Chapter 3

The influence of rewarming after therapeutic hypothermia on outcome after cardiac arrest

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Resuscitation 2012;83:996-1000
Abstract

Introduction
Treatment with hypothermia has been shown to improve outcome after cardiac arrest (CA). Current consensus is to rewarm at 0.25–0.5 °C/h and avoid fever. The aim of this study was to investigate whether active rewarming, the rate of rewarming or development of fever after treatment with hypothermia after CA was correlated with poor outcome.

Methods
This retrospective cohort study included adult patients treated with hypothermia after CA and admitted to the intensive care unit between January 2006 and January 2009. The average rewarming rate from end of hypothermia treatment (passive rewarming) or start active rewarming until 36 °C was dichotomized in a high (≥0.5 °C/h) or normal rate (<0.5 °C/h). Fever was defined as > 38 °C within 72 h after admission. Poor outcome was defined as death, vegetative state, or severe disability after 6 months.

Results
From 128 included patients, 56% had a poor outcome. Actively rewarmed patients (38%) had a higher risk for poor outcome, OR 2.14 (1.01–4.57), p < 0.05. However, this effect disappeared after adjustment for the confounders age and initial rhythm, OR 1.51 (0.64–3.58). A poor outcome was found in 15/21 patients (71%) with a high rewarming rate, compared to 54/103 patients (52%) with a normal rewarming rate, OR 2.61 (0.88–7.73), p = 0.08. Fever was not associated with outcome, OR 0.64 (0.31–1.30), p = 0.22.

Conclusions
This study showed that patients who needed active rewarming after therapeutic hypothermia after CA did not have a higher risk for a poor outcome. In addition, neither speed of rewarming, nor development of fever had an effect on outcome.
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Introduction

Mild therapeutic hypothermia has been shown to decrease mortality and improve neurologic outcome in adult comatose survivors of out-of-hospital cardiac arrest (CA) with ventricular fibrillation (VF) as initial rhythm\textsuperscript{1,2}. This treatment was soon thereafter incorporated in the international guidelines and has become standard care in many countries\textsuperscript{3,4}.

It has been suggested that slow rewarming or the need of active rewarming after hypothermia treatment are signs of extensive brain damage as impaired thermoregulation can be regarded as a failure of the hypothalamus to regulate body temperature\textsuperscript{5,6}. The current recommendation is to rewarm the patients after therapeutic hypothermia at a rate of maximal 0.25-0.5 °C/h, but the optimal rewarming rate is unknown\textsuperscript{3,7}.

Another consensus in the current guidelines is that hyperthermia or fever should be avoided\textsuperscript{3,4}, as hyperthermia is associated with increased cerebral injury in experimental models of forebrain ischemia or asphyxia\textsuperscript{8-10}. In addition, hyperthermia could be a symptom of an infection or cell damage in the anterior region of the hypothalamus. In patients who were not treated with hypothermia after CA, development of fever occurred in up to 83% of the patients, which was associated with an unfavorable neurologic recovery and a prolonged length of stay on the intensive care unit (ICU)\textsuperscript{11-17}. However, randomized controlled trials evaluating if treatment of fever in patients after CA could improve neurologic outcome are lacking.

The aim of this study was to investigate whether active rewarming, the rate of rewarming or the development of fever after treatment with hypothermia after CA was correlated with a poor neurologic outcome. Our hypothesis was that active rewarming, a fast rewarming rate of ≥ 0.5°C/h, or development of fever would be associated with a poor outcome.

Methods

This retrospective cohort study was performed in a 30-bed mixed medical-surgical ICU (Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands). Adult patients, admitted to the ICU between January 2006 and January 2009 who were treated with hypothermia after primary CA, were included. Exclusion criteria for treatment with hypothermia according to our local protocol were signs of a cardiogenic shock (mean arterial pressure < 60mmHg despite use of inotropic drugs or cardiac index < 2.5 l/min/m\textsuperscript{2}),
comatose state due to other causes than CA, and pre-existing diseases with a life expectancy of less than 6 months. Discontinuation of hypothermia treatment due to complications, such as cardiac arrhythmia (ventricular fibrillation, asystole or severe bradycardia) or hemodynamic instability, was an additional exclusion criterion.

