Hyperthermia After Cardiac Arrest Is Associated With an Unfavorable Neurologic Outcome

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Background: Moderate elevation of brain temperature, when present during or after ischemia, may markedly worsen the resulting injury.

Objective: To evaluate the impact of body temperature on neurologic outcome after successful cardiopulmonary resuscitation.

Methods: In patients who experienced a witnessed cardiac arrest of presumed cardiac cause, the temperature was recorded on admission to the emergency department and after 2, 4, 6, 12, 18, 24, 36, and 48 hours. The lowest temperature within 4 hours and the highest temperature during the first 48 hours after restoration of spontaneous circulation were recorded and correlated to the best-achieved cerebral performance categories’ score within 6 months.

Results: Over 43 months, of 698 patients, 151 were included. The median age was 60 years (interquartile range, 53-69 years); the estimated median no-flow duration was 5 minutes (interquartile range, 0-10 minutes), and the estimated median low-flow duration was 14.5 minutes (interquartile range, 3-25 minutes). Forty-two patients (28%) underwent bystander-administered basic life support. Within 6 months, 74 patients (49%) had a favorable functional neurologic recovery, and a total of 86 patients (57%) survived until 6 months after the event. The temperature on admission showed no statistically significant difference (P = .39). Patients with a favorable neurologic recovery showed a higher lowest temperature within 4 hours (35.8°C [35.0°C-36.1°C] vs 35.2°C [34.5°C-35.7°C]; P = .002) and a lower highest temperature during the first 48 hours after restoration of spontaneous circulation (37.7°C [36.9°C-38.6°C] vs 38.3°C [37.8°C-38.9°C]; P < .001) (data are given as the median [interquartile range]). For each degree Celsius higher than 37°C, the risk of an unfavorable neurologic recovery increases, with an odds ratio of 2.26 (95% confidence interval, 1.24-4.12).

Conclusion: Hyperthermia is a potential factor for an unfavorable functional neurologic recovery after successful cardiopulmonary resuscitation.

PATIENTS AND METHODS

PATIENTS

Patients for this study were selected from the population served by the department of emergency medicine of a general hospital, a tertiary care university hospital. The following procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975, as revised in 1983.

The study period ranged from June 1, 1992, through December 31, 1995. Patients older than 18 years who experienced a witnessed cardiac arrest of presumed cardiac cause with subsequent cardiopulmonary resuscitation and return of spontaneous circulation were included in the study. Patients whose cardiopulmonary arrest was associated with trauma, hypothermia, drowning, drug overdose, primary respiratory arrest, and primary neurologic or metabolic reasons were excluded from the study. Patients with pulmonary infiltrates, either clinical or a radiological suggestion of pneumonia, or a C-reactive protein (CRP) level higher than 1.5 mg/dL on admission to the emergency department were excluded; patients with known infection and patients receiving antibiotic therapy were also excluded. Furthermore, we excluded patients whose functional neurologic status could not be assessed, ie, if they died before the withdrawal of sedation and analgesia.

Cardiopulmonary arrest was defined as the absence of spontaneous respiration and a palpable pulse. Return of spontaneous circulation was defined as electrical activity on the electrocardiogram and a palpable pulse for at least 10 minutes. Treatment in the field and in the hospital was according to the American Heart Association’s guidelines for basic and advanced cardiac life support and postresuscitation care. In the hospital, all patients received standard intensive care treatment, such as controlled mechanical ventilation and sedation and analgesia with midazolam hydrochloride, 0.2 mg/kg per hour, and fentanyl citrate, 0.004 mg/kg per hour, for at least 24 hours. Other treatment, such as fluids, vasopressors, fibrinolysis, anticoagulants, and antipryretics, and the initiation and selection of the antibiotic strategy were left to the discretion of the attending physician. No mechanical or external means to reduce the temperature were used.

STUDY DESIGN AND DATA COLLECTION

Data were collected prospectively, as an observational study according to the Utstein style, the recommended guidelines for uniform reporting of data on arrival of patients after out-of-hospital cardiac arrest. Attention has been focused on the periods from collapse (eg, cardiac arrest) until basic and/or advanced life support and from the beginning of life support until the return of spontaneous circulation; the first monitored rhythm in the electrocardiogram; and the recorded history for the individual patients, especially regarding the cause of cardiac arrest. The interval from collapse to first basic and/or advanced life support was defined as no-flow duration, and the interval from the beginning of life support until the return of spontaneous circulation was defined as low-flow duration.

