Timing for Fever-Related Brain Damage in Acute Ischemic Stroke

José Castillo, MD; Antoni Dávalos, MD; Jaume Marrugat, MD; Manuel Noya, MD

Background and Purpose—The association between hyperthermia and early neurological deterioration, increased morbidity, and mortality in acute ischemic stroke is well known. However, the timing at which the cerebral lesion may be aggravated by high temperature has not been firmly established. The aim of this study was to determine the prognostic value of body temperature measured at different times after onset of stroke.

Methods—Axillary temperature was recorded every 2 hours for 72 hours in 260 patients with a hemispheric cerebral infarction of <24 hours’ duration. A potential infectious focus was examined in all patients with hyperthermia (temperature >37.5°C in any of the assessments). Stroke severity was quantified with the Canadian Stroke Scale on admission. The relationship between the highest temperature recorded in each 6-hour interval from stroke onset and stroke outcome (Canadian Stroke Scale and Barthel Index at 3 months) or infarct volume was evaluated by correlation analyses. The importance of the time at which hyperthermia was first detected was assessed by logistic regression analysis.

Results—During the first 72 hours, 158 patients (60.8%) had hyperthermia, and in 57.6% of them an infectious cause was identified. Mortality rate at 3 months was 1% in normothermic patients and 15.8% in hyperthermic patients (P<0.001). The correlation coefficients between the final infarct volume, Canadian Stroke Scale and Barthel Index scores at 3 months, and each temperature recording decreased progressively over time from symptom onset. Hyperthermia initiated within the first 24 hours from stroke onset, but not afterward, was independently related to larger infarct volume (odds ratio [OR]=3.23, 95% CI=1.63 to 6.43; P<0.001) and higher neurological deficit (OR=3.06, 95% CI=1.70 to 5.53; P<0.001) and dependency (OR=3.41, 95% CI=1.69 to 6.88; P=0.002) at 3 months. The infectious origin of hyperthermia was not associated with poorer outcome or greater infarct volume.

Conclusions—The relationship between brain damage and high temperature is greater the earlier the increase in temperature occurs. However, only body temperature within the first 24 hours from stroke onset is associated with poor outcome and large cerebral infarcts. (Stroke. 1998;29:2455-2460.)

Key Words: fever ■ hyperthermia ■ stroke, ischemic ■ stroke outcome ■ temperature

Hyperthermia is a proven factor for cerebral injury in experimental models of focal cerebral ischemia, and its harmful effect persists even if it appears days after the start of ischemia. The association between hyperthermia, even if slight, and early neurological deterioration, increased morbidity, and mortality has also been documented in patients with acute ischemic stroke. However, the timing at which high temperature may aggravate the cerebral lesion has not been firmly established. The relationship between fever and a poor prognosis may be easily explained in patients with central hyperthermia due to extensive infarcts that affect the anterior region of the hypothalamus, but it is unknown whether infectious fever may contribute to greater cerebral damage in patients with small cerebral infarctions located distant to the thermoregulatory center. The objective of this study was to determine the prognostic value of hyperthermia of infectious and noninfectious origin recorded at different times after onset of stroke.

Subjects and Methods
We prospectively studied 297 patients with a cerebral hemispheric infarction confirmed by CT, admitted within the first 24 hours after onset of symptoms (or of sleep, if the patient awoke with stroke). Thirty-seven patients died during the first 3 days of data collection; therefore, 260 patients (59% male; mean age, 69.8±10.2 years) were finally evaluated in the study.

Temperature was taken for 5 minutes in the dry axilla of patients on admission and every 2 hours for 3 days. For the purpose of this study, only the highest temperature recorded in each 6-hour period from the onset of stroke (not from admission) was considered in the

Original Contributions

Stroke is available at http://www.strokeaha.org

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analyses of data. Hyperthermia was defined as an axillary temperature $\geq 37.5^\circ C$ in $\geq 1$ determinations. In all patients with hyperthermia, blood analyses, chest x-ray, hemocultures for aerobic and anaerobic germs, and sputum and urine cultures were performed to exclude a potential infection. If these tests were negative, additional examinations were performed, depending on the symptoms: coproculture (5 patients), spinal tap and cerebrospinal fluid culture (6 patients), catheter culture (3 patients), and bronchial aspirate culture (11 patients). Hyperthermia was considered to be of infectious origin if one of the preceding tests was positive; otherwise, hyperthermia was considered to be of noninfectious origin. Although patients with infectious hyperthermia were treated with antibiotics and those with body temperature $\geq 38^\circ C$ received antipyretics, these drugs were not registered in the database.

