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Multicenter Cohort Study of Out-of-Hospital Pediatric Cardiac Arrest

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Abstract

Objectives—To describe a large cohort of children with out-of-hospital (OH) cardiac arrest with return of circulation (ROC) and to identify factors in the early post-arrest period associated with survival. These objectives were for planning an interventional trial of therapeutic hypothermia after pediatric cardiac arrest.

Methods—A retrospective cohort study was conducted at 15 Pediatric Emergency Care Applied Research Network (PECARN) clinical sites over an 18 month study period. All children 24 hours to 18 years of age with OH cardiac arrest and a history of at least 1 minute of chest compressions with ROC for at least 20 minutes were eligible.

Measurements and Main Results—138 cases met study entry criteria; the overall mortality was 62% (85/138). Event characteristics associated with increased survival were the following: weekend arrests, CPR not ongoing at hospital arrival, arrest rhythm not asystole, no atropine or NaHCO₃, fewer epinephrine doses, shorter duration of CPR, and drowning or asphyxial arrest event. For the 0–12 hour post-arrest ROC period, absence of any vasopressor or inotropic agent (dopamine, epinephrine) use, higher lowest temperature recorded, greater lowest pH, lower lactate, lower maximum glucose and normal pupillary responses were all associated with survival. A multivariate logistic model of variables available at the time of arrest, which controlled for gender, age, race, asystole or ventricular fibrillation/ventricular tachycardia (VF/VT) anytime during the arrest, found the administration of atropine and epinephrine to be associated with mortality. A second model using additional information available up to 12 hours post ROC found 1) preexisting lung or airway disease, 2) etiology of arrest drowning or asphyxia, 3) higher pH and 4) bilateral reactive pupils to be associated with lower mortality. More than 3 doses of epinephrine were associated with poor outcome in 96% (44/46) of cases.

Conclusions—Multiple factors were identified to be associated with survival after OH pediatric cardiac arrest with ROC. Additional information available within a few hours after ROC may diminish outcome associations of factors available at earlier times in regression models. These factors should be considered in the design of future interventional trials aimed to improve outcome after pediatric cardiac arrest.

Keywords

cardiac arrest; out of hospital; return of spontaneous circulation; children; pediatric; cohort study; mortality; outcome; therapeutic hypothermia; randomized controlled trial

INTRODUCTION

Out-of-hospital (OH) cardiac arrest in childhood is often associated with death or poor neurobehavioral outcomes (1–9). Currently, there are no proven therapies effective in ameliorating neurological injury in the pediatric population. Therapeutic hypothermia (TH) is a promising intervention that has been demonstrated to improve outcome in adults following OH ventricular fibrillation or tachycardia (VF/VT) associated cardiac arrest (10,11) and in newborns with hypoxic ischemic encephalopathy (12,13). However, TH for traumatic brain injury has not been shown to be efficacious in adults or children (14,15). A concerning observation in a recently completed clinical trial of TH for traumatic brain injury in children was an unexpected strong trend for worse outcome in those receiving TH (15). Therefore, because of mechanistic differences between age groups and the possibility of patient harm, clinical trials are needed prior to recommending TH for cardiac arrest in children.

To our knowledge, all prior U.S. based reports of OH pediatric cardiac arrest have been either small case series reports from single locations or population studies that described few cases with return of circulation (ROC). Such studies have limited value for planning large multicenter interventional trials as would be required for TH after pediatric cardiac arrest (1–9). In addition, most prior reports lack uniformity in case definitions and outcome measures, which complicates comparison of these studies and limits integration of data in meta-analyses and literature reviews (16, 17). Therefore, findings from the existing literature for OH pediatric cardiac arrest are suboptimal for planning interventional clinical trials.

The Pediatric Emergency Care Applied Research Network (PECARN) is a federally-funded multi-institutional emergency medicine network that conducts research on prevention and management of acute illness and injuries in children (18). Its scope includes the continuum of care from prehospital, to ED, hospital care, and rehabilitation care. This represents an ideal setting to study OH pediatric cardiac arrest interventions and long term follow up. As an initial step in planning a randomized controlled trial (RCT) that would investigate the efficacy of TH and potentially other interventions to improve outcomes in children after cardiac arrest, we conducted a pre RCT cohort study at 15 PECARN sites. The purposes of this study were twofold. The first objective was to describe the patient characteristics, cardiac arrest events, and early post-arrest hospital courses in a large cohort of pediatric patients who received OH CPR for greater than one minute and had a sustained ROC. The second objective was to identify factors most strongly associated with hospital survival outcome in this cohort using information available at the time of ROC, and also within 12 hours following ROC. We hypothesized that in our cohort of pediatric OH cardiac arrest with ROC there would be factors measured in the immediate and early post-arrest period that would be associated with survival. These factors may need to be considered in the design of a future interventional RCT of TH in children.

