Hypothermia Therapy After Pediatric Cardiac Arrest

Dermot R. Doherty, MB BCh, FCARCSI; Christopher S. Parshuram, MB ChB, PhD; Isabelle Gaboury, MSc; Aparna Hoskote, MD, MRCP; Jacques Lacroix, MD, FRCP; Marisa Tucci, MD, FRCP; Ari Joffe, MD, FRCP; Karen Choong, MD, FRCP; Rosemarie Farrell, MSc; Desmond J. Bohn, MB BCh, FRCP; James S. Hutchison, MD, FRCP; on Behalf of the Canadian Critical Care Trials Group

Background—Hypothermia therapy improves mortality and functional outcome after cardiac arrest and birth asphyxia in adults and newborns. The effect of hypothermia therapy in infants and children with cardiac arrest is unknown.

Methods and Results—A 2-year, retrospective, 5-center study was conducted, and 222 patients with cardiac arrest were identified. Seventy-nine (35.6%) of these patients met eligibility criteria for the study (age >40 weeks postconception and <18 years, cardiac arrest >3 minutes in duration, survival for ≥12 hours after return of circulation, and no birth asphyxia). Twenty-nine (36.7%) of these 79 patients received hypothermia therapy and were cooled to 33.7±1.3°C for 20.8±11.9 hours. Hypothermia therapy was associated with higher mortality (P=0.009), greater duration of cardiac arrest (P=0.005), more resuscitative interventions (P<0.001), higher postresuscitation lactate levels (P<0.001), and use of extracorporeal membrane oxygenation (P<0.001). When adjustment was made for duration of cardiac arrest, use of extracorporeal membrane oxygenation, and propensity scores by use of a logistic regression model, no statistically significant differences in mortality were found (P=0.502) between patients treated with hypothermia therapy and those treated with normothermia. Also, no differences in hypothermia-related adverse events were found between groups.

Conclusions—Hypothermia therapy was used in resuscitation scenarios that are associated with greater risk of poor outcome. In an adjusted analysis, the effectiveness of hypothermia therapy was neither supported nor refuted. A randomized controlled trial is needed to rigorously evaluate the benefits and harms of hypothermia therapy after pediatric cardiac arrest. (Circulation. 2009;119:1492-1500.)

Key Words: heart arrest ■ pediatrics ■ cerebral ischemia

Despite relative success in the initial resuscitation from pediatric cardiac arrest, with >60% of victims having return of circulation, the 1-year survival rate of children after cardiac arrest remains poor (<35%).1–5 Hypoxic-ischemic encephalopathy is the most important cause of morbidity and mortality after resuscitation, and its severity is affected by cardiac arrest duration and resuscitation effectiveness.5,6,7 Evidence exists of neurological insult in nearly half of all patients after successful resuscitation.7 Hypothermia therapy holds promise as a neuroprotective treatment after cardiac arrest, and its use is supported by strong basic scientific evidence over the last 15 years.8–14 On the basis of the results of randomized trials, the use of hypothermia therapy in survivors of adult cardiac arrest has been recommended in cardiac arrest treatment guidelines.15–17 Hypothermia therapy has also been reported to reduce the risk of death and disability in neonates with moderate hypoxic-ischemic encephalopathy.18,19 The lim-

Received May 8, 2008; accepted December 8, 2008.

