Multicenter cohort study of out-of-hospital pediatric cardiac arrest*

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Objectives: **To describe a large cohort of children with out-of-hospital cardiac arrest with return of circulation and to identify factors in the early postarrest 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 clinical sites over an 18-month study period. All children from 1 day (24 hrs) to 18 yrs of age with out-of-hospital cardiac arrest and a history of at least 1 min of chest compressions with return of circulation for at least 20 mins were eligible.**

Measurements and Main Results: **One hundred thirty-eight cases met study entry criteria; the overall mortality was 62% (85 of 138 cases). The event characteristics associated with increased survival were as follows: weekend arrests, cardiopulmonary resuscitation not ongoing at hospital arrival, arrest rhythm not asystole, no atropine or $NaHCO_3$, fewer epinephrine doses, shorter duration of cardiopulmonary resuscitation, and drowning or asphyxial arrest event. For the 0- to 12-hr postarrest return-of-circulation 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, and asystole or ventricular fibrillation/ventricular tachycardia 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 hrs after return of circulation found 1) preexisting lung or airway disease; 2) an etiology of arrest drowning or asphyxia; 3) higher pH, and 4) bilateral reactive pupils to be associated with lower mortality. Receiving more than three doses of epinephrine was associated with poor outcome in 96% (44 of 46) of cases.**

Conclusions: **Multiple factors were identified as associated with survival after out-of-hospital pediatric cardiac arrest with the return of circulation. Additional information available within a few hours after the return of circulation 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. (Crit Care Med 2011; 39:141–149)**

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

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 neurologic 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 (VF)- or tachycardia (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 before 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

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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 emergency department, 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 that would investigate the efficacy of TH and potentially other interventions to improve outcomes in children after cardiac arrest, we conducted a pre-randomized controlled trial cohort study at 15 PECARN sites. The purposes of this study were two-fold. The first objective was to describe the patient characteristics, cardiac arrest events, and early postarrest hospital courses in a large cohort of pediatric patients who received OH cardiopulmonary resuscitation (CPR) for >1 min and had a sustained ROC. The second objective was to identify factors most strongly associated with hospital survival outcome in this cohort by using information available at the time of ROC and within 12 hrs 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 postarrest period that would be associated with survival. These factors may need to be considered in the design of a future interventional randomized controlled trial of TH in children.

METHODS

This investigation comes from a National Institute of Child Health and Development-sponsored preclinical trial cohort study conducted by PECARN to precede a randomized clinical trial of TH 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 OH cohorts of cardiac arrest (19). The second paper focused on describing the IH cohort and variables associated with outcome (20). The current study focuses on the OH 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. Patients between 1 day (24 hrs) and 18 yrs of age (inclusive) who experienced an OH cardiac arrest, defined as receiving chest compression for at least 1 min, and who had a ROC for a minimum of 20 mins were eligible for inclusion. Patients who received <1 min of chest compressions, whether or not epinephrine or defibrillation was administered, were excluded. Case classification as OH was assigned if chest compressions were initiated before hospital arrival. Cases with the initiation of chest compressions in the emergency department or other hospital setting were considered to have IH 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 VF/flutter), procedure codes (99.60 CPR 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 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 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 PECARN Central Data Management and Coordinating Center, which 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 preexisting 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, 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 before arrest at 0–6 hrs and >6–12 hrs; 6) pediatric cerebral performance category (PCPC) scores (22) before cardiac arrest and at pediatric intensive care unit (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 the degree of cognitive function and range from 1 to 6, where 1 is normal, 2 is mild disability, 3 is moderate disability, 4 is severe disability, 5 is coma or vegetative state, and 6 is brain death (22).

In addition, the dates and times of important clinical events were recorded, and related time intervals were determined. These intervals included the time from arrest to initiation of CPR, first defibrillation attempt, vascular access, intubation, first epinephrine dose, PICU admission, extracorporeal membrane oxygenation, TH, first seizure, and rehabilitation consultation, as well as the duration of CPR, extracorporeal membrane oxygenation, TH, and 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. Before 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 mins. Physiologic and laboratory data were collected as minimum and maximum values obtained from 0 to 6 hrs and >6 to 12 hrs. 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 hrs, 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 hrs and >6–12 hrs. Similarly, for drugs administered during cardiac arrest in the OH cohort, data were based on any documentation of drugs received either before 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 nonsurvivors by using counts and percentages for

Table 1. Patient characteristics and relationship to hospital survival[a]

