Mild Resuscitative Hypothermia to Improve Neurological Outcome After Cardiac Arrest
A Clinical Feasibility Trial

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Background and Purpose—Recent animal studies showed that mild resuscitative hypothermia improves neurological outcome when applied after cardiac arrest. In a 3-year randomized, prospective, multicenter clinical trial, we hypothesized that mild resuscitative cerebral hypothermia (32°C to 34°C core temperature) would improve neurological outcome after cardiac arrest.

Methods—We lowered patients’ temperature after admission to the emergency department and continued cooling for at least 24 hours after arrest in conjunction with advanced cardiac life support. The cooling technique chosen was external head and total body cooling with a cooling device in conjunction with a blanket and a mattress. Infrared tympanic thermometry was monitored before a central pulmonary artery thermistor probe was inserted.

Results—In 27 patients (age 58 [interquartile range [IQR] 52 to 64] years; 7 women; estimated “no-flow” duration 6 [IQR 1 to 11] minutes and “low-flow” duration 15 [IQR 9 to 23] minutes; admitted to the emergency department 36 [IQR 24 to 43] minutes after return of spontaneous circulation), we could initiate cooling within 62 (IQR 41 to 75) minutes and achieve a pulmonary artery temperature of 33°C 287 (IQR 42 to 401) minutes after cardiac arrest. During 24 hours of mild resuscitative hypothermia, no major complications occurred. Passive rewarming >35°C was accomplished within 7 hours.

Conclusions—Mild resuscitative hypothermia in patients is feasible and safe. A clinical multicenter trial might prove that mild hypothermia is a useful method of cerebral resuscitation after global ischemic states. (Stroke. 2000;31:86-94.)

Key Words: cardiopulmonary resuscitation ■ heart arrest ■ hypothermia ■ outcome

The pathophysiological mechanisms responsible for damage of brain microvasculature and parenchyma before, during, and after resuscitation are multiple. Current cardiac arrest therapy focuses on manual artificial circulation combined with chemical and electrical therapy to restore spontaneous circulation initiating reperfusion. Reoxygenation, although essential and effective in restoring energy charge, also might provoke deleterious chemical cascades. The generation of free radicals in concert with other mediators creates the tissue milieu responsible for the postresuscitation syndrome, which governs the pattern, extent, and onset of multifocal necrosis.

The ability of tissue to survive anoxic no-flow states is drastically reduced in normothermia compared with hypothermia. Hypothermia is “a state of body temperature which is below normal in a homeothermic organism.” Accidental hypothermia is nontherapeutically altered body temperature associated with particular complications and requiring specific treatments. The efficacy of hypothermia in preserving neurological function when instituted before and during certain no-flow cardiovascular states has been well documented both clinically and experimentally in dog outcome models since the 1950s. Recently, mild hypothermia (34°C) was discovered to mitigate brain damage significantly when induced before, during, or after cardiac arrest.

A recently initiated European multicenter trial aims to investigate the effect of mild resuscitative hypothermia for a duration of 24 hours on cerebral recovery in humans after...
cardiac arrest. A preliminary trial was conducted to evaluate safety and feasibility of mild resuscitative hypothermia after cardiac arrest.16,17

Subjects and Methods

This study was approved by the University Hospital Institutional Review Board for Human Research. The study was conducted in accordance with the Declaration of Helsinki and in accordance with all applicable Austrian regulations and standards, including BSI standard EN 540 Clinical Investigation of Medical Devices for Human Subjects, Annex 7, and Annex X of the European Community Medical Device Directive. Prospective informed consent was waived for all patients based on section II.5 of the Declaration of Helsinki. The following specific reasons support waiver of consent in this investigation. The human subject is confronted with a life-threatening situation that necessitates the immediate use of the test treatment. Informed consent cannot be obtained from the subject because of an inability to communicate with or obtain legally effective consent from the subject. Time is insufficient to obtain informed consent from the subject’s legal representative. There is no alternative method of approved or generally recognized therapy available that provides equal or greater likelihood of saving the life of the subject. However, as soon as possible, an extensive informed consent document that encompassed mild resuscitative hypothermia, as well as several related procedures, and research data collection was presented to the patients and/or families and/or their legal representatives.

Patients

From April 1995 to January 1996 prospectively, we analyzed Utstein-style18 collected data of consecutive patients admitted to the Department of Emergency Medicine at the University Hospital after prehospital cardiac arrest. Included were adults with witnessed, nontraumatic, normothermic cardiac arrest of presumed cardiac origin. To exclude the influence of the initial rhythm on patient’s medical management and outcome,19–21 we focused on patients with ventricular fibrillation as the initial ECG pattern recorded by the emergency medical team in the field. Cardiac arrest was defined as the absence of both spontaneous respiration and palpable pulses. Patients were excluded if the duration of cardiac arrest was <5 or >15 minutes and if primary cardiopulmonary resuscitation failed to achieve any return of spontaneous circulation within 60 minutes. Any return of spontaneous circulation was defined as the appearance of a palpable arterial pulse for >5 minutes. Furthermore, we excluded patients with known malignancy, pregnancy, and unfavorable overall or cerebral performance before cardiac arrest,22–24 those with evidence of additional ischemic damage (prolonged [>30 minutes] hypotension [mean arterial pressure <60 mm Hg] or prolonged [>15 minutes] hypoxia [oxygen saturation <0.85]) to the brain before the experimental therapy was initiated, and those who had an additional cardiac arrest within 6 months after the primary event.

