Published in final edited form as:

Pediatr Crit Care Med. 2010 January ; 11(1): 66–74. doi:10.1097/PCC.0b013e3181c58237.

A tertiary care center's experience with therapeutic hypothermia after pediatric cardiac arrest

Ericka L. Fink, MD, Robert S. B. Clark, MD, Patrick M. Kochanek, MD, Michael J. Bell, MD, and R. Scott Watson, MD, MPH

Department of Critical Care Medicine (ELF, RSBC, PMK, MJB, RSW), the Safar Center for Resuscitation Research (ELF, RSBC, PMK, MJB), and Clinical Research, Investigation, the Systems Modeling of Acute Illness (CRISMA) Laboratory (RSW), University of Pittsburgh School of Medicine, and the Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, PA.

Abstract

Objective—To describe the use and feasibility of therapeutic hypothermia after pediatric cardiac arrest.

Design—Retrospective cohort study.

Setting—Pediatric tertiary care university hospital.

Patients—Infants and children (age 1 wk to 21 yrs) without complex congenital heart disease with return of spontaneous circulation after in-hospital or out-of-hospital cardiac arrest from 2000 to 2006.

Intervention—None.

Measurements and Main Results—We studied 181 patients after cardiac arrest, of which 91% were asphyxial in etiology (vs. cardiac) and 52% occurred in-hospital. Overall survival to hospital discharge was 45%. Forty patients received therapeutic hypothermia; all were admitted during or after 2002. Sixty percent of patients in the therapeutic hypothermia group had an initial temperature <35°C. The median therapeutic hypothermia target temperature was 34.0°C (33.5–34.8°C), was reached by 7 hrs (5–8 hrs) after admission in patients who were not hypothermic on admission, and was maintained for 24 hrs (16–48 hrs). Re-warming lasted 6 hrs (5–8 hrs). In the therapeutic hypothermia group, temperature <32°C occurred in 15% of patients and was associated with higher hospital mortality (29% vs. 11%; $p = .02$). Patients treated with therapeutic hypothermia differed from those treated with standard therapy, with more un-witnessed cardiac arrest ($p = .04$), more doses of epinephrine to achieve return of spontaneous circulation ($p = .03$), and a trend toward more out-of-hospital cardiac arrests ($p = .11$). After arrest, therapeutic hypothermia patients received more frequent electrolyte supplementation ($p < .05$). Standard therapy patients were twice as likely as therapeutic hypothermia patients to have a fever (>38°C) after arrest (37% vs. 18%; $p = .02$) and trended toward a higher rate of re-arrest (26% vs. 13%; $p = .09$). Rates of red blood cell transfusions, infection, and arrhythmias were similar between groups. There was no difference in hospital mortality (55.0% therapeutic hypothermia vs. 55.3% standard therapy; $p = 1.0$), and 78% of the therapeutic hypothermia survivors were discharged home (vs. 68% of the standard therapy survivors; $p = .46$). In multivariate analysis, mortality was

independently associated with initial hypoglycemia or hyperglycemia, number of doses of epinephrine during resuscitation, asphyxial etiology, and longer duration of cardiopulmonary resuscitation, but not treatment group (odds ratio for mortality in the therapeutic hypothermia group, 0.47; $p = .2$).

Conclusions—This is the largest study reported on the use of therapeutic mild hypothermia in pediatric cardiac arrest to date. We found that therapeutic hypothermia was feasible, with target temperature achieved in <3 hrs overall. Temperature below target range was associated with increased mortality. Prospective study is urgently needed to determine the efficacy of therapeutic hypothermia in pediatric patients after cardiac arrest.

Keywords

brain injury; cardiopulmonary resuscitation; cardiac arrest; pediatric; outcome

Although cardiac arrest (CA) in infants and children in North America is uncommon, outcomes are dismal. Survival to hospital discharge after out-of-hospital CA is 2% to 28% and is 14% to 42% after in-hospital CA. Many survivors have severe neurologic disability (1–8).

In experimental models of cerebral ischemia-reperfusion injury and CA, hypothermia (HT) mitigated alterations in the cellular environment, namely excitotoxicity, calcium flux, cell signaling, inflammation, free radical and edema formation, apoptosis, and necrosis (9–13). Randomized controlled trials have shown mild (32°C–34°C) HT to be effective in improving neurologic outcome after arrhythmia-induced adult CA and birth asphyxia (14–17). Despite potential complications of HT (e.g., arrhythmias, coagulopathy, and infection), there was no increase in adverse events compared to normothermic control patients (18,19).

No therapy has been shown to improve outcome for pediatric patients after CA, in which the primary etiology is asphyxia (4). Asphyxia is associated with poorer outcomes than arrhythmia-induced CA and has a distinct pathophysiology (20, 21). Nearly 30 yrs ago, Conn et al (22) proposed HYPER therapy as a cerebral resuscitation strategy after return of spontaneous circulation (ROSC) for drowned children, which included moderate HT (30°C), diuretics, hyperventilation (PaCO₂ 30 torr), steroids, phenobarbital (target serum level 50–75 mg/L), neuromuscular blockade, intracranial pressure monitoring, and intracranial pressure-directed therapy. This regimen excluding steroids was retrospectively shown to be associated with neutropenia and increased risk of bacteremia without improving outcome, leading to discontinuation of HT and intracranial pressure-directed therapy in these patients (23).

Contemporary models of global asphyxial CA in prepubertal and adult animals have demonstrated robust neurologic benefits using mild HT, but clinical studies are lacking (13, 24–27). Specifically, studies are needed evaluating the feasibility, safety, and efficacy of mild HT in children, and the National Institutes of Health is supporting a multicenter, randomized, controlled trials investigating therapeutic HT after pediatric CA, which began enrolling subjects in September 2009 later last year (personal communication, Frank Moler, MD, MS; 28).

In 2002, after the publication of two adult HT randomized, controlled trials (14, 15), pediatric critical care physicians at our institution began cooling selected patients who were comatose after CA. Here, we describe our center's experience with the use of HT in children surviving CA.

MATERIALS AND METHODS

Design and Setting

This study was approved by the University of Pittsburgh Institutional Review Board. We performed a retrospective chart review of patients who had in-hospital or out-of hospital CA between July 1, 2000 and August 31, 2006, and were admitted to the pediatric intensive care unit (ICU) at the Children's Hospital of Pittsburgh. Children's Hospital of Pittsburgh is a tertiary care and level I trauma center with > 13,000 admissions per year. The multidisciplinary pediatric ICU has approximately 2400 admissions per year. The cardiac ICU is a separate unit, and the hospital does not have a burn unit. HT was used at the discretion of the attending physician. We had no protocol for its use.