Characteristic	Median (Interquartile Range) Survivors, n = 53	Nonsurvivors, n = 85	p^b
Age (yrs)	3.1 (0.9,10)	2.7 (0.5,12)	.98
Weight (kg)	15.1 (10.5,32)	15 (7.0,35)	.88
	n (%)	n (%)	
Age category (Utstein)			.66
0–30 days	2 (4)	3 (4)	
31 days to <1 yr	11 (21)	28 (33)	
1 yr to <3 yrs	12 (23)	14 (16)	
3 yrs to <8 yrs	10 (19)	10 (12)	
8 yrs to <14 yrs	12 (23)	20 (24)	
14 yrs to <19 yrs	5 (10)	10 (12)	
Gender (male)	36 (68)	58 (70)	.81
Race			.05
White	21 (40)	42 (49)	
Black	13 (25)	28 (33)	
Other/unknown	19 (36)	15 (18)	
Ethnicity			.36
Hispanic	3 (6)	2 (2)	
Not Hispanic	25 (47)	34 (40)	
Unknown	25 (47)	49 (58)	
Insurance type			.13
Commercial	29 (58)	32 (40)	
Medicaid	17 (34)	38 (48)	
Other	4 (8)	10 (13)	
Any chronic preexisting condition	28 (53)	40 (47)	.51
Specific chronic preexisting conditions[c]			
Prenatal conditions or complications	5 (9)	12 (14)	.42
Lung or airway disease	14 (26)	15 (18)	.22
Congenital heart disease	5 (9)	9 (11)	.83
Gastrointestinal	4 (8)	9 (11)	.77
Neurologic	15 (28)	15 (18)	.14

[a]Unavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: age (one), weight (four), gender (two), and insurance type (eight); [b]for comparison between survivors and nonsurvivors, we used the chi-square or Fisher's exact test for categorical variables, Wilcoxon's rank sum test for continuous variables, and the Cochran-Armitage trend test for ordered categorical variables; [c]for chronic preexisting conditions, a condition was assumed not to be present unless specifically noted otherwise.

categorical variables and the median and interquartile range (25th to 75th percentile) for continuous variables. The association of each variable with survival to hospital discharge was examined by using chi-square or Fisher's exact tests for categorical variables and Wilcoxon's 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 were eligible for inclusion in the logistic regression model if the unadjusted *p* value was <.25. In addition, the decision was made *a priori* to include patient age, gender, and asystole or VF/VT anytime during the arrest in the model, regardless of statistical significance. Otherwise, the criteria for variable selection were a significance level of .05 to enter the model and a significance level of .10 to stay in the model. In order to have a stable and generalizable model, variables missing in >20% of cases were not included in the variable selection, nor did we include a variable unless at least five survivors and five nonsurvivors 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 hrs after 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, Cary, NC).

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 nonsurvivors (62%). Survivors and nonsurvivor 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 ($p = .05$), with higher mortality in white and black classifications compared with the other/unknown group. The duration of PICU and hospital stay was longer in survivors than nonsurvivors (6 [2 and 17] vs. 2 [1 and 3] days and 15 [3 and 23] vs. 2 [1 and 3] days; both $p < .01$).

Arrest characteristics are described in Table 2. The OH arrests with ROC occurred most commonly during the daytime hours from 7:00 AM to 6:59 PM (60%) compared with nighttime hours from 7:00 PM to 6:59 AM (40%). Survivors were more likely to have arrested in the daytime than nonsurvivors (68% vs. 55%; $p = .13$), 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 ($p < .01$). 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 were strongly associated with higher mortality ($p < .01$). The first documented arrest rhythm was described as asystole in 46%, pulseless electrical activity in 10%, bradycardia in 10%, VF in 5%, VT in 1.4%, other in 3%, and unknown in 24%. Asystole at any time during the arrest was more common in nonsurvivors than survivors (67% vs. 26%; $p < .01$). 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; seven cases received two or more doses, two cases received one dose, and four cases received no epinephrine. For all arrests, administration of epinephrine, atropine, and sodium bicarbonate during the arrest was associated with greater mortality. The 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) mins vs. 41 (24, 54) mins in nonsurvivors ($p < .01$).

