# THERAPEUTIC HYPOTHERMIA IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE, REFRACTORY INTRACRANIAL HYPERTENSION, OR CEREBRAL VASOSPASM

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**OBJECTIVE:** To evaluate the feasibility and safety of mild hypothermia treatment in patients with aneurysmal subarachnoid hemorrhage (SAH) who are experiencing intracranial hypertension and/or cerebral vasospasm (CVS).

**METHODS:** Of 441 consecutive patients with SAH, 100 developed elevated intracranial pressure and/or symptomatic CVS refractory to conventional treatment. Hypothermia (33–34°C) was induced and maintained until intracranial pressure normalized, CVS resolved, or severe side effects occurred.

**RESULTS:** Thirteen patients were treated with hypothermia alone, and 87 were treated with hypothermia in combination with barbiturate coma. Sixty-six patients experienced poor-grade SAH (Hunt and Hess Grades IV and V) and 92 had Fisher Grade 3 and 4 bleedings. The mean duration of hypothermia was 169 ± 104 hours, with a maximum of 16.4 days. The outcome after 1 year was evaluated in 90 of 100 patients. Thirty-two patients (35.6%) survived with good functional outcome (Glasgow Outcome Scale [GOS] score, 4 and 5), 14 (15.5%) were severely disabled (GOS score, 3), 1 (1.1%) was in a vegetative state (GOS score, 2), and 43 (47.8%) died (GOS score, 1). The most frequent side effects were electrolyte disorders (77%), pneumonia (52%), thrombocytopenia (47%), and septic shock syndrome (40%). Of 93 patients with severe side effects, 6 (6.5%) died as a result of respiratory or multi-organ failure.

**CONCLUSION:** Prolonged systemic hypothermia may be considered as a last-resort option for a carefully selected group of SAH patients with intracranial hypertension or CVS resistant to conventional treatment. However, complications associated with hypothermia require elaborate protocols in general intensive care unit management.

**KEY WORDS:** Hypothermia, Intracranial pressure, Outcome, Subarachnoid hemorrhage, Vasospasm

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In recent years, experience in microneurosurgical techniques, endovascular coiling, and extended resources in neurointensive care has enabled the treatment of patients with severe aneurysmal subarachnoid hemorrhage (SAH) (18, 24, 30, 37). These patients, however, have a high incidence of specific complications, such as severe brain edema with elevations of intracranial pressure (ICP) and cerebral vasospasm (CVS) leading to secondary ischemic infarctions (10, 11, 14).

**ABBREVIATIONS: CT**, computed tomographic; **CVS**, cerebral vasospasm; **GOS**, Glasgow Outcome Scale; **ICP**, intracranial pressure; **SAH**, subarachnoid hemorrhage

Mild hypothermia, showing numerous neuroprotective effects, may serve as an effective treatment option if elevated ICP and/or symptomatic CVS are refractory to conventional treatment (5, 8, 12, 39, 44, 48, 53, 54). Thus far, only a few clinical studies, based on small series of patients with SAH and hypothermia treatment as a result of intracranial hypertension or CVS, have been reported (19, 29, 31, 40, 41).

The purpose of the present study was to evaluate the feasibility and safety of therapeutic hypothermia in patients with SAH and

intracranial hypertension and/or CVS resistant to conventional treatment. The outcome of 100 consecutive patients was studied, focusing especially on possible side effects of the specific treatment.

## PATIENTS AND METHODS

This study was approved as a part of Project E-015/99 by the Ethics Committee of the University of Zurich. Between January 1999 and February 2007, 441 patients with SAH were admitted to the Department of Neurosurgery, University Hospital Zurich, and underwent aneurysm clipping or coiling within 3 days.

### Structured Treatment

All patients were managed according to a standardized treatment protocol for aneurysmal SAH and vasospasm (34). Emergency treatment of elevated ICP consisted of sedation with intubation, osmotherapy (20% mannitol and hypertonic NaCl-hydroxyethyl-starch solution), and thiopental boluses in a dose of 5 to 10 mg/kg. Aneurysm clipping or coiling was performed within hours after emergency diagnostic evaluation with angiography or computed tomographic (CT) angiography. Patients with poor-grade SAH and severe brain edema remained sedated (fentanyl infusion [2–8 μg/kg/h] and midazolam [0.1–0.4 mg/kg/h]) after surgery. A ventricular catheter (Raumedic AG, Münchberg, Germany), an intraparenchymatous probe (Raumedic AG) or, in the early stage of this series, a subdural probe (NMT Neuroscience, Frankfurt, Germany) was inserted. In the absence of elevated ICP (>20 mm Hg) and signs of severe brain edema on a CT scan performed the first day after surgery, sedation was discontinued to assess the patients' neurological status. All patients with SAH were treated with oral nimodipine. In cases of gastrointestinal reflux, nimodipine was administered intravenously. Dexamethasone (16 mg/d) was given for 2 days after hospital admission and then rapidly reduced by 4 mg every second day. Prophylactic antiepileptic treatment with phenytoine or valproate was initiated only in patients with elevated risk of seizures, patients presenting with World Federation of Neurological Societies Grade 3 or higher, patients with bleeding aneurysms in the middle cerebral artery territory, or patients with ischemic infarctions.

