Influence of Admission Body Temperature on Stroke Mortality

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Background and Purpose—The influence of body temperature on stroke outcome remains uncertain. The aim of this study was to investigate the prognostic role of admission body temperature on short-term and long-term mortality in a retrospective cohort study of patients with acute stroke.

Methods—A retrospective cohort of 509 patients with acute stroke, admitted to a tertiary hospital between July 1, 1995, and June 30, 1997, was studied. The relationship between admission body temperature and mortality both in-hospital and at 1-year mortality was evaluated. Body temperature on admission was classified as hypothermia (≤36.5°C), normothermia (>36.5°C and ≤37.5°C), and hyperthermia (>37.5°C). Logistic regression and proportional hazards function analysis were performed after adjustment for clinical predictors of stroke outcome.

Results—In ischemic stroke, mortality was lower among patients with hypothermia and higher among patients with hyperthermia. The odds ratio for in-hospital mortality in hypothermic versus normothermic patients was 0.1 (95% CI, 0.02 to 0.5). The relative risk for 1-year mortality of hyperthermic versus normothermic patients was 3.4 (95% CI, 1.6 to 7.3). A similar but nonsignificant trend for in-hospital mortality was seen among patients with hemorrhagic stroke.

Conclusions—An association between admission body temperature and stroke mortality was noted independent of clinical variables of stroke severity. Hyperthermia was associated with an increase in 1-year mortality. Hypothermia was associated with a reduction in in-hospital mortality. (Stroke. 2000;31:404-409.)

Key Words: mortality ■ stroke, acute ■ temperature

It is well accepted that alterations in body temperature can profoundly affect the mortality from ischemic stroke in laboratory animal models, in which treatment with mild hypothermia (30°C to 34°C) for 3 to 4 hours has been shown to reduce the size of cerebral infarction.1 Accordingly, hypothermia has been suggested as a means of neuroprotection in focal cerebral ischemia.2 In humans, hypothermia is applied in neurosurgery and open-heart surgery to counter the effects of cerebral hypoxic or ischemic insults.3–5 In severe closed head injuries, improved outcomes have been suggested in patients treated with moderate hypothermia.6,7

In contrast, hyperthermia exacerbates ischemic neuronal injury and physiological dysfunction.8–10 Experimental mammalian models provide evidence that ischemic neuronal injury may be increased significantly with even mild hyperthermia of up to 2°C above normal body temperature.11 In human stroke, there have been limited investigations of the influence of body temperature on stroke outcome.11–15; thus, the prognostic role of body temperature is far from conclusive.

In this study we sought to investigate the prognostic significance of hyperthermia and hypothermia on short-term and long-term mortality in patients with acute stroke.

Subjects and Methods

We retrospectively studied patients admitted to a tertiary teaching hospital in the Hunter Region of Australia between July 1, 1995, and June 30, 1997, with a diagnosis of acute stroke (International Classification of Diseases, Ninth Revision codes 430, 431, 433, 434, and 436).16 The principal author reviewed all the medical records of these patients and collected data using a specifically designed form.

The exclusion criteria were as follows: (1) patients whose medical records did not have admission body temperature recorded and (2) patients whose final diagnoses were not clear or were only recorded as acute cerebrovascular accident, without further classification into ischemic or hemorrhagic stroke.

Baseline Measures

Admission consciousness level was classified into conscious, subconscious, or unconscious, which were defined as follows: (1) conscious: alert, appropriate response to verbal commands; (2) subconscious: drowsy or stuporous; and (3) unconscious: coma or no eye opening to verbal stimuli.

Other clinical stroke severity variables, including swallowing difficulty and urinary and fecal incontinence, were noted as positive if present at any time during the acute hospital stay.

Stroke side was classified as affected on both sides if the affected side was only on the right or left side of the patient’s brain or classified as affected on both sides if both sides of the patient’s brain were affected. Hemiparesis was classified as none, single side (left-
or right-side hemiparesis), and both sides. Blood glucose and white blood cell (WBC) count were the earliest record in the medical notes and were recorded as continuous variables. Leukocytosis was defined by a WBC count >11×10^9/L. Brain imaging assessment of infarct or hemorrhage size was not evaluated because late-phase CT scanning and/or MRI scanning was not available in the majority of patients.

The admission body temperature was the first aural temperature recorded in the medical notes. We classified body temperature into 3 groups (hypothermia, normothermia, and hyperthermia) according to the classification previously used by Reith et al. An admission body temperature >37.5°C was defined as hyperthermia; 36.5°C was defined as hypothermia; between this range was defined as normothermia.