From the Department of Anaesthesia, Division of Pediatric Intensive Care (D.R.D.), Children’s Hospital of Eastern Ontario and University of Ottawa, Ottawa, Ontario, Canada; Department of Critical Care Medicine, The Hospital for Sick Children and Interdepartmental Division of Critical Care Medicine, University of Toronto (D.R.D., C.S.P., R.F., D.J.B., J.S.H.), Toronto, Ontario, Canada; Department of Anaesthesia (D.R.D., D.J.B.), The Hospital for Sick Children, Toronto, Ontario, Canada; Chalmers Research Group (I.G.), Children’s Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada; Cardiac Intensive Care Unit (A.H.), Great Ormond Street Hospital for Children, NHS Trust and the Institute of Child Health, London, United Kingdom; CHU mère-enfant Sainte-Justine (J.L., M.T.), Pediatric Intensive Care Division, Department of Pediatrics, Montréal, Québec, Canada; University of Alberta and Department of Pediatrics, Division of Pediatric Intensive Care (A.J.), Stollery Children’s Hospital, Edmonton, Alberta, Canada; Department of Pediatrics, Division of Pediatric Critical Care (K.C.), McMaster Children’s Hospital, Hamilton, Ontario, Canada; and Neuroscience and Mental Health Research Program (J.S.H.), Hospital for Sick Children Research Institute, Toronto, Ontario, Canada.


The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.108.791384/DC1.

Correspondence to James S. Hutchison, Department of Critical Care Medicine, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada MSG 1X8. E-mail jamie.hutchison@sickkids.ca

© 2009 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.108.791384

1492
We hypothesized that hypothermia therapy would be associated with improved outcomes after cardiac arrest. Our objectives were to determine the effect of hypothermia therapy on mortality and functional outcome and to describe any adverse effects of hypothermia therapy.

**Methods**

**Study Design**

A retrospective observational study was done and reported with modifications of the Utstein template. The study protocol was developed with critical appraisal by the Canadian Critical Care Trials Group. Four university-affiliated tertiary pediatric institutions in Canada and 1 in the United Kingdom participated in the study (The Hospital for Sick Children, Toronto, Ontario, Canada; McMaster Hospital, Hamilton, Ontario, Canada; Hôpital Sainte-Justine, Montreal, Quebec, Canada; Stollery Children’s Hospital, Edmonton, Alberta, Canada; and Great Ormond Street Children’s Hospital, London, United Kingdom). Research ethics committees approved the study at each center.

**Patient Selection**

Each participating center searched *International Classification of Diseases, 9th Revision* codes and institutional databases, including Pediatric Intensive Care Unit Evaluations, cardiac arrest, code blue, extracorporeal membrane oxygenation (ECMO), and death databases. The databases were searched from September 1, 2001, through August 31, 2003, for all patients admitted to the hospital who experienced an out-of-hospital or in-hospital cardiac arrest. The pediatric Utstein style was used to define and time events that related to the cardiac arrest. We included patients who had survived a cardiac arrest of sufficient duration to potentially cause a hypoxic-ischemic brain injury and who survived long enough after cardiac arrest for hypothermia therapy to be used. The inclusion criteria were as follows: Patients >40 weeks postconceptional age and <18 years of age; cardiac arrest of at least 3 minutes duration; survival for at least 12 hours after return of spontaneous circulation (or the commencement of rescue ECMO flow); and admission to the intensive care unit after resuscitation. We excluded patients if adequate data could not be extracted from the chart. We also excluded neonates admitted to the neonatal intensive care unit directly from the delivery room with a diagnosis of birth asphyxia, because this population has been studied previously.

**Data Collection**

A case report form and a procedures manual were developed and pretested at The Hospital for Sick Children before implementation at the other centers. Research assistants at each institution were trained with regard to definitions relating to cardiac arrest, “good clinical practice” for case report form completion, and the scoring of outcome measurements before data collection. The following information was abstracted for all patients: Demographics, prearrest medical history, cause of arrest, duration and location of arrest, first-monitored rhythm during arrest, interventions performed during resuscitation, postresuscitative variables (physiological and supportive therapy), interventions performed to control temperature, complications, and outcomes.

Patients were divided into 2 groups, hypothermia therapy and normothermia. The hypothermia therapy group was defined a priori as all patients who were cooled to a temperature of ≤35°C within 6 hours of cardiac arrest for a continuous period of at least 12 hours. This definition was based on reports from laboratory studies and a prospective study in adult humans. All other patients were considered as having received normothermia.