Figure 1 depicts a simple plot of mortality percentage vs. the number of epi-

Table 2. Cardiac arrest event characteristics and relationship to hospital survival[a]

Characteristic	Survivors, n = 53 [n (%)]	Nonsurvivors, n = 85 [n (%)]	p^b
Day of arrest (if unavailable, using CPR, return of circulation, or arrival at hospital)			.01
Weekday	33 (62)	69 (81)	
Weekend	20 (38)	16 (19)	
Time of arrest (if unavailable, using CPR, return of circulation, or arrival at hospital)			.13
Day (7:00 AM to 6:59 PM)	34 (68)	46 (55)	
Night (7:00 PM to 6:59 AM)	16 (32)	38 (45)	
Arrest witnessed	27 (51)	32 (39)	.17
Bystander performed CPR	35 (69)	49 (63)	.50
CPR ongoing at time of arrival to initial hospital	18 (35)	61 (77)	<.01
First monitored rhythm			<.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)	<.01
Ventricular fibrillation/tachycardia rhythm ever reported	8 (15)	22 (26)	.14
Defibrillated before hospital arrival	4 (10)	5 (7)	.72
Drugs administered during arrest			
Fluid bolus	17 (33)	41 (49)	.06
Atropine	11 (21)	56 (67)	<.01
Sodium bicarbonate	10 (19)	46 (55)	<.01
Calcium	1 (2)	9 (11)	.09
Vasopressin	1 (2)	1 (1)	1
Lidocaine	2 (4)	10 (12)	.13
Amiodarone	2 (4)	0 (0)	.15
Number of epinephrine doses			<.01
0	24 (52)	6 (8)	
1	5 (11)	8 (10)	
2	4 (9)	13 (16)	
3	6 (13)	14 (18)	
4	2 (4)	10 (13)	
5	4 (9)	7 (9)	
>5 doses	1 (2)	22 (28)	
Epinephrine doses administered [median (interquartile range)]	0.0 (0.0,3.0)	3.0 (2.0,6.0)	<.01
Epinephrine doses administered [mean ± SD]	1.4 ± 1.8	4.0 ± 2.8	<.01

CPR, cardiopulmonary resuscitation.

[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 before hospital arrival (28), drugs administered (3), and epinephrine administered (12); [b]for comparison between survivors and nonsurvivors, we used Chi-square or Fisher's exact for categorical variables, Wilcoxon's rank sum test for continuous variables, and the Cochran-Armitage trend test for ordered categorical variables.

nephrine doses. The number of epinephrine doses was inversely associated with live hospital discharge ($p < .01$). Three or more doses of epinephrine were administered to 66 patients; 13 (20%) survived to hospital discharge. Only two of these 13 were normal (PCPC score of 1) at hospital discharge. An additional survivor had mild disability (PCPC score of 2), but the baseline PCPC score was unknown in this case. Nine (9) of the 13 (69%) patients had a PCPC score change in at least two categories. Administration of four or more doses of epinephrine was associated with death or poor outcome in 44 of 46 cases with death in 39 (85%), coma or severe disability in four (9%), and moderate disability in one (2%). Only two of 46 (4%) cases were good outcomes defined as normal or mild disability reported at hospital discharge. The maximum number of epinephrine doses documented in a survivor was six (6); however, the PCPC score changed from 1 (normal) to 4 (severe disability) for this patient. The maximum number of epinephrine doses received in a normal survivor (PCPC score of 1) was five.

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 ($p = .04$). Table 4 describes postarrest monitoring and interventions in the 0- to 12-hr time interval after ROC. Survivors and nonsurvivors were similar except for a higher frequency of arterial and central venous catheters in nonsurvivors. An inotropic or vasopressor agent infusion was used nearly twice as commonly in nonsurvivors. Epinephrine was a frequently used agent in both groups. TH was uncommonly utilized in this cohort with <3% of cases receiving this intervention. A subsequent cardiac arrest within 24 hrs was more often observed in nonsurvivors as expected. However, the presence of seizures occurred at similar frequencies in both groups.

In Table 5, physiologic and laboratory values are described for temperature, pH, lactate, and glucose measurements. Nonsurvivors had a lower minimum body temperature than survivors as reported during the early 12-hr postarrest period. Nonsurvivors had a lower minimum pH recorded during the 12-hr period following ROC. The highest recorded lactate and glucose values within 12 hrs after arrest were greater in nonsurvivors. As would be expected, the documentation of bilateral equal responsive pupils during the 12 hrs following the ROC period was associated with increased survival.