Presence of the following comorbid conditions was noted as positive if recorded in the medical notes: hypertension, ischemic heart disease, previous stroke, diabetes mellitus, chronic pulmonary disease, peripheral vascular disease, and atrial fibrillation.

### Outcome Measures

The primary outcomes were in-hospital mortality and 1-year mortality after discharge. The mortality status of patients was provided by the Heart and Stroke Register, which links its patients’ records to mortality data provided by the Registry of Births, Deaths, and Marriages of New South Wales, Australia. The records cover all deaths from residents of the Hunter Region, New South Wales, Australia.

### Statistical Analysis

Continuous variables are expressed as mean±SD or, if skewed, as median with interquartile range. Categorical variables are expressed as percentages. We performed χ² tests in a univariate analysis for screening of variables before multivariate analysis. For in-hospital mortality, multiple logistic regression models were fitted. Exploratory variables included in the model were those with probability value <0.1 from the univariate analysis. The variables with probability value of Wald’s test >0.1 were removed from the model, and the log-likelihood ratio test was performed each time to assess the fit of the more parsimonious model. Temperature (ie, temperature classified as categorical variables or as a continuous variable) was always included in the model. Kaplan-Meier survival curves were obtained to describe 1-year mortality. Cox proportional hazards regression models were fitted for 1-year mortality with the same process as that for in-hospital mortality to select variables. All analyses were performed with the STATA data analysis system (StataCorp, 1997 Stata Software; Release 5.0).

### Results

The initial screening identified 544 patients. Of these patients, 12 and 7 were excluded because the final discharge diagnosis was subarachnoid hemorrhage and transient ischemic attack, respectively. One patient died immediately after admission, 3 patients’ medical records were incomplete, and 12 were excluded because their diagnoses were not clearly classified as ischemic stroke or hemorrhagic stroke. Of the remaining 509 patients in the database, 437 (85.9%) were diagnosed as ischemic and 72 (14.1%) as hemorrhagic stroke. Among the ischemic and hemorrhagic stroke patients, 47 (10.8%) and 39 (54.2%), respectively, died in the hospital. Of the 390 ischemic and 33 hemorrhagic stroke patients who were discharged alive from the hospital, 65 (16.7%) and 7 (21.2%) died within 1 year.

The baseline characteristics of the 509 stroke patients are shown in Table 1. The ischemic stroke patients (mean±SD age, 69.8±10.5 years) were older than hemorrhagic stroke patients (mean±SD age, 66.5±12.7 years) (P=0.020). The sex distribution between the 2 groups was similar. Only 23.2% of ischemic stroke patients were subconscious or unconscious, while of the hemorrhagic stroke patients, 26.4% were subconscious and 40.3% were unconscious on admission. The admission body temperature was significantly higher in the hemorrhagic group (mean±SD, 37.1±0.8°C) than that in ischemic group (mean±SD, 36.7±0.7°C) (P<0.001). Among the 437 ischemic stroke patients, 185 (42.3%) had hyperthermia, 199 (45.5%) normothermia, and 53 (12.1%) hyperthermia, while for those with hemorrhagic stroke, 16 (22.2%) were classified as hyperthermic, 35 (48.6%) normothermic, and 21 (29.2%) hyperthermic. Hypertension was the most common comorbid disease, affecting 58.4% of the ischemic and 62.5% of the hemorrhagic stroke patients.

### Ischemic Stroke

#### In-Hospital Mortality

Admission body temperature was a significant predictor of in-hospital mortality in the final multivariate logistic regression model (Table 2). The odds ratios (ORs) for hyperthermia and hyperthermia versus normothermia were 0.1 (95% CI, 0.02 to 0.5; P=0.004) and 1.4 (95% CI, 0.4 to 4.2; P=0.576), respectively. The difference between hyperthermia and hypothermia was significant, with an OR of 15.8 (95% CI, 2.8 to 90.0; P=0.002) (not shown in the Table). If admission body temperature were entered into the multivariate model as a continuous variable, then each 1°C increase in body temperature would increase the OR for in-hospital mortality by 3.9 (95% CI, 1.9 to 7.8; P<0.001).

In addition to body temperature, other stroke severity variables, such as sub consciously (OR, 11.3; 95% CI, 3.8 to 33.6), unconsciousness (OR, 33.4; 95% CI, 5.0 to 223.4), and swallowing difficulty (OR, 11.9; 95% CI, 4.3 to 32.9), were also significant predictors of in-hospital mortality. The level of blood glucose had a value of P>0.05. When this variable was removed from the model, the log-likelihood ratio test showed that the new model was significantly different from the model presented in Table 2 (P=0.03), and we therefore retained the variable in the final model.

