Induction of Cooling With a Passive Head and Neck Cooling Device  
Effects on Brain Temperature After Stroke

Sven Poli, MD; Jan Purrucker, MD; Miriam Priglinger, MD; Jennifer Diedler, MD; Marek Sykora, MD, PhD; Erik Popp, MD; Thorsten Steiner, MD; Roland Veltkamp, MD; Julian Bösel, MD; André Rupp, PhD; Werner Hacke, MD, PhD; Christian Hametner, MD

Background and Purpose—Therapeutic hypothermia improves clinical outcome after cardiac arrest and appears beneficial in other cerebrovascular diseases. We conducted this study to investigate the relationship between surface head/neck cooling and brain temperature.

Methods—Prospective observational study enrolling consecutive patients with severe ischemic or hemorrhagic stroke undergoing intracranial pressure (ICP) and brain temperature monitoring. Arterial pressure, ICP, cerebral perfusion pressure, heart rate, brain, tympanic, and bladder temperature were continuously registered. Fifty-one applications of the Sovika cooling device were analyzed in 11 individual patients.

Results—Sovika application led to a significant decrease of brain temperature compared with baseline with a maximum of −0.36°C (SD, 0.22) after 49 minutes (SD, 17). During cooling, dynamics of brain temperature differed significantly from bladder (−0.25°C [SD, 0.15] after 48 minutes [SD, 19]) and tympanic temperature (−1.79°C [SD, 1.19] after 37 minutes [SD, 16]). Treatment led to an increase in systolic arterial pressure by >20 mm Hg in 14 applications (n=7 patients) resulting in severe hypertension (>180 mm Hg) in 4 applications (n=3). ICP increased by >10 mm Hg in 7 applications (n=3), led to ICP crisis >20 mm Hg in 6 applications (n=3), and a drop of cerebral perfusion pressure <50 mm Hg in 1 application.

Conclusions—Although the decrease of brain temperature after Sovika cooling device application was statistically significant, we doubt clinical relevance of this rather limited effect (−0.36°C). Moreover, the transient increases of blood pressure and ICP warrant caution. (Stroke. 2013;44:708-713.)

Key Words: acute stroke ■ brain temperature ■ hypothermia ■ induction of cooling ■ intracerebral hemorrhage ■ neuromonitoring ■ neuroprotection

Therapeutic hypothermia improves clinical outcome in patients with global cerebral ischemia after cardiac arrest and in newborns with hypoxic ischemic encephalopathy.1,2 Hypothermia also seems promising in other cerebrovascular diseases, for example, ischemic and hemorrhagic stroke.3–5 In experimental models, the sooner hypothermia was initiated, the more distinctive neuroprotection was.6,7 Although clinical proof is still missing,8 experimental data supports the concept of prehospital induction of cooling. Induction methods should be easily applicable, transportable, safe, and effective in brain cooling. Head cooling devices seem suitable for this purpose. However, the results from the few published clinical trials evaluating cooling efficacy directly in the brain are conflicting.9,10 Theoretical evaluation indicates superiority of combined head and neck cooling compared with pure head cooling only.11 Hence, the Sovika cooling device (HVM Medical, Rotenburg, Germany) covering not only the head but also the anterior and dorsal neck seems promising.

Two recent studies in healthy volunteers showed contradictory data regarding safety. Unfortunately, both trials were limited to monitoring peripheral temperatures only instead of the actual brain temperature.12,13 The aim of our study was to investigate whether the Sovika head and neck cooling device is effective in lowering brain temperature.