**Outcomes**

Mortality at 6 months was the primary outcome. Mortality at 30 days was also recorded. Other outcomes included the following: (1) Pediatric Cerebral Performance Category (PCPC) score assessed at 6 months after cardiac arrest; (2) when the PCPC assessment was possible before cardiac arrest, the ΔPCPC at 6 months was calculated; (3) duration of mechanical ventilation; (4) length of stay in the intensive care unit; (5) length of stay at an acute-care hospital (tertiary care facility); (6) multorgan dysfunction scores and pediatric logistic organ dysfunction scores recorded for 3 days; and (7) data on hypothermia-related adverse events (eg, infections, bleeding or thrombosis, and arrhythmias), recorded for 14 days after cardiac arrest. The decision to cool was recorded, as well as the cooling method(s), time to target temperature, and duration of cooling.

**Data Management and Analysis**

Patient characteristics for each study group are represented as descriptive statistics (unless otherwise noted), mean and SD, or median and interquartile range (IQR). Proportions were compared with χ² tests (or Fisher exact test where appropriate). Temperature and blood pressure were compared between study groups with a linear mixed-effects model, including a fixed effect for time and an interaction term between time and study group. The admission pediatric logistic organ dysfunction score was compared between study groups with Student *t* test. Continuous variables with a skewed distribution were compared between study groups with Mann-Whitney tests. Differences between groups in the numbers of resuscitation drug doses were assessed with Poisson regression models.

Propensity scores were calculated to match case subjects with control subjects by use of a logistic regression model that included age group, primary cause of arrest, arresting rhythm, location of cardiac arrest (in or out of the hospital), duration of cardiac arrest, interventions performed during resuscitation (doses of epinephrine, atropine, calcium, and bicarbonate), and use of ECMO as covariates. The effect of hypothermia therapy on survival at 30 days and 6 months, as well as functional outcome (PCPC score 1 to 3 versus 4 to 6), was assessed with multivariate logistic regression models, adjusted for duration of cardiac arrest and use of ECMO (because these variables have been reported to modify the outcomes), as well as propensity score.

We also analyzed several important subgroups. We compared mortality between the hypothermia therapy and normothermia groups in patients with a primary cardiac cause of their cardiac arrest and in those who died unexpectedly versus expectedly in the regression models. We compared mortality in the out-of-hospital and in-hospital cardiac arrest cases across all 5 centers and in the centers that did and did not use hypothermia therapy. We also described covariables and mortality in the subgroup of patients who were overcooled to <32°C, because overcooling has been associated with worse outcome. Duration of cardiac arrest (from the time of onset of cardiac arrest until return of spontaneous circulation or start of ECMO flow), ventilator days, days in the pediatric intensive care unit, and hospital stay were compared with time-to-event analyses (log-rank test or Breslow test where appropriate).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Results

Patient Characteristics

Within the 2-year time period of the study (September 1, 2001, until August 31, 2003), 222 patients were identified with a cardiac arrest from the databases at the 5 study hospitals (Figure 1). Seventy-nine (35.6%) of these 222 patients met the study entry criteria. The cause of cardiac arrest was cardiac in 55 cases, respiratory in 16, cardiorespiratory in 7 (6 cases of septic shock and 1 case of severe pulmonary hemorrhage), and unknown in 1. Twenty-nine (36.7%) of these 79 patients met our a priori definition of receiving hypothermia therapy. The remaining 50 patients (63.3%) were assigned to the control (normothermia) group.

Four of the 5 hospitals included in the study had pediatric cardiovascular surgery programs. Three of the 5 hospitals had rescue ECMO programs for resuscitation
from cardiac arrest. Demographic factors are shown in Table 1. The majority of the 79 patients included had a chronic illness before the cardiac arrest.