### Treatment of Elevated ICP

If ICP was elevated (>20 mm Hg), treatment with intermittent cerebrospinal fluid drainage, osmotherapy, and mild hyperventilation was initiated. Patients with persistent ICP values greater than 20 mm Hg were eligible for treatment with barbiturate coma (adapted to a burst suppression pattern in continuous electroencephalographic monitoring). All patients under sedation because of intracranial hypertension were treated under extended monitoring of cerebral hemodynamics (monitoring of jugular bulb oxygen saturation, cerebral blood flow, and/or intraparenchymatous oxygen partial pressure) (15, 21, 35). In patients showing signs of brain swelling during or immediately after craniotomy and aneurysm surgery (angry brain), the bone flap was not replaced and duraplasty was performed (primary decompressive craniectomy). The average diameter of craniectomy was 9 cm because of enlarged skin and bone opening in high-grade SAH patients with suspected brain edema. If elevated ICP values (>20 mm Hg) after surgery were resistant to conventional treatment and hypothermia, a secondary decompressive craniectomy with removal of frontal, temporal, and parietal bones (average diameter, 14–15 cm) and duraplasty was performed.

### Treatment of CVS

Transcranial Doppler blood flow measurements were performed daily. A modified triple-H therapy (hypertension with systolic blood pressure > 150 mm Hg, normovolemia to minor hypervolemia, target hematocrit of 30%) was monitored with a PiCCO System (Pulsion Medical Systems AG, Munich, Germany) and induced if signs of CVS were present; e.g., development of delayed ischemic neurological deficits (after exclusion of hydrocephalus, electrolyte disturbance, or infection) in combination with increased transcranial Doppler blood flow velocities (mean middle cerebral artery blood flow velocities > 140 cm/s or increase > 50 cm/s within 24 hours) and/or perfusion deficits in perfusion CT scans. In comatose patients, intraparenchymatous oxygen partial pressure values less than 15 mm Hg or arteriojugular lactate differences greater than -0.2 mmol/L were regarded as highly suspicious for symptomatic CVS. To confirm and exclude CVS in comatose patients, angiography was performed regularly. If patients with delayed ischemic neurological deficits did not improve or worsened, angiography and treatment with percutaneous angioplasty and/or superselective papaverine infusion (total dose, 300 mg) into the vasospastic vessels were performed. In case of CVS recurrence, the papaverine infusion was repeated up to a total of 3 applications. Narrowing of the diameter of the vessel lumen greater than 30% was defined as angiographic evidence of CVS. Symptomatic CVS, resistant to or reoccurring after angioplasty and papaverine, was treated with barbiturate coma. New ischemic lesions that could not be attributed to other causes were considered to be CVS-induced infarctions.

### Hypothermia Treatment

If ICP remained greater than 20 mm Hg and/or CVS was resistant to or recurring after the treatment mentioned above, hypothermia (target body core temperature, 33–34°C) under deep analgosedation was induced and maintained until ICP normalized and/or CVS resolved. Body core temperature was measured by a thermistor in the arterial line and, if tolerated, the rewarming rate was 1°C per day. Contraindications and criteria for early termination of hypothermia were severe pneumonia, signs of septic shock syndrome, coagulation disorder with manifest bleeding, and heart failure. From January 1999 until September 2000, hypothermia was induced and maintained in 10 patients using cooling blankets (Bair Hugger [Arizant Inc., Eden Prairie, MN] and Blanketrol [Cincinnati Sub-Zero, Cincinnati, OH]) and ice bags on the groin, axillae, and neck. Since October 2000 (90 patients), hypothermia was induced and maintained with an intravascular catheter-based heat exchange system (Alsius, Irvine, CA) (33).

The following possible side effects of barbiturate coma and/or hypothermia were recorded: hypernatremia (>150 mmol/L), hyperkalemia (>5 mmol/L), and thrombocytopenia (<100,000/μL). Pneumonia was defined as new or progressive infiltrate in the chest x-ray, together with C-reactive protein values greater than 100 ng/L, a partial pressure of oxygen in arterial blood/fractional inspired oxygen index of less than 300 mm Hg, and positive microbiological cultures of tracheal aspirates. The acute respiratory distress syndrome was defined according to the American European Consensus Conference (partial pressure of oxygen in arterial blood/fractional inspired oxygen index < 300 mm Hg, bilateral infiltrates in chest x-ray, acute onset, pulmonary artery occlusion pressure < 18 mm Hg or no clinical suspicion of left atrial hypertension) (16). Systemic inflammatory response with fever, hyperventilation, and tachycardia could not be deduced from classic symptoms in sedated and hypothermic patients. Therefore, the definition of septic shock syndrome was modified as volume-resistant shock (dosage of norepinephrine > 20 mcg/min or epinephrine > 1 mcg/min), minimum of 1 severe organ

**TABLE 1. Patient characteristics[a]**

| | No. of patients (n = 100) |
|---|---|
| Age (y) ± SD | 49 ± 12.6 |
| Sex, M/F (no.) | 36/64 |
| Admission GCS score, mean ± SD | 8 ± 4.9 |
| Hunt and Hess Grade, no. (%) | |
| *I* | 3 (3) |
| *II* | 21 (21) |
| *III* | 10 (10) |
| *IV* | 29 (29) |
| *V* | 37 (37) |
| Fisher Grade, no. (%) | |
| *1* | 1 (1) |
| *2* | 7 (7) |
| *3* | 31 (31) |
| *4* | 61 (61) |

[a] SD, standard deviation; GCS, Glasgow Coma Scale.

