Impact of Hypothermia Initiation and Duration on Perihemorrhagic Edema Evolution After Intracerebral Hemorrhage

Bastian Volbers, MD; Sabrina Herrmann, MD; Wolfgang Willfarth, MD; Hannes Lücking, MD; Stephan P. Kloska, MD; Arnd Doerfler, MD; Hagen B. Huttner, MD; Joji B. Kuramatsu, MD; Stefan Schwab, MD, PhD; Dimitre Staykov, MD

Background and Purpose—Intracerebral hemorrhage (ICH) causes high morbidity and mortality. Recently, perihemorrhagic edema (PHE) has been suggested as an important prognostic factor. Therapeutic hypothermia may be a promising therapeutic option to treat PHE. However, no data exist about the optimal timing and duration of therapeutic hypothermia in ICH. We examined the impact of therapeutic hypothermia timing and duration on PHE evolution.

Methods—In this retrospective, single-center, case–control study, we identified patients with ICH treated with mild endovascular hypothermia (target temperature 35°C) from our institutional database. Patients were grouped according to hypothermia initiation (early: days 1–2 and late: days 4–5 after admission) and hypothermia duration (short: 4–8 days and long: 9–15 days). Patients with ICH matched for ICH volume, age, ICH localization, and intraventricular hemorrhage were identified as controls. Relative PHE, temperature, and intracranial pressure course were analyzed. Clinical outcome on day 90 was assessed using the modified Rankin scale (0–3=favorable and 4–6=poor).

Results—Thirty-three patients with ICH treated with hypothermia and 37 control patients were included. Early hypothermia initiation led to relative PHE decrease between admission and day 3, whereas median relative PHE increased in control patients (−0.05 [interquartile range, −0.4 to 0.07] and 0.07 [interquartile range, −0.07 to 0.26], respectively; P=0.007) and patients with late hypothermia initiation (0.22 [interquartile range 0.12–0.27]; P=0.037). After day 3, relative PHE increased in all groups without difference. Outcome was not different between patients treated with hypothermia and controls.

Conclusions—Early hypothermia initiation after ICH onset seems to have an important impact on PHE evolution, whereas our data suggest only limited impact later than day 3 after onset. (Stroke. 2016;47:2249-2255. DOI: 10.1161/STROKEAHA.116.013486.)

Key Words: brain edema ■ cerebral hemorrhage ■ induced hypothermia ■ stroke
Concerning duration of TH, ICH patients were cooled for a period of 8 to 10 days after symptom onset in previous studies.\(^{13,22}\) This duration was used based on the pathophysiological background of PHE evolution, which could be shown to peak \(\leq 10\) to 14 days after symptom onset.\(^{4,23}\) However, it remains speculative whether it is necessary to apply TH that long and how duration impacts outcome. Animal studies in ischemic stroke models suggested an association of longer cooling and better neuroprotection.\(^{17,18}\) But because TH is also associated with longer duration of sedation and mechanical ventilation\(^{24}\) as well as a higher risk of pneumonia and sepsis,\(^{25}\) which is suggested to increase in direct proportion to the duration of hypothermia,\(^{17}\) shorter duration of TH may reduce the risk of adverse events with a possible positive impact on outcome. We now evaluated the impact of initiation time and duration of mild TH on PHE evolution.

**Methods**

**Patient Selection**
The study was approved by our institutional review board. Patients with spontaneous ICH admitted between January 2006 and August 2014 treated with mild TH (target temperature 35°C\(^{26}\)) were identified from our institutional database. As control group, patients with spontaneous ICH not treated with hypothermia matched for ICH volume, age, ICH localization, and intraventricular hemorrhage (matching algorithm) were identified from the same database. Spontaneous ICH was assumed when no other cause than hypertension or amyloid angiopathy was found. For final analysis, only patients with at least 1 computed tomography (CT) scan after rewarming were included to sufficiently evaluate PHE evolution in correlation to TH duration. Patients who underwent surgical hematoma evacuation were excluded as well as patients with early withdrawal of therapy or secondary ICH.

**Basic Management**
All patients received standard medical treatment according to our institutional algorithm and the European Stroke Initiative guidelines for monitoring and treatment of ICH.\(^{27,28}\) Body core temperature was measured continuously with a Foley temperature bladder catheter in the hypothermia group, and hourly tympanic temperature was obtained in the control group.\(^{13,22}\) Intracranial pressure (ICP) was monitored in all patients with intraventricular hemorrhage and hydrocephalus or blood in the third/fourth ventricle via extraventricular drainage. In patients with large ICH (>30 cm\(^3\)), ICP monitoring (extraventricular drainage or ICP probe) was considered at the discretion of the treating physician.

