Influence of Prophylactic, Endovascularly Based Normothermia on Inflammation in Patients With Severe Cerebrovascular Disease
A Prospective, Randomized Trial
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Background and Purpose—We analyzed the impact of long-term endovascularly based prophylactic normothermia versus conventional temperature management on inflammatory parameters in patients with severe cerebrovascular disease.

Methods—This was a prospective, randomized, controlled trial comparing the course of inflammatory parameters between the 2 treatment arms: (1) prophylactically endovascular long-term normothermia; and (2) conventional, stepwise fever management with antiinflammatory drugs and surface cooling. Inclusion criteria were (1) spontaneous subarachnoid hemorrhage with Hunt–Hess grade between 3 and 5; (2) spontaneous intracerebral hemorrhage with a Glasgow Coma Scale score of ≤10; or (3) complicated cerebral infarction requiring intensive care unit treatment with a NIH Stroke Scale score of ≥15. Treatment period was 336 hours in subarachnoid hemorrhage patients and 168 hours in patients with complicated stroke or intracerebral hemorrhage patients.

Results—A total of 102 patients (56 female) were enrolled during a 3.5-year period. Overall median total fever burden during the course of treatment was 0.0°C hour and 4.3°C hours in the catheter and conventional group, respectively (P<0.0001). C-reactive protein and interleukin-6 were significantly elevated in the endovascular group (P<0.05). Nonsteroidal antiinflammatory drugs, used as additional treatment of fever, significantly reduced mean C-reactive protein in endovascular treated patients (P<0.01).

Conclusions—The proinflammatory cytokines C-reactive protein and interleukin-6 were significantly elevated in patients receiving prophylactic endovascularly based long-term normothermia. Nonsteroidal antiinflammatory drugs significantly affected the course of proinflammatory parameters; thus, future trials should investigate the role of nonsteroidal antiinflammatory drugs in severe cerebrovascular disease patients and their interaction with temperature management.

Clinical Trial Registration—Trial not registered; enrollment began before July 2005.
(Stroke. 2010;41:2969-2972.)

Key Words: stroke ■ normothermia ■ inflammation ■ nonsteroidal antiinflammatory drugs ■ endovascular cooling

Fever, irrespective of origin, has been clearly demonstrated to be an independent risk factor for unfavorable outcome in cerebrovascular disease patients.1,2 In animal stroke models, prevention of fever by inducing normo- or hypothermia has significantly reduced infarct volume and ameliorated morbidity and mortality.3,4 However, with the exception of post–cardiac arrest, translational studies have consistently failed to show a clear benefit of this intervention regarding good clinical outcome in various neurological diseases including stroke and traumatic brain injury.5,7 Potential side effects of normo-/hypothermia have been discussed to outweigh the neuroprotective effects of temperature reduction.8 In particular, hypothermia has been shown to interact with the inflammatory response through inhibition of leukocyte migration and decrease of proinflammatory response, among other mechanisms, leading to increased rate of infections.9,10 Therefore, analyzing the course of inflammatory parameters in patients with severe cerebrovascular disease under the influence of endovascular cooling could generate hypotheses possibly leading to a better understanding of temperature management and its pathophysiological limitations. The primary goal of our study was to analyze the influence of long-term endovascularly based normothermia in patients with severe cerebrovascular disease onto inflammatory parameters and its effect on neurological outcome. Secondly, interaction of nonsteroidal antiinflammatory drug
(NSAID) application, used for fever control, and its influence on inflammation parameters was subsequently investigated as predefined in our study protocol.

Methods
A detailed description of the study population, inclusion and exclusion criteria, study protocol, and cooling measures used in this study has been published previously. Both study centers strictly followed the identical study protocol. For endovascular cooling, only the Cool Line catheter (without any modification) was used and was always placed in the subclavian vein.

Retrieval of data used in this present analysis was performed prospectively because the original design of the study included analysis of inflammatory parameters as an additional end point. The study protocol was approved by each institutional review board.