For practical reasons, the temperature immediately after admission was monitored with infrared tympanic thermometry (Otostemp LighTouch; Exergen Corporation, Wauertown, Mass); within 30 minutes and during the observation period, it was monitored in the pulmonary artery (Edwards Swan-Ganz VIP catheter; Baxter HealthCare Corporation, Santa Ana, Calif). Information about the method of calibration of temperature probes, the range of linearity of measurement, and the repeatability, reproducibility, and coefficient of variation of each apparatus used to monitor the temperature has been provided elsewhere. The temperature was measured on admission to the emergency department and after 2, 4, 6, 12, 18, 24, 36, and 48 hours. The CRP and fibrinogen levels and the white blood cell count were analyzed on admission and after 12, 24, 36, and 48 hours. Chest x-ray films were reviewed for pulmonary infiltrates every 24 hours (on admission and after 24 and 48 hours).

To define the temperature course and to compare groups, we defined the following variables: the lowest measured temperature within the first 4 hours after return of spontaneous circulation and the highest temperature observed during the first 48 hours after return of spontaneous circulation. The threshold temperature between normothermia and hyperthermia was considered to be 37°C. To account for a possible time effect of elevated body temperature, the area under the temperature curve higher than 37°C was divided by the time when the temperature was elevated.

OUTCOME MEASURES

Cerebral function was assessed prospectively on arrival and at regular intervals for 6 months after the return of spontaneous circulation. Functional neurologic recovery was expressed in cerebral performance categories (CPCs), which are based on the Glasgow overall performance categories. The performance categories are defined as follows: CPC 1, conscious and alert with normal function or only slight disability; CPC 2, conscious and alert with moderate disability; CPC 3, conscious with severe disability; CPC 4, comatose or in a persistent vegetative state; and CPC 5, brain death. The best-achieved CPC score within 6 months was used for calculation. A CPC score of 1 or 2 represents favorable functional neurologic recovery, and a CPC score of 3, 4, or 5 reflects unfavorable functional neurologic recovery.

STATISTICAL ANALYSIS

According to the Utstein style, data are expressed as the median and the interquartile range (IQR). Percentages were determined for dichotomous variables. For the comparison of continuous variables, the Mann-Whitney test was used. The χ² test was used for the comparison of dichotomous variables. A logistic regression analysis was performed to test for independent predictors of unfavorable neurologic recovery. For this age, sex and known predictors of neurologic outcome were included into the model. The required 2-tailed significance level for all tests was set at .05. All data were computed with Microsoft Excel 97 for Windows (Redmond, Wash) and Statistical Product and Service Solutions for Windows, version 8.0 (SPSS Inc, Chicago, Ill).
In 118 patients (78%), cardiac arrest occurred outside of the hospital. In all patients, the estimated median no-flow duration was 5 minutes (IQR, 0-10 minutes) and the median low-flow duration was 14.5 minutes (IQR, 5-25 minutes). Forty-two patients (28%) underwent bystander-administered basic life support; the median no-flow duration in these patients was 1 minute (IQR, 0-2 minutes). The median arterial lactate concentration on admission was 8.7 mmol/L (IQR, 6.0-11.7 mmol/L), and the median pH on admission was 7.30 (IQR, 7.21-7.37). Within 6 months, 74 patients (49%) had a favorable functional neurologic recovery, and a total of 86 patients (57%) survived until 6 months after the event.

The no-flow and low-flow durations, the time from cardiac arrest until restoration of spontaneous circulation, and the cumulative epinephrine dose were significantly lower in patients with a favorable neurologic recovery (Table 1). No significant differences were found comparing the rate of bystander-administered basic life support (Table 1) or the initial electrocardiographic results between groups (Table 2).

The lactate level on admission was significantly lower and pH values on admission were significantly better (Table 1) in patients with a favorable outcome. At 24 hours, lactate levels were lower in patients with a favorable outcome, but this was not statistically significant. The pH value was in normal ranges in both groups.