Inclusion and Exclusion Criteria

We studied infants and children 1 wk to 21 yrs of age admitted to the ICU with ROSC after CA. CA was defined as receipt of chest compressions for pulselessness as determined by a health care worker. We excluded children with congenital heart disease. Subjects were identified by searching the ICU quality-assurance database for an International Classification of Diseases-9 discharge diagnosis of CA (427.5) (29). For patients with multiple CA during the hospitalization, information surrounding the first arrest was used for Utstein-style data collection, and the occurrence of re-arrest was recorded (30). Some patients were dependent on mechanical ventilation before their CA (n = 11), and others became dependent after CA (n = 10).

Data Collection

Etiology of CA was determined by medical record review. When available, we abstracted the duration of time from the beginning of a witnessed CA and the beginning of resuscitation until ROSC, the occurrence of seizures (detected clinically or on electroencephalogram) in the first 4 days after CA, and the number of inotropes and vasopressors (i.e., epinephrine, norepinephrine, vasopressin, milrinone, dopamine, dobutamine) initiated in the first 24 hrs after CA. Temperature, heart rate, and mean arterial blood pressure were documented hourly for clinical care of all ICU patients, but only abstracted for the HT group. We normalized heart rate and mean arterial blood pressure for age and gender (31, 32). Rectal temperatures were measured on most patients, but method of temperature measurement was not uniform.

Definitions

Cardiac rhythm monitoring was not always performed during the period of pulselessness. Therefore, the first monitored rhythm was the first rhythm recorded either during or after the CA. A non-chronic illness was defined as an acute, new medical problem, and chronic illness was defined as a long-standing or recurrent medical problem. We used the National Institute of Diabetes and Digestive and Kidney Diseases definition of hypoglycemia <70 mg/dL and defined hyperglycemia as >250 mg/dL, which is associated with increased mortality in critically ill patients (33). Immunosuppressed patients had cancer, primary immune deficiency, or underwent a solid organ or bone marrow transplantation.

Care After Resuscitation

Although Children's Hospital of Pittsburgh did not have a protocol for care after resuscitation, there were general standards of care. Patients who remained comatose after ROSC received central venous and arterial catheters. Antiepileptic medications were started only if the patient also incurred a traumatic brain injury or had a clinical or electrographic seizure. Pain and sedation medications were used at the discretion of the attending physician.

and were often withheld initially to obtain a neurologic examination. There was no protocol regarding therapy for hyperglycemia in nondiabetic patients; however, practice by ICU attendings may have changed after the publication of a study showing reduced mortality in surgical intensive care adult patients (34). Total parental nutrition was typically instituted by 48 hrs. Enteral feeding was initiated as soon as feasible. We did not routinely obtain electroencephalograms or blood cultures.

Cooling Methods

In patients with severe trauma, hospital policy early in the study period mandated active warming to normothermia in the emergency department (n = 11 standard therapy [ST] patients) with warm lights, intravenous fluids, and bedding. In all other cases, the attending ICU physician decided whether to initiate HT treatment and determined the target temperature, duration, and rate of re-warming. Most ST patients without severe trauma were passively warmed to normothermia.

Induction of HT was accomplished with multiple modalities. Most commonly, we used a cooling blanket (Cincinnati SubZero Plastipad, Cincinnati, OH) positioned under the patient and controlled by an automated cooling system (Gaymar Medi-Therm III, Orchard Park, NY) set to the target temperature. Other methods included surface cooling with ice packets, bath and fan, lowering of the room and ventilator humidifier thermostat, and, occasionally, gastric lavage with iced saline. One patient received 40 mL/kg of intravenous iced saline to induce HT. Nondepolarizing neuromuscular blockers were often used to prevent shivering during induction of HT. Fever ($>38^{\circ}\text{C}$) was treated aggressively in all patients with methods similar to those used for cooling induction, as well as with anti-pyretics (e.g., acetaminophen). Authors have defined fever as any temperature above normal ($>38^{\circ}\text{C}$ or 38.5°C) (35–37). In our ICU, temperatures $>38^{\circ}\text{C}$ provoke a search for an etiology and an effort to actively reduce the temperature because of the risk of higher temperatures and resultant secondary brain injury (38). Re-warming was achieved by increasing the set point of the cooling blanket gradually until the patient reached 36°C , at which time the blanket was turned off to prevent over-warming.

Outcome Measures

The primary outcomes were logistics related to the application of HT and the frequency of adverse events in the first 4 days after CA. Adverse events included hemorrhage, transfusion, positive cultures, electrolyte supplementation, intermittent arrhythmia (any abnormal rhythm documented in the chart that did not precipitate a re-arrest), and rearrest. The number of red blood cell transfusions was obtained from the hospital's blood bank. Positive cultures were defined as any culture positive for bacteria, virus, or fungus from tracheal, blood, cerebrospinal fluid, or urine. A positive tracheal culture was defined as bacterial growth from a tracheal sample with or without leukocytes. There was no protocol for routine surveillance cultures. Although we cannot rule out colonization or contamination, we considered positive cultures from days 1 and 2 likely to represent infection before the CA and those from days 3 and 4 likely to represent nosocomial infection. Electrolytes were replenished when serum levels were below the following thresholds: potassium <3.5 mEq/L, ionized calcium <1.0 mmol/L, magnesium <0.5 mg/dL, and phosphorus <2.5 mg/dL.

Secondary outcomes included mortality and Glasgow Outcome Score (GOS) (assigned in a non-blinded fashion based on medical records for both pre-arrest and hospital discharge status), a variation on the Utstein recommendation (30). GOS categories are defined as: (1) dead; (2) persistent vegetative or minimally conscious state; (3) moderate disability; (4) mild disability; and (5) no disability.

Data Analysis

The data were analyzed for treatment group differences with Fisher's exact tests for categorical variables and Student's *t* tests for normally distributed continuous variables. Wilcoxon rank-sum was used for non-normally distributed data. Associations with outcomes between patients in the HT or ST group were determined by univariate analysis. Variables with $p < .1$ for mortality were included in a multivariable logistic regression model using a backward stepwise method, and variables with the highest p values were eliminated sequentially until all terms in the model were significant ($p < .05$). HT was forced into the final model, although its p value was $> .1$. Initial variables in the multivariable regression included first whole blood pH, initial glucose (<70 mg/dL, 70 – 250 mg/dL, >250 mg/dL), epinephrine doses during resuscitation (0, 1–5, or 6), number of inotropes in the first 24 hrs, location of CA (out-of-hospital vs. in-hospital), etiology of CA (asphyxia vs. cardiac), whether the arrest was witnessed, HT vs. ST, and minutes of cardiopulmonary resuscitation until ROSC. All p values were two-sided. Missing data were not imputed. Data are presented as median (interquartile range [IQR]) or mean $\pm$ SD. Data analysis was performed using Stata software, version 10 (College Station, TX).