Data Collection of Samples
C-reactive protein (CRP) (mg/100 mL), procalcitonin (PCT) (µg/L), and WBCs (G cells/L) were collected daily beginning at enrolment. Interleukin (IL)-10 (pg/mL) and IL-6 (pg/mL) were collected at enrolment and on days 4, 7, 10, and 14 or until end of study, whichever occurred first in both treatment arms. CRP, WBCs, and procalcitonin were chosen as clinically meaningful parameters used routinely to detect inflammation. IL-6 and IL-10 were chosen as 2 representatives of the pro- and antiinflammatory spectrum of interleukins. Blood drawing was performed as defined in our protocol at the time of enrolment and at 7:00 AM for the following days to minimize bias possibly introduced by daytime fluctuation, and samples were immediately processed further thereafter. During study, all laboratory workup protocols were standardized and remained unchanged.

Statistical Methods
To compare longitudinal data of inflammatory parameters, the mean values per patient were calculated and compared between the respective subgroups using Mann–Whitney–Wilcoxon test. The calculation of fever burden and the respective results have been described in detail. The median total fever burden, or area under the curve (AUC) of the fever burden, were compared with Wilcoxon rank-sum tests.

To receive binary outcome measures, modified Rankin score (mRS) was dichotomized (mRS: 0 to 2 and 3 to 6). Risk factors for unfavorable long-term outcome were analyzed by binary logistic regression. Age at stroke, length of stay, application of NSAIDs, treatment allocation, and sex were selected as generally accepted clinically meaningful predictors in patients with severe stroke in this multivariate model.

To verify the difference of CRP between NSAID-treated and nontreated patients generalized estimation equations were calculated with “application of NSAIDs,” day of sampling, and treatment group as factors including important covariates (age, sex). For this analysis, all CRP values were logarithmically transformed. This model (generalized estimation equation) was only applied in the device group. The Figure shows box plots of mean CRP course stratified by NSAID application in the device group (C) and time of enrolment (A and B), and time of enrolment and at 7:00 AM for the following days to minimize bias possibly introduced by daytime fluctuation, and samples were immediately processed further thereafter. During study, all laboratory workup protocols were standardized and remained unchanged.

Inflammatory Parameters and Temperature Management Regimen
Comparing the mean inflammatory parameters over neuro-ICU stay, significant differences could be found for CRP and IL-6 but not for IL-10, PCT, and WBC in the respective treatment groups (Table 1). Interestingly, mean CRP and IL-6 were found to be significantly lower in control patients (P<0.05).

Stepwise predefined conventional fever treatment protocol based on NSAID application was used for both treatment arms if temperature was above 37.9°C. In 86% (n=44) of the patients randomized to the conventional arm and only in 39% (n=20) of the Coolgard patients, these measures were necessary at least once to treat fever. Thus, frequency and overall dose of NSAID administration was significantly elevated in controls (P<0.05). The Figure shows box plots of mean CRP stratified by group and application of NSAID (A and B), time course of CRP stratified by treatment group (C), and time course of CRP stratified by NSAID application in the device

### Table 1. Demographics, Baseline Characteristics, Comparison of Inflammatory Parameters, and Adverse Event Analysis Between the Two Treatment Arms