The temperature on admission was lower in patients with an unfavorable functional neurologic recovery, but without statistical difference (Table 3 and Figure). Within 4 hours after restoration of spontaneous circulation, the temperature in patients with a good functional recovery showed a trend of elevation, while the temperature in patients with a bad functional recovery showed a trend toward a slight decrease. Comparing the lowest temperature within the first 4 hours after restoration of spontaneous circulation, patients with a good functional neurologic recovery had significantly higher values (Table 3). During the following period, the temperature increased in both groups, reaching a significantly lower maximum temperature in patients with a favorable neurologic recovery (Table 3 and Figure). Patients with a good functional neurologic recovery showed a continuum starting at 12 hours after restoration of spontaneous circulation until 36 hours after restoration of spont-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Functional Neurologic Recovery</th>
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<tbody>
<tr>
<td></td>
<td>Good (n = 89)</td>
</tr>
<tr>
<td>Out-of-hospital cardiac arrest†</td>
<td>58 (65)</td>
</tr>
<tr>
<td>No-flow duration, min</td>
<td>0.0 (0.0-1.0)</td>
</tr>
<tr>
<td>Low-flow duration, min</td>
<td>5.0 (2.0-13.3)</td>
</tr>
<tr>
<td>Cardiac arrest to ROSC, min</td>
<td>5.0 (3.0-15.0)</td>
</tr>
<tr>
<td>Countershocks</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Cumulative epinephrine dose, mg</td>
<td>2.0 (1.0-4.0)</td>
</tr>
<tr>
<td>Bystander-administered basic life support†</td>
<td>22 (25)</td>
</tr>
<tr>
<td>pH level on admission to the emergency department, mmol/L</td>
<td>7.34 (7.23-7.40)</td>
</tr>
<tr>
<td>Lactate level on admission to the emergency department, mmol/L</td>
<td>7.4 (4.2-9.9)</td>
</tr>
</tbody>
</table>

*Data are given as the median (interquartile range) body temperature in °C.
†Data are given as the number (percentage) of patients unless otherwise indicated. ROSC indicates restoration of spontaneous circulation.

**Table 2.** Demographic Characteristics and Mortality in Patients With Good and Unfavorable Functional Neurologic Recovery After a Witnessed Cardiac Arrest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good (n = 89)</th>
<th>Unfavorable (n = 62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>61 (53-70)</td>
<td>60 (54-68)</td>
<td>.74</td>
</tr>
<tr>
<td>Male sex</td>
<td>62 (70)</td>
<td>45 (73)</td>
<td>.81</td>
</tr>
<tr>
<td>Body mass index, kg/m²†</td>
<td>26.9 (24.7-29.3)</td>
<td>26.2 (24.6-27.7)</td>
<td>.20</td>
</tr>
<tr>
<td>First ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>3 (3)</td>
<td>0</td>
<td>.27</td>
</tr>
<tr>
<td>VF</td>
<td>63 (71)</td>
<td>37 (60)</td>
<td>.12</td>
</tr>
<tr>
<td>Asystole</td>
<td>9 (10)</td>
<td>14 (22)</td>
<td>.02</td>
</tr>
<tr>
<td>PES</td>
<td>8 (9)</td>
<td>11 (18)</td>
<td>.11</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (7)</td>
<td>0</td>
<td>.08</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 6 mo†</td>
<td>15 (17)</td>
<td>50 (81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>After days†</td>
<td>25 (17-71)</td>
<td>11 (3-24)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Data are given as the number (percentage) of patients unless otherwise indicated. ECG indicates electrocardiogram; VT, ventricular tachycardia; VF, ventricular fibrillation; and PEA, pulseless electrical activity.
†Data are given as the median (interquartile range).