Variables During Resuscitation
Duration of cardiac arrest was a median of 19.5 minutes (range 3 to 109 minutes). The duration of cardiac arrest in the hypothermia therapy group (median 30 minutes, IQR 22.75 to 42 minutes) was longer than in the normothermia group (median 10 minutes, IQR 5 to 29.5 minutes, \(P=0.002\)). The hypothermia therapy group also received more interventions (single-bolus doses) during resuscitation, including epinephrine (\(P=0.006\), atropine, (\(P=0.076\)), sodium bicarbonate (\(P<0.001\)), and calcium (\(P=0.009\); Figure 1) and had a higher serum lactate reading immediately after resuscitation than patients in the normothermia group (median 16.2 versus 7.5 mmol/L, \(P<0.001\); Figure 1). The use of ECMO was also more frequent in the hypothermia therapy group (79.3%) than in the normothermia group (20.4%; \(P<0.001\)). Patients in the hypothermia therapy group also had significantly higher admission pediatric logistic organ dysfunction scores (33.33±11.74) than the normothermia group (22.34±12.14, \(P<0.001\)) which suggests a greater severity of illness before the arrest and resuscitation.

## Temperature Data
Temperature data are shown in Figure 2. A “decision to cool” was documented in 30 (38.0%) of 79 patients; however, 5 of these patients did not reach the target temperature for long enough or within the timeframe to fulfill our a priori definition of hypothermia therapy. An additional 4 patients received hypothermia therapy by our definition, even though no clinical plan was documented in the chart to use therapeutic cooling. The mean temperature for patients receiving hypothermia therapy was 33.7±1.3°C, and the mean duration of hypothermia therapy was 20.8±11.9 hours (range 12 to 69 hours). Temperature within the first 12 hours after cardiac arrest was significantly lower in the hypothermia therapy group than in the normothermia group (\(P<0.001\); Table 1). Hyperthermia was prevented in both groups as recommended by the current International Liaison Committee on Resuscitation guidelines,21 with 8 (16%) of 50 patients in the normothermia group recorded as receiving interventions to control temperature, by use of the temperature control device if the patient was placed on ECMO or active surface cooling in patients not on ECMO. Finally, significant variation was found in the use of hypothermia therapy between reporting centers (\(P=0.004\)), with 2 of 5 centers having no patient treated with hypothermia therapy.

## Mortality
Mortality (unadjusted) was higher at 6 months in the hypothermia therapy group (69.0%) than in the normothermia group (38.0%; odds ratio [OR] 3.62, 95% confidence interval [CI] 1.37 to 9.62, \(P=0.009\); Table 2). The association between hypothermia therapy and mortality declined and lost statistical significance when we adjusted for duration of cardiac arrest, use of ECMO, and propensity score (adjusted OR 1.99, 95% CI 0.45 to 8.85, \(P=0.502\); Table 2). The 30-day mortality rate (unadjusted) was higher in the hypothermia therapy group (58.6%) than in the normothermia group (36.0%), but this did not reach