The following data were retrieved from our patient data management system (PDMS, Metavision, iMDsoft, Sassenheim, The Netherlands): age, gender, presenting rhythm, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, ICU admission temperature, duration of hypothermia, date and time of target temperature, temperature at discontinuation of hypothermia, temperature at start and discontinuation of active rewarming, duration of active rewarming, date and time of return to normal body temperature (36°C), and development of fever (defined as body temperature above 38°C) within the first 72 h after admission.

According to our local protocol, target temperature (32-34°C) was induced with intravenous infusion of 4°C Ringer’s lactate (maximum of 30 ml/kg) and maintained for 24 h with surface cooling with the Blanketroll® II, Cincinatti Sub-Zero Medical, Cincinatti, Ohio, United States of America. Patient’s temperature was measured either via blood or pharyngeal probe. Active rewarming was indicated when patients did not reach normal body temperature after 12 h of passive rewarming. Every patient admitted after CA received a daily dose of paracetamol 4000 mg. The protocol did not contain treatment recommendations in case of development of fever after the hypothermia period.

The period of rewarming was defined as the duration (h) from end of hypothermia treatment (passive rewarming group) or time of start active rewarming until normal body temperature. The average increase in body temperature per hour was calculated and dichotomized in a high rate of rewarming (defined as ≥ 0.5°C/h) or a normal rate of rewarming (defined as < 0.5°C/h).

Neurologic outcome was assessed with the Glasgow Outcome Scale (GOS) 6 months after admission via a telephone interview with the patient, a legal representative or his/her general practitioner. The primary outcome of the study was poor outcome, defined as death, vegetative state, or severe disability (GOS 1–3). As a secondary outcome we used mortality.

**Statistical analysis**

Patient characteristics were described according to their distribution. Variables were expressed as mean and standard deviation (normally distributed) or as medians and
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interquartile ranges (IQR, not normally distributed). Categorical variables were expressed as percentages (n). Statistical significance was considered to be at p < 0.05. When appropriate, statistical uncertainty was expressed by 95% confidence intervals (CIs). Differences between baseline characteristics for the passive rewarming versus active rewarming group were calculated with the independent Student’s t-test, χ²-test or the Mann-Whitney U test. The goal of the primary analysis was to quantify the net effect of the application of active rewarming on outcome, controlling for other variables. Exploration of interaction (effect modification) and confounding was considered methodologically relevant. We first focused on the crude (uncorrected) effect of active rewarming (independent variable) on poor outcome (dependent variable). Then statistically (univariate analysis p ≤ 0.10) and clinically relevant covariates were added as an interaction term. If the interaction term appeared to be significant (p < 0.05), the relation between active rewarming and poor neurologic outcome could be different for various levels of the covariate. This would indicate the need for separate models for the levels of the covariate. If a significant interaction was not found, the model was examined for confounding. Confounding was defined as ≥ 10% change in the coefficient of the central determinant (active rewarming) as a consequence of adding a covariate. All analyses were performed with SPSS 18.1 (IBM Corporation, Armonk, New York, United States).

Results

A total of 136 patients were included. Eight patients were excluded from further analysis as treatment with hypothermia was prematurely ended due to complications, the majority due to cardiac arrhythmia or hemodynamic instability. Patient characteristics and differences between the active and passive rewarming group are presented in Table 1. The patients who needed active rewarming were significant older than those who rewarmed spontaneously (p < 0.01). A poor outcome was found in 72/128 patients (56%) of the complete group after 6 months. Mortality was 68/128 patients (53%). Age, APACHE II and initial rhythm were significant risk factors for poor outcome (Table 2). These factors were no effect modifiers, but age and initial rhythm were both identified as confounders for active rewarming and the rewarming rate. Age, initial rhythm and APACHE II were confounders for development of fever.