**TABLE 2. Location of ruptured aneurysms**

| | No. of aneurysms (n = 100) |
|---|---|
| Ruptured aneurysms in anterior circulation, no. (%) | 86 (86) |
| *Internal carotid artery* | 13 (13) |
| *Ophthalmic artery* | 1 (1) |
| *Posterior communicating artery* | 9 (9) |
| *Proximal anterior cerebral artery* | 1 (1) |
| *Anterior communicating artery* | 30 (30) |
| *Distal anterior cerebral artery* | 5 (5) |
| *Middle cerebral artery* | 27 (27) |
| Ruptured aneurysms in posterior circulation, no. (%) | 14 (14) |
| *Posterior inferior cerebellar artery* | 2 (2) |
| *Superior cerebellar artery* | 1 (1) |
| *Basilar tip aneurysm* | 10 (10) |
| *Posterior cerebral artery* | 1 (1) |
| Multiple aneurysms, no. (%) | 24 (24) |

dysfunction (Sequential Organ Failure Assessment score > 2 for a single organ system), and positive microbiological cultures in tracheal aspirate, urine, blood, or on catheters (17). Cerebrospinal fluid infection was defined by positive microbiological cultures in the cerebrospinal fluid, routinely collected from patients with ventricular drainage 3 times a week, or if clinical signs occurred. Subcutaneous pus was defined as wound infection calling for neurosurgical revision.

### Outcome Measurements

Neurological outcome was assessed after 3 and 12 months by a neurologist in the outpatient clinic using the Glasgow Outcome Scale (GOS) score, with GOS 1 denominating death, GOS 2 vegetative state, GOS 3 severe disability, GOS 4 moderate disability, and GOS 5 mild or no disability (27).

### Statistical Analysis

Neurological outcome between the patient groups was compared by applying Fisher's exact test.

## RESULTS

### *Patient and Treatment Characteristics*

Between January 1999 and February 2007, a total of 441 patients with SAH were admitted and treated with early aneurysm clipping or coiling. Of these patients, 100 (23.1%) were treated with hypothermia because of intractable intracranial hypertension and/or refractory CVS, both occurring concurrently or subsequently during the course of the illness. Ninety-six patients were treated with clipping and 4 patients with coiling. Patient characteristics and the location of the aneurysms are given in Tables 1 and 2. Thirteen percent of the patients were treated with hypothermia alone because of the presence of contraindications for barbiturate coma, and 87 patients were treated with hypothermia in combination with barbiturate coma. Severe SAH of Hunt and Hess Grades IV and V occurred in 66%, and Fisher Grades 3 and 4 in 92%, respectively. The mean duration of hypothermia treatment was 169 ± 104 hours, with a maximum length of 16.4 days. Primary and/or secondary decompressive craniectomy because of persistent ICP greater than 20 mm Hg despite hypothermia treatment was performed in 52 patients (52%). External ventricular drains were inserted in 76 patients (76%). Thirty-two patients (32%) needed definitive ventriculoperitoneal or vetriculoatrial shunting during primary hospitalization.

### Outcome

Overall outcome characteristics are summarized in Table 3. The GOS score was evaluated 3 and 12 months after hospital discharge. In 10 patients, the 12-month evaluation has not been performed to date. Good functional outcome (GOS score, 4–5) was achieved in 30 patients (30.0%) after 3 months and in 32

**TABLE 3. Outcome in all patients treated with systemic hypothermia**

| Glasgow Outcome Scale | No. of patients after 3 months (n = 100) | No. of patients after 12 months (n = 90) |
|---|---|---|
| 5—Mild or no disability, no. (%) | 9 (9) | 17 (18.9) |
| 4—Moderate disability, no. (%) | 21 (21) | 15 (16.7) |
| 3—Severe disability, no. (%) | 23 (23) | 14 (15.6) |
| 2—Vegetative state, no. (%) | 8 (8) | 1 (1.1) |
| 1—Death, no. (%) | 39 (39) | 43 (47.8) |

**TABLE 4. Outcome of age- and complication-related subgroups[a]**

| Glasgow Outcome Scale | Patients older than 60 years (n = 13) | Patients younger than 60 years (n = 77) | ICP group[b] (n = 28) | CVS group[c] (n = 28) | ICP/CVS group[d] (n = 34) |
|---|---|---|---|---|---|
| 5—Mild or no disability, no. (%) | 2 (15.4) | 15 (19.5) | 3 (10.7) | 10 (35.7) | 4 (11.8) |
| 4—Moderate disability, no. (%) | 0 | 15 (19.5) | 4 (14.3) | 6 (21.4) | 5 (14.7) |
| 3—Severe disability, no. (%) | 2 (15.4) | 12 (15.6) | 4 (14.3) | 4 (14.3) | 6 (17.6) |
| 2—Vegetative state, no. (%) | 0 | 1 (1.3) | 0 | 0 | 1 (2.9) |
| 1—Death, no. (%) | 9 (69.2) | 34 (44.2) | 17 (60.7) | 8 (28.6) | 18 (52.9) |

[a] ICP, intracranial pressure; CVS, cerebral vasospasm.
[b] Patients with intracranial pressure greater than 20 mm Hg.
[c] Patients with symptomatic cerebral vasospasm.
[d] Patients with intracranial pressure greater than 20 mm Hg and symptomatic cerebral vasospasm, concurrently.

patients (35.6%) after 12 months. The number of patients surviving severely disabled (GOS score, 3) or in a vegetative state (GOS score, 2) decreased from 31.0% (n = 31) to 16.7% (n = 15) between the evaluation periods. The overall mortality rate after 12 months was 47.8%.

The 12-month outcome of patients divided into subgroups regarding age and indications for hypothermia treatment is displayed in Table 4. Because of the high intergroup difference in sample size without significance, patients younger than 60 years tended to survive more often with good functional outcome, as compared with patients aged older than 60 years (39 versus 15.4%, not significant). The indications for hypothermia in all 100 patients were intractable intracranial hypertension alone (ICP group, 30%), resistant CVS alone (CVS group, 36%), and both (ICP/CVS group, 34%). GOS evaluation after 12 months in the ICP and combined ICP/CVS group was similar regarding good functional outcome (25.0 and 26.5%, not significant) and mortality (60.7 and 52.9%, not significant). In the CVS group, good functional outcome after 1 year was achieved significantly more often as compared with the ICP group (57.1 versus 25.0%, $P = 0.02$) and the ICP/CVS group (57.1 versus 26.5%, $P = 0.025$).