---

### Table 1. Demographics Before Cardiac Arrest

<table>
<thead>
<tr>
<th></th>
<th>Normothermia (n=50)</th>
<th>Hypothermia Therapy (n=29)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23 (46.0)</td>
<td>16 (55.2)</td>
<td>0.640</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>0–12 mo</td>
<td>22 (44.0)</td>
<td>22 (75.9)</td>
<td></td>
</tr>
<tr>
<td>1–18 y</td>
<td>28 (56.0)</td>
<td>7 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Chronic diagnosis</td>
<td>45 (84.0)</td>
<td>22 (81.5)</td>
<td>0.308</td>
</tr>
<tr>
<td>Cardiac</td>
<td>37 (88.1)</td>
<td>19 (86.4)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (4.8)</td>
<td>2 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>3 (7.1)</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>&lt;14 Days after surgery</td>
<td>28 (56.0)</td>
<td>19 (65.5)</td>
<td>0.480</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>21 (75.0)</td>
<td>17 (89.5)</td>
<td></td>
</tr>
<tr>
<td>Other surgery</td>
<td>7 (25.0)</td>
<td>2 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Place of cardiac arrest</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Out-of-hospital</td>
<td>3 (6.0)</td>
<td>1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>In-hospital (all)</td>
<td>47 (94.0)</td>
<td>28 (96.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>PICU</td>
<td>28 (59.6)</td>
<td>19 (67.9)</td>
<td></td>
</tr>
<tr>
<td>Ward areas</td>
<td>9 (19.1)</td>
<td>3 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>4 (8.5)</td>
<td>1 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operating room</td>
<td>3 (6.4)</td>
<td>2 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>1 (2.1)</td>
<td>2 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.1)</td>
<td>1 (3.6)</td>
<td></td>
</tr>
<tr>
<td>PACU</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Cause of cardiac arrest</td>
<td></td>
<td></td>
<td>0.835</td>
</tr>
<tr>
<td>Cardiac</td>
<td>34 (68.0)</td>
<td>21 (72.4)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>11 (22.0)</td>
<td>5 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Cardiorespiratory</td>
<td>4 (8.0)</td>
<td>3 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arresting rhythm</td>
<td></td>
<td></td>
<td>0.227</td>
</tr>
<tr>
<td>Asystole/bradycardia</td>
<td>30 (60.0)</td>
<td>24 (82.8)</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachyarrhythm</td>
<td>11 (22.0)</td>
<td>2 (6.9)</td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>3 (6.0)</td>
<td>1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (12.0)</td>
<td>2 (6.9)</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac arrest indicates the index cardiac arrest; PICU, pediatric intensive care unit; PACU, post–anesthesia care unit; and PEA, pulseless electrical activity.

All data are expressed as n (%).

*Other: neurological=1, genetic=1, renal=1.
For patients who had solely a cardiac origin of their cardiac arrest, after the removal of those patients who had either a respiratory or cardiorespiratory cause of their cardiac arrest from the analysis, no difference was found in mortality (unadjusted and adjusted) between the hypothermia and normothermia groups. Among those patients who died, no statistical difference was found between the 2 treatment groups in the number of patients who died unexpectedly at 6 months (deaths without do-not-resuscitate orders in place) or those whose deaths were expected (individuals with do-not-resuscitate orders placed, or those from whom life-sustaining supports were withdrawn; Figure 1; \( P = 0.731 \)).

The mortality rate was 100% in patients with an out-of-hospital cardiac arrest and 46.7% in patients with an in-hospital cardiac arrest. Survival was inversely associated with duration of cardiac arrest, with a median duration of 29 minutes in nonsurvivors and 10 minutes in survivors \( ( P = 0.001 ) \). Mortality rates at 6 months varied between 24% and 100% across the 5 study centers \( ( P = 0.023 ) \).

When the regression models were run on the subsample of patients coming from the 3 of 5 centers where hypothermia therapy was used, mortality (unadjusted) was found to be significantly higher in the hypothermia group than in the normothermia group \( ( P = 0.019 ) \). The difference did not remain significant once the model was adjusted for duration of cardiac arrest, use of ECMO, and propensity score \( ( P = 0.197 ) \).

For normothermia patients, mortality in the 2 centers that did not use hypothermia therapy was 6 (60%) of 10 patients, whereas mortality in the sites that used hypothermia therapy was 13 (32.5%) of 40 patients, but this difference was not statistically significant \( ( P = 0.150 ) \).

**Functional and Other Outcomes**

The proportion of patients with an unfavorable outcome (PCPC of 4 to 6) at 6 months after cardiac arrest was higher in the hypothermia therapy group (unadjusted OR 2.92, 95% CI 1.10 to 7.69, \( P = 0.031 \); Table 2). When we adjusted for duration of cardiac arrest, use of ECMO, and propensity score \( ( P = 0.197 ) \). For normothermia patients, mortality in the 2 centers that did not use hypothermia therapy was 6 (60%) of 10 patients, whereas mortality in the sites that used hypothermia therapy was 13 (32.5%) of 40 patients, but this difference was not statistically significant \( ( P = 0.150 ) \).
Hypothermia-Related Adverse Events

The multiorgan dysfunction score was higher in the hypothermia therapy group on the first 3 days after cardiac arrest ($P=0.004$, $P=0.011$, and $P<0.001$ for day 1, 2, and 3, respectively; Figure 2). Mean arterial blood pressure was recorded for up to 72 hours after cardiac arrest. Data were analyzed by age group, and blood pressure was found to be significantly lower in the hypothermia therapy group in patients 1 to 12 months of age ($P=0.002$) and patients 1 to 18 years of age ($P=0.017$). No difference in blood pressure was found between groups for patients 1 to 4 weeks of age ($P=0.343$).