Active rewarming was performed in 49/128 patients (38%). The majority of the patients (31/49) needed active rewarming because normal body temperature was not achieved while rewarming spontaneously. Other reasons for active rewarming were hemodynamic instability, cardiac arrhythmia, temperature drop, expectation not to rewar
spontaneously (all ≤ 3 patients), or unknown (13/49 patients). Binary logistic regression showed that patients who needed active rewarming had a higher chance for poor outcome, OR 2.14 (95% CI 1.01-4.57), \( p < 0.05 \) (Table 3). However, after adjustment for age and initial rhythm as confounders, this effect disappeared OR 1.51 (0.64-3.58), \( p = 0.35 \). For mortality similar results were found, crude logistic regression analysis showed an OR 1.71 (0.82-3.57), \( p = 0.15 \). After adjustment for age, initial rhythm and APACHE II as confounders, the OR was 1.24 (0.51-3.00), \( p = 0.64 \).

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
<th>All patients ((n = 128))</th>
<th>Active rewarming ((n = 49))</th>
<th>Passive rewarming ((n = 79))</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, ( n ) (%)</td>
<td>97 ( (76) )</td>
<td>34 ( (69) )</td>
<td>63 ( (80) )</td>
<td>0.18</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>61.6 ( (13.2) )</td>
<td>65.6 ( (12.9) )</td>
<td>59.2 ( (12.9) )</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>OHCA, ( n ) (%)</td>
<td>106 ( (83) )</td>
<td>38 ( (78) )</td>
<td>68 ( (86) )</td>
<td>0.21</td>
</tr>
<tr>
<td>First rhythm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF/VT</td>
<td>95 ( (74) )</td>
<td>32 ( (65) )</td>
<td>63 ( (80) )</td>
<td>0.16</td>
</tr>
<tr>
<td>Non-VF/VT</td>
<td>29 ( (23) )</td>
<td>14 ( (29) )</td>
<td>15 ( (19) )</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4 ( (3) )</td>
<td>3 ( (6) )</td>
<td>1 ( (1) )</td>
<td></td>
</tr>
<tr>
<td>APACHE II, median (IQR)</td>
<td>26 ( (18-31) )</td>
<td>26 ( (19-32) )</td>
<td>25 ( (17-31) )</td>
<td>0.37</td>
</tr>
<tr>
<td>Admission temperature, median (IQR)</td>
<td>35.1 ( (34.3-35.9) )</td>
<td>34.8 ( (34.0-35.8) )</td>
<td>35.3 ( (34.6-35.9) )</td>
<td>0.06</td>
</tr>
<tr>
<td>Length of ICU stay (days), median (IQR)</td>
<td>5.0 ( (3.3-7.0) )</td>
<td>5.0 ( (4.0-8.0) )</td>
<td>5.0 ( (3.0-7.0) )</td>
<td>0.25</td>
</tr>
<tr>
<td>Outcome at 6 mo, ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>68 ( (53) )</td>
<td>30 ( (61) )</td>
<td>38 ( (48) )</td>
<td></td>
</tr>
<tr>
<td>Vegetative state</td>
<td>0 ( (0) )</td>
<td>0 ( (0) )</td>
<td>0 ( (0) )</td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>4 ( (3) )</td>
<td>3 ( (6) )</td>
<td>1 ( (1) )</td>
<td></td>
</tr>
<tr>
<td>Moderate disability</td>
<td>15 ( (12) )</td>
<td>7 ( (14) )</td>
<td>8 ( (10) )</td>
<td></td>
</tr>
<tr>
<td>Good recovery</td>
<td>38 ( (30) )</td>
<td>8 ( (16) )</td>
<td>30 ( (38) )</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 ( (2) )</td>
<td>1 ( (2) )</td>
<td>2 ( (3) )</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; IQR = interquartile range; OHCA = out-of-hospital cardiac arrest; VF = ventricular fibrillation; VT = ventricular tachycardia; APACHE II = Acute Physiology And Chronic Health Evaluation II; ICU = Intensive Care Unit
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**Table 2** Potential risk factors influencing outcome

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.03 (0.45-2.33)</td>
<td>0.95</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.01-1.08)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>IHCA</td>
<td>1.73 (0.65-4.60)</td>
<td>0.27</td>
</tr>
<tr>
<td>APACHE II</td>
<td>1.10 (1.05-1.16)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-VF/VT</td>
<td>15.12 (3.39-67.40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission</td>
<td>0.83 (0.62-1.10)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

