Effects of Poststroke Pyrexia on Stroke Outcome
A Meta-Analysis of Studies in Patients

Cother Hajat, MRCP; Shakoor Hajat, MSc; Pankaj Sharma, PhD

Background and Purpose—The effect of pyrexia on cerebral ischemia has been extensively studied in animals. In humans, however, such studies are small and the results conflicting. We undertook a meta-analysis using all such published studies on the effect of hyperthermia on stroke outcome.

Methods—Three databases were searched for all published studies that examined the relationship of raised temperature after stroke onset and eventual outcome. Combined probability values and odds ratios were obtained. A heterogeneity test was performed to ensure that the data were suitable for such an analysis. Morbidity and mortality were used as outcome measures.

Results—Nine studies were identified totaling 3790 patients, providing our study with 99% power to detect a 9% increase in morbidity and 84% power to detect a 1% increase in mortality for the pyrexic group. The combined odds ratio for mortality was 1.19 (95% CI, 0.99 to 1.43). A heterogeneity test was highly nonsignificant (P>0.05) for mortality, suggesting that the data were sufficiently similar to be meta-analyzed. Combined probability values were highly significant for both morbidity (P<0.0001) and mortality (P<0.00000001).

Conclusions—The results from this meta-analysis suggest that pyrexia after stroke onset is associated with a marked increase in morbidity and mortality. Measures should be taken to combat fever in the clinical setting to prevent stroke progression. The possible benefit of therapeutic hypothermia in the management of acute stroke should be further investigated. (Stroke. 2000;31:410-414.)

Key Words: fever ■ meta-analysis ■ outcome ■ stroke

Stroke remains one of the leading causes of morbidity and mortality in the western world. Several factors have been implicated in influencing the extent of cerebral damage in acute stroke, such as high or low systolic blood pressure, elevated blood glucose, and a high temperature. Rodent models have consistently shown hyperthermia to be a reliable predictor of stroke outcome. One study found that elevation of rat body temperature to 40°C 24 hours after induced cerebral infarction resulted in a 3-fold increase in cerebral infarct volume. Significant results were also obtained after experimental traumatic injury, with a 2.6-fold increase in rat mortality and a 13-fold increase of cerebral contusion volume. Other studies have found significant effects on stroke outcome in rats with lesser degrees of hyperthermia. Furthermore, it has been shown that induced hypothermia has a protective effect up to 1 hour after focal permanent ischemia. In humans, however, the relationship between fever and stroke outcome has been far less extensively investigated, with studies incorporating small numbers of patients and, as recently emphasized, providing conflicting results. There are no large-scale prospective studies assessing outcome between normothermic and hyperthermic patients.

We sought to undertake a meta-analysis on all published studies to investigate the effect of body temperature on stroke outcome in humans. Combining the results of such studies has the advantage of increasing the power of small, and often underpowered, studies by pooling data.

Methods
Three computer databases (MEDLINE, BIDS, and the Cochrane Library) were searched for all published studies that investigated the effect of body temperature after the onset of stroke on stroke outcome. In addition, all articles identified with our electronic search had their bibliographies searched for other potential sources of data, revealing 1 additional study suitable for inclusion. Unpublished data for 2 of these studies were acquired through personal communication from the authors. Morbidity and mortality were used as measures of outcome. Demographic details such as age and sex were documented together with statistical information such as sample size, exclusion criteria, outcome measures, probability value, and odds ratios (ORs). Most of the studies estimated the OR by multiple linear regression with the exception of 3 studies that used univariate analysis and Cox regression analysis.

A combined OR was obtained for mortality by taking weighted means by the method of Woolf and was tested for heterogeneity with a χ² index. Individual probability values were amalgamated for
Results

Nine studies were identified as suitable for inclusion,7–10,13–17 1 of which was not in the English language10 and 1 of which was published in abstract form,8 totaling 3790 patients (49.8% male; mean age, 73.0 years) (Table). This provided our study with 99% power to detect a 9% increase in morbidity and 84% power to detect a 1% increase in mortality for the pyrexial group.