Five (17.2%) of the 29 hypothermia therapy patients were overcooled to $32^\circ C$. The duration of cardiac arrest in these 5 patients ranged from 12 to 79 minutes, postresuscitation lactate levels ranged from 13.4 to 35 mmol/L, and pediatric logistic organ dysfunction scores range from 22 to 52. Three of these 5 patients died. No statistically significant differences were found between the hypothermia therapy and normothermia groups in infectious complications or other hypothermia-related adverse events for 14 days after return of circulation (Table 3). Normothermic patients were more likely to receive nitroprusside than hypothermia therapy patients (56.0% versus 27.6%) on day 1 ($P=0.019$). No other differences were found for other inotropic supports (dopamine, epinephrine, or norepinephrine) or use of a phosphodiesterase inhibitor (milrinone) for 3 days after cardiac arrest (data not shown).

Table 2. Mortality and Functional Outcome

<table>
<thead>
<tr>
<th></th>
<th>Normothermia (n=50)</th>
<th>Hypothermia Therapy (n=29)</th>
<th>Unadjusted OR (95% CI)</th>
<th>$P$</th>
<th>Adjusted OR (95% CI)</th>
<th>Adjusted $P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-d Mortality</td>
<td>18 (36.0)</td>
<td>17 (58.6)</td>
<td>2.52 (0.99–6.45)</td>
<td>0.054</td>
<td>2.50 (0.55–11.49)</td>
<td>0.238</td>
</tr>
<tr>
<td>6-mo Mortality</td>
<td>19 (38.0)</td>
<td>20 (69.0)</td>
<td>3.62 (1.37–9.62)</td>
<td>0.009</td>
<td>1.99 (0.45–8.85)</td>
<td>0.502</td>
</tr>
</tbody>
</table>

PCPC before cardiac arrest

1–3 45 (90.0) 21 (72.4) 2.92 (1.10–7.69) 0.031 2.00 (0.45–9.01) 0.364

4–6 5 (10.0) 8 (27.6) 1.000 1.000

PCPC after cardiac arrest

1–3 29 (58.0) 9 (32.1) 1.000 1.000

4–6 21 (42.0) 19 (67.9) 1.000 1.000

All data are expressed as n (%).

Table 3. Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Normothermia (n=50)</th>
<th>Hypothermia Therapy (n=29)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac tachyarrhythmia</td>
<td>9 (18.0)</td>
<td>5 (17.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ventricular</td>
<td>7 (14.0)</td>
<td>4 (13.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Supraventricular</td>
<td>2 (4.0)</td>
<td>1 (3.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Subsequent cardiac arrest</td>
<td>13 (26.0)</td>
<td>2 (6.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>17 (34.0)</td>
<td>9 (31.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Clinically significant infection</td>
<td>11 (22.0)</td>
<td>6 (20.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (12.0)</td>
<td>7 (24.1)</td>
<td>0.211</td>
</tr>
<tr>
<td>Septicemia</td>
<td>1 (2.0)</td>
<td>2 (6.9)</td>
<td>0.551</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4 (8.0)</td>
<td>2 (6.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Wound</td>
<td>16 (32.0)</td>
<td>14 (48.3)</td>
<td>0.141</td>
</tr>
<tr>
<td>Renal replacement</td>
<td>8 (16.0)</td>
<td>2 (6.9)</td>
<td>0.316</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Arterial occlusion</td>
<td>1 (2.0)</td>
<td>1 (3.4)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Therapeutic hypothermia was used more often in infants than in older children, and admission pediatric logistic organ dysfunction scores were higher than in the normothermia group. Many intrarresuscitation and postresuscitation variables were associated with the use of hypothermia therapy, which included longer durations of cardiac arrest, more pharmacological interventions during resuscitation, greater postresuscitation lactic acid levels, higher multiorgan dysfunction scores, and more renal replacement therapies. These factors are known to be associated with worse outcome in