Methods

Study Design  
We conducted a prospective single center observational study enrolling consecutive patients with (severe) ischemic or hemorrhagic stroke admitted to our neurocritical care unit between January and
Table 1. Inclusion/Exclusion Criteria

<table>
<thead>
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<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Ischemic or hemorrhagic stroke</td>
<td>Skin lesions not allowing a secure application of the Sovika head and neck cooling device</td>
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<tr>
<td>Combined intracranial pressure/temperature brain probe</td>
<td>Concomitant other physical or pharmacological cooling interventions</td>
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<td>Brain, bladder, or tympanic temperature &gt;37.1°C</td>
<td>Life expectancy &lt;24 h</td>
</tr>
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<td>Written informed consent by patient or legal representative</td>
<td>Known cryoglobulinemia and cold agglutinins</td>
</tr>
<tr>
<td>Brain, bladder, or tympanic temperature &gt; 38.0°C</td>
<td>Known vasospastic vascular disorder (e.g., Raynaud phenomenon or thromboangiitis obliterans)</td>
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<tr>
<td>Concomitant other physical or pharmacological cooling interventions</td>
<td>Brain, bladder, or tympanic temperature &gt; 38.0°C</td>
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<td>Known vasospastic vascular disorder (e.g., Raynaud phenomenon or thromboangiitis obliterans)</td>
<td>Combined intracranial pressure/temperature brain probe</td>
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</table>

Cooling Protocol

Cooling of all cerebrovascular patients was conducted in 2 steps following our standard operating procedure to achieve normothermia (36.0°C–37.1°C): first, if body core temperature exceeded 37.1°C, the Sovika cooling device was applied; second, if body core temperature remained >37.1°C after 1 hour or the initial body core temperature was >38.0°C, pharmacological measures (acetaminophen or metamizole) were taken and whole-body-surface cooling was initiated. If, in later time course, temperature rose again, the cooling protocol restarted from the beginning. This lead to >1 application of the Sovika cooling device in most patients.

Statistics

Statistical analysis was computed with MATLAB v7.12 (MathWorks, Natick, MA) and SAS v9.2 (SAS, Cary, NC). Start of cooling (0 minutes) was predefined as the time point when the Sovika cooling device was fully applied to the patients’ head. Baseline of brain and body temperatures includes all 15 minutes until start of cooling (average of −15 to 0 minutes). Baseline of the neurovital parameters was limited to 10 minutes (average of −15 to −5 minutes). A period of 5 minutes before cooling start was excluded to avoid artifacts caused by positioning of the patient before cooling device application. To obtain robust estimates, baseline data were compared with the pooled data of equally long posttreatment intervals. To capture maximal treatment effects, the posttreatment interval of interest was 0 to 10 minutes postcooling for neurovital parameters and 45 to 60 minutes postcooling for temperature (indicated by shaded areas in Figures 1 and 2). Primary statistical analysis was limited to the first application of the Sovika cooling device for each patient. Student test for dependent measurements was used. A second analysis included all subsequent applications. To account for the different number of applications per subject, a mixed-model analysis was applied. To analyze the relative differences among brain, tympanic, and bladder temperature, ANOVA with 2 dependent factors (brain and bladder, or brain and tympanic temperature) and time was computed. Pearson correlation analysis was applied to test influence of age, sex, body weight, body height, body mass index, body surface area, brain temperature at baseline, time from stroke onset to cooling, and inflammatory response before application (C-reactive protein, leukocytes) on brain cooling. P<0.05 was considered significant.

Results

Eleven patients with a total of 51 applications of the Sovika cooling device were analyzed. Baseline characteristics are shown in Table 2. In the following, we present the results of the primary statistical analysis (11 initial applications). Results of the secondary analysis including all 51 applications (initial and subsequent) are mainly shown in the Table and Figure in the online-only Data Supplement.

Brain Temperature

At baseline, brain temperature in mean was 37.15°C (SD, 0.21). After 1 hour of cooling, brain temperature was reduced an average of 0.32°C (SD, 0.2; P<0.001; Figure 1). The maximum decrease in brain temperature was −0.36°C (SD, 0.22) after 49 minutes (SD, 17). We found no significant correlation between the extent of brain cooling and age (r=0.47), sex (r=0.42), body weight (r=0.11), body height (r=−0.28), body mass index (r=0.27), body surface area (r=0.04), brain temperature (r=−0.12) at baseline, time from stroke onset to cooling (r=−0.09), or inflammatory status (C-reactive protein [r=0.07], leukocytes [r=−0.04]) before application of the Sovika cooling device.