Three of the 9 studies9,14,16 showed significantly higher morbidity and mortality in pyrexial patients (Table). In 2 additional studies,10,15 mortality was the only outcome measured and was significantly higher with associated pyrexia. Another 2 studies13,17 found mortality, but not morbidity, to be associated with pyrexia. In the first of these studies,10 this was true only of a subgroup of patients admitted within 6 to 12 hours of onset of stroke; a second subgroup admitted 12 to 24 hours after onset of stroke showed no association between pyrexia and mortality. Mortality was not found to be associated with pyrexia in the remaining 2 studies,7,8 in which it was used as the sole outcome measure (Table).

Three additional studies18–20 were identified but were not suitable for inclusion. The first of these18 found that recovery of neurological deficit after stroke was greater in apyrexial than in pyrexial patients, but the significance of these results could not be calculated because of the small numbers of patients used. Furthermore, these authors were unable to accurately distinguish between cerebral infarction and hemorrhage because of lack of availability of CT scans when this study was published, thus compromising the potential accu-

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>n</th>
<th>Mean Age, y/% Male</th>
<th>Outcome Measures</th>
<th>Morbidity</th>
<th>Mortality</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Reith et al (1996)14</td>
<td>Admission &lt;6 h</td>
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<td></td>
<td>(1) temp &lt;37.4°C</td>
<td>293</td>
<td>74.2 (±11.3)/</td>
<td>Scandinavian Stroke Scale at discharge</td>
<td>During hospital stay</td>
<td>0.0024</td>
<td>*</td>
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<tr>
<td></td>
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<td>50%</td>
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<tr>
<td>Jorgensen et al (1996)13</td>
<td>Admission 6–12 h</td>
<td>166</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>(1) temp ≤37.4°C</td>
<td></td>
<td></td>
<td>Scandinavian Stroke Scale at discharge</td>
<td>During hospital stay</td>
<td>0.37</td>
<td>*</td>
</tr>
<tr>
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<td></td>
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<tr>
<td></td>
<td>Admission 12–24 h</td>
<td>232</td>
<td></td>
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</tr>
<tr>
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<tr>
<td></td>
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<tr>
<td>Azzimondi et al (1995)15</td>
<td>Admission at any time</td>
<td>141</td>
<td>77.2 (±10.1)/</td>
<td></td>
<td>...</td>
<td>30 d</td>
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<tr>
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<td>41</td>
<td></td>
<td></td>
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<tr>
<td>Castillo et al (1994)16</td>
<td>Admission ≤24 h</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) temp ≤37.5°C</td>
<td>123</td>
<td>66.6/</td>
<td>Neurological, Barthe, and Glasgow scores at 6 mo</td>
<td>6 mo</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>(2) temp &gt;37.5°C</td>
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<td>50.8%</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Terent and Andersson (1981)9</td>
<td>Admission at any time</td>
<td>196</td>
<td></td>
<td></td>
<td>*</td>
<td>Complete paresis</td>
<td>3 mo</td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>(2) temp &gt;38.0°C</td>
<td>42</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Castillo et al (1998)17</td>
<td>Admission ≤24 h</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>(1) temp ≤37.5°C</td>
<td>158</td>
<td>69.8 (±10.2)/</td>
<td>Canadian Stroke Scale at 3 mo, Barthel Index at 3 mo</td>
<td>3 mo</td>
<td>0.142</td>
<td>1.68</td>
</tr>
<tr>
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<td>(2) temp &gt;37.5°C</td>
<td>102</td>
<td>59%</td>
<td></td>
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</tr>
<tr>
<td>Sharma and Ross (1998)7</td>
<td>Admission ≤24 h</td>
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<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td></td>
<td>(1) temp ≤37.0°C</td>
<td>209</td>
<td>74/</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(2) temp &gt;37.0°C</td>
<td>87</td>
<td>44.8%</td>
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<tr>
<td>MacWalter et al (1998)4</td>
<td>Admission ≤24 h</td>
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<td></td>
<td></td>
<td></td>
<td>...</td>
<td>12 mo</td>
</tr>
<tr>
<td></td>
<td>(1) temp ≤37.5°C</td>
<td>1555</td>
<td>73.3 (±10.9)/</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(2) temp &gt;37.5°C</td>
<td>73</td>
<td>48.6%</td>
<td></td>
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<td></td>
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<tr>
<td>Huo and Zhao (1997)10</td>
<td>Admission ≤24 h</td>
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<td></td>
<td></td>
<td>...</td>
<td>During hospital stay</td>
<td>...</td>
</tr>
<tr>
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<td>(1) temp ≤37.5°C</td>
<td>203</td>
<td>Range 40–78/</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(2) temp &gt;37.5°C</td>
<td>17</td>
<td>59.5%</td>
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</tbody>
</table>