The interval from the time of collapse (presumed time of cardiac arrest) to 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 or termination of resuscitative efforts was termed low-flow duration. Data were obtained through interviews with the ambulance physicians, paramedics, bystanders, and families. The recording of periods of time during cardiac arrest is an estimate and cannot be quantified accurately. Owing to the fact that only 1 person was responsible for collecting the patients’ charts according to the Utstein style of collecting data,18 highly accurate data were available for every patient. Because witnesses were personally interviewed, impression surrounding the exact time of recognition of collapse and the accurate time of the emergency medical activation was minimized.

General Management

Acute care included basic and advanced cardiac life support performed by the ambulance service personnel or in-hospital emergency medical technicians and physicians per standard protocol.1 In the emergency department, after initial neurological evaluation and assessment of respiratory and hemodynamic function, the patient was provided with standardized treatment as described below. Eligibility for the study was assessed as soon as possible at the hospital. Standard medical management of all patients required Foley catheters, arterial catheters, central venous catheters, and intubation. Sedation and analgesia were performed with midazolam and fentanyl, titrated for 32 hours to facilitate respiratory management and to avoid stress induced by invasive procedures. Relaxation was done by neuromuscular blockade with pancuronium for 32 hours. The lowest dose that would permit complete muscle relaxation was used. Neuromuscular relaxants are essential to maintain hypothermia and to prevent shivering with a subsequent rise in the systemic and cerebral metabolic rates.25,26 Ventilators were set to maintain an arterial oxygen saturation of >0.95 with PaO2 between 100 and 150 mm Hg and PaCO2 between 40 and 45 mm Hg. Arterial pH was kept between 7.37 and 7.45 by use of a-stat management (temperature-uncorrected PaO2 and pH).7,27 Positive end-expiratory pressure <5 mm Hg was used carefully to reduce FiO2. Mean arterial blood pressure was kept >60 mm Hg, and decreases in systemic blood pressure were treated primarily with crystalloid fluids or hydroxyl ethyl starch. Vasopressors such as epinephrine, norepinephrine, and dopamine, and dobutamine were used if sufficient blood pressure control could not be achieved with fluids alone. Fluid balance was controlled; neither dextrose nor free water was given, to avoid generation of cerebral edema. To minimize hyperglycemia, no glucose was used in intravenous fluids. Serum blood glucose was kept between 5.5 and 11.1 mmol/L (100 and 200 mg/dL) and hematocrit between 0.30 and 0.45. Potassium was supplemented if the serum potassium level was <4 mmol/L. Thrombolytic therapy was given as indicated. Parenteral nutrition or enteric feeding was begun as soon as practical. Maintenance of fluid and electrolyte homeostasis was a standard requirement, and monitoring was performed either by pulmonary artery catheterization or by evaluation of fluid intake and output. Optimal head position (30°) was provided, and movements of the head were done carefully to avoid too much torsion and flexion of the neck. Laboratory studies were performed as clinically indicated. Brain death was determined and certified according to legally and ethically accepted methods.29 Life support was maintained for ≥3 days in all except certified brain-dead patients. In all patients who responded to pain in any manner, life support was maintained for ≥7 days.

Temperature Management and Cooling Procedures

The target temperature was a core temperature of 33±1°C, which was defined as mild resuscitative hypothermia and which has shown benefit in former and recent prospective, randomized, controlled human trials.30–33 This low core temperature was achieved by external head and body cooling. Through a water-circulating system (Plastipads, Cincinnati Sub-Zero Products, Inc), fluid flowed through the blankets and the temperature-controlling device (Blanketrol II Hypothermia System, Cincinnati Sub-Zero Products, Inc). The blankets were placed within a special mattress consisting of air cushions (TheraKair, Kinetic Concepts, Inc), which avoided direct patient contact with the blankets. Air, which was now temperature controlled by the blankets, flowed in alternating cushions to avoid constant cooling of one part of the patient’s body, eg, a skin segment. In addition, head and body cooling was performed with a lightweight mattress with tiny holes (Polar Bair, Augustin Medical, Inc) and constant cold air flow (Polar Bair, Augustin Medical, Inc). Active cooling was started immediately on arrival of the patient at the emergency department by placing the patient on the precooled mattress. Active cooling was stopped 24 hours after arrival in the emergency department. The period of 24 hours was thought to be a compromise of minimum time needed to achieve a benefit34,35 and maximum time tolerated for possible side effects.36 No active external rewarming procedures were performed. Temperature was primarily monitored and controlled with intermittent infrared tympanic thermometry measurements (Ototemp
LighTouch, Exergen Corporation). LighTouch models accurately measure arterial temperature via heat balance at the ear (AHBE method), providing reproducible measurements for immediate verification of both temperature and user technique. After placement of a pulmonary artery catheter (Edwards Swan-Ganz VIP catheter, Baxter Healthcare Corporation), core temperature was measured continuously. Additional temperature probes were placed in the esophagus (Mon-a-therm general purpose, 12F, Mallinckrodt Medical Inc) and in the bladder (Thermistor-tipped urinary catheter, Metronic Electronics Inc). 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.37 Potential adverse effects of hypothermia,36 such as abnormal bleeding, hemodynamic instability, arrhythmias, electrolyte disturbances, infectious diseases, and renal failure, have been recorded.