RESULTS

In the 6-yr study period, 399 children had the discharge diagnosis CA, 181 of whom met entry criteria and were included in this study (Fig. 1). Forty subjects received HT. Baseline patient characteristics were similar between HT and ST groups (Table 1), with the exception that more immunosuppressed patients were in the ST group ($p = .1$). Only one-third of children had no chronic illnesses.

Details of CA, Resuscitation, and Management After Resuscitation

Ninety percent of children with CA had asphyxia as the cause of their CA, and 55% of CA occurred in-hospital (Tables 2 and 3). Important differences existed between HT and ST groups with regard to duration of cardiopulmonary resuscitation to ROSC, doses of epinephrine during resuscitation, and witnessed arrest status.

Logistics of Hypothermia Treatment

All 40 children receiving HT were admitted during or after 2002. The median temperature on presentation to the ICU was lower in the HT vs. ST group (34.2°C [32.3°C – 35.3°C] vs. 35.4°C [33.6°C – 36.3°C]; $p < .01$). The majority (60%) of children in the HT group presented to the ICU with temperatures at or below the target temperature and therefore required only maintenance cooling. Temperature $<36^{\circ}\text{C}$ or $>38^{\circ}\text{C}$ on arrival to the ICU was associated with increased mortality (vs. 36°C – 38°C ; $p < .01$). The median HT target temperature was 34.0°C (33.5°C – 34.8°C), was reached by 7 hrs (5–8 hrs) in patients who had temperature above target on admission, and was maintained for 24 hrs (16–48 hrs). A cooling blanket was used for 84% of HT patients. Re-warming lasted 6 hrs (5–8 hrs). Eleven children, six with trauma before 2002, were actively warmed to normothermia. Three of these patients progressed to brain death, one died without brain death, and seven survived.

Safety

The HT and ST groups had similar rates of hemorrhage, receipt of red blood cell transfusions, intermittent arrhythmias, infection, and seizures in the first 4 days of admission (Table 4).

Three children had bradycardia (<60 beats per minute) for >1 hr (range, 2–11 hrs) during HT (Figs. 2A, B, C). All were older than 12 yrs, with corresponding normal to high blood pressures, and all had a GOS of 5 (normal) on hospital discharge. Mean arterial blood

pressure did not change significantly on re-warming in the HT group, but heart rate increased after re-warming.

Patients in the HT group received more frequent potassium, magnesium, and phosphorus supplementation than those in the ST group ($p < .05$) and trended toward more calcium supplementation ($p = .08$). Patients in the HT group also received more insulin infusions in the first 4 days, both for the entire study period ($p < .01$) and for patients admitted in or after 2002 ($p = .02$).

Patients in the HT group with temperature $<32^{\circ}\text{C}$ had increased hospital mortality compared with patients whose temperature remained $\geq 32^{\circ}\text{C}$ (73% vs. 43%; $p = .02$), even excluding patients with admission temperature $<30^{\circ}\text{C}$ ($p = .03$). However, there was a trend toward fewer re-arrests in children treated with HT vs. ST (5 [13%] vs. 36 [26%]; $p = .09$).

Fever ($>38^{\circ}\text{C}$) in the first 4 days occurred more frequently in the ST group vs. the HT group (38% vs. 18%; $p = .02$). Three children in the HT group had fever in the first 24 hrs on re-warming. Neither mortality nor GOS was associated with fever in the first 4 days.

Outcomes

Mortality was similar between groups (55.0% HT vs. 55.3% ST; $p = 1.0$). Mortality did not improve over time and ranged from 34% to 70% per year. Extracorporeal membrane oxygenation (ECMO) was not associated with mortality overall (5 of 11 [45%] ECMO patients died vs. 95 of 170 [56%] non-ECMO; $p = .54$) or within each group (HT mortality: 40% ECMO vs. 57% non-ECMO; $p = .6$; ST mortality: 50% ECMO vs. 56% non-ECMO; $p = 1.0$). However, mortality was only 27% in children who had ROSC after cardiopulmonary resuscitation without epinephrine ($n = 48$) vs. 65% in children requiring at least one dose of epinephrine to achieve ROSC ($n = 133$). In bivariate and multivariate analysis, HT was not associated with survival. (Table 5).

DISCUSSION

To our knowledge, this is the largest study reporting on the use of HT after pediatric CA. We found that mild HT in children after ROSC is feasible using resources readily available in this tertiary pediatric ICU. However, we also identified important safety issues related to cooling below target temperature and depletion of electrolytes.

HT for neuroprotection after CA from asphyxia has been studied prospectively only in neonates, but inpatient adults treated with HT after pulseless electrical activity or asystole demonstrated a trend toward better outcome in an observational study (18). Current American Heart Association guidelines recommend the use of HT for adults remaining comatose after CA from ventricular arrhythmia and the consideration of HT for comatose survivors of pediatric CA (39).

Time to target temperature in our patients was comparable to that reported in adult and neonatal randomized, controlled trials, although the median target temperature in this cohort was higher (34°C vs. 32°C – 34°C) (14, 15, 17), and almost half of the children who attained ROSC had an initial temperature $<35^{\circ}\text{C}$. The higher target temperatures may reflect inexperience with the use of HT, lack of evidence of benefit in pediatric patients after CA, or caution in patients thought to be at higher risk for adverse effects from HT (e.g., patients with trauma or arrhythmia). Similar to other studies of children with acute brain injury, abnormal temperature on presentation to the ICU was associated with increased mortality (40–48). Temperature below target range in the HT group occurred less frequently (15%) than in an adult cohort (63%) (49), suggesting that temperature may be easier to control in

children. It is not clear, however, if presence of a poikilothermic state is reflective of severe injury and thus an increased risk of death, and/or if temperature below target range itself causes an increase in mortality.

We were surprised that 38% of children in the ST group had fever in the first 4 days after CA. Given the well-documented detrimental effects of fever in animal models of brain ischemia, this could represent an important target for improvement by health care providers and cooling technologies. Since 2002, our trauma protocol has been modified to discontinue active warming of children with brain injury (38).

Patients in the HT group tended to be treated with ECMO more frequently, but ECMO was not associated with a higher or lower mortality risk. Children with congenital heart disease, who were excluded from this study, have benefitted the most from ECMO cardiopulmonary resuscitation (50, 51). The use of neuromuscular blockade was greater in the HT group, to provide more precise patient temperature control, to prevent shivering, and to promote ventilator synchrony. The greater number of days with an artificial airway in patients treated with HT may be a consequence of the intervention itself (patients remained intubated until re-warming was completed).