Temp indicates temperature. *Data not given by that study.
racy of our meta-analysis. The second study compared differences in body temperature between patients with stable and progressing stroke and concluded that body temperature was independently related to progressing stroke \((P<0.0001)\). This study was not, however, included in the meta-analysis for 2 reasons: first, it did not directly compare survival or outcome between pyrexial and apyrexial patients, and second, the study analyzed temperature as a continuous variable and did not stratify patients into pyrexial and apyrexial groups. A 12th study in Japanese was identified with our search protocol. However, the authors sought to find a relationship between changes in blood pressure and body temperature and the site of the lesion only in stroke patients who were autopsied. Hence, this study did not meet the inclusion criteria of our meta-analysis and was therefore also excluded.

The combined OR for mortality was 1.19 (95% CI, 0.99 to 1.43) (Figure ). The result of the heterogeneity test \((P>0.05)\) indicated that the studies were similar enough to be meta-analyzed. Combining the probability values of individual studies suggested that both morbidity \((P<0.0001)\) and mortality \((P<0.0000001)\) were significantly higher in the pyrexial versus apyrexial patient groups.

**Discussion**

There is a considerable body of evidence from the animal literature that raised body temperature after the onset of stroke is associated with poor outcome. However, most human studies have been undertaken on small numbers of patients and give conflicting results. In our study there were inadequate OR values available for a combined OR to be calculated for morbidity. The combined OR for mortality suggested a 19% increase in mortality in pyrexial versus apyrexial patients, but the lower CI just crossed the line for no effect. This result may be because of the 5 OR values available, the vast majority of patients were from 2 of the studies that showed no correlation between pyrexia and mortality and hence may have heavily influenced the combined OR. However, the combined probability value, calculated with data from all 9 studies, is more representative and importantly was highly significant for both morbidity and mortality. From the results of our meta-analysis, we can conclude that hyperthermia after the onset of stroke has a significantly detrimental effect on stroke outcome.

The etiology of hyperthermia after stroke is not always evident. Patients with intraventricular or subarachnoid hemorrhages and brain stem infarcts are thought to have greater “central” or “neurogenic” fever. In our analysis patients with subarachnoid hemorrhage were excluded by 1 of the studies. A second study excluded subdural and epidural hemorrhages, and 2 additional studies excluded all hemorrhages. The remaining investigators included all causes of stroke. Clearly, this could lead to discrepancies in the results of individual studies and should be borne in mind during the interpretation of this meta-analysis. Naturally, superimposed infection may also account for pyrexia. One study excluded patients with any evidence of infection. Three other studies also investigated evidence of infection. Of these, 1 study found infection to be present in <20% of their pyrexial patients. Unlike body temperature, neither infection nor leukocytosis had a significant effect on stroke outcome. The second study found the presence of bronchopneumonia in 50% of pyrexial patients. The third study found that 57.6% of hyperthermic patients had an infectious cause (mainly pulmonary and urinary sources). However, coexistent infection within the first 3 days of stroke was not independently associated with poor prognosis. Results from previous investigators generally support these findings but also emphasize that fever may be directly related to the size of the cerebral lesion. Combined, this suggests that the presence of infection in the studies included in our meta-analysis would not have accounted for, or even contributed to, the associated poor outcome.

