater degree of ischemic damage.

Starting time, duration, and depth of hypothermia are important factors in reducing ischemic infarction volume. However, the usefulness of deep therapeutic hypothermia for cerebral ischemia has been limited by adverse effects such as myocardial arrhythmia, hypotension, blood hypercoagulability, and hemodynamic instability. On the other hand, it has been stated that mild hypothermia at 33°C to 35°C is not associated with cardiovascular instability or other side effects in experimental models. We chose mild hypothermia of 32°C because clinical application and continuity can be accomplished both easily and safely, without severe complications.

Although the most protective effect is reported when hypothermia is started during or before ischemia, we started hypothermia 1 hour after MCAO because this is more relevant for clinical issues. The length of hypothermia is also important for cerebral protection. Since it may be difficult in small animals to maintain anesthesia and hypothermia for a prolonged time without severe side effects, we chose a 5-hour period of mild hypothermia, starting 1 hour after onset of ischemia. In the clinical setting, mild hypothermia can be administered over a long time period of 72 hours without severe side effects. A recently published study reported a significant reduction in infarction size and improved long-term neurological outcome after prolonged but delayed postischemic hypothermia in transient focal cerebral ischemia in rats. However, it is necessary to clarify the effects of prolonged mild hypothermia on permanent focal ischemia to apply this strategy in the very early phase of cerebral ischemia before reperfusion is initiated. Recently, the beneficial effect of mild prolonged hypothermia in severe MCA infarction in humans has been reported.

Preliminary experiment 1 was performed to evaluate the efficacy of permanent hypothermia. Permanent hypothermia has shown to be very potent in reducing infarction size 6 hours after MCAO. Our results are in concordance with the results of Baker et al reporting a significant reduction in infarction size as determined by TTC staining 6 hours after permanent MCAO occlusion and hypothermia of 24°C. Morphological protection measured 6 hours after MCAO occurred mainly in the cortex and was not significant in the basal ganglia. Although the validity of infarction size determined by TTC staining 6 hours after permanent MCAO has not been rigorously confirmed by electron microscopy, other studies have used TTC staining to determine necrosis within such a time frame. Despite this limitation, TTC staining 6 hours after MCAO reveals that permanent mild hypothermia may significantly reduce infarction size. Zhang and coworkers demonstrated that hypothermia is protective when induced 1 hour after transient ischemia in a focal stroke model. In a model of transient focal cerebral ischemia, infarction volume was significantly reduced (32%) when mild hypothermia was induced immediately after reperfusion and maintained for a prolonged period. However, a delay in hypothermia until 30 minutes after reperfusion failed to achieve statistical significance.

Although the effects of hypothermia on reversible cerebral ischemia have been extensively studied, less attention has been paid to the effects of mild hypothermia in models of permanent focal cerebral ischemia. In the clinical setting, the possibility of hypothermia being useful only in transient ischemia is less encouraging since vascular occlusion often does not resolve for many hours or days, if ever. In the literature, results of the effect of hypothermia on permanent focal ischemia are controversial. Both Baker et al and Kader et al were able to demonstrate that moderate hypothermia permanently reduces infarction size when administered before or as early as 1 hour after onset of ischemia. In contrast, Ridenour et al reported that hypothermia failed to modify permanent focal ischemia. This is in accord with our results: 5 hours of mild hypothermia postponed the evolution of infarction but did not significantly reduce definite infarction volume. The phenomenon of delayed neurodegeneration is well established for global ischemia models and has been reported recently in a focal ischemia model. Thus, hypothermia may delay death in those neurons that have been irreversibly damaged.