Cardiovascular Monitoring
For cardiovascular monitoring, catheters were placed in the radial artery, the pulmonary artery, and a central vein as soon as possible. Arterial, pulmonary, and central venous pressure were displayed on a multichannel monitor (HP series 600 monitor, product No. M-1166A, Hewlett-Packard). Hemodynamic parameters, such as cardiac output and pulmonary arterial wedge pressure, were measured intermittently based on hemodynamic needs but at least every 6 hours with a Swan-Ganz catheter (Baxter Healthcare Corporation). Simultaneously, blood gas samples were taken. Cardiac index, systemic vascular resistance index, and pulmonary vascular resistance index were calculated.38 Transducers (Baxter pressure monitoring kit, Bentley Laboratories Europe BV) were positioned at the level of the midaxillary line. These transducers were set at zero to atmosphere and calibrated against a mercury manometer. Continuous tracings, such as ECG, \( \text{SaO}_2 \), \( P_{E T C O_2} \), pressures, and temperatures, were displayed on a multichannel monitor (HP series 600 monitor, Hewlett-Packard) and as analog readout (HP series No. J11 with 8-channel analog output option, Hewlett-Packard). The analog output function card provided 8 channels of analog output for connection to the data acquisition system, Deweport 2000 (Dewetron GesmbH).39 Both wave and numeric output were supported. An interface cable that met the specifications of Hewlett-Packard (resistance of 1 conductor <60 mΩ/m, capacity of 1 conductor with other wires grounded <400 pF/m) was used. With this analog output, the most important hemodynamic variables were recorded. All data sampling was computer controlled, and data processing was done on a portable workstation with integrated signal amplifiers, 16-bit precision A/D conversion, and Pentium microprocessor, combined in 1 instrument, and the data analysis software Dasylab40 (version 2; Data Acquisition System; Dasytec). Typically, the data consisted of 5-minute recordings. All data were time correlated (time-shift correction of the Hewlett-Packard monitor), calibrated, and simultaneously sampled with gap-free 128 Hz on each channel to an internal high-speed SCSI hard disk.

Neurological Evaluation
Cerebral function was assessed prospectively on arrival and at regular intervals during the 6 months following return of spontaneous circulation. The method, which is based on the Glasgow outcome performance categories,42 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, certified brain death or dead by traditional criteria. The best CPC score achieved between 3 days and within 6 months was used for calculation. A CPC score of 1 or 2 was considered good, whereas a CPC score of 3 or 4 was rated as poor functional neurological outcome. In agreement with the Utstein style,18 neither long-dated neuropsychological data, imaging data, or EEG data were used for outcome evaluation.

Statistical Analysis
According to the Utstein style, data are expressed as median and interquartile range (IQR).45 Laboratory data and hemodynamic parameters are measured as median and 95% CI. A nonoverlapping of the ranges was considered statistically significant (\( P \) value <0.05). Percentages were determined for dichotomous variables.43 Temperature measurement in the pulmonary artery (\( T_p \)) was considered a “gold standard” and was compared with the temperature measured in the esophagus (\( T_e \)) and the temperature measured in the urinary bladder (\( T_b \)). Agreement between the 2 methods was assessed according to a method described by Bland and Altmann.44 All data were computed with Microsoft Excel for Windows, version 5.0, and SPSS for Windows, version 6.0.

Results
Patients
Within an observation period of 9 months, 31 of 153 cardiac arrest patients were treated with mild resuscitative hypothermia. Four patients had to be excluded from analysis: 2 had asystole as the first diagnosed rhythm, cooling was terminated in 1 patient after 10 hours because of acute hemorrhage due to liver rupture, and 1 patient could not be cooled sufficiently because the cooling mattress was not used appropriately.

General Management
The median age of the remaining 27 patients was 58 (IQR 52 to 64) years, with a median body surface area of 1.91 (IQR 1.86 to 2.04) m\(^2\). Seven patients (26%) were female. In all patients, cardiac arrest occurred out of hospital.