METHODS

This investigation comes from a NICHD sponsored pre clinical trial cohort study conducted in the PECARN research network to precede a randomized clinical trial of therapeutic hypothermia after pediatric cardiac arrest. Three manuscripts were planned *a priori* to be

submitted for publication. The first paper reported group differences between in-hospital (IH) and out of hospital (OH) cohorts of cardiac arrest (19). The second paper focused on describing the in-hospital cohort and variables associated with outcome (20). The current study focuses on the out of hospital arrest cohort. It is a retrospective cohort study of OH pediatric cardiac arrest occurring between July 1, 2003 and December 31, 2004 at 15 sites associated with the PECARN network. Patients between one day (24 h) and 18 years of age (inclusive) who experienced an OH cardiac arrest defined as receiving chest compression for at least one minute and who had a ROC for a minimum of 20 minutes, were eligible for inclusion. Patients who received less than 1 minute of chest compressions, whether or not epinephrine or defibrillation was administered, were excluded. Case classification as OH was assigned if chest compressions were initiated prior to hospital arrival. Cases with the initiation of chest compressions in the ED or other hospital setting were considered to have in-hospital cardiac arrest and were excluded from this report. The inclusion and exclusion criteria were selected to identify a cohort of patients similar to those who would be potentially eligible for a future interventional trial of TH.

Patients were identified by medical record ICD-9 codes (427.5 cardiac arrest, and 437.4 ventricular fibrillation/flutter), procedure codes (99.60 cardiopulmonary resuscitation not otherwise specified, 99.63 closed chest cardiac massage, and 99.62 other electric counter shock of heart), institutional arrest logs (e.g. CPR committee or Quality Assurance Committee), morbidity and mortality reviews, emergency department records, trauma records, Pediatric Risk of Mortality (PRISM) scores (21), and other site specific mechanisms. If a patient experienced more than one cardiac arrest during the study time period, only the first arrest meeting eligibility criteria was included. The study was approved with a waiver of informed consent granted by the Institutional Review Board at all 15 clinical sites and the data coordinating center.

The PECARN Central Data Management and Coordinating Center (CDMCC) at the University of Utah trained investigators and data abstractors at each site to review patient records and collect data. Training included review of a manual of operations, teleconferences, and comparative coding of hypothetical patient records. During data collection, a sample of nearly 20% of records coded by data abstractors was reviewed by the site investigators for 27 key data fields. Overall agreement was > 96%. Data fields reviewed by the site investigator that did not match with those of the abstractor were flagged for resolution. All data were double-entered into a secure, encrypted Internet site and electronically submitted to the CDMCC. The CDMCC performed a secondary review to ensure data quality, and site abstractors were queried to resolve data discrepancies.

Data collected included 1) patient characteristics such as age, gender, race, ethnicity, weight, insurance type, and chronic pre-existing conditions; 2) event characteristics such as first and subsequent monitored cardiac rhythms, drugs administered, intravenous access and airway management, and use of defibrillation or open-chest CPR; 3) etiology of cardiac arrest; 4) hospital course such as subsequent arrests, seizures, use of extracorporeal membrane oxygenation (ECMO), TH, other intensive care interventions and monitoring devices, and drug therapies; 5) physiologic and laboratory data such as vital signs, blood gases and chemistries, and pupillary reflexes prior to arrest at 0–6 hrs and >6–12 hrs; 6) Pediatric Cerebral Performance Category (PCPC) scores (22) prior to cardiac arrest, and at PICU and hospital discharge; and 7) outcomes such as survival to PICU and hospital discharge, PICU and hospital discharge location, and need for supplemental oxygen, enteral tube feedings, tracheostomy or mechanical ventilation at hospital discharge. PCPC scores measure degree of cognitive function and range from 1 to 6 where 1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative state, and 6 = brain death (22).

In addition, dates and times of important clinical events were recorded and related time intervals determined. These intervals included the time from arrest to initiation of CPR, first defibrillation attempt, vascular access, intubation, first epinephrine dose, PICU admission, ECMO, TH, first seizure, and rehabilitation consultation, as well as the duration of CPR, ECMO, TH, PICU and hospital stay. Utstein style definitions were used for most variables in which such definitions exist (23, 24).

Several steps were taken to prepare the data for analysis. Prior to analysis, we reviewed time intervals for invalid or extreme values. If a value was considered impossible or extremely unlikely based on a valid range for that variable, it was set to missing for the analysis. For example, the time to first epinephrine dose after arrest was set to missing if it was negative, or if the value was greater than 120 minutes. Physiologic and laboratory data were collected as minimum and maximum values obtained from 0–6 h and >6–12 h. If there was only one value provided for a time interval, this value was assigned to both the minimum and maximum. To obtain the minimum value for the first 12 h, we took the minimum of both time intervals, and the same approach was used for the maximum. A value was only considered missing if it was missing across both 0–6 h and >6–12 h. Similarly, for drugs administered during cardiac arrest in the OH cohort, data were based on any documentation of drugs received either prior to hospital arrival or in the hospital.

Statistical Analyses

Each analysis was restricted to patients having full data on relevant variables. Each variable was described for survivors and non-survivors using counts and percentages for categorical variables and the median and interquartile range (IQR) (25th – 75th percentile) for continuous variables. The association of each variable with survival to hospital discharge was examined using Chi-square or Fisher's exact tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. The Cochran-Armitage test for trend was used for ordered categorical variables.