Comparison of Brain With Tympanic and Bladder Temperature

Bladder temperature at baseline (mean, 37.22°C; SD, 0.20) was similar to brain temperature, whereas tympanic temperature

accuracy±0.2°C, Smiths Medical). Sampling rate of data acquisition was 1 per minute using Draeger software and stored on a commercially available hard disc. Computed tomography scans were indicated by the neurological intensive care attendings independent of the study. In all patients, computed tomography scans before and after the cooling application were evaluated for bleeding complications by independent neuroradiologists.
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(710)

(36.5°C; SD, 0.41) was significantly lower (P<0.001).

After 1 hour of cooling, bladder temperature was reduced an average of 0.18°C (SD, 0.15; P=0.003), with a maximum decrease of −0.25°C (SD, 0.15) after 48 minutes (SD, 19). The difference between brain and bladder temperature became significant (P=0.006). Tympanic temperature was reduced an average of 1.69°C (SD, 1.19; P<0.001), with a maximum decrease of −1.79°C (SD, 1.19) after 37 minutes (SD, 16). During cooling, dynamics of brain temperature differed significantly from bladder (P<0.001) and tympanic temperatures (P=0.002).

**Vital Parameters and Safety**

After the application of the Sovika cooling device, we observed a transient increase of the arterial and the CPP (Figure 2). Although increase of systolic arterial pressure (SAP) compared with baseline did not reach level of significance (mean, 10.15 mm Hg; SD, 15.49; P=0.055) and mean arterial pressure only increased an average of 6.66 mm Hg (SD, 9.92; P=0.05), 3 patients had an increase of SAP >20 mm Hg, resulting in an absolute SAP >180 mm Hg in 1 patient. Analyzing all 51 applications, an increase in SAP >20 mm Hg was observed in 7 individual patients in a total of 14 applications, leading to an absolute SAP >180 mm Hg in 4 applications (n=3 patients). Mean ICP was not elevated after the Sovika application (0.24 mm Hg; SD, 2.07; not significant). Although we did not observe critical ICP changes in the 11 initial applications, ICP increased >10 mm Hg in 7 (n=3 patients) of all 51 applications leading to ICP crisis >20 mm Hg in 6 applications (n=3 patients) and a drop of CPP <50 mm Hg in 1 application. Mean CPP after Sovika application increased an average of 6.46 mm Hg (SD, 9.53; P=0.048). Heart rate did not change significantly during application (mean, −0.17 bpm; SD, 2.48; not significant). No bleeding complications were observed in computed tomography scans.

**Discussion**

Therapeutic hypothermia effects clinical relevant neuroprotection after cardiac arrest, is recommended in current resuscitation guidelines,1,16 and appears beneficial in stroke.3–5 To maximize neuroprotection, laboratory data suggest the shortest possible interval between symptom onset and hypothermia,6,7 providing a rationale for preliminary studies to find optimal methods for prehospital induction of cooling that could then be tested in larger trials. The Sovika head and neck cooling device was designed for prehospital cooling. The objective of our study was to investigate the relationship between surface head and neck cooling with the Sovika device and brain temperature. After the 1-hour treatment period in 11 patients, brain temperature was reduced by an average of –0.32°C.
A smaller decrease in brain temperature resulted when taking all 51 applications into account (−0.18°C). The only previously available data on brain temperature acquired during passive external head cooling were published in 1992. In 3 patients, no or only a marginal decrease was observed. In contrast to the passive external head cooling used by Mellergård, the Sovika cooling device features supplementary neck coverage. Head plus neck versus head only coverage was suggested to be superior in cooling deeper brain regions. Hence, the decrease of brain temperature in our patients could be attributed to the additional neck cooling, the bigger sample size, or both. Although change of brain temperature was statistically significant, the achieved cooling rate is very low compared with alternative cooling methods already tested prehospital. Using intranasal cooling with the RhinoChill device, it was possible to reduce brain temperature by a mean of −0.53°C (SD, 0.24) in only 15 minutes, which is significantly more than the decrease we found after 1 hour of surface head/neck cooling with the Sovika (mean, −0.32°C; SD, 0.2; P=0.012, please see Table and Figure in the online-only Data Supplement).