#### One-Year Mortality

The final Cox regression model after variable selection is shown in Table 3. Hyperthermia was a significant factor in predicting 1-year mortality. The relative risk for hyperthermia versus normothermia was 3.4 (95% CI, 1.7 to 6.3; P=0.004); however, the difference between hyperthermia and normothermia was not significant (P=0.454). When the admission body temperature was entered into the multivariate model as a continuous variable, then for each 1°C increase in temperature, the risk of death at 1-year mortality would increase by 2.1 (95% CI, 1.4 to 3.2; P=0.001).

Older age (>65 years), swallowing difficulty on admission, and some comorbid diseases (hypertension, ischemic heart disease, and peripheral vascular disease) were also significant predictors of 1-year mortality (Table 3).

Kaplan-Meier survival curves were constructed to assess the association between 1-year survival and level of
admission body temperature (Figure). The 1-year survival probability in the hyperthermia group was significantly lower than that in the normothermia group (log-rank \( P = 0.002 \)). The 1-year survival in the hypothermia group was higher than that of normothermia group; however, the log-rank test shows that this result was not statistically significant (\( P = 0.186 \)).

### Hemorrhagic Stroke

Seventy-two stroke patients were diagnosed as having a hemorrhagic stroke. Age (>65 years), level of consciousness, urinary and fecal incontinence, both sides of the brain affected, and hemiparesis were all significant predictors of in-hospital mortality. Body temperature was not a statistically significant predictor (\( P = 0.108 \)), but there was a trend toward the mortality rate being highest in the hyperthermia group and lowest in the hypothermia group. Because of the smaller number of patients with hemorrhagic stroke, impaired conditions of consciousness (subconsciousness, unconsciousness) were combined into a single group in the data analysis. The admission body temperature was not significant after being included in the multivariate model. After it was excluded from the model, the log-likelihood ratio test showed that admission body temperature was not significantly related to in-hospital mortality (\( P = 0.777 \)). The only 3 variables in the final model that significantly predicted in-hospital mortality were impaired consciousness, fecal incontinence, and hyperglycemia.

Body temperature was also not a significant predictor of 1-year mortality for hemorrhagic stroke in the univariate analysis. Since only 33 hemorrhagic stroke patients were discharged alive from the hospital, and 7 (21.2%) died within 1 year, the numbers were insufficient to perform a statistical analysis for 1-year mortality.

### Table 1. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ischemic Stroke (n=437)</th>
<th>Hemorrhagic Stroke (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>69.8±10.5</td>
<td>66.5±12.7</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>57.2</td>
<td>54.2</td>
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<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke severity, %</strong></td>
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<tr>
<td>Consciousness level</td>
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<td></td>
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<tr>
<td>Consciousness</td>
<td>76.9</td>
<td>33.3</td>
</tr>
<tr>
<td>Subconsciousness</td>
<td>18.8</td>
<td>26.4</td>
</tr>
<tr>
<td>Unconsciousness</td>
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<td>Swallowing difficulty</td>
<td>17.9</td>
<td>52.8</td>
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<tr>
<td>Urinary incontinence</td>
<td>11.2</td>
<td>48.6</td>
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<tr>
<td>Fecal incontinence</td>
<td>8.2</td>
<td>44.4</td>
</tr>
<tr>
<td>Both sides of brain affected</td>
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<td>22.2</td>
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<tr>
<td><strong>Hypothermia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4.1</td>
<td>19.4</td>
</tr>
<tr>
<td>Single side</td>
<td>93.4</td>
<td>77.8</td>
</tr>
<tr>
<td>Both sides</td>
<td>2.5</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/L, median (interquartile range)*</td>
<td>6.9 (5.8, 8.1)</td>
<td>7.8 (6.7, 9.6)</td>
</tr>
<tr>
<td>WBC count, ( \times 10^9 ) L, mean±SD</td>
<td>9.2±2.8</td>
<td>10.7±3.7</td>
</tr>
<tr>
<td>Temperature, °C, mean±SD</td>
<td>36.7±0.7</td>
<td>37.1±0.8</td>
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<tr>
<td>Hypothermia ((&lt;36.5°C)), %</td>
<td>42.3</td>
<td>22.2</td>
</tr>
<tr>
<td>Normothermia ((36.5) to 37.5°C), %</td>
<td>45.5</td>
<td>48.6</td>
</tr>
<tr>
<td>Hyperthermia ((&gt;37.5°C)), %</td>
<td>12.1</td>
<td>29.2</td>
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<tr>
<td><strong>Comorbidities, %</strong></td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>58.4</td>
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<td>Ischemic heart disease</td>
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<td>Previous stroke</td>
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<td>Diabetes</td>
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<td>Chronic pulmonary disease</td>
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<td>18.1</td>
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<td>Peripheral vascular disease</td>
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</tr>
<tr>
<td>Atrial fibrillation</td>
<td>15.6</td>
<td>13.9</td>
</tr>
</tbody>
</table>