**Table 3.** Body Temperature in Patients With Good and Unfavorable Functional Neurologic Recovery After a Witnessed Cardiac Arrest

<table>
<thead>
<tr>
<th>Body Temperature*</th>
<th>Good (n = 89)</th>
<th>Unfavorable (n = 62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission to the emergency department</td>
<td>35.6 (34.2-36.0)</td>
<td>35.3 (34.0-35.9)</td>
<td>.39</td>
</tr>
<tr>
<td>Minimum</td>
<td>36.0 (35.2-36.2)</td>
<td>35.2 (34.7-35.7)</td>
<td>.001</td>
</tr>
<tr>
<td>Maximum</td>
<td>37.6 (36.9-38.6)</td>
<td>38.3 (37.8-38.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Δ(+37)</td>
<td>0.25 (0.00-0.78)</td>
<td>0.66 (0.17-1.00)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Data are given as the median (interquartile range) body temperature in °C.
†Data are given as the median (interquartile range) body temperature in degrees Celsius.
Temperature curves within 48 hours after successful cardiopulmonary resuscitation. Data are expressed as the median.

taneous circulation, with a following downward trend of the temperature curve, in contrast to patients with a bad functional neurologic recovery, who had the continuum until 48 hours after restoration of spontaneous circulation (Figure). Comparing the weighted mean temperature (the area under the temperature curve higher than 37°C when divided by the time the temperature was elevated), patients with a favorable neurologic recovery had significantly lower values than did patients with an unfavorable neurologic recovery (Table 3).

C-reactive protein and fibrinogen levels were lower in the group with a favorable outcome; however, a statistically significant difference was found at 24 hours after restoration of spontaneous circulation only for the CRP level (Table 4). The course of CRP showed a maximum 36 hours after restoration of spontaneous circulation, with a following decrease, more pronounced in the group with a favorable outcome. The white blood cell count showed no trend at all during the observation period. Signs of pneumonia in the chest x-ray film were found in 11 (7.3%) of the patients after 24 hours (P = .65), and in 12 (7.9%) of the patients after 48 hours (P = .65), without a statistically significant difference between groups. After 24 and after 48 hours, significantly fewer patients with a favorable neurologic recovery received antibiotic treatment (33 patients [37%] compared with 39 patients [63%] [P = .006] and 36 patients [40%] compared with 40 patients [65%] [P = .009], respectively). Within the first 48 hours after successful cardiopulmonary resuscitation, no patient received antipyretics.

Variables showing a significant difference between groups in a univariate analysis were included into a logistic regression model (age, male sex, no-flow duration, low-flow duration, out-of-hospital cardiac arrest, pH level on admission, lactate level on admission, and highest temperature observed during the first 48 hours after return of spontaneous circulation). The number of counter-shocks and the cumulative epinephrine dose (measured in milligrams) were not included, to keep the number of cases for calculation high in the model. The logistic regression model showed that fever going over the threshold temperature of 37°C was a strong independent predictor for an unfavorable functional neurologic recovery (Table 5). For each degree Celsius higher than 37°C, the association with an unfavorable neurologic recovery increases, with an odds ratio of 2.26 (95% confidence interval, 1.24-4.12).

This investigation of the influence of body temperature on functional neurologic recovery showed that hyperthermia (a temperature higher than the threshold value of 37°C) was associated with an unfavorable functional neurologic recovery after cardiopulmonary resuscitation of persons who experienced cardiac arrest with a presumed cardiac cause. Each degree Celsius higher than 37°C showed an increased association with the risk of severe disability, coma, or a persistent vegetative state (CPC 3-4), with an odds ratio of 2.26.

One cause of hyperthermia after cardiopulmonary resuscitation might be infection. Global ischemia during and after cardiac arrest leads to gut ischemia, which makes translocation of bacteria or toxins possible. Another reason for infection could be pulmonary aspiration due to the comatose state. Gaussorgues and Gueugniaud and colleagues showed that 39% of patients had 2 or more blood cultures that were positive for infection within 12 hours after cardiopulmonary resuscitation.

No data were available on the underlying causes of fever, but the higher risk of poor neurologic recovery suggested that high temperature was an independent component of poor prognosis. In patients who experience stroke, the most frequent cause of fever 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. In agreement with studies of patients who experienced stroke, we found that patients with a higher temperature had a worse prognosis for neurologic recovery.