Despite similar initial serum glucose concentration after ROSC, insulin infusions were used twice as frequently in the HT group, which may be a reflection of HT-related hyperglycemia. As in patients with traumatic brain injury and congenital heart surgery, hyperglycemia was associated with increased mortality (52–56). Hypoglycemia on ICU presentation was also associated with increased mortality, perhaps reflecting a poor stress response or long-standing nutrient deprivation causing cellular energy depletion. Hypoglycemia induces neuronal cell death in the same vulnerable areas as does hypoxia-ischemia (the CA1 hippocampus, cerebral cortex, basal ganglia, and thalamus), and likely exacerbates neuronal cell death after CA (57). Optimal glucose management after CA in children is unknown and may be a critical element in management after resuscitation.

As in the adult and neonatal randomized, controlled trials, HT was not associated with increased arrhythmias, severe bleeding events, or red cell transfusions (14–17). We also found no difference in the incidence of seizures or positive cultures. Groups had similar rates of sepsis or septic shock as the etiology of CA.

Patients in the HT group received more electrolyte supplementation. Although this finding is similar to adult traumatic brain injury patients treated with HT (who are at particular risk for low levels of phosphorus and magnesium), it has not been previously reported in the CA literature (58–61). Potential mechanisms mediating electrolyte depletion are: cold diuresis, which increases water and electrolyte losses and has greatest effect during active cooling; osmotic diuresis from hyperglycemia; increased insulin use in the HT group; and intracellular shifts of electrolytes during HT (58–61).

Hemodynamic changes can occur during HT and re-warming. Cardiac output decreases during HT secondary to decreased heart rate and decreased stroke volume and increased afterload from peripheral vasoconstriction. It typically increases back to baseline during re-warming (62, 63). Mean arterial blood pressure can decrease on re-warming, which can be partly explained by peripheral vasodilation inducing a relative hypovolemic state. This occurred in only one patient in our study, suggesting that care was taken to avoid this complication (64). Finally, the metabolism and effects of commonly used medications are influenced by systemic HT and may result in altered hemodynamics (65).

Patients in our study had higher survival rates than those in previous reports (3, 4), at least partially because we included only patients who survived to ICU admission. Also, we

included all patients receiving cardiopulmonary resuscitation who had pulselessness documented by a health care worker, even if the event was brief (e.g., a plugged endotracheal tube in the ICU). One-third of the patients did not require bolus epinephrine for ROSC, and they had twice the survival rates of patients receiving epinephrine. Finally, large reviews of pediatric CA include data from hospitals that do not specialize in pediatric care.

Study Limitations

In this observational study, we were unable to fully adjust for the effects of selection bias or effects of temporal trends. We therefore cannot determine the efficacy of HT in children after CA. The purpose of the study was to describe our experience using HT and help care providers anticipate and prevent adverse events. Data collection was limited by available documentation. Children with congenital heart disease, a group with better outcome after CA, were excluded. GOS was assigned retrospectively in a non-blinded fashion using medical record entries. GOS is a gross measure of function and may not accurately depict outcome in infants. Our study does not include data on long-term outcomes or detailed cognitive function. Testing for infection and electrolyte levels was not standardized. There was no protocol for routine cultures in patients, and many children had cultures taken on the day of presentation with CA, whether signs and symptoms of sepsis were present, potentially biasing our data. Although electroencephalogram pattern has been associated with outcome after pediatric CA, we did not measure it in this study (66).

Rectal temperature probes are routinely used in our ICU, largely because they are simple to use. However, they may less accurately measure core temperature than other methods (67–72).

CONCLUSIONS

Pediatric patients with CA are in urgent need of proven interventions that improve outcome. Details regarding the optimal implementation of therapeutic HT in children after CA are needed. Common complications associated with HT may blunt its effectiveness, but that may be preventable. We believe that the efficacy of mild HT warrants prospective study in pediatric patients after CA.

Acknowledgments

Special thanks to Suruchi Batra and Ronald Radocay for assistance in data acquisition. The authors are grateful to the department of medical records at the Children's Hospital of Pittsburgh. The authors thank the nursing staff of the ICU for their efforts with regard to HT management. The authors thank Stephen Wisniewski, PhD, Associate Dean for Research, Graduate School of Public Health, University of Pittsburgh, for his expert statistical review. The authors appreciate the generous support from the National Institutes of Health/National Institute of Child Health and Human Development 5K12 HD047349-02 (ELF) and K23 HD046489 (RSW).

REFERENCES

1. Kuisma M, Suominen P, Korpela R. Paediatric out-of-hospital cardiac arrests- epidemiology and outcome. *Resuscitation*. 1995; 30:141–150. [PubMed: 8560103]
2. Reis AG, Nadkarni V, Perondi MB, et al. A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. *Pediatrics*. 2002; 109:200–209. [PubMed: 11826196]
3. Young KD, Gausche-Hill M, McClung CD, et al. A prospective population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. *Pediatrics*. 2004; 114:157–164. [PubMed: 15231922]

4. Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA*. 2006; 295:50–57. [PubMed: 16391216]
5. de Mos N, van Litsenburg RR, McCrindle B, et al. Pediatric in-intensive-care-unit cardiac arrest: Incidence, survival, and predictive factors. *Crit Care Med*. 2006; 34:1209–1215. [PubMed: 16484906]
6. Hickey RW, Painter MJ. Brain injury from cardiac arrest in children. *Neurol Clin*. 2006; 24:147–158. viii. [PubMed: 16443136]
7. Donoghue AJ, Nadkarni V, Berg RA, et al. Out-of-hospital pediatric cardiac arrest: An epidemiologic review and assessment of current knowledge. *Ann Emerg Med*. 2005; 46:512–522. [PubMed: 16308066]
8. O'Rourke PP. Outcome of children who are apneic and pulseless in the emergency room. *Crit Care Med*. 1986; 14:466–468. [PubMed: 3698611]
9. Zeevalk GD, Nicklas WJ. Hypothermia and metabolic stress: Narrowing the cellular site of early neuroprotection. *J Pharmacol Exp Ther*. 1996; 279:332–339. [PubMed: 8859011]
10. Ji X, Luo Y, Ling F, et al. Mild hypothermia diminishes oxidative DNA damage and prodeath signaling events after cerebral ischemia: A mechanism for neuroprotection. *Front Biosci*. 2007; 12:1737–1747. [PubMed: 17127418]
11. D'Cruz BJ, Fertig KC, Filiano AJ, et al. Hypothermic reperfusion after cardiac arrest augments brain-derived neurotrophic factor activation. *J Cerebral Blood Flow Metab*. 2002; 22:843–851.
12. Roka A, Vasarhelyi B, Bodrogi E, et al. Changes in laboratory parameters indicating cell necrosis and organ dysfunction in asphyxiated neonates on moderate systemic hypothermia. *Acta Paediatr*. 2007; 96:1118–1121. [PubMed: 17590199]
13. Ohmura A, Nakajima W, Ishida A, et al. Prolonged hypothermia protects neonatal rat brain against hypoxic-ischemia by reducing both apoptosis and necrosis. *Brain Dev*. 2005; 27:517–526. [PubMed: 15899566]
14. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002; 346:557–563. [PubMed: 11856794]
15. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002; 346:549–556. [PubMed: 11856793]
16. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet*. 2005; 365:663–670. [PubMed: 15721471]
17. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005; 353:1574–1584. [PubMed: 16221780]
18. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med*. 2007; 35:1041–1047. [PubMed: 17334257]
19. Jacobs S, Hunt R, Tarnow-Mordi W, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev*. 2007; 17:CD003311. [PubMed: 17943788]
20. Young KD, Seidel JS. Pediatric cardiopulmonary resuscitation: A collective review. *Ann Emerg Med*. 1999; 33:195–205. [PubMed: 9922416]
21. Siesjo BK, Katsura K-I, Zhao Q, et al. Mechanisms of secondary brain damage in global and focal ischemia: A speculative synthesis. *J Neurotrauma*. 1995; 12:943–956. [PubMed: 8594224]
22. Conn AW, Edmonds JE, Barker GA. Cerebral resuscitation in near drowning. *Pediatr Clin North Am*. 1979; 26:691. [PubMed: 492801]
23. Bohn DJ, Biggar WD, Smith CR, et al. Influence of hypothermia, barbiturate therapy, and intracranial pressure monitoring on morbidity and mortality after near-drowning. *Crit Care Med*. 1986; 14:529–534. [PubMed: 3709193]
24. Logue ES, McMichael MJ, Callaway CW. Comparison of the effects of hypothermia at 33 degrees C or 35 degrees C after cardiac arrest in rats. *Acad Emerg Med*. 2007; 14:293–300. [PubMed: 17296802]
25. Fink EL, Marco CD, Donovan HA, et al. Brief induced hypothermia improves outcome after asphyxial cardiopulmonary arrest in juvenile rats. *Develop Neurosci*. 2005; 27:191–199.

26. Agnew DM, Koehler RC, Guerguerian AM, et al. Hypothermia for 24 hours after asphyxial cardiac arrest in piglets provides striatal neuroprotection that is sustained 10 days after rewarming. *Pediatr Res.* 2003; 54:253–262. [PubMed: 12736390]
27. Xiao F, Safar P, Radovsky A. Mild protective and resuscitative hypothermia for asphyxial cardiac arrest in rats. *Am J Emergency Med.* 1998; 16:17–25.
28. Moler FW. Planning therapeutic hypothermia after pediatric cardiac arrest trial. *Crit Care Med.* 2006; 34:A421.
29. WHO. 5th Edition. Los Angeles, CA: Practice Management Information Corporation; 1998. World Health Organization International Classification of Diseases.
30. Zaritsky A, Nadkarni V, Hazinski MF, et al. Recommended guidelines for uniform reporting of pediatric advanced life support: The pediatric Utstein style. A statement for healthcare professionals from a task force of the American Academy of Pediatrics, the American Heart Association, and the European Resuscitation Council. *Pediatrics.* 1995; 96(4 Pt 1):765–779. [PubMed: 7567346]
31. Report of the Second Task Force on Blood Pressure Control in Children 1987: Task Force on Blood Pressure Control in Children. National Heart, Lung, Blood Institute, Bethesda, Maryland. *Pediatrics.* 1987; 79:1–25. [PubMed: 3797155]
32. Park, M. *Pediatric Cardiology for Practitioners.* 3rd Edition. Mosby: St. Louis; 1996.
33. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc.* 2003; 78:1471–1478. [PubMed: 14661676]
34. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001; 345:1359–1367. [PubMed: 11794168]
35. Mackowiak PA. Concepts of fever. *Arch Intern Med.* 1998; 158:1870–1881. [PubMed: 9759682]
36. Baraff LJ, Bass JW, Fleisher GR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. *Ann Emerg Med.* 1993; 22:1198–210. [PubMed: 8517575]
37. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005; 6:2–8. [PubMed: 15636651]
38. Hickey RW, Kochanek PM, Ferimer H, et al. Induced hyperthermia exacerbates neurologic neuronal histologic damage after asphyxial cardiac arrest in rats. *Crit Care Med.* 2003; 31:531–535. [PubMed: 12576962]
39. AHA. 2005 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: pediatric advanced life support. *Pediatrics.* 2006; 117:e1005–e1028. [PubMed: 16651281]
40. Clifton GL, Miller ER, Choi SC, et al. Hypothermia on admission in patients with severe brain injury. *J Neurotrauma.* 2002; 19:293–301. [PubMed: 11939497]
41. Martin RS, Kilgo PD, Miller PR, et al. Injury-associated hypothermia: an analysis of the 2004 National Trauma Data Bank. *Shock.* 2005; 24:114–118. [PubMed: 16044080]
42. Wang HE, Callaway CW, Peitzman AB, et al. Admission hypothermia and outcome after major trauma. *Crit Care Med.* 2005; 33:1296–1301. [PubMed: 15942347]
43. Vayrynen T, Kuusma M, Maatta T, et al. Medical futility in asystolic out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand.* 2007; 8:8.
44. Biggart MJ, Bohn DJ. Effect of hypothermia and cardiac arrest on outcome of near-drowning accidents in children. *J Pediatr.* 1990; 117(2 Pt 1):179–183. [PubMed: 2380813]
45. Natale JE, Joseph JG, Helfaer MA, et al. Early hyperthermia after traumatic brain injury in children: Risk factors, influence on length of stay, and effect on short-term neurologic status. *Crit Care Med.* 2000; 28:2608–2615. [PubMed: 10921603]
46. Peres Bota D, Lopes Ferreira F, Melot C, et al. Body temperature alterations in the critically ill. *Intensive Care Med.* 2004; 30:811–816. [PubMed: 15127194]
47. Clemmer TP, Fisher CJ Jr, Bone RC, et al. Hypothermia in the sepsis syndrome and clinical outcome. The Methylprednisolone Severe Sepsis Study Group. *Crit Care Med.* 1992; 20:1395–1401. [PubMed: 1395659]