Logistic regression with forward stepwise variable selection was used to explore and describe independent variables most strongly associated with mortality. Variables were screened with the appropriate univariate test described above and eligible for inclusion in the logistic regression model if the unadjusted p-value was < 0.25. In addition, the decision was made *a priori* to include patient age, gender and asystole or ventricular fibrillation/ventricular tachycardia (VF/VT) anytime during the arrest in the model regardless of statistical significance. Otherwise, the criteria for variable selection were a significance level to enter the model of 0.05 and significance level to stay in the model of 0.10. In order to have a stable and generalizable model, variables missing in > 20% of cases were not included in variable selection, nor did we include a variable unless at least 5 survivors and 5 non-survivors had the characteristic of interest.

Using the approach outlined above, two final logistic regression models were built. The first model included only variables available before and during the arrest. The second model additionally considered variables collected in the first 12 hours post-arrest. Adjusted odds ratios and 95% confidence intervals were calculated for each model. The c-statistic, or area under the receiver operating characteristic curve, is also reported. All analyses were conducted in SAS version 9.1 (SAS Institute Inc., North Carolina).

RESULTS

A total of 138 pediatric OH cardiac arrest cases with ROC were submitted from the 15 PECARN associated sites over the 18-month period. There were 53 survivors (38%) and 85 non-survivors (62%). Survivors and non-survivor groups were similar with respect to age,

gender, Hispanic ethnicity, insurance type and the frequency of chronic conditions (Table 1). Race classification was associated with mortality ($p=0.05$), with higher mortality in white and black classifications compared to the other/unknown group. Duration of PICU and hospital stay was longer in survivors than non-survivors (6.0 (2.0, 17.0) vs. 2.0 (1.0, 3.0) and 15.0 (3.0, 23.0) vs. 2.0 (1.0, 3.0) days, both $p<0.01$).

Arrest characteristics are described in Table 2. OH arrests with ROC occurred most commonly during the daytime hours 7AM to 6:59 PM (60%) compared to nighttime hours 7 PM to 6:59 AM (40%). Survivors were more likely to have arrested in the daytime than non-survivors (68% vs. 55%; $p=0.13$), but statistical significance was not seen possibly due to small sample size. Arrests occurring on weekends (Saturday or Sunday) were associated with higher survival than on weekdays ($p<0.01$). Witnessed arrests occurred in 44% and bystander CPR was documented in 65%, but neither was associated with outcome. Ongoing chest compressions at hospital arrival occurred in 61% and was strongly associated with higher mortality ($p<0.01$). First documented arrest rhythm was described as asystole in 46%, pulseless electrical activity (PEA) in 10%, bradycardia in 10%, VF 5%, VT 1.4 %, other in 3% and unknown in 24%. Asystole at any time during the arrest was more common in non-survivors than survivors (67% vs. 26%, $p<0.01$). Fourteen patients had bradycardia described as the initial rhythm in this cohort. The number of doses of epinephrine received by this group was documented in 13 of the 14 cases; 7 cases received 2 or more doses, 2 cases received 1 dose and 4 cases received no epinephrine. For all arrests, administration of epinephrine, atropine and sodium bicarbonate during the arrest was associated with greater mortality. Duration of CPR was known and documented in only 69 of the 138 cases. Survivors had a median duration of CPR of 18.5 (3.5, 28.5) minutes versus 41.0 (24.0, 54.0) minutes in non-survivors ($p<0.01$).

Figure 1 depicts a simple plot of mortality percent versus number of epinephrine doses. Number of epinephrine doses was inversely associated with live hospital discharge ($p<0.01$). Three or more doses of epinephrine were administered to 66 patients; 13 (20%) survived to hospital discharge. Only 2 of these 13 were normal (PCPC=1) at hospital discharge. An additional survivor had mild disability (PCPC=2), but the baseline PCPC was unknown in this case. Nine (9) of the 13 (69%) had PCPC change of at least 2 categories. Administration of four or more doses of epinephrine was associated with death or poor outcome in 44/46 cases with death in 39 (85%), comatose or severe disability in 4 (9%), and moderate disability 1 (2%). In only 2/46 (4%) cases were good outcomes defined as normal or mild disability at hospital discharge reported. The maximum number of epinephrine doses documented in a survivor was six (6), however, PCPC changed from 1 (normal) to 4 (severe disability) for this patient. The maximum number of epinephrine doses received in a normal survivor (PCPC=1) was 5.

The most common causes attributed for the arrest are listed in Table 3. Patients with an etiology of drowning / asphyxia were more likely to survive to hospital discharge than patients with other arrest etiologies ($p=0.04$). Table 4 describes post-arrest monitoring and interventions in the 0 to 12 hour time interval after ROC. Survivors and non-survivors were similar except for a higher frequency of arterial lines and central venous lines in non-survivors. An inotropic or vasopressor agent infusion was used nearly twice as commonly in non-survivors. Epinephrine was a frequently used agent in both groups. TH was uncommonly utilized in this cohort with fewer than 3% of cases receiving this intervention. A subsequent cardiac arrest within 24 h was more often observed in non-survivors as expected. However, the presence of seizures occurred at a similar frequency in both groups.