### Side Effects

The rate of side effects occurring during hypothermia and until Day 7 after rewarming is listed in Table 5. Of the 100 patients, 93 (93%) developed at least 1 side effect, possibly associated with hypothermia treatment. Hypernatremia and hyperkalemia occurred in 61 and 35 patients, limiting the duration of hypothermia and barbiturate coma in 31 and 28 cases, respectively. Among the 13 patients treated with hypothermia alone without barbiturate coma, hypernatremia occurred in 8 and hyperkalemia in 3 patients. One patient had to be treated with hemodiafiltration because of hyperkalemia. None of the patients died as a result of electrolyte disorders. Apart from atrial fibrillation, which could be kept under control with amiodarone, no hemodynamic relevant cardiac arrhythmias occurred. A thrombocyte count of less than 100/μL blood was observed in 47 patients and in 9 patients (69%) treated with hypothermia alone. One severe bleeding complication from a catheter insertion site with femoral hematoma and need for surgery occurred. Eighty-three patients suffered from severe infections, more than 50% of them in terms of ventilator-associated pneumonia. Of the 13 patients treated with hypothermia alone, 10 (77%) developed severe infections. Clinically manifested venous thrombosis was validated by ultrasonography in 8 patients. Six patients died of severe side effects (respiratory or multi-organ failure) known to be associated with barbiturate coma and hypothermia.

## DISCUSSION

In patients with refractory intracranial hypertension, mortality and disability rates increase up to 95 and 100%, respectively

**TABLE 5. Side effects during hypothermia treatment**

| Side effects | All patients (n = 100) |
|---|---|
| Electrolyte disorders | |
| *Hypernatremia (>150 mmol/L)* | 61 (61%) |
| *Hyperkalemia (>5 mmol/L)* | 35 (35%) |
| Coagulopathy | |
| *Thrombocytopenia (<100.000/μL)* | 47 (47%) |
| Severe infections | |
| *Ventilator-associated pneumonia* | 52 (52%) |
| *Catheter-associated urinary tract infection* | 17 (17%) |
| *Cerebrospinal fluid infection* | 6 (6%) |
| *Surgical wound infection* | 5 (5%) |
| *Intravascular catheter-related bloodstream infection* | 3 (3%) |
| Septic shock syndrome | 40 (40%) |
| Acute respiratory distress syndrome | 16 (16%) |
| Clinical symptomatic venous thrombosis | 8 (8%) |

(11, 22, 38). Symptomatic CVS, if resistant to treatment, leads to a devastating outcome (13, 14, 30). In our study population, after all, good functional outcome was achieved in more than one-third of all patients (GOS score of 4–5 in 35.6% of patients) experiencing resistant intracranial hypertension and/or CVS.

During the past decades, promising studies on intraoperative hypothermia during aneurysm surgery as an attempt to reduce ischemic injury have been published (7, 23, 28, 42, 49, 50). Todd et al. (56), applying intraoperative hypothermia in a randomized study in 1001 patients with good-grade SAH, however, demonstrated no improvement in neurological outcome 3 months after aneurysm surgery. This suggests that only a carefully selected subgroup of patients, with specific complications induced by SAH, may benefit from hypothermia treatment at a particular time and for a certain duration.

In the present series, good functional outcome could be achieved in 39% of patients younger than 60 years and in 15.4% of those older than 60 years. A recent multivariate analysis of the 4 tirilazad trials demonstrated that increasing age is associated with unfavorable outcome (47). In a recent analysis of 350 patients with SAH in 22 Italian neurosurgical centers, Citerio et al. (10) found, on the basis of a logistic regression model, that age older than 60 years was an independent predictor of unfavorable outcome (odds ratio, 3; 95% confidence interval, 1.7–5.3). This effect may be even more pronounced in a subgroup of patients with high severity grade, most severe illness course, and a treatment procedure associated with severe side effects.

The most encouraging results were achieved in patients with resistant CVS without intracranial hypertension (good functional outcome in 57.1%). Hypothermia was induced as early and fast as possible if symptoms of CVS, refractory to conventional treatment, occurred. Several models of ischemia demonstrated that hypothermia, induced during or early after ischemia, is effective in minimizing neuronal damage after SAH (20, 44, 54). Piepgras et al. (44) investigated the mean apparent diffusion coefficient as a marker of ischemic damage after SAH with normothermia and hypothermia, induced up to 60 minutes after SAH in rats. They concluded that initiation and duration of the hypothermia period seems to be of importance. Thomé et al. (54, 55) demonstrated that pre- and postinsult hypothermia (32°C) reverses acute cerebral perfusion pressure-independent hypoperfusion after cisternal blood injection in rats. Kawamura et al. (32) demonstrated the neuroprotective effects of hypothermia via reduction of the stress response after experimental SAH. As intracranial hypertension is a late consequence of global cerebral edema after SAH, these animal studies encourage early induction of hypothermia in high-grade SAH; e.g., as soon as signs of brain swelling are visible in admission CT scans or intraoperatively.