**Endovascular Hypothermia**
TH was performed according to our institutional protocol as described previously.\(^{13,22}\) A 9.3F, 38-cm catheter central line (ICY, IC-3893; Zoll Medical) and a temperature management device (Thermogard; Zoll Medical) were used. For patients treated with TH outside of clinical studies, informed consent had been obtained from relatives or legal representatives to receive TH as individual rescue therapy if necessary. Here, TH duration was left at the discretion of the treating physician, and in other cases, it was defined according to a study protocol.\(^{13,22}\) The standard rewarming rate was 0.5°C/24 h. TH was defined as sufficient if bladder temperature was <36.0°C.\(^{26}\)

**Assessment of Clinical Data**
Clinical characteristics including the frequency of elevated ICP (>20 mm Hg lasting \(>5\) minutes or patient presents with symptoms related to elevated ICP (deterioration of consciousness, anisocoria))\(^{29}\) up to day 14 after admission (ICP burden) and fever burden (number of days with temperature \(\geq 37.5°C\))\(^{30}\) were obtained from medical records.

**Neuroimaging and Assessment of PHE and ICH Volume**
Neuroimaging was performed on a fourth-generation CT scanner (SOMATOM-Sensation-64, SOMATOM-Definition-AS+; Siemens-Healthcare, Erlangen, Germany). A sequential or helical CT scan was obtained. Reconstruction algorithms for CT images are summarized in Table 1 in the online-only Data Supplement. CT images were acquired and reconstructed parallel to the orbitomeatal plane. Absolute volumes of ICH and PHE were obtained using a validated semiautomatic volumetric algorithm as previously published.\(^{31}\) Different time points of CT scans were merged to time clusters for better comparison (days 1, 2–3, 4–6, 7–9, and 10–12). An additional time cluster (days 13–15) was analyzed if available. Relative PHE (rPHE) was calculated as a ratio of PHE volume and initial ICH volume.\(^{32}\) To analyze a possible PHE rebound after rewarming, the percentage of rPHE change between the last CT scan before rewarming and the first scan after rewarming was compared with the percentage of rPHE change between the first and second CT scan after rewarming and the last and next to last CT scan before rewarming. To account for different time intervals between these CT scans in individual patients and the effect of time on the natural course of PHE evolution, \(r\) rPHE change was calculated per day (\(\Delta rPHE\)).

**Outcome Variables**
PHE evolution was compared between patients treated with TH in correlation with the day of TH initiation (early [on admission (day 1) or day 2 after admission] versus late [day 4–5]) and TH duration (short duration [4–8 days] and long duration [9–15 days]) and control patients. rPHE was used for this comparison. Median and dichotomized modified Rankin scale (mRS) scores (favorable outcome=mRS score 0–3 and poor outcome=mRS score 4–6) on day 90 were analyzed. Temperature evolution was analyzed, as well as burden of elevated ICP episodes (ICP burden), as known adverse events after rewarming.\(^{17,13}\)

**Statistics**
Baseline data were summarized as mean and SD, number and percentage, or median and interquartile range (IQR) as appropriate. Statistical analyses were performed using the IBM SPSS Statistics 21 software package (IBM-Corporation, Armonk, NY). Mann–Whitney U test with exact significance was used for comparison of rPHE and temperature between groups if Kolmogorov–Smirnov test indicated a non-normal distribution. Independent \(t\) test was used for comparison of continuous variables between groups with normally distributed data. Dichotomous variables between groups were compared using Fisher exact test and \(\chi^2\). Ordinal variables were analyzed with the Wilcoxon rank–sum test with exact testing if necessary. Linear regression was used to analyze relationship between continuous interval variables. Missing data for analyzed parameters led to exclusion from this analysis. A \(P\) value <0.05 was considered statistically significant. Statistical tests were 2 sided.