48. Tobin J, Reddihough D. Hypothermia in children with severe neurological disabilities. *J Paediatr Child Health*. 1994; 30:176–178. [PubMed: 8198855]
49. Merchant RM, Abella BS, Peberdy MA, et al. Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med*. 2006; 34(12 Suppl):S490–S494. [PubMed: 17114983]
50. Morris MC, Wernovsky G, Nadkarni VM. Survival outcomes after extracorporeal cardiopulmonary resuscitation instituted during active chest compressions following refractory in-hospital pediatric cardiac arrest. *Pediatr Crit Care Med*. 2004; 5:440–446. [PubMed: 15329159]
51. Thiagarajan RR, Laussen PC, Rycus PT, et al. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. *Circulation*. 2007; 116:1693–1700. [PubMed: 17893278]
52. Jeremitsky E, Omert LA, Dunham CM, et al. The impact of hyperglycemia on patients with severe brain injury. *J Trauma*. 2005; 58:47–50. [PubMed: 15674149]
53. Cochran A, Scaife ER, Hansen KW, et al. Hyperglycemia and outcomes from pediatric traumatic brain injury. *J Trauma*. 2003; 55:1035–1038. [PubMed: 14676647]
54. Falcao G, Ulate K, Kouzekanani K, et al. Impact of postoperative hyperglycemia following surgical repair of congenital cardiac defects. *Pediatr Cardiol*. 2008; 5:5.
55. Wintergerst KA, Buckingham B, Gandrud L, et al. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics*. 2006; 118:173–179. [PubMed: 16818563]
56. Kinoshita K, Kraydieh S, Alonso O, et al. Effect of posttraumatic hyperglycemia on contusion volume and neutrophil accumulation after moderate fluid-percussion brain injury in rats. *J Neurotrauma*. 2002; 19:681–692. [PubMed: 12165130]
57. Suh SW, Hamby AM, Swanson RA. Hypoglycemia, brain energetics, and hypoglycemic neuronal death. *Glia*. 2007; 55:1280–1286. [PubMed: 17659530]
58. Boylan JW, Hong SK. Regulation of renal function in hypothermia. *Am J Physiol*. 1966; 211:1371–1378. [PubMed: 5956552]
59. Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality—Part 2: Practical aspects and side effects. *Intensive Care Med*. 2004; 30:757–769. [PubMed: 14767590]
60. Aibiki M, Kawaguchi S, Maekawa N. Reversible hypophosphatemia during moderate hypothermia therapy for brain-injured patients. *Crit Care Med*. 2001; 29:1726–1730. [PubMed: 11546972]
61. Polderman KH, Peerdeman SM, Girbes AR. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. *J Neurosurg*. 2001; 94:697–705. [PubMed: 11354399]
62. Gebauer CM, Knuepfer M, Robel-Tillig E, et al. Hemodynamics among neonates with hypoxic-ischemic encephalopathy during whole-body hypothermia and passive rewarming. *Pediatrics*. 2006; 117:843–850. [PubMed: 16510666]
63. Fugelseth D, Satas S, Steen PA, et al. Cardiac output, pulmonary artery pressure, and patent ductus arteriosus during therapeutic cooling after global hypoxia-ischaemia. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88:F223–F228. [PubMed: 12719397]
64. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxicischemic encephalopathy. *Pediatrics*. 2000; 106(1 Pt 1):92–99. [PubMed: 10878155]
65. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. *Crit Care Med*. 2007; 35:2196–2204. [PubMed: 17855837]
66. Nishisaki A, Sullivan J 3rd, Steger B, et al. Retrospective analysis of the prognostic value of electroencephalography patterns obtained in pediatric in-hospital cardiac arrest survivors during three years. *Pediatr Crit Care Med*. 2007; 8:10–17. [PubMed: 17251876]
67. Maxton FJ, Justin L, Gillies D. Estimating core temperature in infants and children after cardiac surgery: A comparison of six methods. *J Adv Nurs*. 2004; 45:214–222. [PubMed: 14706007]
68. Robinson JL, Seal RF, Spady DW, et al. Comparison of esophageal, rectal, axillary, bladder, tympanic, and pulmonary artery temperatures in children. *J Pediatr*. 1998; 133:553–556. [PubMed: 9787697]

69. Rumana CS, Gopinath SP, Uzura M, et al. Brain temperature exceeds systemic temperature in head-injured patients. *Crit Care Med.* 1998; 26:562–567. [PubMed: 9504587]
70. Henker RA, Brown SD, Marion DW. Comparison of brain temperature with bladder and rectal temperatures in adults with severe head injury. *Neurosurgery.* 1998; 42:1071–1075. [PubMed: 9588552]
71. Stone JG, Young WL, Smith CR, et al. Do standard monitoring sites reflect true brain temperature when profound hypothermia is rapidly induced and reversed? *Anesthesiology.* 1995; 82:344–351. [PubMed: 7856892]
72. Crowder CM, Tempelhoff R, Theard MA, et al. Jugular bulb temperature: Comparison with brain surface and core temperatures in neurosurgical patients during mild hypothermia. *J Neurosurg.* 1996; 85:98–103. [PubMed: 8683289]

Figure 1. Study flowchart. Hypothermia (*HT*) data are presented as mean ± SD and median (interquartile range). *ROSC*, return of spontaneous circulation; *h*, hour; *n*, number.

Figure 2.

Physiologic variables of the hypothermia therapy (*HT*) group. *A*, Temperatures of the *HT* group (mean $\pm$ standard error) during the time before *HT*, *HT*, re-warming, and after re-warming phases. Because there was no *HT* protocol, each data point contains a variable number of patients. *B* and *C*, Mean arterial blood pressure and heart rate, normalized for age and gender. The arrow in (*C*) denotes increased heart rate after re-warming.

Table 1

Patient characteristics

Variable	Total, n = 181	ST, n = 141	HT, n = 40	<i>p</i> ^a
Age in yrs				.8
Mean ± SD	6.0 ± 6.2	6.0 ± 6.2	6.0 ± 6.6	
Median (IQR)	2.9 (0.7–11.2)	2.9 (1.1–11.1)	2.4 (.4–11.8)	
Gender, male/female (% male)	104/77 (57.5)	80/61 (56.7)	24/16 (60.0)	.9
Race/ethnicity, n (%) ^b				1.0
White	126 (70.0)	97 (69.3)	29 (72.5)	
Black	29 (16.1)	23 (16.4)	6 (15.0)	
Other/unknown	25 (13.9)	20 (14.3)	5 (12.5)	
Insurance status, n (%) ^b				.7
Public	111 (62.7)	87 (63.5)	24 (60.0)	
Private	58 (32.8)	43 (31.4)	15 (37.5)	
Self-pay	8 (4.52)	7 (5.1)	1 (2.5)	
Pre-existing illness, n (%)				.6
None	55 (35.7)	43 (35.2)	12 (37.5)	
Not chronic	35 (22.7)	26 (21.3)	9 (28.1)	
Chronic	64 (41.6)	53 (43.4)	11 (34.3)	
Immunosuppressed, n (%)	17 (9.4)	16 (11.3)	1 (2.5)	.1

ST, standard therapy; HT, hypothermia therapy; IQR, interquartile range.