In Table 5, physiologic and laboratory values are described for temperature, pH, lactate and glucose measurements. Non-survivors had a lower minimum body temperature than

survivors reported during the early 12 h post-arrest period. Non-survivors had a lower minimum pH recorded during the 12 h period following ROC. Highest recorded lactate and glucose values within 12 h post-arrest were greater in non survivors. As would be expected, documentation of bilateral equal responsive pupils during the 12 h period following ROC period was associated with increased survival.

PCPC at baseline and at hospital discharge was available for most cases in this cohort (127/138 [50 survivors and 77 non-survivors]). Overall, 83% (105/127) of cases had a normal PCPC (=1) prior to the arrest. Twenty-seven (54%) survivors had a PCPC of 1 or 2 at hospital discharge. There were 30 survivors (60%) with no change in PCPC at discharge; 20 (40%) survivors had a change in PCPC of 1 or greater. Overall, 62% (31/50) of survivors had a PCPC at hospital discharge of 1 or 2, or no change from baseline PCPC. Mortality (including patients with missing PCPC data), was 85/138 (62%).

Table 6 summarizes two logistic regression models for variables with information available upon ROC and with additional information available through 12 hour post-arrest. After controlling for patient age, gender, race and cardiac rhythm asystole or ventricular fibrillation/ventricular tachycardia (VF/VT) anytime during the arrest, the number of epinephrine doses and administration of atropine were associated with mortality (area under curve 0.83). In the second model additional information reported through 12 h was utilized. A history of preexisting lung disease, etiology of arrest of drowning or asphyxia, higher minimum pH, and the presence of bilateral reactive pupils at anytime up to 12 h were each associated with lower mortality (area under curve 0.86).

Figure 2 depicts the probability of death based on minimum pH during the initial 12 h after arrest for patients with and without drowning/asphyxial arrest. Predicted probabilities are based on an “average” cardiac arrest patient with median age (2.9 years) and values for all other variables based on most frequently observed in population, ie, white male with asystole arrest rhythm and pupils not responsive at some point during 12 hours post-arrest. For a given pH, patients with drowning/asphyxial arrest had lower mortality.

DISCUSSION

Currently there exist inadequate data in the literature upon which to plan interventional clinical trials in children achieving ROC following cardiac arrest. Most U.S. reports in this population are limited by small numbers of cases in series reports and/or single geographic locations (1,16,17). As such, the existing literature is inadequate for planning large multicenter interventional clinical trials aimed to improve neurobehavioral outcomes in this population. The current pre-clinical trial planning cohort study was conducted over a relatively short period of 18 months at 15 PECARN children’s hospitals and represents one of the largest experiences of OH cardiac arrest with ROC cases from a U.S. pediatric population. The participating sites were diversely located across eastern, northern and western regions of the US; the network has limited representation in the most southern states where submersion type events may be more common year round than in other regions. Despite this limitation, our report is likely more generalizable to the overall U.S. pediatric population than existing reports. We believe this is the first report in the literature to focus specifically on OH pediatric cardiac arrest with ROC in a broad based U.S. population.

New findings related to OH pediatric cardiac arrest with ROC were observed in this investigation. First, we observed age was not associated with survival when examined either as a continuous variable or as Utstein style age categories. Previous studies have reported age to be associated with survival; however, the largest prior report included cases without ROC (1). This likely accounts for the different study findings, as cases without ROC

constitute a larger proportion of the total than the subset of cases with ROC (1, 17,18). Second, we observed weekend arrests to be associated with better outcomes following pediatric cardiac arrest in the OH setting and to our knowledge this has not been reported previously. Possible explanations might be the greater availability of adult caregivers during weekends or less traffic and quicker response times by EMS. This is in contrast to observations in adults with in-hospital cardiac arrest, where higher mortality on weekends and night shifts has been demonstrated (25).

Post-arrest factors occurring within 12 h of arrest were also observed to be associated with survival. Higher lowest temperature measured during the 0–12 hour period was associated with better survival. This may be explained by longer duration of CPR associated with lower body temperature. Biochemical measurements during the 0–12 hour period for lower pH, higher lactate and higher glucose were also associated with increased mortality. On clinical exam, the presence of bilateral reactive pupils in the immediate 12 hour period post ROC was associated with higher survival.

