Admission Body Temperature Predicts Long-Term Mortality After Acute Stroke

The Copenhagen Stroke Study

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Background and Purpose—Body temperature is considered crucial in the management of acute stroke patients. Recently hypothermia applied as a therapy for stroke has been demonstrated to be feasible and safe in acute stroke patients. In the present study, we investigated the predictive role of admission body temperature to the long-term mortality in stroke patients.

Methods—We studied 390 patients with acute stroke admitted within 6 hours from stroke onset. Admission clinical characteristics (age, sex, admission stroke severity, admission blood glucose, cardiovascular risk factor profile, and stroke subtype) were recorded for patients with hypothermia (body temperature ≤37°C) versus patients with hyperthermia (body temperature >37°C). Univariately the mortality rates for all patients were studied by Kaplan-Meier statistics. To find independent predictors of long-term mortality for all patients, Cox proportional-hazards models were built. We included all clinical characteristics and body temperature as a continuous variable.

Results—Patients with hyperthermia had more severe strokes and more frequently diabetes, whereas no difference was found for the other clinical characteristics. For all patients mortality rate at 60 months after stroke was higher for patients with hyperthermia (73 per 100 cases versus 59 per 10 cases, \(P = 0.001\)). When body temperature was studied in a multivariate Cox proportional-hazards model, a 1°C increase of admission body temperature independently predicted a 30% relative increase (95% CI, 4% to 57%) in long-term mortality risk. For 3-month survivors we found no association between body temperature and long-term survival when studied in a multivariate Cox proportional hazard model (hazards ratio, 1.11 per 1°C; 95% CI, 0.82 to 1.52).

Conclusion—Low body temperature on admission is considered to be an independent predictor of good short-term outcome. The present study suggests that admission body temperature seems to be a major determinant even for long-term mortality after stroke. Hypothermic therapy in the early stage in which body temperature is kept low for a longer period after ictus could be a long-lasting neuroprotective measure. (Stroke. 2002;33:1759-1762.)

Key Words: body temperature ■ mortality ■ prognosis ■ stroke

In animal stroke models, body temperature has been studied extensively over the past 20 years.1 Lowering body temperature through hypothermic therapy has been demonstrated to be a strong neuroprotective measure.2–4 Elevation of body temperature has been shown to result in more extensive brain damage in animal stroke models.5,6 In human stroke, low admission body temperature seems to improve short-term survival and neurological recovery, and to result in less extensive brain damage on computed tomography scans.7 In addition, low acute body temperature appears to be associated with less release in humans of glutamate, which is a marker of ischemia-induced damage to brain tissue.8 However, whether the association between low body temperature acutely after stroke and a favorable outcome is only a temporary phenomenon or low body temperature on admission provides long-lasting improvements remains unknown.

Recently, there have been a few small studies of the feasibility and safety of hypothermic therapy in patients with acute stroke,9,10 and this seems to be possible and well tolerated even in awake stroke patients.11 At least 1 randomized clinical trial of hypothermia in acute stroke patients has been launched recently by a Danish research team. Furthermore, it is a widely accepted practice to avoid hyperthermia in the early stages after acute stroke.12

In this study, we sought to evaluate whether body temperature on admission is an independent predictor of long-term prognosis after stroke. The purpose of the study was 2-fold, as follows: (1) to determine the relation between admission
body temperature and long-term mortality in all patients admitted within 6 hours from onset and (2) to determine long-term mortality in those of the patients surviving 3 months.

Methods

We included all patients with acute stroke (onset within 6 hours) admitted consecutively, during a 25-month period from 1991 to 1993, to the stroke unit at Bispebjerg Hospital (Copenhagen, Denmark). The study is prospective and community-based, as has previously been described in detail.13 Hospital care is free, and a very high proportion (88%) of the stroke patients in the area were admitted to this hospital serving a well-defined catchment area of nearly 240,000 inhabitants in the city of Copenhagen.14 No selection of patients was performed with regard to age, severity of stroke, or medical condition before admission. All treatment, rehabilitation, and diagnostic procedures were performed within the stroke unit. Patients were not discharged until the rehabilitation team decided that no further in-hospital improvement could be expected. Therefore, no referral to other departments or hospitals for further rehabilitation was necessary.