Bystander basic life support was performed in only 10 patients (37%). The no-flow duration was 6 (IQR 1 to 11) minutes; the low-flow duration was 15 (IQR 9 to 23) minutes. For return of spontaneous circulation, 3 (IQR 2 to 6) countershocks were needed, and the median cumulative amount of epinephrine administered intravenously during cardiopulmonary resuscitation was 6 (IQR 3 to 7) mg.

Patients arrived in the emergency department 36 (IQR 24 to 43) minutes after return of spontaneous circulation. In the emergency department, initial neurological evaluation without any sedation showed a Glasgow Coma Scale score of 3 and good respiratory (\( \text{PaO}_2 \geq 335 \) [IQR 212 to 461] mm Hg) and hemodynamic (mean arterial pressure 84 [IQR 74 to 95] mm Hg) function. Eligibility was assessed within 3 minutes.

During the first 24 hours after admission, midazolam 0.2 (0.16 to 0.23) mg ⋅ kg\(^{-1}\) ⋅ h\(^{-1}\) and fentanyl 0.003 (0.003 to 0.004) mg ⋅ kg\(^{-1}\) ⋅ h\(^{-1}\) were needed, and pancuronium 0.02 (0.01 to 0.02) mg/kg was given hourly. Arterial oxygen saturation was maintained at >0.95, PaO\(_2\) between 104 (IQR 91 to 118) and 90 (IQR 80 to 102) mm Hg, and Paco\(_2\) between 39 (IQR 35 to 41) and 34 (IQR 32 to 37) mm Hg. To maintain arterial blood pressure >60 mm Hg, crystalloids (292 [IQR 244 to 406] mL/h) were needed during the first 24 hours. Hydroxyl ethyl starch was not required. All patients had a positive fluid balance of 3280 (IQR 2160 to 4930) mL and a urine output of 167 (IQR 82 to 264) mL/h within the first 24 hours. Despite this positive fluid balance, the pulmonary arterial wedge pressure and the ratio of PaO\(_2\) to FiO\(_2\) did not show a change toward a fluid overload. Adult respiratory distress syndrome was not found in the patients who required
prolonged mechanical ventilation. Epinephrine was needed in 8 patients and norepinephrine in 6; dopamine was administered in 25 patients and dobutamine in 22. Thrombolytic therapy was given to 1 patient.

Serum blood glucose was between 14.9 and 6.9 mmol/L (269 and 125 mg/dL) and hemoglobin between 144 and 120 g/L (14.4 and 12.0 g/dL) within the cooling period (Table 1). At admission, arterial pH was 7.28 (IQR 7.19 to 7.35) and was maintained between 7.42 and 7.40 until rewarming (Table 1). Base excess (extracellular fluid) and pH showed a tendency toward normal values within the first 4 hours and showed stable normal values during cooling and rewarming (Table 1). Serum lactate decreased from 8.6 (IQR 6.5 to 11.0) mmol/L on arrival at the emergency department to 1.6 (IQR 1.3 to 4.70) mmol/L 12 hours thereafter, showed a further decrease during the cooling period, and was 1.6 (IQR 0.8 to 3.0) mmol/L after rewarming (Table 1). Potassium levels were between 3.7 and 4.2 mmol/L (Table 1). Renal function (creatinine and blood urea nitrogen), together with diuresis, was not impaired (Table 1). None of the patients needed hemofiltration owing to oliguric renal failure. Complications such as sepsis, coagulopathy, neutropenia, or thrombocytopenia (Table 1) and frostbite on the skin did not occur in any patient.

There were no deaths during the time of resuscitative mild hypothermia. In 2 patients, the cooling procedure was terminated after 14 hours because of hemodynamic instability. During the hospital stay, 3 patients died of heart failure. Therapy was withdrawn in 8 patients when prognosis was considered hopeless, eg, brain death was diagnosed.

**Temperature Management and Cooling Procedures**

On arrival at the emergency department, the patients had a temperature of 35.3°C (IQR 34.9°C to 36.0°C), and active cooling was started within 5 minutes. The surface temperature of the precooled mattress was 4°C. The target temperature was reached within 4 (IQR 3 to 5) hours after start of the external active cooling procedure. Active cooling was performed for 24 hours. The core temperature was >35°C within 7 hours after termination of active cooling (Figure).

The mean bias between $T_p$ and $T_E$ was 0.1°C (IQR 0.1°C to 0.2°C), the upper limit of agreement was 0.8°C, and the lower limit of agreement was −0.6°C. The mean bias between $T_p$ and $T_B$ was −0.1°C (−0.2°C to −0.1°C), the upper limit of agreement was 0.8°C, and the lower limit of agreement was −1°C.