**Results**

**Patients’ Characteristics**
Fifty-three patients with ICH were sufficiently treated with TH. Six patients were excluded because of surgical hematoma evacuation, 2 patients because of insufficient data sets, and 3 patients because of early do-not-resuscitate orders during the first few days after TH initiation. Nine patients did not receive another CT scan after rewarming because of the discretion of the treating physician. In 3 patients, TH was initiated late, and in 30 patients early. Of those patients with early TH initiation, 21 patients received TH up to day 4 to 8 (short duration) and 9 patients up to day 9 to 15 (long duration; \(n=4\) because of study protocol\(^{13,22}\) and \(n=5\) because of persistently increased PHE or...
In patients with early TH initiation, rPHE of patients with early TH initiation decreased between neuroimaging on admission and on day 3, whereas it increased in patients with late TH initiation (median rPHE difference between day 1 and 3 [ΔrPHE]=−0.05 [IQR −0.4 to 0.07] and +0.22 [IQR, 0.12−0.27] respectively; \( P=0.037 \)) and in control patients during that time interval (median ΔrPHE=+0.07 [IQR, −0.07 to 0.26]; \( P=0.007 \) compared with patients with early hypothermia initiation). This early rPHE increase did not differ between patients with late TH initiation and control patients (\( P=0.296 \)). rPHE evolution between days 3 and 9 did not differ between control patients and patients with early and late TH initiation (data not shown). Median peak rPHE was lower in patients with early TH initiation than in control patients (1.27 [IQR, 0.94–1.71] and 1.56 [IQR, 1.06–2.03], respectively; \( P=0.045 \)), whereas there was no difference between patients with late TH initiation and control patients (\( P=0.461 \)). Figure 1 illustrates mean rPHE evolution up to day 9.

**Influence of Hypothermia Duration on PHE Evolution**

Patients with early TH initiation (\( n=30 \)) were included for following analyses. Mean early PHE evolution between admission and day 3 did not differ between patients with short and long TH duration (mean difference, 0.03; 95% CI, −0.29 to 0.24). Between day 3 and day 12, PHE increased to the same extent in patients with short and long TH duration and control patients (Figure 2). In a subset of patients with neuroimaging up to day 15 (\( n=17 \) with short and \( n=8 \) with long hypothermia duration), there was also no difference in mean rPHE evolution between days 12 and 15 (mean difference, 0.12; 95% CI, −0.13 to 0.36).

**PHE Evolution During and After Rewarming**

PHE evolution in TH patients did not differ between the time before rewarming (median ΔrPHE% between next to last and peak).
last CT scan before rewarming: 3.4 [IQR, −10.3 to 9.2]) and the time during rewarming (median ΔrPHE% between the last CT scan before and the first CT scan after rewarming: 4.0 [IQR, −4.7 to 13.6]; P=0.408). Also, there was no difference between PHE evolution during and after rewarming (median ΔrPHE% between the first and second CT scan after rewarming: 2.3 [IQR, −10.2 to 12.2]; P=0.968), indicating that no rPHE rebound after rewarming occurred. We could not find a correlation between TH duration and PHE evolution during rewarming (R²=0.04; P=0.301).

Temperature Evolution

Evolution of maximum daily temperature is illustrated in Figure 3. After rewarming, temperature increased to a median of >37.5°C, which indicates presence of fever. There was a trend toward a linear relationship between TH duration and fever burden within 10 days after rewarming (R²=0.12; P=0.059).

Intracranial Pressure

ICP burden in general did not differ between control patients and patients treated with TH (Table). However, temporal distribution was different. During hypothermia, median ICP burden was lower in patients with short TH duration than in control patients (0 [IQR, 0] and 0 [IQR, 0–1], respectively; P=0.022), whereas it was equal after rewarming (0 [IQR, 0–3.5] and 0 [IQR, 0–1], respectively; P=0.297). In patients with long TH duration, median ICP burden did not differ in comparison to control patients during TH (1 [IQR, 0–11] and 1 [IQR, 0–8], respectively; P=0.94) but was higher after rewarming (2 [IQR, 0–18.5] and 0 [IQR, 0], respectively; P=0.003). After rewarming, there was no linear relationship between temperature and ICP burden (R²=0.001; P=0.611).

Functional Outcome

mRS scores on day 90 was available for 29 control patients and 29 TH patients. Four control patients (14%) and 5 TH patients (17%) had a favorable outcome (P=0.999). Analyzing only patients with early TH initiation, 4 patients (15%) had a favorable outcome on day 90 (P=0.868 compared with control patients). Median mRS score on day 90 did not differ between TH and control patients (Table). Figure 4 shows mRS scores on day 90 assessed in patients with early TH initiation and control patients.

Discussion

We could show that TH especially in the acute phase after ICH seems to have an important impact on PHE evolution. Our findings support the current pathophysiological understanding of secondary neuronal damage after ICH, its association with PHE in neuroimaging, and the suggested impact of hypothermia on it.