Stroke was defined according to the World Health Organization criteria.15 The study does not include patients with transient ischemic attacks or subarachnoid hemorrhage.

The Scandinavian Stroke Scale (SSS) was used to assess stroke severity.16 The SSS evaluates level of consciousness; eye movement; power in arm, hand, and leg; orientation; aphasia; facial paresis; and gait on a total score from 0 (worst) to 58 (best).17 The score was recorded on admission, weekly during hospital stay, and at discharge by the same neurologist (H.S.J.). The long-term follow-up data on mortality and date of death were obtained from the Danish Central Registry of Persons where date of death for all residents in Denmark are recorded through a unique 10-digit identification code containing information on birth date. Another experienced neurologist (L.P.K.) who was blinded to data obtained on admission prospectively recorded the follow-up data. Follow-up was performed during the year 1999 with December 29, 1999, as censoring date.

For classification of stroke subtype (hemorrhage or infarction), computed cerebral tomography was performed with a Siemens Somatom DR scanner, and the same experienced reader of computed cerebral tomograms read the scans.

The following prognostic factors were accounted for in the statistical analyses: age, sex, initial stroke severity, stroke subtype, ischemic heart disease, hypertension, atrial fibrillation, diabetes, intermittent claudication, smoking, daily intake of any type of alcohol (eg, wine, spirits, or beer), previous stroke, preexisting disability, and admission blood sugar. Diabetes, atrial fibrillation, ischemic heart disease, preexisting disability, hypertension, and smoking were defined according to standard criteria.7 Body temperature was obtained immediately after admission to the hospital and was recorded by tympanic measurements.

Univariately, comparison between patients with hypothermia and hyperthermia was performed by Student’s t test for continuous variables and by χ² test for dichotomized variables. Mortality rates at 60 months were estimated by the log-rank test. Cumulative survival plots were calculated by the Kaplan-Meier statistics to evaluate survival for hypothermia versus hyperthermia patients any time between index stroke and 5 years after onset. To study admission body temperature as an independent predictor for long-term mortality after stroke onset, a Cox proportional-hazards model was built, because multiple factors were thought to influence long-term mortality. All variables given in Table 1 were included in the initial model using the forward procedure including admission body temperature as a continuous variable. Then, unimportant variables were removed one by one until only variables with a P<0.2 remained. The analysis was then performed using the backward procedure. To ensure that hazards were proportional throughout the study period for all dichotomized variables, log-minus-log plots were performed for each dichotomized variable. The required 2-tailed level of significance for all tests was set at 0.05.

Results

In Table 1, the basic clinical characteristics are given stratified in 2 groups according to admission body temperature. Hypothermia was present in 45.9% of the 390 patients included. Patients who were hyperthermic on admission had
more severe strokes as compared with hypothermic patients (SSS score 30.2 versus 36.5 points, \(P=0.001\)) and more frequently had diabetes (14.2% versus 22.8%, \(P=0.04\)). No differences between hypothermic and hyperthermic patients were found for the other clinical characteristics considered.

The Figure gives the cumulated survival for all patients admitted within 6 hours with hypothermia versus hyperthermia calculated by the Kaplan-Meier statistics. At 5 years after stroke onset, mortality rate among patients with hyperthermia was 73 per 100 cases versus 59 per 100 cases among those with hypothermia on admission (\(P=0.001\); log-rank test). In a multivariate model (Table 2) using Cox proportional-hazards analysis (including body temperature as a continuous parameter), we found that a decrease of admission body temperature by 1°C was an independent predictor of increased long-term survival (hazards ratio [HR], 1.30; 95% CI, 1.04 to 1.63). The covariates admission stroke severity (HR, 1.32 per 10-point-higher SSS score; 95% CI, 1.20 to 1.43), age (HR, 1.69 per 10-year decrease; 95% CI, 1.43 to 2.00), atrial fibrillation (HR, 0.66; 95% CI, 0.48 to 0.93), and admission blood glucose (HR, 1.04 per 1 mmol/L decrease; 95% CI, 0.98 to 1.09) were also in the final model.