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**TABLE 1. Blood Chemical Values, Hematologic and Coagulation Values, and Arterial Blood Gas Values Uncorrected for Temperature**

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>12 h</th>
<th>24 h</th>
<th>36 h</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood chemical values</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>3.8 (3.5–3.9)</td>
<td>3.7 (3.5–3.8)</td>
<td>3.7 (3.6–4.0)</td>
<td>4.2 (3.9–4.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>139 (138–139)</td>
<td>141 (139–141)</td>
<td>139 (138–142)</td>
<td>139 (135–142)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>122 (113–116)</td>
<td>101 (66–112)</td>
<td>73 (60–97)</td>
<td>83 (73–88)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urea nitrogen, mmol/L</td>
<td>7.0 (5.8–7.9)</td>
<td>7.0 (5.4–9.7)</td>
<td>5.7 (4.5–8.2)</td>
<td>4.8 (3.3–6.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Total bilirubin, μmol/L</td>
<td>10 (7–14)</td>
<td>15 (9–27)</td>
<td>16 (11–34)</td>
<td>15 (7–18)</td>
<td>NS</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>53 (30–88)</td>
<td>77 (51–125)</td>
<td>72 (32–98)</td>
<td>55 (24–126)</td>
<td>NS</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>53 (35–73)</td>
<td>52 (35–78)</td>
<td>38 (35–58)</td>
<td>37 (26–102)</td>
<td>NS</td>
</tr>
<tr>
<td>Amylase, U/L</td>
<td>87 (80–118)</td>
<td>138 (76–423)</td>
<td>190 (45–397)</td>
<td>187 (48–362)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipase, U/L</td>
<td>82 (66–124)</td>
<td>35 (18–63)</td>
<td>35 (10–234)</td>
<td>33 (10–109)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>14.9 (11.8–17.8)</td>
<td>8.7 (6.6–10.4)</td>
<td>6.9 (6.6–10.3)</td>
<td>7.1 (6.6–10.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.05 (0.05–0.05)</td>
<td>0.85 (0.05–1.2)</td>
<td>4.59 (3.22–5.40)</td>
<td>9.28 (7.54–11.80)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>8.6 (6.5–11.0)</td>
<td>1.60 (1.3–3.9)</td>
<td>1.8 (1.0–4.7)</td>
<td>1.6 (0.8–3.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Hematologic and coagulation values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White-cell count, G/L</td>
<td>13.4 (11.9–14.9)</td>
<td>11.2 (8.7–16.0)</td>
<td>8.0 (6.4–11.4)</td>
<td>7.2 (6.2–1.32)</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count, G/L</td>
<td>227 (211–300)</td>
<td>182 (134–235)</td>
<td>157 (118–100)</td>
<td>157 (125–178)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>144 (138–148)</td>
<td>133 (123–141)</td>
<td>129 (114–133)</td>
<td>120 (114–135)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.1 (2.6–3.6)</td>
<td>3.2 (2.8–3.7)</td>
<td>3.5 (3.0–3.6)</td>
<td>4.0 (2.4–4.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>0.79 (0.51–0.99)</td>
<td>0.56 (0.24–0.79)</td>
<td>0.57 (0.16–0.77)</td>
<td>0.54 (0.07–0.66)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Arterial-blood gas values uncorrected for temperature</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.28 (7.19–7.35)</td>
<td>7.42 (7.34–7.45)</td>
<td>7.38 (7.34–7.44)</td>
<td>7.40 (7.36–7.44)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>335 (212–461)</td>
<td>104 (91–118)</td>
<td>89 (83–95)</td>
<td>90 (80–102)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Base excess (extracellular fluid), mmol/L</td>
<td>−8.30 (−13.40 to −4.70)</td>
<td>−3.50 (−4.10 to −0.30)</td>
<td>−1.55 (−2.70 to −1.00)</td>
<td>0.00 (−2.70–1.40)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are median (95% CI). n=27.

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Cardiovascular Monitoring

Arrhythmias occurred in 7 patients. There were 11 short episodes of ventricular fibrillation and 6 of ventricular tachycardia. In 1 of these patients, the cooling procedure was terminated after 16 hours because of recurrent ventricular fibrillation. Mean arterial pressure decreased slightly, but mean pulmonary pressure and pulmonary artery wedge pressure did not change (Table 2) during the first 24 hours. The initial cardiac index on arrival in the emergency department was 2.6 (1.9 to 3.2) L \cdot \text{min}^{-1} \cdot \text{m}^{-2} and decreased slightly within the next 4 hours during the initial cooling period. At the end of cooling, cardiac index increased again and showed a further increase to 3.1 (IQR 2.4 to 3.6) L \cdot \text{min}^{-1} \cdot \text{m}^{-2} at normothermia. The systemic vascular resistance index was 2379 (1512 to 3035) dyne \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2} on admission and rose within the first 4 hours of cooling. Thereafter, it

Serial changes of the temperature of the cooling mattress (A) and of the core temperature measured in the pulmonary artery (B), the esophagus (C), and the urinary bladder (D) from admission (0 hours) until 36 hours after arrival in the emergency department. Data are shown as median and IQR.