The pathophysiological background of PHE caused by ICH includes many detrimental pathways leading to secondary neuronal damage and death, for example, excitotoxicity and glutamate release (cytotoxic edema), blood–brain barrier damage (vasogenic edema), induction of inflammatory and proapoptotic pathways, and release of toxic blood breakdown products and thrombin. Most of those processes are initiated within minutes to hours after the occurrence of ICH and may continue for a period of ≥72 hours. Animal studies have revealed a rise of proinflammatory mediators within hours after cerebral injury and a simultaneous complement system activation, which possibly causes significant additional injury through phagocytic actions of macrophages and further stimulation of immune reactions. Thus, at least in the initial stages of acute brain injury, a hyperinflammatory state can be assumed. Glutamate release and consecutive excitotoxicity occurs within minutes after cellular damage. There are also hints that cerebral thermopooling may increase in certain brain areas within minutes to days after cerebral injury. This may lead to local cerebral hyperthermia to date known in ischemic brain conditions, which may further increase damage to injured neurons.

Many of these detrimental pathways mainly associated with the occurrence of cytotoxic PHE may be blocked by...
hypothesis in these earliest stages, leading to a decreased early PHE evolution: hypothermia is associated with decreased excitotoxic damage, altered and inhibited apoptotic signals, reduced neuronal calcium influx, decreased cerebral metabolic rate, decreased release of excitatory amino acids, inhibited inflammation, and reduced disruption of the blood–brain barrier.17,18 Thus, in accordance with our results, early initiation of TH—which could already be shown to be feasible and safe13—seems to be important for a sufficient treatment of PHE evolution. Although only 3 patients received lately initiated TH, we observed higher rPHE in those patients, rather comparable with controls than with patients who received early TH. This finding may indicate that TH is possibly more valuable as a preventive measure for PHE rather than a treatment capable of reducing PHE that has already occurred. However, no definite conclusion can be drawn from our limited data.

As previous research could repeatedly show, early PHE increase is associated with increased peak PHE and poor outcome.6,4 Therefore, at least hypothetically, therapeutic inhibition of early PHE evolution may result in better outcome. To date, only a few clinical studies examining mild TH in ICH patients exist12,22; however, none of them delivered data on long-term outcome apart from mortality. We could not show an association of TH with functional outcome. Of course, outcome data from our cohort should be interpreted cautiously considering the retrospective study design and the small sample size. Several other considerations may also explain these findings:

There are no data about the optimal duration of TH. Studies of our own group maintained TH for 10 days in patients with ICH to inhibit PHE evolution, which roughly represents the known natural PHE increase up to day 8 to 12 after symptom onset.4 Concerning PHE evolution, our data suggest that a shorter duration may be sufficient. We could not find an impact of TH on PHE evolution later than day 3 after symptom onset. Animal studies in ischemic stroke models suggest an interdependence of the timing of TH initiation and duration to achieve neuroprotection. If TH is initiated early, a shorter cooling duration might be effective, whereas in case of a delayed initiation, a prolonged cooling period seems to be necessary for neuroprotective effects.18 However, a longer period of TH might be associated with a higher proportion of adverse events. In studies of hypothermia in patients with ischemic stroke, it seems that complications occur in direct proportion to the duration and depth of cooling, with the most common problems being pneumonia and sepsis.17 We could not find increased rates of pneumonia in patients treated with TH, which might be explained by the high pneumonia rate in the control group. But we detected some interesting aspects concerning fever burden as a possible surrogate marker of inflammatory activity. As a logical consequence of targeted temperature control, fever burden was lower in patients treated with TH than in control patients. However, analyzing the temporal distribution of fever burden, we found a strong tendency that patients with longer TH duration suffer a higher fever burden after rewarming than patients with shorter TH duration. Because fever burden is known to negatively influence outcome in ICH patients7,30 as a mere temperature-associated effect independently from any infectious disease,34 a possible fever rebound after longer TH duration may outweigh the above-mentioned positive effects of TH during the early stages after ICH.

Another known problem may be the rewarming period itself.17 Data derived from ischemic stroke research suggest that overly rapid rewarming can lead to massive edema increase and reflex ICP elevation17 with possible herniation.33 We could not find a relevant PHE increase after rewarming using our rewarming protocol.13,22 Only in patients with insufficient ICP control during TH, we also observed an increased ICP burden after rewarming. Thus, in accordance with other studies,17,33 we concluded that this effect was not associated with our rewarming algorithm. However, no general statement about rewarming procedures can be made in our cohort.