The only previous large US based report to describe both survival and neurological outcome in a pediatric OH arrest with ROC cohort was by Young et al (1). This was a secondary analysis of a dataset from a clinical trial of OH airway management conducted between 1994 and 1997 from two counties in the Los Angeles area. After excluding cases that did not have ROC, 165 cases with OH cardiac arrest with ROC were described (1). Overall, 51 (31%) cases were discharged home alive, while 114 (69%) died during hospitalization. Of those who survived to hospital discharge, good PCPC (1 or 2) occurred in 16/51 (31%), no change from previously abnormal neurologic status in 11/51 (22%), and poor outcome 3–5 occurred in 24/51 (47%). Nearly half (26) of the 51 survivors did not receive epinephrine. In our cohort, 138 cases with cardiac arrest and ROC occurred over 18 months at 15 PECARN children's hospitals. Overall, 62% (85/138) of cases died, while 38% (53/138) survived. Of survivors with available PCPC information (n=50), 27 (54%) had a PCPC of 1 or 2 at hospital discharge; 4 (8%) had no change from previously abnormal PCPC, and 19 (38%) had a poor outcome (score 3–5). Approximately 50% of survivors of OH cardiac arrest did not receive epinephrine, similar to the Young report.

Previous reports have attempted to describe a specific number of epinephrine doses in which outcome was universally poor so that futility of the resuscitation intervention could be assured. More than 2 or 3 doses of epinephrine have been reported as such cut points in the past (1,3). In 1996, Schindler reported no survivors of pediatric cardiac arrest if more than 2 doses of epinephrine were required. Young more recently reported in 2004 greater than 3 epinephrine doses to be universally associated with poor survival outcome (1). In our cohort, 46 patients had greater than three doses of epinephrine. Only 7 of these 46 children survived with live hospital discharge. Six of the 7 had normal PCPC reported prior to cardiac arrest; at hospital discharge one survivor was comatose, three had severe disability, one had an outcome of moderate disability, and one had normal outcome. One case had unknown baseline PCPC and had mild disability (PCPC=2) at discharge. Overall, 44/46 (96%) had poor outcome defined as death or PCPC > 2. Therefore, four or more doses of epinephrine cut point was usually, but not always, associated with poor outcome in our experience. Finally, we believe caution is required as future interventions (i.e. therapeutic hypothermia) may alter any arbitrary cut points (epinephrine doses, duration of cardiac arrest, biomarker measurements, etc), resulting in inaccurate prognostication.

We performed exploratory logistic regression analyses to determine which factors were most strongly associated with outcome at the time of ROC, while controlling for patient age, gender, race and cardiac rhythm asystole or ventricular fibrillation/ventricular tachycardia (VF/VT) anytime during the arrest. Similar analyses were also performed with additional

information available up to 12 h after ROC. For variables available at the completion of the CPR (Model 1), only the use of epinephrine and atropine were independently associated with reduced survival (AUC 0.83). In a model with additional factors available out to 12 hours following arrest (Model 2), preexisting lung or airway disease, etiology of arrest drowning or asphyxia, higher pH, and reactive pupils were all associated with lower mortality (AUC 0.86).

A major limitation of the existing pediatric cardiac arrest literature concerns long-term neurological outcome of survivors. In our report, neurological outcome could only be ascertained at hospital discharge with the simple clinical score PCPC (20). Optimally, outcome would be assessed at follow up periods of at least a year or more with more extensive neurobehavioral assessment tools. Limited reports have suggested that following cardiac arrest the status of children at hospital discharge is similar to that measured at 12 month follow up (26). Detailed neurobehavioral testing on a large number of cases has not been reported at one year or longer follow-up after pediatric OH cardiac arrest. This may be needed to detect more subtle changes in long-term neurobehavioral outcome (27). 'Good' outcome has been defined in some large reports as a PCPC score 1, 2, or 3 for in-hospital cardiac arrest (28). For society and individual families, a decline in even one level is likely to represent a huge burden in terms of family adjustment, school performance and long term functioning in society. Long term follow up with age appropriate neurobehavioral testing may detect more subtle changes in brain function following 'successful' resuscitation than can be detected with gross measurement by PCPC or similar scales.

Another limitation of our study commonly observed in other cardiac arrest reports concerns missing data for some variables of interest. For example, initial cardiac arrest rhythm has often been missing information even in optimal settings of cardiac arrest. One study from the National Registry of Cardiopulmonary Resuscitation (NRCPR) database of pediatric in-hospital cardiac arrests, reported missing first documented rhythm occurring in 22% of cases (28). In spite of the fact that most in-hospital cardiac arrests occurred in monitored settings (PICU and ED) and records were abstracted by trained personnel, missing information is common. Therefore, it is not surprising that our OH cohort had missing information for initial rhythm in 24%, a rate similar to that in the NRCPR. An exception is the study of OH cardiac arrest by Young et al who reported arrest rhythms in 548/601 cases (91%). This was possibly due to real time contact of EMS paramedic personnel by study investigators. The authors described that they were able to complete data for rhythm classification even if it was not available in the EMS record. This was primarily the result of reclassification of the rhythms recorded on EMS forms as PEA (1). An additional limitation of our retrospective cohort study was that we could not capture information on the training of the individuals performing resuscitation or whether standard PALS guidelines were followed. Because we only examined cases with ROC for at least 20 minutes, it is likely at least partially effective resuscitation was provided at some point to result in ROC.