### TABLE 2. Hemodynamic and Oxygenation Parameters

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Reaching Target Temperature (4 ± 3 h)</th>
<th>End of Cooling (24 ± 1 h)</th>
<th>Reaching Temperature ≥35°C (30 ± 3 h)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>106 (88–124)</td>
<td>80 (73–90)</td>
<td>81 (67–84)</td>
<td>94 (80–105)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>84 (74–95)</td>
<td>84 (81–93)</td>
<td>76 (70–84)</td>
<td>76 (66–80)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>26 (17–27)</td>
<td>26 (21–33)</td>
<td>25 (22–27)</td>
<td>28 (25–34)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure, mm Hg</td>
<td>15 (12–20)</td>
<td>17 (13–21)</td>
<td>16 (15–18)</td>
<td>16 (12–19)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index, L \cdot \text{min}^{-1} \cdot \text{m}^{-2}</td>
<td>2.6 (1.9–3.2)</td>
<td>2.3 (1.7–2.9)</td>
<td>2.7 (2.0–3.0)</td>
<td>3.1 (2.4–3.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}</td>
<td>2379 (1512–3035)</td>
<td>2652 (1951–3436)</td>
<td>1805 (1387–2493)</td>
<td>1460 (1164–1732)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, dyne \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}</td>
<td>244 (180–379)</td>
<td>332 (229–436)</td>
<td>237 (182–321)</td>
<td>265 (202–344)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Oxygenation parameters**

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Reaching Target Temperature (4 ± 3 h)</th>
<th>End of Cooling (24 ± 1 h)</th>
<th>Reaching Temperature ≥35°C (30 ± 3 h)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen delivery index, mL \cdot \text{min}^{-1} \cdot \text{m}^{-2}</td>
<td>503 (379–665)</td>
<td>482 (353–691)</td>
<td>455 (397–653)</td>
<td>473 (423–636)</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen consumption index, mL \cdot \text{min}^{-1} \cdot \text{m}^{-2}</td>
<td>94 (72–139)</td>
<td>87 (76–93)</td>
<td>79 (73–107)</td>
<td>100 (63–159)</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen availability, mL/min</td>
<td>1150 (750–1379)</td>
<td>942 (696–1375)</td>
<td>898 (790–1273)</td>
<td>933 (878–1255)</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen extraction ration, %</td>
<td>0.2 (0.16–0.23)</td>
<td>0.2 (0.13–0.23)</td>
<td>0.19 (0.15–0.22)</td>
<td>0.22 (0.13–0.26)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are median (95% CI). n=27.
decreased to 1805 (1387 to 2493) dyne \cdot s \cdot cm^{-2} \cdot m^{-2} and showed a further decrease in the following rewarming period to 1460 (1164 to 1732) dyne \cdot s \cdot cm^{-2} \cdot m^{-2}. These changes were not significant, although a trend could be seen (Table 2).

**Neurological Evaluation**

Clinical seizures occurred in none of the patients. Fourteen patients had a CPC score of 1 or 2, considered a good outcome, and 2 patients had a CPC score of 3 or 4, rated as a poor functional neurological outcome. Eleven patients died before a neurological evaluation could be performed.

**Discussion**

This pilot trial assessing mild resuscitative hypothermia after cardiac arrest\(^{16,17}\) showed that it was safe and feasible to mildly cool patients after ventricular fibrillation cardiac arrest.

Surface cooling was initiated within 62 (IQR 41 to 75) minutes after cardiac arrest. The target temperature (33 ± 1°C) was reached after 287 (IQR 242 to 401) minutes and was maintained for an additional 24 hours. Thereafter, patients were passively rewarmed and reached a temperature >35°C after 7 hours. The outcome was measured at 6 months, with the CPC score subdivided into good outcome (CPC 1 or 2), poor outcome (CPC 3 or 4), or death. After 6 months, good neurological recovery was achieved by 14 patients (52%), 2 (7%) had poor neurological recovery, and 11 (41%) died. Compared with historic controls in our department, this represents a 2-fold improvement in outcome. There were no major complications that could be directly related to treatment with mild hypothermia. Similar results were obtained by Bernard et al\(^{30}\) and Yanagawa et al.\(^{31}\) Both studies showed significant improvement in outcome in comatose survivors of out-of-hospital cardiac arrest with cooling for 12 hours\(^{30}\) or 48 hours.\(^{31}\) The latter study\(^{31}\) showed an increase in pneumonic complications.