^aST vs. HT;

^b numbers of subjects for race/ethnicity, insurance status, and pre-existing illness do not equal column totals because of missing data. Race/ethnicity data were available for 180, insurance data for 177, and pre-existing illness for 154 subjects.

Table 2

Etiology of cardiac arrest^a

Etiology ^b	Total, n = 180	All ST, n = 140	ST After 2001, n = 95	HT, n = 40	p ^c	Mortality by Etiology, %
Pulmonary disease, ^d n (%)	43 (23.8)	36 (25.5)	28 (29.5)	7 (17.5)	.8	42
Trauma	23 (12.7)	21 (14.9)	16 (16.8)	2 (5.0)	.09	70
Sepsis or septic shock	22 (12.2)	18 (12.8)	14 (14.7)	4 (10.0)	.6	64
SIDS	17 (9.4)	11 (7.8)	5 (5.3)	6 (15.0)	.08	76
Submersion	15 (8.3)	8 (5.7)	4 (4.2)	7 (17.5)	.02	40
Cardiac ^e	14 (7.7)	9 (6.4)	5 (5.3)	5 (12.5)	.05	29
Hemorrhage, non-trauma	10 (5.5)	6 (4.3)	4 (4.2)	4 (10.0)	.08	60
Inflicted TBI	9 (5.0)	8 (5.7)	5 (5.3)	1 (2.5)	1.0	78
Neurologic disease, non-trauma	9 (5.0)	8 (5.7)	5 (5.3)	1 (2.5)	1.0	78
Status epilepticus	7 (3.9)	5 (3.5)	1 (1.1)	2 (5.0)	.1	71
Abdominal catastrophe	4 (2.2)	3 (2.1)	3 (3.2)	1 (2.5)	1.0	75
Abnormal electrolytes	3 (1.7)	3 (2.1)	2 (2.1)	0 (0.0)	1.0	0
Toxic ingestion	1 (0.6)	1 (0.7)	1 (1.1)	0 (0.0)	1.0	0
Other	3 (1.7)	3 (2.1)	2 (2.1)	0 (0.0)	1.0	33

ST, standard therapy; HT, hypothermia therapy; SIDS, sudden infant death syndrome; TBI, traumatic brain injury.

^aEtiologies were available for 180 of the 181 study patients (and 140 of the 141 ST patients);^betiologies are mutually exclusive;^cST vs. HT, all patients 2002 to 2006 only;^dincludes asthma, pulmonary infections, and aspiration;^eincludes cardiomyopathy, arrhythmia, and heart transplant recipients for cardiomyopathy.

Table 3

Details of cardiac arrest, resuscitation, treatment, and outcome

Characteristic	Total, n = 181	ST, n = 141	HT, n = 40	<i>p</i> ^a
Primary etiology, n (%)				.4
Asphyxia	164 (91.1)	129 (92.1)	35 (87.5)	
Cardiac	16 (8.9)	11 (7.9)	5 (12.5)	
Location, n (%)				.11
In-hospital	94 (54.9)	78 (55.3)	16 (40.0)	
Out-of-hospital	87 (45.1)	63 (44.7)	24 (60.0)	
Witnessed, n (%)	136 (75.6)	111 (79.3)	25 (62.5)	.04
Interval of CA to ROSC, ^b mins				.02
Mean ± SD	14.5 ± 14.5	13.5 ± 14.8	18.2 ± 13.0	
Median (IQR)	10 (4–20)	8 (3–15)	15 (10–26)	
Interval of CPR to ROSC, ^c mins				.06
Mean ± SD	15.0 ± 14.4	14.5 ± 14.8	17.4 ± 12.6	
Median (IQR)	10 (5–20)	9 (4–20)	15 (8–26)	
First monitored rhythm, ^d n (%)				.06
PEA/bradycardia	82 (53.9)	69 (58.0)	13 (39.4)	
Asystole	47 (30.9)	32 (26.9)	15 (45.5)	
VT/VF	19 (12.5)	16 (13.4)	3 (9.1)	
Sinus tachycardia/NSR	4 (2.6)	2 (1.7)	2 (6.1)	
Epinephrine doses				.03
Mean ± SD	2.2 ± 2.5	2.0 ± 2.3	3.0 ± 3.0	
Median (IQR)	2 (0–3)	1.5 (0–3)	2 (1–4)	
ECMO, n (%)	11 (6.1)	6 (4.3)	5 (12.5)	.07
Initial glucose, mg/dL, mean ± SD	224 ± 123	224 ± 129	223 ± 98	1.0
Initial lactate, mmol/L, mean ± SD	8.5 ± 6.9	8.5 ± 7.2	8.5 ± 6.2	1.0
Temperature on ICU admission, °C				.02
Mean ± SD	34.6 ± 2.2	34.8 ± 2.1	33.9 ± 2.2	
Median (IQR)	35.1 (33.3–36.1)	35.4 (33.6–36.3)	34.2 (32.3–35.3)	
Number of inotropes during first 24 hrs				.4
Mean ± SD	1.5 ± 1.4	1.5 ± 1.4	1.7 ± 1.4	
Median (IQR)	1 (0–3)	1 (0–3)	2 (.5–3)	
Insulin infusion during first 24 hrs, n (%)	58 (32.2)	35 (25.0)	23 (57.5)	<.01
Hydrocortisone infusion during first 24 hrs, n (%)	67 (37.2)	52 (37.1)	15 (37.5)	1.0
Neuromuscular blockade during first 24 hrs, n (%)	50 (27.8)	28 (20.0)	22 (55.0)	<.01
Duration of artificial airway, days				.04
Mean ± SD	15.7 ± 33.2	14.9 ± 28.4	18.4 ± 46.8	
Median (IQR)	4 (2–13)	4 (1–13)	7 (3–13)	
ICU length of stay, days				.5
Mean ± SD	20.1 ± 38.7	20.1 ± 35.9	20.0 ± 47.7	
Median (IQR)	6 (1–19)	5 (1–24)	7 (2–18)	

Characteristic	Total, n = 181	ST, n = 141	HT, n = 40	<i>p</i> ^a
Hospital length of stay, days				.5
Mean ± SD	25.6 ± 43.6	25.0 ± 40.7	27.4 ± 53.2	
Median (IQR)	8 (2–32)	8 (2–32)	9 (3–25)	
Seizures during first 4 days, n (%)	32 (17.7)	24 (17.0)	8 (20.0)	.6
Pre-CA GOS, mean ± SD	4.5 ± 0.8	4.5 ± 0.8	4.7 ± 0.6	.5
Hospital discharge GOS, mean ± SD	2.4 ± 1.6	2.4 ± 1.6	2.4 ± 1.7	.9
Mortality, n (%)	100 (55.2)	78 (55.3)	22 (55.0)	1.0
Withdrawal of technological support, n (%)	64 (35.4)	51 (36.2)	13 (32.5)	1.0
Brain dead, n (%)	10 (5.5)	7 (5.0)	3 (7.5)	.7

CA, cardiac arrest; ROSC, return of spontaneous circulation; IQR, interquartile range; ICU, intensive care unit; ST, standard therapy; HT, hypothermia therapy; GOS, Glasgow Outcome Scale; CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; VT, ventricular tachycardia; VF, ventricular fibrillation; NSR, normal sinus rhythm; V-A ECMO, venous-arterial extracorporeal mechanical oxygenation.