In Table 3, the final Cox proportional-hazards model for 3-month survivors is shown. In this model, admission body temperature was not an independent predictor of long-term survival (\(P=0.50\)), when adjusted for other covariates. Instead, covariates such as admission stroke severity (HR, 1.18 per 10-point-higher SSS score; 95% CI, 1.01 to 1.32), age (HR, 1.85 per 10-year decrease; 95% CI, 1.51 to 2.26), atrial fibrillation (HR, 0.63; 95% CI, 0.41 to 0.95), and hypertension (HR, 0.67; 95% CI, 0.48 to 0.94) were independent predictors of survival 3 months after onset.

**Discussion**

A few previous studies have suggested that a lower admission body temperature is associated with a better short-term outcome. We found only 1 study looking at prognosis beyond the first few months after onset in relation to body temperature.\(^{18}\) In this study hyperthermia raised the risk of 1-year mortality by a factor of 3.4 relative to normothermic patients. However, in this study no validated measure for admission stroke severity was used, and the study was retrospective, based on medical records.

For all patients included in the present study, we found significantly higher mortality rates among patients with hyperthermia as compared with hypothermic patients. But this could be explained by the more severe strokes for patients with hyperthermia on admission, because stroke severity was not adjusted for in the Kaplan-Meier analysis. Therefore, we had to evaluate the relative mortality risk adjusted for differences in admission stroke severity and risk factor profile. In the multivariate survival analysis, admission body temperatures were entered as a continuous variable rather than as a dichotomized variable to detect the independent predictive impact of differences in body temperature. For all patients, we found a 1-degree difference in admission body temperature to correspond to a 30% difference in the relative risk of long-term mortality. However, it may be that this relation is only due to a temporary effect early after stroke, resulting in a sustained favorable mortality rate for patients with a low admission body temperature. This may be the case as the survival curves are converging after 2 to 3 months, and we failed to show admission body temperature per se to be associated with survival for those patients still alive 3 months after stroke. Nevertheless, this study only studied the spontaneous relationship. It may be that if body temperature is kept low for a longer period of time acutely after admission, a more robust and long-lasting effect will emerge.

The explanation for the possible neuroprotective effect of low body temperature in acute stroke remains largely speculative. However, most studies point toward a slowing down of the neurodegenerative processes in the penumbra.\(^{19}\) The penumbra consists of a hypoperfused zone of neurons surrounding the initial necrotic area, which are still alive but without the ability to perform normal activity.\(^{20}\) These neu-

**TABLE 2. Cox Regression Analysis (Final Model) for All Patients (n=294): Overall \(\chi^2<0.0001\)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Covariate</th>
<th>Coeff (b)</th>
<th>SE (b)</th>
<th>(P)</th>
<th>Hazards Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>Temperature (per 1°C decrease)</td>
<td>0.23</td>
<td>0.11</td>
<td>0.03</td>
<td>1.30</td>
<td>1.04–1.57</td>
</tr>
<tr>
<td></td>
<td>Blood glucose (per 1 mmol/L decrease)</td>
<td>0.04</td>
<td>0.02</td>
<td>0.09</td>
<td>1.04</td>
<td>0.98–1.09</td>
</tr>
<tr>
<td></td>
<td>Severity (per 10-point increase)</td>
<td>0.03</td>
<td>0.004</td>
<td>(&lt;0.0001)</td>
<td>1.32</td>
<td>1.20–1.43</td>
</tr>
<tr>
<td></td>
<td>Age (per 10-year decrease)</td>
<td>0.05</td>
<td>0.009</td>
<td>(&lt;0.0001)</td>
<td>1.69</td>
<td>1.43–2.00</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>0.41</td>
<td>0.17</td>
<td>0.01</td>
<td>0.66</td>
<td>0.48–0.93</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>0.12</td>
<td>0.16</td>
<td>0.23</td>
<td>0.89</td>
<td>0.63–1.12</td>
</tr>
</tbody>
</table>

Coef (b) denotes regression coefficient; SE, standard error.
rons are at risk of degenerating if reperfusion is not established within a reasonable time. If temperature is decreased in the penumbra, a subsequent slowing down of the neurodegenerative processes may result. This means that the time window for reperfusion to be established will be widened, and more neurons in the penumbra will be able to survive and regain their function.

The present study suggests that the neuroprotective effect of low body temperature go beyond the first few weeks after stroke onset. We speculate that if hypothermia proves to be an efficient therapy in acute stroke patients, this is likely to have long-lasting implications for mortality. Trials on hypothermia applied deliberately in acute stroke patients are warranted.

References


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