To date, Benson et al\(^{32}\) and Williams and Spencer\(^{33}\) have published preliminary experience with the use of moderate resuscitative hypothermia in patients resuscitated from cardiac arrest. However, no other publications have followed these promising reports. Historic, dubious experiments during the 1940s, alternative therapies that were thought to be more effective, and concerns regarding possible complications, including arrhythmias, coagulopathy, and pulmonary infection, discouraged further experimentation or application of resuscitative hypothermia until moderate resuscitative hypothermia after cardiac arrest was evaluated in the 1980s by Gisvold et al\(^{45}\) in monkeys and by Leonov et al\(^{14}\) in dogs, showing a less impressive benefit than the subsequent series of dog studies with mild resuscitative hypothermia.\(^{15}\) These showed highly significant benefit in a reproducible manner.

Hypothermia is a state of body temperature below normal in a homeothermic organism. In contrast to accidental hypothermia, hypothermia used, for example, with cardiopulmonary bypass, neurosurgery, or cardiac arrest is administered in a controlled way. Hypothermia is graded into 4 levels\(^{46}\): mild (34°C to 36°C), moderate (28°C to 33°C), deep (17°C to 27°C), and profound (4°C to 16°C).\(^{5}\)

Hypothermia has been used for several years with certain surgical procedures and circulatory arrest states. Clinical and experimental results showed a pronounced protective effect of hypothermia during specific ischemic states.\(^{90–12}\) It is also well established that postischemic hypothermia reduces the amount of cell death in certain brain regions.\(^{47–50}\) Recent studies have demonstrated a minimum duration and therapeutic window of mild hypothermia of ≥ 3 hours when applied within the first 30 minutes after onset of ischemia.\(^{51}\) A later start of hypothermia could also accomplish a benefit, because there is evidence that the postischemic damage process lasts for several days.\(^{52,53}\)

In the last several years, various laboratory cerebral outcome studies have been performed to investigate hypothermia initiated after an ischemic state. Sterz et al\(^{15}\) presented a dog model of cardiac arrest in which mild hypothermia (33.3 ± 0.6°C) initiated immediately after return of spontaneous circulation demonstrated a significant improvement in neurological outcome. In that study, the core body temperature was lowered by means of cold-water (4°C) head cooling and nasal irrigation in combination with air convection cooling by a fan and blanket. The target temperature was reached within 30 minutes after return of spontaneous circulation and was maintained for 90 minutes, with passive return to normal values 4 hours after return of spontaneous circulation. Investigating the long-term effect of delayed, postischemic mild to moderate hypothermia (24 hours with a delay of 1 hour) in a gerbil model of 5-minute forebrain ischemia, Colbourne and Corbett\(^{34}\) showed 70% CA1 protection compared with normothermic controls after 6 months. Although this was a significant (90%) reduction in 30-day survival, it showed for the first time a persistent, if not permanent, neuroprotection due to postischemic hypothermia. Yanamoto et al\(^{19}\) only saw a trend toward reduction of the infarct volume in a model of 3-hour transient focal ischemia in rats with a mild hypothermia duration of 21 hours and a delay of 30 minutes. Possibly, the ischemic time was too long to determine any benefit under hypothermic conditions. There is considerable evidence that resuscitative hypothermia has maximum benefit when applied immediately after any return of spontaneous circulation. In a study by Kuboyama et al\(^{54}\) using a ventricular fibrillation cardiac arrest dog model, the benefit of mild resuscitative cerebral hypothermia was diminished if not induced immediately with reperfusion after cardiac arrest. A delay of 15 minutes in initiation of cooling after reperfusion may not improve functional outcome, although it may slightly decrease tissue damage. In contrast, several other studies\(^{34,51,55–59}\) have suggested a benefit of delayed resuscitative hypothermia. Baker et al\(^{60}\) showed that in the setting of permanent middle cerebral artery occlusion, hypothermia markedly decreases brain injury even when its induction is delayed for up to 1 hour after the onset of ischemia.

Former and recent prospective, randomized, controlled human trials have suggested a benefit of mild resuscitative hypothermia in seriously injured patients.\(^{61}\) Traumatic brain injury,\(^{62–65}\) and adult respiratory distress syndrome.\(^{66}\) A study on traumatic brain injury treated with mild hypothermia demon-
strated an improvement of outcome at 3 and 6 months in patients with primary Glasgow Coma Scale scores of 5 to 7.67

There have been several cooling techniques suggested for clinical use, including ice bags, blankets containing circulating coolant, cold carotid artery infusions,86 single carotid artery perfusion with extracorporeally cooled blood,69 a helmet with chemical cooling capabilities,70 a cooling cap filled with −3°C solution,71 ice-water nasal lavage,72 cardio-pulmonary bypass,14 and cold peritoneal lavage.73 Most of these methods are quite invasive and carry the potential of dermal injuries or other complications; therefore, we chose a rather unusual surface cooling method. We used external head cooling with a blanket Bair Hugger and systemic external cooling by means of a Blanketrol II in conjunction with a specially designed TheraKai mattress.16,17 With this setup, we could reach a target core (pulmonary artery) temperature of 33 ± 1°C within 287 (IQR 242 to 401) minutes after cardiac arrest. This temperature was maintained for 24 hours, and the patients were passively rewarmed over another 7 hours. The TheraKai mattress had the advantage of additional kinetic therapy and thus prevented injury to the skin. This setup of cooling via blankets plus air blowing (4°C) was in the beginning the only available method to achieve the best effect of surface cooling by convection and conduction. This was rather complicated and not as effective as desired; however, it avoided an initial increase of temperature, which could have had a therapeutic effect.70 Earlier initiation of cooling would lead to a better outcome. Even so, we think it was justified to pursue delayed cooling, then let patients get warm.74 In addition, this first use of this new cooling technique should give the manufacturer the opportunity and motivation to construct a simpler cooler using noninvasive but effective cooling techniques. In the future, we will use a system of external cooling with cold air by means of a modified TheraKai mattress and body blankets supplied by a single integrated air source.