^aST vs. HT;

^bN = 126 total, 101 ST, and 25 HT patients. Time from pulselessness to ROSC;

^cN = 138 total, 111 ST, and 27 HT patients. Time from initiation of CPR to ROSC;

^dN = 152 total, 119 ST, and 33 HT patients.

Table 4

Adverse events in the first 4 days

Type of Event	Total, n = 181	ST, n = 141	HT, n = 40	<i>p</i> ^a
Arrhythmias, n (%)				
Intermittent	9 (6.0)	6 (4.3)	3 (7.5)	.4
Re-arrest	41 (22.7)	36 (25.5)	5 (12.5)	.09
Positive culture, n (%) ^{b,c}	97 (53.6)	73 (51.8)	24 (60.0)	.17
Days 1 and 2	81 (44.8)	62 (44.3)	19 (47.5)	.3
Tracheal aspirate	50	34	16	
Blood	17	15	2	
Urine	8	8	0	
Cerebrospinal fluid	2	2	0	
Viral	4	3	1	
Days 3 and 4	16 (8.8)	11 (7.9)	5 (12.5)	.2
Tracheal aspirate	8	4	4	
Blood	4	4	0	
Urine	1	1	0	
Cerebrospinal fluid	3	2	1	
Viral	0	0	0	
Number of RBC transfusions,				.15
Mean ± SD	3.8 (7.7)	3.7 (8.4)	4.2 (4.5)	
Median (IQR)	2 (1–4)	2 (1–3)	2 (1–7)	
Hemorrhage, n (%)	8 (4.4)	7 (5.0)	1 (2.5)	1.0
Central nervous system	1	1 ^d	0	
Pulmonary	1	1 ^e	0	
Gastrointestinal	5	4 ^f	1 ^g	
Genitourinary	1	1 ^h	0	
Doses of electrolytes, n (%)				
Potassium				<.01
0 doses	85 (47.0)	78 (55.3)	7 (17.5)	
1–3 doses	40 (22.1)	31 (22.0)	9 (22.5)	
4 doses	56 (30.9)	32 (22.7)	24 (60.0)	
Magnesium				<.01
0 doses	134 (74.0)	111 (78.1)	23 (57.5)	
1–3 doses	42 (23.2)	29 (20.6)	13 (30.5)	
4 doses	5 (2.8)	1 (.7)	4 (10.0)	
Calcium				.08
0 doses	161 (89.0)	129 (91.5)	32 (80.0)	
1–3 doses	16 (8.8)	9 (6.4)	7 (17.5)	
4 doses	4 (2.2)	3 (2.1)	1 (2.5)	
Phosphorus				<.01

Type of Event	Total, n = 181	ST, n = 141	HT, n = 40	<i>p</i> ^a
0 doses	140 (77.3)	117 (83.0)	23 (57.5)	
1–3 doses	39 (21.6)	22 (15.6)	17 (42.5)	
4 doses	2 (1.1)	2 (1.4)	0 (.0)	
Fever, n (%) ⁱ	59 (33%)	52 (37%)	7 (18%)	.02
Temperature below target, n (%)				.02 ^j
<32°C			6 (15.0)	
<31°C			5 (12.5)	
<30°C			4 (10.0)	

RBC, red blood cells; ST, standard therapy; HT, hypothermia; IQR, interquartile range.

^aST vs. HT;

^bbacterial infection, unless noted otherwise;

^cpositive cultures with the same organism and site for a patient were counted once;

^dpatient with gunshot wound to head;

^epatient on extracorporeal membrane oxygenation (ECMO);

^ftwo patients with liver failure/short gut syndrome, one patient with multi-system trauma, one patient with sepsis after multi-visceral transplantation;

^gpatient with postoperative coagulopathy and gastrointestinal hemorrhage;

^hpatient on ECMO;

ⁱfever was defined as ≥38°C;

^j*p* value is comparing hospital mortality among HT patients with temperature <32°C vs. ≥32°C.

Table 5

Univariate and multivariate analysis for mortality

Variable	Odds Ratio	<i>p</i>	95% CI
<i>Univariate analysis for mortality</i>			
First whole blood pH	0.01	<.01	0.00–0.10
Initial glucose 70–250 mg/dL	1		Reference group
Initial glucose <70 mg/dL	3.36	.04	1.03–10.93
Initial glucose >250 mg/dL	5.31	<.01	2.67–10.53
No epinephrine bolus during resuscitation	1		Reference group
1–5 epinephrine doses	3.98	<.01	1.96–8.09
6 epinephrine doses	28.8	.002	3.43–241.6
Number of inotropes first 24 hrs	1.48	<.01	1.17–1.87
OOH (vs. IH) location of CA	2.48	<.01	1.35–4.53
Cardiac (vs. asphyxia) etiology	0.16	.01	0.04–0.60
Witnessed (vs. non-witnessed)	0.42	.02	0.20–0.87
VT/VF (vs. PEA/asystole)	0.59	.3	0.22–1.55
Age	1.04	.08	0.99–1.10
Male	1.14	.7	0.63–2.07
HT (vs. ST)	0.99	1.0	0.49–2.00
Interval of CA to ROSC ^a	1.06	<.01	1.03–1.10
Interval of CPR to ROSC ^b	1.07	<.01	1.04–1.11
<i>Multivariate analysis for mortality</i>			
HT vs. ST ^c	0.47	.2	0.15–1.45
First serum glucose <70 or >250 vs. 70–250 mg/dL mg/dL ^c	4.52	<.01	1.86–10.97
1–5 epinephrine doses ^d	2.47	.09	0.87–7.06
6 epinephrine doses ^d	27.27	.02	1.81–411.60
Cardiac vs. asphyxia etiology ^c	0.10	.02	0.02–.65
Interval of CPR to ROSC	1.05	.02	1.01–1.09

IH, in-hospital; OOH, out-of-hospital; CI, confidence interval; CA, cardiac arrest; VT, ventricular tachycardia; VF, ventricular fibrillation; PEA, pulseless electrical activity; HT, hypothermia therapy; ST, standard therapy; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

^aBased on 126 subjects for which these data were available;

^bbased on 138 subjects for which these data were available;

^csecond variable listed was the reference for the analysis;

^dvs. no doses of epinephrine.