Small studies testing experimental active head cooling devices reported cooling rates of up to −0.6°C in deep (n=2 patients) and −1.84°C in superficial brain regions (−0.8 cm from cortex; n=8 patients). Cold fluid circulating through these devices provides sustained heat exchange, but the need of an external liquid pump and electric power supply limits prehospital use. No such active head cooling devices are commercially available.

The low cooling efficiency we found with the Sovika device could be attributed to a selection bias in our study: only patients exceeding 37.1°C of brain, bladder, or tympanic temperature were enrolled. Starting temperature (central venous) in a study on patients immediately after stroke onset, the real future target group, was significantly lower than mean (brain) temperature at baseline in our group of stroke patients: 36.35°C (SD, 0.49) compared with 37.15°C (SD, 0.21), respectively (P<0.001, please see Table and Figure in the online-only Data Supplement).

### Table 2. Baseline Characteristics

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<th>BH, cm</th>
<th>BMI, kg/m²</th>
<th>BSA, m²</th>
<th>Brain Temp, °C</th>
<th>CRP, mg/L</th>
<th>WBC, /μL</th>
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<td>38</td>
<td>8.3</td>
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#indicates number of applications of the Sovika cooling device; BH, body height; BMI, body mass index; brain temp, brain temperature at baseline; BSA, body surface area, Mosteller-formula; BWt, body weight; CRP, C-reactive protein; f, female; ICH, intracerebral hemorrhage; IS, ischemic stroke; m, male; NIHSS, National Institutes of Health Stroke Scale score at admission; time to cooling, time from stroke onset to initial application of the Sovika cooling device; and WBC, white blood count.
The aforementioned RhinoChill device was reported much faster and more efficient even in a group of neurological patients with an average brain temperature of 38.1°C at baseline.17

Tympanic temperature approximates body core temperature under normothermic conditions and, for practical reasons, is preferred in the prehospital setting.18 Consistent with the 2 recent trials, we found a large drop of in tympanic temperature starting immediately after external head cooling with the Sovika was applied reaching −1.69°C in mean after 1 hour of cooling.12,13 Others reported a similar decrease of tympanic temperature using different passive head cooling devices.20,21 Recording brain and tympanic temperature simultaneously, we clearly demonstrate that this drop is a local cooling effect overestimating, by far, the effect on brain temperature.22

Bladder temperature (mean, −0.18°C), however, underestimates the effect on brain temperature (mean, −0.32°C) during cooling with the Sovika device. This may be attributable to selective brain cooling as concluded by Wang et al22 or may be a delayed response of bladder temperature during rapid temperature changes when compared with other body core temperatures.23

Regarding treatment effects on blood pressure Koehn et al13 and Kallmünzer et al12 reported conflicting data in healthy volunteers. Interestingly, Koehn et al13 observed an immediate increase of blood pressure on cooling onset followed by a steady increase over a 2-hour time period, whereas the blood pressure increase in our study was also immediate, but transient (Figure 2). Kallmünzer et al12 did not observe any relevant blood pressure changes. However, because autonomic regulation and stress responses are known to be often impaired in stroke patients, direct comparisons of the 2 trials with our data should be drawn with caution. Taking into account that 2 of 3 existing trials on the Sovika device detected an increase of blood pressure, other cohorts may be prone to blood pressure increase as well. Especially, in patients within the hyperacute phase of hemorrhagic stroke, an increase of >20 mm Hg may cause deleterious hematoma expansion or rebleeding,24 further limiting the prehospital use of the Sovika cooling device for patients with unknown disease entities and missing neuromonitoring, even though we did not observe any intracranial bleeding complications in our patients.