Stroke severity was quantified with the use of the Canadian Stroke Scale (CSS) on admission, on day 7, and at 3 months. The functional capacity of the patient was evaluated with the Barthel Index (BI) at 3 months. All CT examinations were performed on a CT Systec 3000 Plus (GEC) scanner with a 512$\times$512 matrix display. A cerebral CT was performed on all patients on admission; a second CT was completed between days 4 and 7 after the patient’s inclusion in the study. The final infarct volume was calculated with the CT scan performed on days 4 to 7 according to the following formula: $0.5a\times b\times c$, where $a$ and $b$ are the largest perpendicular diameters measured on the CT and $c$ is slice thickness. Infarct size was measured by one radiologist who was unaware of each patient’s clinical results.

Twenty-six patients (10%) died between day 3 and the last evaluation at 3 months, and 7 patients were not present at the final visit. The value of 0 was imputed to the CSS and BI scores at 3 months in those patients who died before the end of the study, and the CSS score at day 7 was carried forward as the CSS score at 3 months in those who were lost to follow-up after the first week.

**Statistical Analyses**

Proportions were compared with the $\chi^2$ test. Comparison between 2 groups of continuous variables was performed with the Student’s $t$ test or the Mann-Whitney test, depending on whether or not the distribution was normal.

Correlations between the highest body temperature recorded at each 6-hour period and stroke outcome measures at 3 months (CSS and BI scores) or final infarct volume were performed with Spearman’s and Pearson’s analyses, respectively. A log transformation of infarct volume was performed to achieve a normal distribution. Correlation coefficients obtained at each interval from stroke onset were plotted in charts showing the magnitude of the relationship between temperature and the outcome variables.

The importance of the time at which hyperthermia was recorded during the first 72 hours for stroke outcome was assessed by stepwise logistic regression analysis. CSS and BI at 3 months and the ultimate infarct volume were considered 2 categories because they were not normally distributed. Cutoff values for CSS (0, good outcome: $\geq 7$ points; 1, poor outcome: $<7$ points), BI (0, good outcome: $\geq 60$ points; 1, poor outcome: $<60$ points) and infarct volume (0, small: $<30$ cm$^3$; 1, large: $\geq 30$ cm$^3$) were calculated as described by Robert et al.,$^{14}$ with consideration of the mean values in normothermic and hyperthermic patients. The time interval from stroke onset at which hyperthermia was initially recorded (0 to 24 hours, 24 to 48 hours, 48 to 72 hours), age, the highest temperature recorded during the study period, and coexistent infections within the first 3 days (1=yes, 0=no) were included as covariates. This procedure allowed us to determine whether high temperature initiated in a particular interval from symptom onset was related to stroke outcome and infarct volume independently of the absence of fever in the subsequent intervals as a result of treatment.

**Results**

During the first 72 hours after symptom onset, 158 patients (60.8%) developed hyperthermia. Hyperthermia was first recorded within the first 24 hours in 91 patients, from 24 to 48 hours in 49, and from 48 to 72 hours in 18 patients. The number of patients with and without hyperthermia in each time period is shown in Figure 1.

Body temperature on admission was significantly higher in the 37 excluded patients who died within the first 3 days of hospitalization than in the study population ($37.8\pm0.5^\circ C$ versus $36.9\pm0.7^\circ C$; $P=0.028$). Thirty-three of the 37 excluded patients had hyperthermia, in 28 of them initiated within the first 24 hours from onset and in 5 afterward. Among the 260 survivors at the third day, mortality rate at 3 months was 1% in normothermic patients and 15.8% in patients who developed hyperthermia within the first 72 hours ($P<0.001$). Mortality was higher when hyperthermia
was recorded in the first 48 hours than later (17.1% versus 5.6%; \(P=\text{NS}\)).