Discussion

We report the use of hypothermia therapy after cardiac arrest in a cohort of pediatric patients from 5 university-affiliated centers. Hypothermia therapy was used after cardiac arrest in one third of these patients and in 3 of 5 study centers, and its use was associated with higher mortality and worse functional outcome than with normothermia. However, when regression modeling was used to adjust for duration of cardiac arrest, use of ECMO, and propensity scores, hypothermia therapy no longer had a statistically significant adverse impact on survival or functional outcome. The majority of patients in the present study, 75 (94.9%) of 79, had in-hospital cardiac arrests.
cardiac arrest and may explain the worse outcome in the hypothermia therapy group.1,32–34 A greater proportion of patients in the hypothermia therapy group received ECMO. However, no statistical difference was found between the 2 groups relative to hypothermia-related adverse effects or use of inotropes. Also, no statistically significant differences were found in the median duration of days ventilated, pediatric intensive care unit days, or days spent in the hospital among survivors.

The American Heart Association and the International Liaison Committee on Resuscitation recommend that hypothermia therapy (32°C to 34°C for 12 to 24 hours) should be considered if the child remains comatose after resuscitation.21 This recommendation was extrapolated from adult data by an expert panel.20 Previous experience with therapeutic hypothermia in pediatrics apart from intraoperative hypothermia for congenital cardiac surgery is limited. Hypothermia (<32°C) on admission after ice-water near drowning has been associated with intact survival, but hypothermia therapy combined with hyperventilation and barbiturate coma was associated with a high rate of infectious complications with no clear improvement in outcome after near drowning.35,36 In the present study, during hypothermia therapy, patients were cooled to varying temperature ranges and for varying durations. Patients were also rewarmed at varying rates. Five of 29 patients were overcooled to <32°C, and this has been associated with adverse outcomes.31 Rewarming too rapidly after hypothermia therapy has also been associated with hypotension and with increased mortality after traumatic brain injury in children.37 It is clear that centers in the present study were not using guidelines for hypothermia therapy and re war ming. We recommend that guidelines for cooling and rewar ming be used in the future to decrease variability in care and improve patient safety.38 Hyperthermia is common after return of spontaneous circulation and is associated with increased mortality.39 In the patients enrolled in the present study, hyperthermia was actively prevented as recommended by the current International Liaison Committee on Resuscitation guidelines.21 Therapeutic hypothermia has been reported to be safe in neonates after birth asphyxia.18,19,40–42 Whole-body hypothermia therapy has been shown to reduce the risk of death and disability in subgroups of infants after moderate to severe ischemic encephalopathy.18,19 One explanation for the different findings of the present study from other reports in adults and newborns is that pediatric patients with cardiac arrest are not a homogenous population. In the adult studies, patients were resuscitated after ventricular tachyarrhythmia, whereas the neonatal studies describe another relatively homogenous population with birth asphyxia. In-hospital pediatric patients with cardiac arrest often have chronic diseases, and usually, they have an insidious physiological deterioration that leads to cardiac arrest, which may affect the patient’s overall outcome.43,44

A recent survey of pediatric intensivists reported that many physicians were aware of the adult therapeutic hypothermia literature. Thirty-eight percent occasionally used hypothermia therapy and 9% always used hypothermia therapy after pediatric cardiac arrest.45 In the present study, use of hypothermia therapy for cardiac arrests was also variable across study sites, with 2 of 5 centers not using hypothermia therapy.