We observed a relevant ICP increase in 7 of all 51 applications of the Sovika device within the first minutes. A rapid increase within seconds is frequently associated with a stress response or triggering of autonomic dysfunctions via the vagal or glossopharyngeal nerves or carotid bodies,25 whereas an increase within minutes is likely because of local venous obstruction.26 The latter may result from bilateral jugular vein compression when the part of the Sovika device covering the anterior neck is fitted. The advantage regarding cooling efficacy via supplementary neck coverage may be disadvantageous regarding venous drainage leading to rise in ICP. ICP crisis >20 mm Hg, as observed after 6 of 51 applications, may compromise cerebral perfusion (CPP <50 mm Hg observed in 1 patient).

As our study was designed as a prospective observational study enrolling consecutive patients, it has some limitations. Patients were not randomized, and no control group was analyzed. The nature of the study made blinded design unfeasible; furthermore, the study was only conducted at a single site. Although the sample size of our study was rather small, focusing on critically ill cerebrovascular patients at our neurointensive care unit allowed us to not only provide actual brain temperature data but also safety considerations by using continuous neuromonitoring. To our knowledge, only 3 additional patients treated with other passive head cooling devices had brain temperature monitoring so far.9

Conclusions
Although the decrease of brain temperature after Sovika cooling device application was statistically significant, a mean cooling rate of −0.32°C per hour is rather weak compared with other induction methods.6,17 Moreover, the transient increases of blood pressure and ICP warrant caution when using the Sovika head and neck cooling device. As tympanic and bladder temperature do not reflect the actual brain temperature and tend either to over- or underestimate cooling effects, our study emphasizes that brain temperature monitoring is mandatory for evaluation of (new) cooling methods.

Sources of Funding
No financial support was received. Sovika cooling and storage devices were allocated by HVM Medical, Rotenburg, Germany.

Disclosures
Dr Poli receives speaker’s fees from C.R. Bard, BeneChill, EMCOOLs, and ZOLL Medical, project funding from ZOLL Medical and EMCOOLs, and supplies and equipment from BeneChill, Covidiën, EMCOOLs, HVM Medical, Raumedic, and ZOLL Medical. The other authors have no conflicts to report.

References


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doi: 10.1161/STROKEAHA.112.672923

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/3/708

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/01/24/STROKEAHA.112.672923.DC1
ONLINE SUPPLEMENT

Titel
Induction of Cooling with a Passive Head and Neck Cooling Device - Effects on Brain Temperature After Stroke
Supplemental Methods

Statistics
A two-sample t-test adjusted for heterogeneous variances was used to compare brain temperature of our sample at baseline and after one hour of cooling with the central venous temperature at baseline reported by Lyden et al. in table 1 page 415 \(^1\) and the brain temperature achieved after 15 min of intranasal cooling with the RhinoChill\(^\text{®}\) device reported by Abou-Chebl et al. on page 2166 \(^2\) respectively. \(P < 0.05\) was considered significant.
Supplemental Tables

S1. Secondary statistical analysis of all 51 applications (initial and subsequent) of the Sovika® cooling device (n = 11 patients) comparing baseline values of brain, bladder, tympanic temperatures and vital parameters to post-treatment intervals covering the maximal treatment effects (indicated by gray shaded areas in Figure 2 and 3). Mixed-model analysis was applied to account for the different number of applications per subject. $P < 0.05$ was considered significant.

### Temperatures*  
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<td>Tympanic</td>
<td>$(\Delta ^\circ C)$</td>
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*Baseline -15 to 0 min versus post-treatment +45 to +60 min

### Vital parameters**  
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**Baseline -15 to -5 min versus post-treatment 0 to +10 min
**Supplemental Figures**

*S2.* Left: Individual brain temperature curves of each patients (P1 to P11) including all 51 applications (initial and subsequent) of the Sovika® cooling device. Right: Mean curves of brain, bladder and tympanic temperatures of each patient.
Supplemental References