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>CoolGard (n=51)</th>
<th>Control (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (mean±SD)</td>
<td>26.8±4.9</td>
<td>26.6±5.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Age, yr (mean±SD)</td>
<td>58.5±12.8</td>
<td>58.7±14.4</td>
<td>0.95</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>21 (41)</td>
<td>25 (49)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>4 (8)</td>
<td>6 (12)</td>
<td>0.60</td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>19 (37)</td>
<td>22 (43)</td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>28 (55)</td>
<td>23 (45)</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>18 (35)</td>
<td>14 (27)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>49 (96)</td>
<td>44 (86)</td>
<td>0.16</td>
</tr>
<tr>
<td>Infectious</td>
<td>49 (96)</td>
<td>41 (80)</td>
<td>0.03</td>
</tr>
<tr>
<td>Noninfectious</td>
<td>19 (37)</td>
<td>20 (39)</td>
<td>1.00</td>
</tr>
<tr>
<td>Major adverse event, n (%)</td>
<td>25 (49)</td>
<td>20 (39)</td>
<td>0.43</td>
</tr>
<tr>
<td>Infectious</td>
<td>4 (8)</td>
<td>8 (16)</td>
<td>0.36</td>
</tr>
<tr>
<td>Noninfectious</td>
<td>17 (33)</td>
<td>11 (22)</td>
<td>0.27</td>
</tr>
<tr>
<td>Longitudinal data of inflammatory</td>
<td>10.8±6.0</td>
<td>8.6±5.6</td>
<td>0.03</td>
</tr>
<tr>
<td>parameters (mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/100 mL</td>
<td>10.3±3.3</td>
<td>10.5±2.8</td>
<td>0.84</td>
</tr>
<tr>
<td>WBCs, G cells/L (mean±SD)</td>
<td>11.3±17.2</td>
<td>10.9±16.5</td>
<td>0.72</td>
</tr>
<tr>
<td>IL-10, pg/mL (mean±SD)</td>
<td>95.2±82.2</td>
<td>72.7±83.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Procalcitonin, µg/L (mean±SD)</td>
<td>0.4±1.1</td>
<td>0.7±1.4</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Treatment groups are compared using t tests (continuous variables), Fisher’s exact tests (dichotomous variables), and Mann–Whitney–Wilcoxon test (inflammatory variables). All tests are based on a 2-sided type I error of 0.05. Patients who experience ≥1 event of a given infection type or ≥1 event overall are counted only once for that infection type and overall infection types. The no. of patients at each time point experiencing at least 1 adverse event of a given infection type are compared using Fisher’s exact tests.

Results
Baseline Characteristics and Fever Burden
For a detailed analysis regarding these parameters, please refer to the results in the previously published article. The median total AUC regarding fever burden was significant higher in the control group (4.3°C hours) than in the Coolgard group (0.0°C hour; P<0.0001; Wilcoxon rank-sum test).
group only (D). Generalized estimation equations yielded a significant effect of NSAID application ($P<0.01$), day of sampling ($P<0.001$), and their interaction on CRP ($P<0.01$) independent of age and sex in the device group.

**Outcome**

No difference in overall neurological outcome could be found in the 6-month follow-up. Using a binary logistic regression analysis and dichotomizing outcome (favorable [mRS, 0 to 2] versus unfavorable [mRS, 3 to 6]) yielded only age to be associated with unfavorable outcome (Table 2). Application of NSAID reached statistical tendency ($P=0.10$) with reduced odds ratio for unfavorable outcome (Table 2).

**Discussion**

This prospective, randomized trial is the first study to analyze inflammatory parameters in patients with severe cerebrovascular disease under the influence of long-term endovascularly based normothermia versus conventional active temperature management. Although fever has been identified to be an independent predictor and risk factor of unfavorable outcome, especially in patients with severe neurological disease, many studies have consistently failed to ameliorate outcome by inducing normo- or hypothermia.$^{5,6,8}$ It has been speculated that the inflammatory response might be negatively altered through thermoregulatory measures possibly nullifying a potential benefit of normothermia.$^{6,8–10}$ In our study, (pro)inflammatory parameters such as CRP and IL-6 were significantly decreased in the control group using stepwise conventional temperature control measures. This is of utmost interest because, although strictly following the predefined protocol, fever burden was an impressive 4-fold higher in the control group than in the device group. When keeping in mind that AUC contributing to fever burden was only calculated if bladder temperature was $>37.9^\circ$C, it is even more surprising that levels of CRP and IL-6 were significantly lower in control patients.