CSS score on admission was significantly lower in hyperthermic patients (4.9±2.5) than in normothermic patients (6.9±1.9) \((P<0.001)\). At 3 months, poor outcome in neurological deficit (49.4% versus 13.7%; \(P<0.001\)) and functional capacity (46.2% versus 11.8%; \(P<0.001\)) was more frequent in patients with hyperthermia. CT showed a large cerebral infarct in 9.8% of normothermic patients and in 39.2% of hyperthermic patients \((P<0.001)\).

The relationship between brain damage and high temperature was greater the earlier the increase in temperature. The correlation coefficients between the final infarct volume, CSS and BI scores at 3 months, and each temperature recording decreased progressively over time from symptom onset (Figure 2).

In 91 (57.6%) of 158 patients with hyperthermia within the first 72 hours, an infectious cause was found (bronchopulmonary infection in 47 patients, urinary infection in 40 patients, sepsis in 4 patients, thrombophlebitis in 9 patients, and salmonellosis in 1 patient). The proportion of patients with hyperthermia of infectious and noninfectious origin in each time period is shown in Figure 3. Body temperature was higher in patients with hyperthermia of infectious etiology than in those with hyperthermia of noninfectious origin in all the time periods studied, although this difference only reached statistical significance from 36 hours onward (data not shown). Mortality was greater in patients with infectious hyperthermia than in those with noninfectious hyperthermia (22% versus 7.5%; \(P<0.013\)), although patients with infections did not have a higher stroke severity on admission in comparison with those with fever of noninfectious origin.
The final infarct volume (46 ± 62 versus 36 ± 38 cm³; \( P = 0.54 \)) and functional capacity at 3 months (BI: 48 ± 43 versus 61 ± 36; \( P = 0.14 \)) were not significantly different between the groups of patients with infectious and noninfectious hyperthermia, although the former group had a significantly higher stroke severity at the end of the follow-up (CSS: 5.4 ± 3.6 versus 6.8 ± 2.8; \( P = 0.035 \)).

The correlation coefficients between stroke severity at 3 months, final infarct volume, and each body temperature recording were similar in patients with infectious and noninfectious hyperthermia during the first 30 hours from symptom onset. From 30 to 72 hours, the coefficients decreased more notably in cases of infectious hyperthermia (Figure 4).

Logistic regression analyses showed that hyperthermia initiated within the first 24 hours from stroke onset, but not afterward, was independently related to large infarct volumes and poor outcome in neurological deficit and functional ability at 3 months (Table). Coexistent infections within the first 3 days were not independently associated with poor prognosis.

### Multiple Logistic Regression Analyses of Infarct Volume and Stroke Outcome

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Infarct Volume</th>
<th>Greater Neurological Deficit at 3 mo</th>
<th>Poor Functional Capacity at 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>( P )</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.99–1.05)</td>
<td>0.173</td>
<td>1.04 (1.01–1.07)</td>
</tr>
<tr>
<td>Infection</td>
<td>0.72 (0.32–1.62)</td>
<td>0.427</td>
<td>0.92 (0.43–2.01)</td>
</tr>
<tr>
<td>Highest temperature, °C</td>
<td>2.81 (1.34–5.89)</td>
<td>0.006</td>
<td>1.68 (0.84–3.40)</td>
</tr>
<tr>
<td>Time at which hyperthermia was initiated</td>
<td>( P )</td>
<td>0.001</td>
<td>( P )</td>
</tr>
<tr>
<td>0–24 h</td>
<td>3.23 (1.63–6.43)</td>
<td>&lt;0.001</td>
<td>3.06 (1.70–5.53)</td>
</tr>
<tr>
<td>24–48 h</td>
<td>1.14 (0.52–2.51)</td>
<td>0.736</td>
<td>1.47 (0.78–2.80)</td>
</tr>
<tr>
<td>48–72 h</td>
<td>0.23 (0.05–1.09)</td>
<td>0.064</td>
<td>0.33 (0.10–1.03)</td>
</tr>
</tbody>
</table>

### Discussion

In experimental models of cerebral ischemia, even moderate hyperthermia is a factor that increases cerebral lesion and volume of infarcted tissue.\(^1\)\(^–\)\(^4\),\(^6\)\(^–\)\(^14\) Hyperthermia facilitates the transformation of ischemic penumbra into infarction and accelerates the development of ischemic necrosis.\(^1\)\(^–\)\(^2\),\(^5\)\(^–\)\(^14\) In the human acute stroke, it has also been demonstrated that hyperthermia is an independent risk factor of poor outcome and that it is associated with greater morbidity and mortality\(^9\)\(^–\)\(^11\) and larger infarct volumes.\(^11\) The present results are in accord with the previous findings. We have found an independent relationship between high body temperature within the first 24 hours and larger infarct volume, higher neurological deficit, and dependency at 3 months.