OR = Odds ratio; CI = confidence interval; IHCA = In-hospital cardiac arrest; APACHE II = Acute Physiology and Chronic Health Evaluation II; VF = ventricular fibrillation; VT = ventricular tachycardia

**Table 3** Analysis of the influence of active rewarming

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active rewarming</td>
<td>2.14 (1.01-4.57)</td>
<td>0.048</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.74 (0.79-3.83)</td>
<td>0.17</td>
</tr>
<tr>
<td>Adjusted for age and VF/VT</td>
<td>1.51 (0.64-3.58)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

OR = Odds ratio; CI = confidence interval; VF = ventricular fibrillation; VT = ventricular tachycardia

The rewarming rate could not be calculated in 4 patients because of missing data. A high rewarming rate was present in 21/124 patients (17%), of whom 15 (71%) had a poor outcome and 1 patient was lost to follow-up. Of the 103 patients with a normal rewarming rate, 54 (52%) had a poor outcome and 2 patients were lost to follow-up. A high rewarming rate was not associated with a significant higher risk for poor outcome, OR 2.61 (0.88-7.73), p = 0.08. After adjustment for age and initial rhythm, the OR was 2.27 (0.69-7.46), p = 0.18. For mortality the OR was 2.29 (0.81-6.43), p = 0.12. After adjustment for age, the OR was 1.70 (0.58-4.96), p = 0.33.

Patients who needed active rewarming had a higher chance to have a high rewarming rate, as in total 17/21 patients (81%) with a high rewarming rate were patients who needed active rewarming, OR 9.9 (3.1-31.7), p < 0.001.
Almost half of the patients (47%) developed fever within 72 h after admission. In the passive rewarming group, significantly more patients developed fever compared with the active rewarming group, 55% versus 35%, respectively ($p = 0.03$). Development of fever within 72 h after admission was not associated with poor outcome (OR 0.64 (0.31-1.30), $p = 0.22$), as well as after adjustment for the confounders age, initial rhythm and APACHE II (OR 0.94 (0.40-2.17), $p = 0.88$). Fever was also not associated with mortality (OR was 0.63 (0.31-1.28), $p = 0.20$, after adjustment for the confounders the OR was 0.84 (0.36-1.96), $p = 0.69$). The median length of stay on the ICU was 5.0 days for patients with fever (IQR 4.0-8.0), as well as for patients without fever (IQR 3.0-7.0), $p = 0.17$.

**Discussion**

This study showed that patients who needed active rewarming after therapeutic hypothermia after CA did not have a higher risk for a poor outcome. Univariate analysis showed a significant effect of active rewarming on outcome, but this effect could be contributed to age and/or initial rhythm. In addition, neither speed of rewarming, nor development of fever had an effect on outcome. However, the number of patients who had a high rewarming rate was very small and robust conclusions on the effect of rapid rewarming cannot be drawn from our study. Similar results were found for mortality.

Treatment with therapeutic hypothermia is considered beneficial in patients after CA because induced hypothermia is associated with lower levels of proinflammatory cytokines and free radicals, reduced hyperexcitatory state, a lower cerebral metabolic rate, reduced permeability of the blood-brain barrier and anticoagulant effects$^{19}$. Furthermore, lower temperatures possibly decrease intracranial pressure$^{19,20}$. The hypothalamus is regarded to integrate and execute thermoregulatory responses to body or environment temperature changes. A structural lesion due to trauma, tumor or anoxia can lead to hypothermia$^{5,6}$. Failure to rewarm after hypothermia treatment spontaneously is often interpreted as a sign of extensive brain damage, but studies to confirm or reject this assumption are lacking. In our study, patients who needed active rewarming had a higher risk for poor outcome, but after adjustment for age or initial rhythm, there was no association left.