Some notable population differences exist between our report and that of Young et al (1). The latter report included newly born cardiac arrest cases (5%), while ours excluded these cases. This age group had a higher survival than older infants (36% vs 4%) (1). The newborn group was a planned exclusion in our study since TH for newborns with hypoxic ischemic encephalopathy was being actively evaluated in several completed or ongoing trials (12,13), and the NRCPR recommends newborns be analyzed separately. Additionally, in our cohort cases up to 18 years of age were included while Young et al did not report data on cases more than 40 kg or 12 yrs of age. Their population originated from two counties near Los Angeles and may not be generalizable to the rest of US. Our 15 centers were wide spread and well represented across the US, with the exception of southern sites. In spite of these distinct differences, our findings are relatively similar.

It should be emphasized that our report differs from others in the literature in several important respects. Since our primary goal was to collect feasibility information for interventional TH trials in children after cardiac arrest, we excluded cases that did not survive the initial resuscitation event to have ROC for at least 20 minutes. For this reason, comparison of our findings directly with other reports that often included cases without ROC would need to account for this difference. In a recent literature review of out of hospital cardiac arrest reported approximately 70% of out of hospital arrests in children not to have ROC (17). Another difference is that we had study-specific inclusion and exclusion criteria. For example, since we were planning a clinical trial of TH after pediatric cardiac arrest, we were primarily interested in a population with at least some risk of mild to severe hypoxic-ischemic brain injury. Therefore, we excluded all cases that received less than a minute of chest compressions, regardless of whether epinephrine or defibrillation was administered. Finally, we excluded cases less than 24 hours of age (newborn) since TH studies have been and are being conducted in this population.

A simple requirement of a minimum of 1 minute of chest compressions was used for our definition of cardiac arrest as inclusion criteria in planning a future RCT of TH after cardiac arrest. We did not use the existing NRCPR definition of in-hospital cardiac arrest, which emphasizes documentation in the medical record of the absence of a palpable pulse or a rhythm not associated with a pulse. Pulse detection or absence of it is an extremely unreliable and problematic physical finding to accurately measure in adults under optimal conditions; trained pediatric caregivers perform poorly as well (29–31); an expert group has ranked it as a high research priority (31). An American Heart Association-affiliated expert group recently proposed a different ‘pragmatic definition’ for OH cardiac arrest to include ‘receives chest compressions by EMS personnel’ (32).

In conclusion, this multicenter cohort study is one of the largest to date and reports new associations related to OH pediatric cardiac arrest with ROC outcomes. Weekend arrests (Saturday or Sunday) were associated with higher survival than those occurring on weekdays. We observed greater than 3 epinephrine doses to be associated with poor outcome (96%), although good outcome did occur infrequently (4%). In a multivariate model that used information available up to 12 hours after ROC and controlled for patient age, gender, race, and cardiac rhythm asystole or VF/VT at anytime during the arrest, we observed factors most strongly associated with lower mortality to be 1) a history of preexisting lung disease, 2) etiology of arrest drowning or asphyxia, 3) higher minimum pH, and 4) the presence of bilateral reactive pupils. Using information only available up to ROC, number of epinephrine doses and atropine use were most strongly associated with higher mortality. Finally, investigators should be aware that when planning clinical trials related to cardiac arrest, variables associated with outcome in prior reports that include cases with and without ROC may not be associated with outcome in the subset with ROC. Pre-clinical trial cohort studies may clarify such associations and assist in the planning of clinical trials.

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Appendix

We acknowledge the efforts of the following individuals participating in PECARN at the time this study was initiated.

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Figure 1.

Simple plot of mortality percent versus number of epinephrine doses received

Numbers on graph depict the number of cases who receiving the described epinephrine doses 12 missing cases from total of 138

Number of epinephrine doses was inversely associated with live hospital discharge ($p < 0.01$).

Figure 2.

Predicted probabilities of death for lowest pH values within 12 hours of ROC^a

^a Based on logistic regression Model 2 (including variables prior to, during, and up to 12 hours after cardiac arrest). The predicted probabilities are based on an “average” cardiac arrest patient with median age (2.9 years) and values for all other variables based on most frequently observed in population, ie, white male with asystole arrest rhythm and pupils not responsive at some point during 12 hours post-arrest.

Table 1Patient Characteristics and Relationship to Hospital Survival^a

	Survivors (N=53)	Non-survivors (N=85)	P- Value ^b
	Median (IQR)	Median (IQR)	
Age (years)	3.1 (0.9, 10.0)	2.7 (0.5, 12.0)	0.98
Weight (kg)	15.1 (10.5, 32.0)	15.0 (7.0, 35.0)	0.88
	<i>n (percent)</i>	<i>n (percent)</i>	
Age category (Utstein)			0.66
0 to 30 days	2 (4)	3 (4)	
31 days to < 1 year	11 (21)	28 (33)	
1 year - < 3 years	12 (23)	14 (16)	
3 years - < 8 years	10 (19)	10 (12)	
8 years to < 14 years	12 (23)	20 (24)	
14 years to < 19 years	5 (10)	10 (12)	
Gender (male)	36 (68)	58 (70)	0.81
Race			0.05
White	21 (40)	42 (49)	
Black	13 (25)	28 (33)	
Other/Unknown	19 (36)	15 (18)	
Ethnicity			0.36
Hispanic	3 (6)	2 (2)	
Not Hispanic	25 (47)	34 (40)	
Unknown	25 (47)	49 (58)	
Insurance type			0.13
Commercial	29 (58)	32 (40)	
Medicaid	17 (34)	38 (48)	
Other	4 (8)	10 (13)	
Any chronic pre-existing condition	28 (53)	40 (47)	0.51
Specific chronic pre-existing conditions ^c			
Prenatal conditions or complications	5 (9)	12 (14)	0.42
Lung or airway disease	14 (26)	15 (18)	0.22
Congenital heart disease	5 (9)	9 (11)	0.83
Gastrointestinal	4 (8)	9 (11)	0.77
Neurological	15 (28)	15 (18)	0.14

^aUnavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: age (1), weight (4), gender (2), insurance type (8).

^bFor comparison between survivors and non-survivors, we used Chi-square or Fisher's exact test for categorical variables, Wilcoxon rank-sum test for continuous variables, and the Cochran-Armitage trend test for ordered categorical variables.

^cFor chronic pre-existing conditions, a condition was assumed to be not present unless specifically noted otherwise.

Table 2Cardiac Arrest Event Characteristics and Relationship to Hospital Survival^a

	Survivors (N=53)	Non-survivors (N=85)	P-Value ^b
	n (percent)	n (percent)	
Day of arrest (if unavailable, using CPR, ROC, or arrival at hospital)			0.01
Weekday	33 (62)	69 (81)	
Weekend	20 (38)	16 (19)	
Time of arrest (if unavailable, using CPR, ROC, or arrival at hospital)			0.13
Day (7:00 am – 6:59 pm)	34 (68)	46 (55)	
Night (7:00 pm – 6:59 am)	16 (32)	38 (45)	
Arrest witnessed	27 (51)	32 (39)	0.17
Bystander performed CPR	35 (69)	49 (63)	0.50
CPR ongoing at time of arrival to initial hospital	18 (35)	61 (77)	< 0.01
First monitored rhythm			< 0.01
Asystole	13 (25)	51 (60)	
Bradycardia	9 (17)	5 (6)	
Pulseless electrical activity	3 (6)	11 (13)	
Ventricular fibrillation/ tachycardia	5 (9)	4 (5)	
Other / Unknown	23 (43)	14 (16)	
Asystole rhythm ever reported	14 (26)	57 (67)	< 0.01
Ventricular fibrillation/ tachycardia rhythm ever reported	8 (15)	22 (26)	0.14
Defibrillated prior to hospital arrival	4 (10)	5 (7)	0.72
Drugs administered during arrest			
Fluid bolus	17 (33)	41 (49)	0.06
Atropine	11 (21)	56 (67)	< 0.01
Sodium Bicarbonate	10 (19)	46 (55)	< 0.01
Calcium	1 (2)	9 (11)	0.09
Vasopressin	1 (2)	1 (1)	1.00
Lidocaine	2 (4)	10 (12)	0.13
Amiodarone	2 (4)	0 (0)	0.15
Number of epinephrine doses			< 0.01
0 doses	24 (52)	6 (8)	
1 dose	5 (11)	8 (10)	
2 doses	4 (9)	13 (16)	
3 doses	6 (13)	14 (18)	
4 doses	2 (4)	10 (13)	
5 doses	4 (9)	7 (9)	
> 5 doses	1 (2)	22 (28)	
	Median (IQR)	Median (IQR)	

	Survivors (N=53)	Non-survivors (N=85)	P-Value ^b
	n (percent)	n (percent)	
Epinephrine doses administered	0.0 (0.0, 3.0)	3.0 (2.0, 6.0)	< 0.01
	Mean $\pm$ SD	Mean $\pm$ SD	
Epinephrine doses administered	1.4 $\pm$ 1.8	4.0 $\pm$ 2.8	< 0.01

^a Unavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: time of arrest (4), arrest witnessed (3), bystander CPR (9), CPR ongoing at arrival (8), defibrillated prior to hospital arrival (28), drugs administered (3), epinephrine administered (12).

^b For comparison between survivors and non-survivors, we used Chi-square or Fisher's exact for categorical variables, Wilcoxon rank-sum test for continuous variables, and the Cochran-Armitage trend test for ordered categorical variables.

Table 3Etiology of Cardiac Arrest and Relationship to Hospital Survival^a

	Survivors (N=53)	Non-survivors (N=85)	P-Value ^b
	n (percent)	n (percent)	
Cardiac (not congenital heart disease)			
Arrhythmia	7 (13)	6 (7)	0.24
Other	4 (8)	3 (4)	0.43
Congenital heart disease	1 (2)	5 (6)	0.40
Respiratory			
Acute life threatening event	7 (13)	15 (18)	0.47
Respiratory failure	12 (23)	25 (30)	0.36
Drowning / Asphyxia	22 (42)	21 (25)	0.04
Other	1 (2)	9 (11)	0.09
Neurological	1 (2)	4 (5)	0.65
Drug overdose / ingestion	1 (2)	3 (4)	1.00
Trauma	3 (6)	12 (14)	0.12
Electrolyte imbalance / terminal condition	3 (6)	2 (2)	0.37

^aPatients could have multiple categories identified for etiology of arrest. There was one patient (a non-survivor) who did not have any information documented for etiology of arrest. This patient was excluded from percentage calculations.