To date, only a few clinical case reports or small series applying hypothermia to minimize damage after SAH have been published. Of a series of 12 patients with life-threatening refractory CVS treated with barbiturate coma, Kassell et al. (29) treated 3 with hypothermia (30–32°C body core temperature). Overall, 11 of the 12 patients died. In the 3 patients treated with hypothermia, profound alterations in acid-base and fluid balance occurred. Kawamura et al. (31) evaluated 6 patients with World Federation of Neurological Societies Grade 4 and 5 bleeding admitted within 6 hours from symptom onset and treated with hypothermia for 4 to 5 days applying positron emission tomography. Three patients recovered with good functional outcome according to the Barthel Index. Inamasu and Ichikizaki (26) treated 11 patients with poor-grade SAH and intracranial hypertension refractory to mannitol with hypothermia (35°C) for 3 days. Although ICP control could be achieved in all but 2 patients, 8 patients died and 3 survived severely disabled or in a persistent vegetative state. Nagao et al. (40) treated 9 patients with poor-grade SAH. Three patients survived with good functional outcome, 1 was moderately disabled, and 5 patients died. In a later series, Nagao et al. (41) performed hypothermia treatment (32–34°C) in 8 patients with severe CVS showing progressive ischemic neurological deficits that were refractory to conventional therapies, and in patients who underwent delayed aneurysm clipping with delayed neurological deficits. Good recovery after 5 to 10 days of hypothermia treatment could be achieved in 5 patients and moderate disability could be achieved in 2 patients.

Prolonged systemic hypothermia may be associated with severe side effects, thus possibly negating potential benefits (9, 19, 29, 44, 45). The mean duration of hypothermia in our patients was 7 days (up to a maximum of 16 days) and was adjusted to the duration of ICP elevations and the persistence of CVS, matching the occurrence and severity of side effects. The incidence of side effects was high, compared with studies applying hypothermia treatment for 12 to 24 hours (4, 25), suggesting that the longer patients are treated with hypothermia, the more often side effects might occur (4, 19, 25). Nearly all of our patients showed side effects that are associated with and/or possibly induced by hypothermia treatment.

With 52, 40, and 16%, respectively, the incidence of ventilator-associated pneumonia, septic shock syndrome, and acute respiratory distress syndrome was high. Hypothermia and barbiturate coma suppress inflammatory reactions, inhibit neutrophil and macrophage function, and release proinflammatory cytokines (1, 6, 36, 52). However, only 6 patients died from respiratory or multi-organ failure. In 1999, a strict protocol for treatment of elevated ICP and CVS, as well as prevention and treatment of side effects of systemic hypothermia and barbiturate coma, was introduced in our neurocritical care unit (34, 37). Thrombocytopenia, occurring in nearly half of the patients, was counteracted vigorously by administration of platelets. Hemorrhagic diathesis, because of platelet dysfunction, and changed kinetic of clotting enzymes are known to be associated with long-term hypothermia treatment (2, 57). Therefore, in our patients, we transfused platelets when they dropped below 100/μL. Furthermore, regarding hypothermia treatment, our protocol limits the use of other drugs and plasma substitutes hampering platelet aggregation, such as hydroxyethyl starch solution and valproate, while preferring fluid and volume substitution with cristalloids and fresh frozen plasma. With this

regimen, only 1 patient experienced severe bleeding complications.

Several studies have reported electrolyte disorders induced by hypothermia and barbiturate treatment (1, 9, 46). Although hypernatremia may be controlled with desmopressin and slow infusion of slightly hypo-osmotic cristalloids, one has to be especially alert to the occurrence of potentially dangerous hyperkalemia, which occurred in one-third of our patients. Although rebound hyperkalemia after severe hypokalemia refractory to potassium therapy is described to be associated with barbiturate coma, and most patients were treated with both hypothermia and barbiturates, it also occurred in 3 patients treated with hypothermia alone (9). Polderman et al. (46) found that hypothermia in trauma patients was commonly associated with hypokalemia, hypophosphatemia, and hypomagnesemia. Normo- and hypothermic patients, however, were sedated with pentobarbital to a burst suppression pattern. No electrolyte disorders were found in normothermic patients, and there were no reports on rebound hyperkalemia during rewarming (46). Therefore, as Cairns et al. (9) already concluded regarding barbiturate treatment, serum electrolytes have to be monitored closely during hypothermia and barbiturate treatment, and clinicians may tolerate or treat asymptomatic hypokalemia very carefully, rather than risk severe rebound hyperkalemia. Other general supportive intensive care measures such as tight glucose control, complicated by hypothermia-induced insulin resistance, as well as treatment of hypomagnesemia and cardiac arrhythmias, and controlled slow rewarming because of imminent rebound brain edema and pyrexia after rewarming are of high importance (3, 45, 51). Possible side effects of hypothermia have to be detected early and treated proactively and vigorously to avoid that hypothermia adversely effects outcome. Clinicians applying systemic hypothermia should be carefully aware of its physiological and pathophysiological consequences leading to beneficial as well as potentially deleterious effects.

### Limitations of the Study

A major limitation of the present study, especially regarding the analysis of side effects, is the fact that, in most cases, hypothermia was combined with barbiturate coma and osmotherapy. Therefore, infections as a result of immunosuppression and electrolyte disorders in several cases may not have been induced by hypothermia alone, but also by thiopenthal infusion, mannitol, or hypertonic hydroxyethyl starch solution (19, 52). Furthermore, a multicenter study with randomized concurrent controls is desirable to define the true impact of hypothermia treatment in patients with SAH and resistant intracranial hypertension and/or CVS.

## CONCLUSION

Prolonged systemic hypothermia with a target body core temperature of 33 to 35°C may be considered as a last-resort option for a carefully selected group of younger SAH patients with resistant intracranial hypertension or CVS. Good functional outcome in these patients with most severe complications can be achieved in more than one-third of the cases. However, in most patients treated with long-term hypothermia, severe side effects occur and, therefore, require elaborated protocols in general intensive care unit management and experienced medical and nursing staff; e.g., staff especially trained regarding possible complications associated with hypothermia treatment.

### Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

## REFERENCES


1. Aibiki M, Maekawa S, Ogura S, Kinoshita Y, Kawai N, Yokono S: Effect of moderate hypothermia on systemic and internal jugular plasma IL-6 levels after traumatic brain injury in humans. **J Neurotrauma** 16:225–232, 1999.
2. Ao H, Moon JK, Tashiro M, Terasaki H: Delayed platelet dysfunction in prolonged induced canine hypothermia. **Resuscitation** 51:83–90, 2001.
3. Badjatia N, Topcuoglu MA, Buonanno FS, Smith EE, Nogueira RG, Rordorf GA, Carter BS, Ogilvy CS, Singhal AB: Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage. **Crit Care Med** 33:1603–1609, 2005.
4. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. **N Engl J Med** 346:557–563, 2002.
5. Bigelow WG, Lindsay WK, Harrison RC, Gordon RA, Greenwood WF: Oxygen transport and utilization in dogs at low body temperatures. **Am J Physiol** 160:125–137, 1950.
6. Biggar WD, Bohn D, Kent G: Neutrophil circulation and release from bone marrow during hypothermia. **Infect Immun** 40:708–712, 1983.
7. Botterell EH, Lougheed WM, Morley TP, Vandewater SL: Hypothermia in the surgical treatment of ruptured in tracranial aneurysms. **J Neurosurg** 15:4–18, 1958.
8. Busto R, Dietrich WD, Globus MY, Ginsberg MD: Postischemic moderate hypothermia inhibits CA1 hippocampal ischemic neuronal injury. **Neurosci Lett** 101:299–304, 1989.
9. Cairns CJ, Thomas B, Fletcher S, Parr MJ, Finfer SR: Life-threatening hyperkalaemia following therapeutic barbiturate coma. **Intensive Care Med** 28:1357–1360, 2002.
10. Citerio G, Gaini SM, Tomei G, Stocchetti N: Management of 350 aneurysmal subarachnoid hemorrhages in 22 Italian neurosurgical centers. **Intensive Care Med** 33:1580–1586, 2007.
11. Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA: Global cerebral edema after subarachnoid hemorrhage: Frequency, predictors, and impact on outcome. **Stroke** 33:1225–1232, 2002.
12. Deng HB, Han HS, Cheng DM, Sun GH, Yanari MA: Mild hypothermia inhibits inflammation after experimental stroke and brain inflammation. **Stroke** 34:2495–2501, 2003.
13. Dorsch NW: Cerebral arterial spasm—A clinical review. **Br J Neurosurg** 9:403–412, 1995.
14. Dorsch NW: Therapeutic approaches to vasospasm in subarachnoid hemorrhage. **Curr Opin Crit Care** 8:128–133, 2002.
15. Fandino J, Kaku Y, Schuknecht B, Valavanis A, Yonekawa Y: Improvement of cerebral oxygenation patterns and metabolic validation of superselective intraarterial infusion of papaverine for the treatment of cerebral vasospasm. **J Neurosurg** 89:93–100, 1998.
16. Ferguson ND, Frutos-Vivar F, Esteban A, Fernández-Segoviano P, Aramburu JA, Nájera L, Stewart TE: Acute respiratory distress syndrome: Underrecognition by clinicians and diagnostic accuracy of three clinical definitions. **Crit Care Med** 33:2228–2234, 2005.
17. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL: Serial evaluation of the SOFA score to predict outcome in critically ill patients. **JAMA** 286:1754–1758, 2001.