The conventional temperature control protocol was mainly based on application of antiinflammatory drugs such as NSAID. As previously discussed, fever burden was significantly higher in the control group, leading to significant increased application of NSAID in controls ($P<0.05$). In the endovascular group, application of NSAID led to a significant decrease of CRP, adjusted for age and gender, in comparison with device patients without NSAID. It has been speculated that inhibition of cyclooxygenase through NSAIDs might have a (neuro)protective effect interacting in the inflammatory process.$^{12,13}$ This finding could have an enormous impact on the design of future studies: because endovascular cooling has been shown to be efficacious and feasible in constantly maintaining target temperature, the combination with antiinflammatory drugs may likely have additional neuroprotective effects.$^{5,11}$ When interpreting our results, one must keep in mind that the clear causative relationship between NSAID

### Table 2. Predictors of Unfavorable Neurologic Long-Term Outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.09</td>
<td>1.04 – 1.13</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Endovascular group</td>
<td>Reference Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1.56</td>
<td>0.5 – 4.88</td>
<td>0.44</td>
</tr>
<tr>
<td>No NSAID</td>
<td>Reference Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID applied</td>
<td>0.36</td>
<td>0.1 – 1.24</td>
<td>0.1</td>
</tr>
<tr>
<td>LOS neuro-ICU</td>
<td>1.01</td>
<td>0.99 – 1.04</td>
<td>0.35</td>
</tr>
<tr>
<td>Sex</td>
<td>0.58</td>
<td>0.2 – 1.68</td>
<td>0.31</td>
</tr>
</tbody>
</table>

To receive binary outcome measures mRS was dichotomized (mRS, 0–2 [favorable outcome] vs 3–6 [unfavorable outcome]). Model was calculated using binary logistic regression. Odds ratio indicates risk of unfavorable neurologic long-term outcome (mRS 3–6). LOS, length of stay.
application, inflammatory response, and favorable patient outcome remains unclear, but our study generates hypotheses warranting future trials investigating this question. In a recently published study, improvement of outcome in febrile stroke patients could be achieved by high-dose paracetamol administration. One might speculate that this improvement might even be increased with additional use of prophylactic endovascular temperature control.

When interpreting inflammatory parameters, infectious adverse events (AEs) must be considered as a confounding factor. In our population, overall AEs were evenly distributed, whereas infectious AEs were significantly elevated in the device group. Because almost all device patients had at least 1 infectious AE during study period (96%), a selection bias possibly influencing CRP or NSAID application is unlikely. Speculating on the elevation of CRP and IL-6, infectious AEs might partly explain this difference; however, if this is the only reason, it remains unclear why PCT, WBC, and IL-10 were not influenced.

The antibiotic treatment regime was not prospectively evaluated and therefore not included as outcome parameter in the study design. However, the antibiotic management could have had an important influence on the course of inflammatory parameters. One must be aware that this is a relevant limitation of our study, and future trials should address this important interaction in a prospective manner in detail. Detecting infections in endovascular cooled patients can be difficult because parameters used in routine clinical care might be masked as in our cohort: patient temperature (through active cooling), PCT, and WBC were not elevated in the device group in comparison with the control group, whereas infectious AEs were significantly elevated in the device group in comparison with the control group, possibly indicating by the tendency of our results.

One important limitation of the study is that the sample size calculation of this trial was based on detecting a difference in mean fever burden of 25°C hours (ie, power of 99%). To study improvement of outcome by NSAID application, a significantly higher sample size may be assumed, possibly indicated by the tendency of our results.

**Sources of Funding**

This study was supported in part by an unrestricted research grant from Alsius Corp, (Irvine, Calif). Alsius Corp was neither involved in study design, collection, analysis, and interpretation of data nor writing the report. Alsius did not suppress any data or outcome analysis carried out as predefined in the study protocol. Audit of source data and statistical analyses were conducted by independent institutes.

**Disclosures**

None.

**References**

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Stroke. 2010;41:2969-2972; originally published online October 28, 2010; doi: 10.1161/STROKEAHA.110.591933
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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