*Restricted to 416 ischemic and 64 hemorrhagic stroke patients.
Discussion

Our findings suggest that admission body temperature is an independent predictor of both short- and long-term mortality in ischemic stroke when one controls for other clinical indicators of stroke severity. Among ischemic stroke patients, hypothermia was associated with a significant reduction of in-hospital mortality (OR, 0.1; 95% CI, 0.02 to 0.5). Conversely, hyperthermia was associated with an increased level of 1-year mortality (relative risk, 3.4; 95% CI, 1.6 to 7.3). A similar trend for in-hospital mortality was seen among patients with hemorrhagic stroke, but this was not statistically significant; however, the power to examine this association was low because of small numbers.

The retrospective design of this study precluded evaluation of infarct size based on brain imaging measurements. Since previous studies have noted an association between infarct size or infarct volume and body temperature, an important limitation in our analysis is that infarct size could not be included in the multivariate model. Reith et al, however, noted that body temperature remained independently associated with stroke mortality after adjustment for infarct size in a multivariate analysis. We cannot, however, rule out a confounding effect of infarct size on the association between body temperature and stroke mortality.

Four previous reports have pointed out a possible association between body temperature and stroke mortality. In a prospective study of 177 patients with acute cerebral infarction, Castillo et al found that the difference in body temperature between those who died within 6 months and those who survived was highly significant (P < 0.001). However, multivariate analysis was not used. Azzimondi et al analyzed the data of 183 patients and determined that high fever (maximum temperature recorded during the first 7 days, ≥37.9°C) was an independent factor for a worse prognosis. In both studies, the numbers of patients were small, and important potential confounders and predictive factors such as age and major comorbid conditions were not considered.

Reith et al, in a consecutive study of 390 stroke patients, determined that body temperature was independently related to stroke mortality. For each 1°C increase in body tempera-
The presence of infection on admission to the hospital could not be accurately determined retrospectively. Elevated WBC count, however, was found not to predict stroke outcome in this analysis. This finding is consistent with earlier work that found neither infection nor leukocytosis to be related to in-hospital stroke mortality.13

The mechanisms of a beneficial effect of hypothermia and a harmful effect of hyperthermia in experimental animal models have not been fully elucidated. In ischemic stroke, a central area of irreversibly damaged tissue is surrounded by a zone of hypoperfused and functionally impaired but potentially viable tissue, the “ischemic penumbra.”24,25 Temperature may have a significant effect on neuronal survival in the ischemic penumbra. Hypothermia decreases the cerebral metabolic rate and thus decreases the ischemic-induced accumulation of lactate, while hyperthermia increases lactic acidosis, producing acceleration of neuronal death.8,26 Hypothermia attenuates posts ischemic excitotoxic glutamate release27 and free radical production,28 both proposed mechanisms of late neuronal death. The neuroprotective effects of hypothermia may be more relevant in ischemic stroke, in which the presence of a penumbral region in humans is strongly supported by positron emission tomography imaging studies.29,30 In hemorrhagic stroke, however, evidence points toward absence of a penumbral region.31 This observation may have relevance for the lack of influence of temperature on hemorrhagic stroke mortality noted in this study.

The results of our study suggest that there is an association between admission body temperature and both short- and long-term mortality in patients with ischemic stroke. Hypothermia was associated with an increase in 1-year mortality, and hypothermia was associated with a reduction in in-hospital mortality. The potential effect of infarct or hemorrhage size on the association between body temperature and stroke mortality was not tested because of the retrospective nature of the study. Further evaluation of the influence of temperature on stroke outcome (in terms of both mortality and functional outcome) will require prospective studies in which lesion size and the presence of infection can be accurately ascertained and stroke morbidity measured.

Acknowledgments
This study would not have been possible without the collaboration of the staff of Heart and Stroke Register, the Hunter Area Health Service, who provided the primary data of the stroke patients. The authors wish to thank the staff of the Medical Information Department, John Hunter Hospital, who made available all the relevant medical records, and Rachel O’Connell, who provided statistical support for the data analysis.

References


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*Stroke*. 2000;31:404-409
doi: 10.1161/01.STR.31.2.404

*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

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