The present study has some limitations, such as its retrospective design. Our conclusion that no difference in outcome was found between the 2 intervention groups in the adjusted analysis might reflect a lack of statistical power. Given a mortality rate of ≈40% in the normothermia group, we would need 165 patients in each of the hypothermia therapy and normothermia groups to detect an OR of 2.0 with 80% power and a 2-sided α=0.05. Although we found no increase in adverse events associated with the use of hypothermia therapy, adverse event rates are typically underestimated in retrospective studies, because they are not recorded sometimes. Wide variability in resuscitation outcome was found among the 5 contributing centers. The subgroups varied in type of arrest and treatment, and these variations may have had substantial effects on outcome. The conclusions should be interpreted with caution in light of the heterogeneity of the patients and their treatment.

In conclusion, hypothermia therapy was associated with a worse mortality and functional outcome, but the association was lost when the analysis was adjusted for duration of cardiac arrest, ECMO, and propensity scores. No difference was found between the groups in adverse events for 14 days after return of circulation. The present study strongly supports the need for randomized controlled clinical trials before therapeutic hypothermia becomes a standard of care after resuscitation from pediatric cardiac arrest.

Acknowledgments
We thank Rose Gaiteiro, the study research coordinator, and the research assistants at the study sites.

Sources of Funding
This study was supported by The Hospital for Sick Children Foundation seed grant No. 27 and the Heart and Stroke Foundation of Ontario grant No. NAS360. Dr Doherty was supported by an Ontario Ministry of Health Trauma Fellowship.

Disclosures
None.

References
Hypothermia After Pediatric Cardiac Arrest


Hypothermia therapy is currently recommended for the treatment of ventricular arrhythmia–induced cardiac arrest in adults. Very few data exist on the use of hypothermia therapy in children with cardiac arrest. We report factors associated with the use of hypothermia therapy in 79 children who survived for ≥12 hours after return of circulation after cardiac arrest. Approximately one third of these patients were treated with hypothermia therapy of at least 12 hours’ duration. Clinicians were more likely to use hypothermia therapy in children with a more prolonged cardiac arrest or when extracorporeal membrane oxygenation was used as part of the resuscitation. When controlling for the duration of cardiac arrest and use of extracorporeal membrane oxygenation in a regression analysis, hypothermia therapy was not associated with improved or worsened mortality or neurological outcome. Randomized controlled trials are urgently needed to assess the risks and benefits of hypothermia therapy in children with cardiac arrest before strong recommendations can be made.
Hypothermia Therapy After Pediatric Cardiac Arrest
Dermot R. Doherty, Christopher S. Parshuram, Isabelle Gaboury, Aparna Hoskote, Jacques Lacroix, Marisa Tucci, Ari Joffe, Karen Choong, Rosemarie Farrell, Desmond J. Bohn and 
James S. Hutchison
on Behalf of the Canadian Critical Care Trials Group

Circulation. 2009;119:1492-1500; originally published online March 9, 2009;
doi: 10.1161/CIRCULATIONAHA.108.791384
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/119/11/1492

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2009/03/09/CIRCULATIONAHA.108.791384.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/
Supplemental Material

Methods and Results

A secondary objective of our study was to determine if the use of hypothermia therapy in pediatric patients with cardiac arrest increased following the publication of 2 randomized controlled trials of hypothermia therapy following ventricular arrhythmia-induced cardiac arrest in adults. These landmark studies were published in the same issue of the New England Journal of Medicine in February, 2002.(1,2) Our retrospective study assessed use of hypothermia therapy for 6 months before and for 18 months after the publication of these studies. We found no difference in the rate of use of hypothermia therapy in pediatric patients before and after publication of these 2 studies (Appendix Figure).


Appendix figure legend: Cumulative plot of pediatric patients with cardiac arrest that were treated with hypothermia therapy or normothermia in 5 children’s hospitals. The dotted line represents the month of publication of 2 studies demonstrating the efficacy of hypothermia therapy in adults with cardiac arrest.