Castillo et al studied the effect of hyperthermia at different times after the onset of stroke. Hyperthermia within 72 hours of stroke significantly increased mortality.
hyperthermia within the first 24 hours after stroke, however, caused significantly greater morbidity. When hyperthermia occurred after 24 hours, it was not an independent risk factor for poor outcome.\textsuperscript{11} Since none of the other studies stratified patients according to time of onset of hyperthermia, only the 72-hour data were used in our analyses. Clearly, the extent of cerebral damage is related to the timing of hyperthermia onset, and this important relationship has been shown previously in both experimental and clinical studies.\textsuperscript{2,5,14}

The mechanism for the poor outcome seen after hyperthermia remains speculative. The area of reversibly impaired neuronal function surrounding the infarcted tissue, known as the ischemic penumbra, is thought to be the site where temperature-dependent stroke progression occurs. Several mechanisms have been postulated to explain this effect of hyperthermia. Neurotransmitters associated with poor cerebral infarct outcome, such as glutamate, \(\gamma\)-aminobutyric acid, and glycine, have been shown to increase during hyperthermia and to diminish with hypothermia.\textsuperscript{23} Increased free radical production is another possible mechanism.\textsuperscript{23} The temperature-sensitive blood-brain barrier is a possible means of stroke progression due to hyperthermia. Indeed, protein transfer across the blood-brain barrier that occurs after periods of normothermic global ischemia is attenuated during intraischemic hypothermia (30°C to 33°C) and markedly increased during intraischemic hyperthermia (39°C) in rats.\textsuperscript{24} Temperature has a significant influence on intracerebral metabolism. Animal studies have shown temperature-dependent changes in the levels of ATP,\textsuperscript{25,26} phosphocreatine,\textsuperscript{26} and calcium/calmodulin-dependent protein kinase II\textsuperscript{27} after periods of global cerebral ischemia.

Although the results of this study are strongly positive, its limitations must be recognized. These include the well-documented problems associated with all meta-analyses,\textsuperscript{28} particularly, but not confined to, publication bias. Furthermore, there were clear differences between the parameters used for patient inclusion into the individual studies. The subtypes of stroke included in each study are heterogeneous. Since different etiologies and severities of stroke are thought to cause neurogenic pyrexia to differing extents, this could have influenced the final result. Other discrepancies between studies included the statistical methods used, the means of testing for morbidity, the duration at which morbidity and mortality were measured, and, in particular, the measurement of pyrexia. Indeed, pyrexia was measured at varying times after the onset of stroke in different studies, ranging from a single reading on admission\textsuperscript{14} to pyrexia within 7 days of admission.\textsuperscript{9,15} The definition of pyrexia was also discrepant between studies, ranging from >37.0°C to \(\geq38.0^\circ\text{C}\).\textsuperscript{9} One study further subdivided pyrexial patients into those with low and high fever.\textsuperscript{15} However, for the purpose of our analyses patient groups were dichotomized into those with no (or low) fever and those with high fever (Table 1). The discrepancy in the proportion of patients with pyrexia, which varied from 4.5%\textsuperscript{8} to 60.8%,\textsuperscript{17} could be explained neither by the definition of pyrexia nor by the duration of time for which body temperature was monitored after the stroke.

If these limitations of meta-analyses are accepted, our results clearly suggest a detrimental effect of hyperthermia on stroke outcome, with some evidence of greater effect with early onset of pyrexia.\textsuperscript{17} This obviously leads to the question of whether hyperthermia could, conversely, offer a beneficial effect. In the setting of acute traumatic brain injury, induced hypothermia has been shown to significantly improve outcome for up to 6 months in patients with initial Glasgow Coma Scale scores of 5 to 7.\textsuperscript{29} Interestingly, induced hypothermia after head injury has been shown to reduce lactate production (representative of cerebral ischemia) as well as intracranial hypertension.\textsuperscript{30} Moreover, induced moderate hypothermia (33°C) for 48 to 72 hours in 25 patients with middle cerebral artery territory infarction with elevated intracranial pressure (within 14±7 hours of stroke onset) significantly reduced intracranial pressure, with the investigators suggesting improved long-term outcome among survivors.\textsuperscript{31}

The message from this study is that careful emphasis should be placed on the fastidious control of pyrexia, particularly in the early poststroke period. We await further clinical trials on the possible beneficial effects of therapeutic hypothermia. Until then, normothermia must remain the goal in the management of acute stroke.

**Acknowledgments**

We would like to thank Dr J.C. Sharma and Dr R. MacWalter for kindly supplying unpublished data from their studies, and Dr J. Hon for his help with translation. Pankaj Sharma is a BHF Clinician Scientist and a Fulbright Scholar.

**References**

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*Stroke.* 2000;31:410-414
doi: 10.1161/01.STR.31.2.410

*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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