^bChi-square or Fisher's exact used for comparison between survivors and non-survivors.

Table 4Post-Arrest Hospital Course (0–12 Hours) and Relationship to Hospital Survival^a

	Survivors (N=53)	Non- survivors (N=85)	P-Value ^b
	n (percent)	n (percent)	
ICU interventions and monitoring devices			
Cardiac monitor	47 (96)	83 (99)	0.55
Pulse oximeter	47 (96)	83 (99)	0.55
Peripheral intravenous catheter	45 (92)	71 (85)	0.22
Intraosseous access	8 (16)	23 (27)	0.15
Central venous catheter / CVP	31 (63)	69 (82)	0.02
Arterial catheter	26 (53)	64 (76)	0.01
Mechanical ventilation	42 (86)	80 (95)	0.10
Therapeutic hypothermia	1 (2)	2 (2)	1.00
ECMO	1 (2)	2 (2)	1.00
Drug therapies			
Antiarrhythmics	10 (20)	23 (27)	0.37
Anticonvulsants	12 (24)	23 (27)	0.71
Any inotrope or vasopressor	22 (45)	71 (85)	< 0.01
Dopamine	10 (20)	38 (45)	< 0.01
Dobutamine	2 (4)	15 (18)	0.02
Epinephrine	19 (39)	57 (68)	< 0.01
Norepinephrine	0 (0)	5 (6)	0.16
Milrinone or inamrinone	1 (2)	5 (6)	0.41
Vasopressin	1 (2)	9 (11)	0.09
Other inotrope or vasopressor	5 (10)	13 (15)	0.39
Subsequent arrests w/in 24 hrs of initial CA	5 (9)	26 (31)	< 0.01
Seizures (any time post-arrest)	11 (22)	24 (29)	0.33

^aUnavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: ICU intervention and monitoring devices (5) [except therapeutic hypothermia (0)], drug therapies (5).

^bChi-square or Fisher's exact used for comparison between survivors and non-survivors.

Table 5
Physiologic and Laboratory Values (0–12 Hours Post-Arrest) and Relationship to Hospital Survival^a

	Survivors (N=53)		Non-survivors (N=85)		P-Value ^b
	N	Median (IQR)	N	Median (IQR)	
Minimum temperature, °C	52	35.5 (33.7, 36.2)	81	33.5 (32.3, 34.8)	< 0.01
Maximum temperature, °C	52	37.9 (37.1, 38.8)	81	37.5 (36.4, 39.0)	0.70
Minimum pH	46	7.17 (7.08, 7.34)	77	6.90 (6.77, 7.06)	< 0.01
Maximum pH	46	7.40 (7.35, 7.46)	77	7.37 (7.27, 7.45)	0.05
Maximum lactate, mmol/L	27	3.5 (2.1, 10.0)	49	10.4 (5.7, 14.8)	< 0.01
Minimum glucose, mg/dL	46	124 (100, 168)	80	143 (93, 250)	0.35
Maximum glucose, mg/dL	46	215 (150, 294)	80	318 (249, 389)	< 0.01
	N	n (percent)	N	n (percent)	
Two responsive pupils	51	31 (60.8)	80	11 (13.8)	< 0.01

^aUnavailable (missing) values were excluded from calculations of summary statistics.

^bFor comparison between survivors and non-survivors, Chi-square test was used for categorical variables and Wilcoxon rank-sum test was used for continuous variables.

Table 6Logistic Regression Models for Hospital Mortality^{a,b}

Model	Variable	Odds Ratio	95% CI	P-value
Model 1 (N=121)				
	Epinephrine Doses	1.44	1.12 – 1.86	<0.01
	Atropine administered during arrest	3.47	1.25 – 9.66	0.02
Model 2 (N=115)				
	Preexisting lung or airway disease	0.26	0.07 – 0.90	0.03
	Etiology of arrest of drowning / asphyxia	0.25	0.08 – 0.80	0.02
	pH (0.10 point change)	0.73	0.58 – 0.92	0.01
	Both pupils reactive	0.18	0.06 – 0.59	<0.01

^aEach model controlled for gender, age, race, and asystole or VF/VT ever documented during arrest.

^bArea under the curve (AUC) as estimated by c-statistic was 0.83 for Model 1 and 0.86 for Model 2.

Model 1 (pre-arrest and arrest variables only) If race (final p-value = 0.10) removed from model selection process, then the variable for etiology of arrest of drowning/asphyxia enters into the model instead. All other variables were unchanged. The c-statistic for the model with drowning/asphyxia was also 0.83.

Model 2 (adding in variables from 12 hours post-arrest) If race (final p-value = 0.09) removed from model selection process, then the final model is unchanged (that is, all variables the same except race is not included).