Third, in our cohort, patients treated with TH suffered larger secondary hematoma expansion. This difference may also have had an important impact on outcome. Because of the retrospective design, no statements concerning causality can be made. Although temperature-dependent effects on coagulation have been described, clinically relevant changes in platelet function and clotting do not seem to occur in mild TH levels of 35°C.28 Furthermore, in some patients, the decision to use TH was taken as an escalation measure of treatment after hematoma growth had occurred.

**Figure 3.** Median maximum daily temperature evolution in patients with hypothermia up to day 4 to 8 (short duration) and day 9 to 15 (long duration) and control patients.

**Figure 4.** Modified Rankin Scale (mRS) score on day 90 of patients with early hypothermia initiation (hypothermia; n=26) and control patients (n=29).
There are several limitations to our study: it is a monocenter retrospective study with a small sample size, especially in the group with late hypothermia initiation. In most of the included patients, treatment decisions concerning onset and duration of hypothermia were taken individually at the discretion of the treating physician. This fact does not allow us to draw any conclusion considering clinical outcomes. Other individual treatment decisions may also have influenced the radiological and clinical course in our patients: insufficient ICP reduction or further PHE increase may have lead to longer hypothermia duration. Vice versa, a limited early PHE increase without elevated ICP values may have led to the decision to withdraw TH early in some patients. Prospective data are needed. However, the present uniformity of basic management protocols at our institution limits treatment variations to a certain degree.

Because temperature measurement during TH was performed in the bladder, no definitive statement about brain temperature is yet possible.36 However, this procedure is commonly used in hypothermia studies. Also, in control patients, tympanic temperature was measured. In some control patients without extra-ventricular drainage or ICP probes, we could not perform ICP monitoring and used clinical and radiological findings instead to estimate ICP burden. This may have led to inconsistent findings. Because there was no data available about PHE evolution in patients with strict normothermia (37.0°C [=fever prevention]), we cannot exclude that mere prevention of fever, which was frequently present in our control group, could also sufficiently influence PHE evolution. Further investigation is warranted. CT scans were not performed regularly at the same time after symptom onset. Thus, we analyzed edema volumes using time clusters of ≤2 days each, which might pose possible bias. However, we used a semiautomatic threshold-based volumetric method, which was validated against magnetic resonance imaging and yields reliable observer-independent results.31

**Conclusions**

Our data suggests that early initiation of TH after onset of ICH may result in better control of PHE evolution. An influence of TH on PHE evolution in the later course of time was not obvious.

**Disclosures**

None.

**References**


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Stroke. 2016;47:2249-2255; originally published online July 21, 2016;
doi: 10.1161/STROKEAHA.116.013486

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SUPPLEMENTAL MATERIAL

Impact of mild endovascular hypothermia initiation and duration on perihemorrhagic edema evolution after intracerebral hemorrhage

Bastian Volbers\textsuperscript{1} MD, Sabrina Herrmann\textsuperscript{1} MD, Wolfgang Willfarth\textsuperscript{1} MD, Hannes Lücking\textsuperscript{2} MD, Stephan P. Kloska\textsuperscript{2} MD, Arnd Doerfler\textsuperscript{2} MD, Hagen B. Huttner\textsuperscript{1} MD, Joji B. Kuramatsu\textsuperscript{1} MD, Stefan Schwab\textsuperscript{1} MD, PhD, Dimitre Staykov\textsuperscript{1,3} MD.

\textsuperscript{1}Neurological Department, University of Erlangen-Nuremberg
\textsuperscript{2}Neuroradiological Department, University of Erlangen-Nuremberg
\textsuperscript{3} Department of Neurology, Hospital of the Brothers of St. John, Eisenstadt, Austria

Supplemental Table I: Reconstruction algorithms for used CT scanners

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<td>helical scan 4.8 mm</td>
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<td>Definition AS+</td>
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<td></td>
<td>helical scan 4.8 mm</td>
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</table>

Supplemental Table II: Further clinical characteristics of all included ICH patients: mean (standard deviation (SD)), median (interquartile range (IQR)), n(%) as appropriate; renal insufficiency was diagnosed if serum creatinine on admission was >1.2 mg/dl; *independent t-test, +\chi^2/Fisher’s exact test, # Mann-Whitney-U/Wilcoxon Rank sum test.

<table>
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<tr>
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<th>Patients treated with hypothermia (n=33)</th>
<th>Control group (n=37)</th>
<th>p-value</th>
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<td>20(54)</td>
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<td>[median(IQR)]</td>
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<td>Mechanical ventilation</td>
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<td>Length of stay</td>
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