18. Fogelholm R, Hernesniemi J, Vapalahti M: Impact of early surgery on outcome after aneurismal subarachnoid hemorrhage. A population-based study. **Stroke** 24:1649–1654, 1993.
19. Gasser S, Khan N, Yonekawa Y, Imhof HG, Keller E: Long-term hypothermia in patients with severe brain edema after poor-grade subarachnoid hemorrhage: Feasibility and intensive care complications. **J Neurosurg Anesthesiol** 15:240–248, 2003.
20. Grote E, Hassler W: The critical first minutes after subarachnoid hemorrhage. **Neurosurgery** 22:654–661, 1988.
21. Hegner T, Krayenbühl N, Hefti M, Yonekawa Y, Keller E: Bedside monitoring of cerebral blood flow in patients with subarachnoid hemorrhage. **Acta Neurochir Suppl** 77:131–134, 2001.
22. Heuer GG, Smith MJ, Elliott JP, Winn HR, LeRoux PD: Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. **J Neurosurg** 101:408–416, 2004.
23. Hindman BJ, Todd MM, Gelb AW, Loftus CM, Craen RA, Schubert A, Mahla ME, Torner JC: Mild hypothermia as a protective therapy during intracranial aneurysm surgery: A randomized prospective pilot trial. **Neurosurgery** 44:23–33, 1999.
24. Hirai S, Ono J, Yamaura A: Clinical grading and outcome after early surgery in aneurysmal subarachnoid hemorrhage. **Neurosurgery** 39:441–447, 1996.
25. Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. **N Engl J Med** 346:549–556, 2002.
26. Inamasu J, Ichikizaki K: Mild hypothermia in neurologic emergency: An update. **Ann Emerg Med** 40:220–230, 2002.
27. Jennett B, Snoek J, Bond MR, Brooks N: Disability after severe head injury: Observations on the use of the Glasgow Outcome Scale**. J Neurol Neurosurg Psychiatry** 44:285–293, 1981.
28. Karibe H, Sato K, Shimizu H, Tominaga T, Koshu K, Yoshimoto T: Intraoperative mild hypothermia ameliorates postoperative cerebral blood flow impairment in patients with aneurysmal subarachnoid hemorrhage. **Neurosurgery** 47:594–601, 2000.
29. Kassell NF, Peerless SJ, Drake CG, Boarini DJ, Adams HP: Treatment of ischemic deficits from cerebral vasospasm with high dose barbiturate therapy. **Neurosurgery** 7:593–597, 1980.
30. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL: The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results**. J Neurosurg** 73:18–36, 1990.
31. Kawamura S, Suzuki A, Hadeishi H, Yasui N, Hatazawa J: Cerebral blood flow and oxygen metabolism during mild hypothermia in patients with subarachnoid haemorrhage. **Acta Neurochir (Wien)** 142:1117–1122, 2000.
32. Kawamura Y, Yamada K, Masago A, Katano H, Matsumoto T, Mase M: Hypothermia modulates induction of hsp70 and c-jun mRNA in the rat brain after subarachnoid hemorrhage. **J Neurotrauma** 17:243–250, 2000.
33. Keller E, Imhof HG, Gasser S, Terzic A, Yonekawa Y: Endovascular cooling with heat exchange catheters: A new method to induce and maintain hypothermia. **Intensive Care Med** 29:939–943, 2003.
34. Keller E, Krayenbühl N, Bjeljac M, Yonekawa Y: Cerebral vasospasm: Results of a structured multimodal treatment. **Acta Neurochir Suppl** 94:65–73, 2005.
35. Keller E, Nadler A, Alkadhi H, Kollias SS, Yonekawa Y, Niederer P: Noninvasive measurement of regional cerebral blood flow and regional cerebral blood volume by near-infrared spectroscopy and indocyanine green dye dilution. **Neuroimage** 20:828–839, 2003.
36. Kimura A, Sakurada S, Ohkuni H, Todome Y, Kurata K: Moderate hypothermia delays proinflammatory cytokine production of human peripheral blood mononuclear cells. **Crit Care Med** 30:1499–1502, 2002.
37. Lerch C, Yonekawa Y, Muroi C, Bjeljac M, Keller E: Specialized neurocritical care, severity grade, and outcome of patients with aneurysmal subarachnoid hemorrhage. **Neurocrit Care** 5:85–92, 2006.
38. Le Roux PD, Winn HR: Intracranial aneurysms and subarachnoid hemorrhage management of the poor grade patient. **Acta Neurochir Suppl** 72:7–26, 1999.
39. Maher J, Hachinski V: Hypothermia as a potential treatment for cerebral ischemia. **Cerebrovasc Brain Metab Rev** 5:277–300, 1993.
40. Nagao S, Irie K, Kawai N, Kunishio K, Ogawa T, Nakamura T, Okauchi M: Protective effect of mild hypothermia on symptomatic vasospasm: A preliminary report. **Acta Neurochir Suppl** 76:547–550, 2000.
41. Nagao S, Irie K, Kawai N, Nakamura T, Kunishio K, Matsumoto Y: The use of mild hypothermia for patients with severe vasospasm: A preliminary report. **J Clin Neurosci** 10:208–212, 2003.
42. Ogilvy CS, Carter BS, Kaplan S, Rich C, Crowell RM: Temporary vessel occlusion for aneurysm surgery: Risk factors for stroke in patients protected by induced hypothermia and hypertension and intravenous mannitol administration. **J Neurosurg** 84:785–791, 1996.
43. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, Rordorf G, Schwamm LH, Koroshetz WJ, McDonald CT: Fever in subarachnoid hemorrhage: Relationship to vasospasm and outcome. **Neurology** 56:1299–1304, 2001.
44. Piepgras A, Elste V, Frietsch T, Schmiedek P, Reith W, Schilling L: Effect of moderate hypothermia on experimental severe subarachnoid hemorrhage, as evaluated by apparent diffusion coefficient changes. **Neurosurgery** 48:1128–1135, 2001.
45. Polderman KH: Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality—Part 2: Practical aspects and side effects. **Intensive Care Med** 30:757–769, 2004.
46. Polderman KH, Peerdeman SM, Girbes AR: Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. **J Neurosurg** 94:697–705, 2001.
47. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL: Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. **Stroke** 38:2315–2321, 2007.
48. Rosomoff HL, Holaday DA: Cerebral blood flow and cerebral oxygen consumption during hypothermia. **Am J Physiol** 179:85–88, 1954.
49. Sato K, Sato K, Yoshimoto T: Systemic and cerebral haemodynamics during craniotomy under mild hypothermia in patients with acute subarachnoid haemorrhage. **Acta Neurochir (Wien)** 142:1013–1020, 2000.
50. Spetzler RF, Hadley MN, Rigamonti D, Carter LP, Raudzens PA, Shedd SA, Wilkinson E: Aneurysms of the basilar artery treated with circulatory arrest, hypothermia, and barbiturate cerebral protection. **J Neurosurg** 68:868–879, 1988.
51. Steiner T, Friede T, Aschoff A, Schellinger PD, Schwab S, Hacke W: Effect and feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarction of the middle cerebral artery. **Stroke** 32:2833–2835, 2001.
52. Stover JF, Stocker R: Barbiturate coma may promote reversible bone marrow suppression in patients with severe isolated traumatic brain injury. **Eur J Clin Pharmacol** 54:529–534, 1998.
53. Sutton LN, Clark BJ, Norwood CR, Woodford EJ, Welsh FA: Global cerebral ischemia in piglets under conditions of mild and deep hypothermia. **Stroke** 22:1567–1573, 1991.
54. Thomé C, Schubert G, Piepgras A, Elste V, Schilling L, Schmiedek P: Hypothermia reduces acute vasospasm following SAH in rats. **Acta Neurochir Suppl** 77:255–258, 2001.
55. Thomé C, Schubert GA, Schilling L: Hypothermia as a neuroprotective strategy in subarachnoid hemorrhage: A pathophysiological review focusing on the acute phase. **Neurol Res** 27:229–237, 2005.
56. Todd MM, Hindman BJ, Clarke WR, Torner JC; Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators: Mild intraoperative hypothermia during surgery for intracranial aneurysm. **N Engl J Med** 352:135–145, 2005.
57. Valeri CR, Feingold H, Cassidy G, Ragno G, Khuri S, Altschule MD: Hypothermia-induced reversible platelet dysfunction. **Ann Surg** 205:175–181, 1987.