A wide variety of methods of temperature measurement (brain temperature via ventricular catheter, tympanic probe, esophageal probe, rectal probe, or Swan-Ganz catheter) are available. Brain temperature may be dissociated from systemic temperature by 0.2°C to 1°C, although differences are usually small.75 Measurement of tympanic temperature, irrespective of brain temperature, has the advantage of being noninvasive, fast, and easily applicable and therefore has been used routinely to fulfill the eligibility criteria. Because the purpose of this trial was to investigate the effect of mild resuscitative hypothermia, no major effort was made to compare different temperature-monitoring methods. As soon as possible, Swan-Ganz catheter measurements were taken instead of tympanic temperature, because they are more reliable under surface cooling conditions. In addition, we showed that the temperature course at different body sites (pulmonary artery, esophagus, and bladder) showed no major differences.

There are concerns about potential adverse effects of hypothermia.37 There have been reports of an association between hypothermia, trauma, and abnormal bleeding.76 Hypothermia prolongs prothrombin and partial thromboplastin times77 and also has an adverse effect on platelet function.78 In the present study, no significant bleeding complications and no influence on major coagulation parameters due to mild resuscitative hypothermia were found. One patient excluded from analysis was found to have liver rupture due to traumatic injury within the scope of incorrect external chest compressions performed during basic life support by bystanders. Another patient, who received thrombolytic therapy, developed small hematomas on the right upper extremity due to numerous unsuccessful venipuncture attempts.

The impact of hypothermia on the cardiovascular system is discussed controversially. There are concerns that resuscitative hypothermia may cause hemodynamic instability after resuscitation from cardiac arrest, because many of these patients have myocardial ischemia. Sinus bradycardia is common; however, junctional bradycardia and atrial fibrillation with a slow ventricular response rate may be seen when the temperature drops to 30°C. Ventricular irritability and fibrillation are increasingly common below 25°C to 28°C.5,70 However, if the core temperature is kept above 30°C, there is little risk of significant bradycardia or ventricular fibrillation due to hypothermia.81 In 1 of our patients with malignant arrhythmias, the attending physician decided to stop cooling after 16 hours. However, the patient continued to have arrhythmogenic hemodynamic instability after normothermia had been achieved. Hypokalemia, which commonly occurs as core temperature decreases, results from the movement of potassium into cells and may worsen the arrhythmogenic effect.82 However, hypokalemia was not seen in our patients. Cardiac contractility, measured in a variety of ways, increases until temperature reaches ~25°C.79 Thus, stroke volume may increase and cardiac output may be maintained.83 On the other hand, some have reported decreased ejection fraction and cardiac output, particularly with hypothermic times of 10 to 24 hours or more.84 Because of an increase in systemic vascular resistance,16,85 blood pressure is little affected. It was not necessary to stop cooling because of hemodynamic effects of mild resuscitative hypothermia in any of our patients. Several authors have commented on an increased incidence of neutropenia, septicemia, and pneumonia in children with anoxic brain injury after near drowning86 and in head-injured patients treated with hypothermia.87 This may reflect inhibition of neutrophile release or other factors.88 None of our patients developed infectious diseases, eg, sepsis syndrome. Moderate hypothermia is known to increase urine output despite decreased renal blood flow, due to decreased solute reabsorption.89 In all of our patients, we observed an increased need for volume replacement due to high urinary output during the cooling period.

In conclusion, mild resuscitative hypothermia in patients after cardiac arrest is feasible, and it is expected that a clinical multicenter trial will prove that it may be a useful method of cerebral resuscitation after global ischemic states and therefore promote the prevention of neuromental diseases.

Appendix

Additional members of the HACA Study Group were as follows: Erga Cerchiari, MD, Centrale Operativa SSUEm Milano 1, 1° Servizio di Anestesia e Rianimazione, Ospedale Niguarda Ca’Gamba, Milano, Italy; Patrick Martens, MD, Department Anesthesie en Kritische Zorgen, A.Z. Sint-Jan van het OCMW, Brugge.
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References


Mild Resuscitative Hypothermia to Improve Neurological Outcome After Cardiac Arrest: A Clinical Feasibility Trial
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