However, the aim of our study was not to focus on causes of infection after cardiopulmonary resuscitation but to correlate hyperthermia to neurologic recovery. We did not focus on the data of bacterial screening (blood culture or Uricult results or the presence of tracheal fluid), as results mainly come late and are of less help in the empirical start of antibiotic therapy; we only compared markers of infection (white blood cell count, fibrinogen level, and CRP level) and suggested pneumonia and/or signs of pneumonia on the chest x-ray film within patient groups (those with a favorable and an unfavorable neurologic recovery), and found no statistically significant differences for all of these variables.

On the other hand, there was a statistically significant difference in the application of antibiotic drugs 24 and 48 hours after cardiac arrest and successful cardiopulmonary resuscitation. Patients with an unfavorable neurologic recovery had a significantly higher rate of antibiotic treatment. As antibiotic treatment within the first 48 hours after successful cardiopulmonary resuscitation was started because of fever, elevated markers of infection, and signs of pneumonia in the chest x-ray film, the main reason for this significant difference seems to
be the higher temperature in patients with an unfavorable neurologic recovery.

Takino and Okada5 showed that patients with an unfavorable functional neurologic recovery (prolonged coma and brain death) more often had initial hypothermia (temperature <35°C), but the number of cases is few and most patients experienced prolonged coma or brain death. In our study, we found that patients with an unfavorable functional neurologic recovery showed a decrease of temperature within the first 4 hours after restoration of spontaneous circulation; compared with patients with a good functional neurologic recovery, they had significantly lower temperatures. Patients with an unfavorable functional neurologic recovery had a significantly higher highest temperature observed and weighted mean temperature (the area under the temperature curve higher than 37°C) when divided by the time the temperature was elevated) within 48 hours after restoration of spontaneous circulation. This temperature course might be due to impaired temperature control after cardiac arrest and successful cardiopulmonary resuscitation and might correlate with the amount of postischemic central nervous system damage. The usual temperature homeostasis showed an initial decrease and fever thereafter in patients with an unfavorable neurologic outcome. This study does not establish that temperature elevation worsened outcome, and it may be that enhanced initial brain damage indeed elevated the temperature.

From animal studies, we know by which mechanisms hyperthermia may influence the ischemic brain and can worsen cerebral ischemia. The cellular mechanism seems rather nonspecific but tends to collectively involve key items rendering neurons resistant to ischemic damage. The release of neurotransmitters in global ischemia is accentuated by hyperthermia and diminished by hypothermia. In an animal study23 of prosencephalon ischemia in rats, hyperthermic rats showed a signiﬁcant increase of ganglionic glutamate levels and a trend toward higher levels thereafter compared with normothermic rats. An additional mechanism is the production of cortical oxygen radical in the recirculation period, which showed no elevation in moderate hypothermic ischemia, a 2- to 3-fold elevation in the normothermic period, and a 4- to 5-fold elevation in hyperthermic ischemia.24-25 In addition, hyperthermia influences the brain metabolism by adenosine triphosphate depletion and by less complete recovery of adenosine triphosphate levels and by adenylyl energy changes in cortical and subcortical regions.26 These changes in adenosine triphos-
phate metabolism in combination with metabolic insults are highly correlated with the release of endogenous glutamate and aspartate.

Furthermore, hyperthermia markedly enhances calpain activation and spectrin proteolysis in cortical pyramidal neurons soon after the onset of reperfusion, which became marked by 4 and 24 hours, in association with morphological evidence of irreversible neuronal injury.

Various methods of temperature measurement are available (eg, the brain temperature may be measured via a ventricular catheter, a tympanic probe, a vesical probe, or a Swan-Ganz catheter). The brain temperature may be dissociated from the systemic temperature by 0.2°C to 0.1°C, although differences are usually small. Measurement of tympanic temperature has the advantage of being noninvasive, fast, and easily applicable and, therefore, has been used routinely. Swan-Ganz catheter measurements were taken if there was an indication for invasive hemodynamic monitoring.

In conclusion, hyperthermia during recovery after primary successful cardiopulmonary resuscitation worsens ischemic damage. Although the cause and effect of elevated temperature on survival are not proved, it seems prudent to rigorously control temperature in such patients. An elevated temperature should be aggressively treated and should not exceed normal values for a long time. This is especially true in view of the fact that mild resuscitative hyperthermia, used for resuscitation in patients who experience cardiac arrest, seems to mitigate neurologic damage.

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REFERENCES