Patients who needed active rewarming in our study were significantly older compared to patients who rewarmed spontaneously. A possible explanation for this difference could be the altered thermoregulatory responses in older patients. The pathophysiology of this mechanism has not been fully elucidated, but reduced subcutaneous fat, peripheral vasoconstriction, cardiac output, and muscle mass are considered as contributors$^{21}$.
Clinical studies about the optimal rewarming rate in patients treated with hypothermia after cardiac arrest are lacking, but current consensus is to rewarm patients at a maximum rate of 0.25-0.5 °C/h\textsuperscript{3,4,7}. In experimental studies, rapid rewarming was associated with increased cerebral injury and cerebral metabolic rate\textsuperscript{22-25}. There are clinical studies about the effects of rewarming in patients with cardiac surgery, stroke or traumatic brain injury, but the pathophysiology is different from the patients with primary cardiac arrest. Grigore et al. prospectively investigated the effect of rewarming rate in 165 patients after treatment with deep hypothermia (28-32°C) during cardiac surgery, and found worsened cognitive outcome in the fast rewarming group after 6 weeks using a multivariable linear regression analysis\textsuperscript{26}. Other studies in patients who were treated with hypothermia after stroke or traumatic brain injury (TBI) showed that rewarming could cause an increase of intracranial pressure, but results for TBI patients are conflicting\textsuperscript{20,27-29}. We found a trend towards an association with poor outcome in patients who rewarmed at ≥ 0.5 °C/h, but the number of patients who had a high rewarming rate was very small and after adjustment for confounders (age and initial rhythm), the trend disappeared.

Another recommendation in the current guidelines is that hyperthermia or fever should be avoided\textsuperscript{3,4}. Beside infections, hyperthermia can be a symptom of cell damage in the anterior hypothalamus. Experimental studies showed increased cerebral injury in models of forebrain ischemia or asphyxia with hyperthermia\textsuperscript{8-10}. Important effects of fever are the induction of the inflammatory cascade and an increase of neuronal excitotoxicity with neurotransmitter release, free radical production, and increased intracellular glutamate concentrations\textsuperscript{30}. Previous studies in patients not treated with hypothermia after CA showed that the 20-83% developed fever within 24-72 h after admission\textsuperscript{11,13,14,16}. The definition of fever varied, but an association with poor outcome was found\textsuperscript{11,14-17}. Zeiner et al. found an OR of 2.26 for each degree Celsius higher than 37 °C for poor outcome\textsuperscript{15}. Diringer et al. found that an elevated body temperature was associated with 3.2 additional ICU days and 4.3 additional hospital days\textsuperscript{12}. In our study, almost half of the patients had a temperature above 38°C within the first 72 h after admission. Fever was not associated with poor outcome, nor with length of ICU stay. Length of hospital stay was not investigated.

In our study 56% of the patients had a poor outcome after 6 months, which is comparable with a large international prospective study of 975 patients of whom 54% had a poor outcome after 6-12 months\textsuperscript{31}. A recent multicenter prospective cohort study performed in the Netherlands found a poor outcome in 53% of the patients after 6 months\textsuperscript{32}. 
A limitation of this study is the retrospective design and data were collected from one hospital. Therefore, the findings of this study could not be applied without any restraint into daily clinical practice. Our local protocol stated that active rewarming was indicated when patients did not reach normal body temperature after 12 h of passive rewarming. This implicated that the active rewarming and passive rewarming groups were not equal. It would have been better if these groups could be defined and differed from the beginning. A prospective randomized study investigating the effects of the method of rewarming and treatment of fever would address to the study questions. Such a study would be quite a challenge as large numbers of patients and strict treatment protocols would be needed.

Another limitation is the number of patients included, especially the small number of patients with a high rewarming rate. This limits robust conclusions from this study due to a possible type II error.

Many questions remain about the optimal method of hypothermia treatment in patients after CA. Currently, the optimal target temperature is studied in the international multicenter Target Temperature Management Study (NCT01020916), which investigates whether controlled temperature of 36°C has a similar effect as a controlled temperature of 33°C. Further studies should investigate the best methodology and rate of rewarming, fever treatment, optimal sedation regimens and best methods to monitor patients during hypothermia treatment.

Conclusions

This study showed that patients who needed active rewarming after therapeutic hypothermia after CA did not have a higher risk for a poor outcome. In addition, our results suggested that neither speed of rewarming, nor development of fever had an effect on outcome.

References

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