Experimental and clinical studies have emphasized the importance of the time of onset of hyperthermia on the magnitude of the cerebral injury.\(^1\)\(^–\)\(^3\),\(^14\)\(^–\)\(^15\) Larger lesions are provoked when hyperthermia coincides with the onset of cerebral ischemia.\(^1\)\(^–\)\(^3\),\(^14\) Similarly, hypothermia yields beneficial effects when it is simultaneously induced with the development of ischemia, but it is not effective if its onset is
hours afterward.\textsuperscript{16,17} Models of focal and global cerebral ischemia have been developed with delayed induction of hyperthermia to reproduce the clinical situation in humans, showing the persistence, even 24 hours afterward, of the pernicious effects of an increase in temperature.\textsuperscript{5,6}

The timing for hyperthermia-related brain damage in acute ischemic stroke had not been investigated previously. In the present study body temperature was monitored during 72 hours, ie, during the period in which most of progressing strokes occur. According to our results, the relationship between the intensity of hyperthermia and stroke outcome or infarct volume is stronger the earlier the fever develops, and body temperature within the first 24 hours is the key value associated with greater cerebral damage; when hyperthermia appears afterward it is not an independent factor of poor outcome. The use of antipyretics in some patients, a fact that was not recorded in this study, could modify body temperature profile after admission. Nevertheless, its influence in our results is unlikely since we used a logistic model that allowed us to determine whether high temperature initiated in a particular interval from symptom onset was related to stroke outcome and infarct volume independently of the absence of fever in the subsequent intervals as a result of treatment.

The most frequent etiology of fever in acute stroke is infection, but hyperthermia is occasionally an expression of cell necrosis or of changes in thermoregulatory mechanisms that occur when lesions are located in the anterior region of the hypothalamus.\textsuperscript{12,18–20} However, we cannot rule out the occurrence of infectious and noninfectious hyperthermia during the first 30 hours of evolution but decreased more notably in cases of infectious hyperthermia from 30 hours onward (coefficients >0.2, $P<0.001$).

Figure 4. Distribution of correlation coefficients between each temperature recording and Canadian Stroke Scale (CSS) score at 3 months (top, Spearman's correlation) and log-transformed final infarct volume (bottom, Pearson's correlation) in patients with hyperthermia of infectious and noninfectious origin within the first 72 hours. Note that the coefficients were similar in patients with infectious and noninfectious hyperthermia during the first 30 hours of evolution but decreased more notably in cases of infectious hyperthermia from 30 hours onward (coefficients >0.2, $P<0.001$).
more prone to aspiration and urinary complications and therefore to infection. In our study infection was demonstrated in 58% of the patients who developed hyperthermia, while in 42% of patients fever could be due to tissue necrosis itself or to changes in thermoregulation. The relationship between hyperthermia within the first 24 hours from symptom onset and stroke outcome or infarct volume was independent of the infectious or noninfectious origin of fever. However, after 30 to 36 hours from onset, the significant correlation between infarct volume, neurological deficit at 3 months, and body temperature disappeared in patients with infections. These facts support the hypothesis that in some patients fever could be directly related to larger cerebral infarctions or to the acute phase response in more severe strokes.\footnote{Dinarello CA. The acute phase response. In: Bennett JC, Plum F, eds. Cecil Textbook of Medicine. Philadelphia, Pa: WB Saunders Co; 1996: 1535–1537.}

In conclusion, the relationship between the degree of hyperthermia and stroke outcome or infarct volume is highest when it begins within 24 hours of onset of symptoms. While further studies are needed to confirm these results, our main efforts should be directed toward an immediate and effective reduction of body temperature when it is \( > 37.5 \)°C, particularly within the first 24 hours of cerebral ischemia, since most likely only high temperature in this period independently contributes to poor prognosis.

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References

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