Several studies reported beneficial effects of combined treatment, such as brief hypothermia and anti-inflammatory and antipyretic drugs. Coimbra et al found that postischemic hypothermia alone only delayed neuronal damage after global ischemia in rats, but combined treatment with hypothermia and dipyrone, an anti-inflammatory drug, significantly reduced permanent neuronal damage. Using the rat model of endovascular MCAO, Karibe et al demonstrated that early mild hypothermia can extend the therapeutic window for reperfusion to at least 3 hours of ischemia. In Wistar rats, the therapeutic window to reduce infarction size has been shown to be 2 hours, the point at which restoration of cerebral blood flow did not significantly reduce infarction size compared with permanent focal ischemia. Whether hypothermia produces permanent reduction in definite infarction size is controversial. However, even if hypothermia only delays the onset of permanent neuronal damage, it may well increase the window of opportunity for some other form of therapy, such as pharmacological neuroprotection or craniectomy.

Our results demonstrated that the combination of craniectomy and transient mild hypothermia yields a significant additional benefit, since this combination resulted in additional reduction of infarction size (group E, 9.10 ± 2.41%) and improved neurological score compared with controls (P < 0.01) and craniectomy alone (P < 0.05). Although both craniectomy and hypothermia reduce cortical infarction, there might be an additive effect by different mechanisms. Postischemic hypothermia may extend ischemic neuronal viability long enough for collateral blood flow to develop or until a transient period of ischemia subsides. Hypothermia may also lower ICP and the critical threshold of cerebral blood flow necessary to maintain neuronal viability, expanding the “is-
chemic penumbra” of potentially viable tissue. Early decompres-
sive craniectomy may further decrease ICP, thereby increasing
cortical cerebral perfusion pressure. Functionally compromised
but viable (penumbral) brain may thus be able to survive.10

However, some clinical data suggest that globally elevated
ICP is not a common phenomenon in the initial phase of large
hemispheric infarctions. Thus, lethal compartmental shifts
can occur even in the face of normal global ICP, leading to
increased mortality. In our study concurrent ICP monitoring
and cerebral blood flow measurements, ie, with the use of
laser-Doppler flowmetry, need to be performed with crani-
ectomy. However, since a main objective of this study was to
investigate the effects of craniectomy per se, invasive laser-
Doppler flowmetry and ICP monitoring were not performed.

Rewarming after temporary hypothermia must be consid-
ered the “critical phase” of hypothermic therapy since there
might be a rebound increase in ICP.18 This may be an
explanation of why temporary hypothermia only delayed the
delerious effects caused by hypothermia in our experiment
and thus did not result in any substantial improvement. In
contrast, when craniectomy has already been performed,
rewarming might be of minor relevance because ICP is
already reduced by craniectomy.

Finally, there are some limitations when one tries to
extrapolate from our results to human stroke. The time course
of cerebral ischemia in rats is different from that in humans,
and the quality of leptomeningeal collateral blood flow also
differs substantially.44 However, our experimental results
indicate that decompressive craniectomy as an early second-
ary prevention of cerebral ischemia may limit further evolu-
tion of cerebral ischemia. Clinically, hemicraniectomy is
technically a simple procedure that could be performed with
minimal ancillary support and, in contrast to thrombolytic
therapy, without increased risk of hemorrhage.

In conclusion, our results suggest that decompressive
 craniectomy early after vessel occlusion significantly reduces
infarction size and improves neurological performance in
MCA infarction in rats. Temporary postischemic mild hypo-
thermia postpones the evolution of infarction but does not
significantly reduce definite infarction size or improve neu-
rological outcome by itself. Compared with craniectomy
alone, the combination of hypothermia and decompressive
 craniectomy yields a significant additional beneficial effect
on infarction size and neurological outcome 24 hours after
MCAO.

In the clinical setting, postischemic hypothermia may
provide an approach to potentially reduce ongoing neuronal
damage and may be effective in extending the therapeutic
window for delayed treatment modalities such as crani-
ectomy. The clinical relevance of our experimental results 24
hours after MCAO needs to be addressed in further studies,
with a special focus on long-term outcome.

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hypoperfusion, blood-brain barrier disruption, brain edema, and neuronal

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