## COMMENTS

Seule et al. have evaluated the feasibility and safety of mild hypothermia treatment in aneurysmal subarachnoid hemorrhage (SAH) patients with intracranial hypertension and/or cerebral vasospasm (CVS). Results demonstrate that 35.6% of patients obtained good func-

tional outcomes, with the most frequent side effects being electrolyte disorders, pneumonia, thrombocytopenia, and septic shock. The authors concluded that systemic hypothermia should be viewed as a last resort option for selected patients with elevated intracranial pressure (ICP) or refractory vasospasm, as complications may be severe. Although elevated brain temperatures can worsen outcomes after stroke and traumatic brain injury (1, 2), this article by Seule et al. provides evidence that lowering systemic temperatures in the acute period after brain injury is associated with significant side effects. At this point, a trial of postoperative hypothermic treatment in aneurysmal SAH may be warranted.

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1. Cairns CJ, Andrews PJ: Management of hyperthermia in traumatic brain injury. **Curr Opin Crit Care** 8:106–110, 2002.
2. Reith J, Jørgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, Olsen TS: Body temperature in acute stroke: Relation to stroke severity, infarct size, mortality, and outcome. **Lancet** 347:422–425, 1996.

This is a tremendously thought-provoking article. The authors address the use of significant hypothermia in SAH patients in the intensive care unit setting; hence, most patients are in poor grade. The authors' management philosophy thus goes against the "Lund Concept" of essentially normalizing all parameters. Nevertheless, the concept herein is of cerebral protection with hypothermia, and the authors give rationale and evidence for its use, along with barbiturate coma, in severe cases of SAH as a last resort. The reporting of a significant associated morbidity is to be commended. The article is sure to provoke interesting responses from the readership.

**Neil Kitchen**
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The authors evaluated the feasibility and safety of mild hypothermia treatment in 100 patients with aneurysmal SAH who had intracranial hypertension and/or CVS. Hypothermia (33–34°C) was induced and maintained until ICP normalized, CVS resolved, or severe side effects occurred. The mean duration of hypothermia was 169 ± 104 hours. The most frequent side effects were electrolyte disorders (77%), pneumonia (52%), thrombocytopenia (47%), and septic shock syndrome (40%).

The present report is of great interest for neurosurgeons and neurointensivists, since it describes the largest published series of patients treated with moderate hypothermia and barbiturate coma. As the authors emphasize, the efficacy of the treatment cannot be assessed in the present study because no control group was introduced. However, their results are encouraging with regard to mortality and functional outcome rates among patients with resistant elevated ICP and CVS. In our experience, repeated angiographic supraselective intra-arterial treatment, more than 3 times if necessary, is the best option for severe resistant CVS.

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This study evaluated the feasibility and safety of mild hypothermia to treat ruptured aneurysm patients with refractory vasospasm, increased ICP, or both. One hundred consecutive patients were managed with mild hypothermia (33–34°C), with side effects that included electrolyte disorders, pneumonia, thrombocytopenia, and sepsis. Nearly half of the patients died, but good outcomes were observed in one-third of patients. The authors conclude that hypothermia can be used safely as a last resort in these patients, who otherwise have a grim prognosis. Although it seems reasonable to add hypothermia to the management of these patients, a larger study, similar to the Intraoperative Hypothermia for Aneurysm Surgery Trial, will be needed to demonstrate a therapeutic effect.

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This article adds to a number of published studies on hypothermia in patients with SAH. The investigators focus on poor-grade and critically ill patients, in contrast to a randomized trial of intraoperative hypothermia, the Intraoperative Hypothermia for Aneurysm Surgery Trial, which found no effect of hypothermia during surgery on outcome among good-grade patients with ruptured aneurysms and SAH (1). There was a slight increase in complications, mainly infection, when hypothermia was used. The differences are that the group from Zurich used prolonged postoperative hypothermia for a mean of 7 days, and many of the patients were in poor clinical grades. The study was not randomized. Most patients underwent craniotomy and aneurysm clipping, although 4% were treated endovascularly. A high rate of complications was observed, and, in the absence of randomization, the impact on outcome cannot be ascertained. Even in the hands of these experts, with access to every kind of monitoring and technology available, it is not clear that hypothermia helped. The authors achieved good outcome or moderate disability on the Glasgow Outcome Scale in 36% of patients. Forty-eight percent died. In comparison, the tirilazad studies in the 1990s found that, of the 789 World Federation of Neurosurgical Society Grade 4 and 5 patients with SAH, 38% had good outcome or moderate disability, and 37% died. The search for simple, neuroprotective strategies will continue.

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1. Todd MM, Hindman BJ, Clarke WR, Torner JC: Mild intraoperative hypothermia during surgery for intracranial aneurysm. **N Engl J Med** 352:135–145, 2005