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

Table 6 summarizes two logistic regression models for variables with information available upon ROC and with additional information available through 12 hrs after

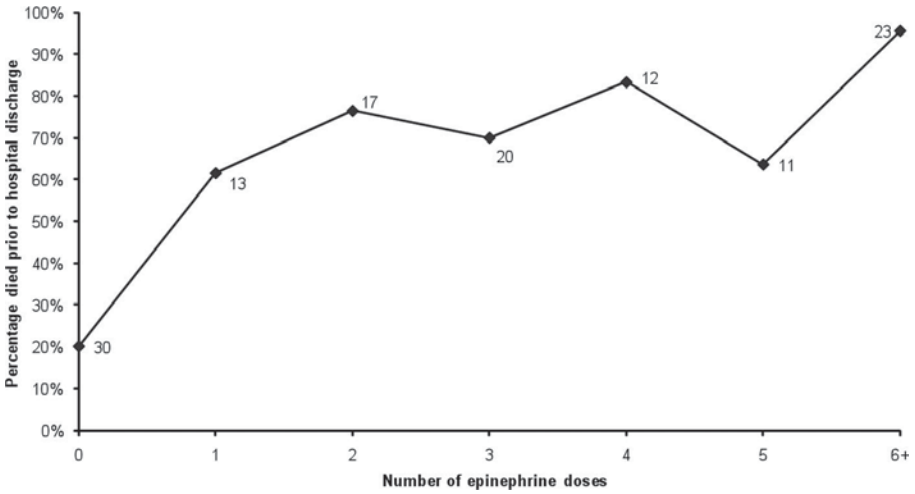

Figure 1. Simple plot of mortality percentage vs. number of epinephrine doses received. Numbers on graph depict the number of cases that were receiving the described epinephrine doses. There were 12 missing cases from a total of 138. The number of epinephrine doses was inversely associated with live hospital discharge ($p < .01$).

Table 3. Etiology of cardiac arrest and relationship to hospital survival[a]

Etiology	Survivors, n = 53 n (%)	Nonsurvivors, n = 85 n (%)	p^b
Cardiac (not congenital heart disease)			
Arrhythmia	7 (13)	6 (7)	.24
Other	4 (8)	3 (4)	.43
Congenital heart disease	1 (2)	5 (6)	.40
Respiratory			
Acute life threatening event	7 (13)	15 (18)	.47
Respiratory failure	12 (23)	25 (30)	.36
Drowning/asphyxia	22 (42)	21 (25)	.04
Other	1 (2)	9 (11)	.09
Neurologic	1 (2)	4 (5)	.65
Drug overdose/ingestion	1 (2)	3 (4)	1
Trauma	3 (6)	12 (14)	.12
Electrolyte imbalance/terminal condition	3 (6)	2 (2)	.37

[a]Patients could have multiple categories identified for etiology of arrest. There was one patient (a nonsurvivor) who did not have any information documented for etiology of arrest. This patient was excluded from percentage calculations; [b]chi-square or Fisher's exact was used for comparison between survivors and nonsurvivors.

arrest. After controlling for patient age, gender, race, and cardiac rhythm asystole or VF/VT anytime during the arrest, the number of epinephrine doses and administration of atropine were associated with mortality (area under curve .83). In the second model additional information reported through 12 hrs was utilized. A history of preexisting lung disease, etiology of arrest drowning or asphyxia, higher minimum pH, and the presence of bilateral reactive pupils at anytime up to 12 hrs were each associated with lower mortality (area under curve .86).

Figure 2 depicts the probability of death based on minimum pH during the initial 12 hrs 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 yrs) and values for all other variables based on most frequently observed in population, i.e., white male with asystole arrest rhythm and pupils not responsive at some point during 12 hrs after 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 preclinical 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 United States; 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 that 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, because 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 emergency medical services (EMS). This is in contrast to observations in adults with IH cardiac arrest, where higher mortality on weekends and night shifts has been demonstrated (25).

Postarrest factors occurring within 12 hrs of arrest were also observed to be associated with survival. A higher lowest temperature measured during the 0- to 12-hr 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- to 12-hr period for lower pH, higher lactate, and higher glucose were also associated with increased

Table 4. After arrest hospital course (0–12 hrs) and relationship to hospital survival[a]

Hospital Course	Survivors, n = 53 n (%)	Nonsurvivors, n = 85 n (%)	p^b
Intensive care unit interventions and monitoring devices			
Cardiac monitor	47 (96)	83 (99)	.55
Pulse oximeter	47 (96)	83 (99)	.55
Peripheral intravenous catheter	45 (92)	71 (85)	.22
Intraosseous access	8 (16)	23 (27)	.15
Central venous catheter/pressure	31 (63)	69 (82)	.02
Arterial catheter	26 (53)	64 (76)	.01
Mechanical ventilation	42 (86)	80 (95)	.10
Therapeutic hypothermia	1 (2)	2 (2)	1
Extracorporeal membrane oxygenation	1 (2)	2 (2)	1
Drug therapies			
Antiarrhythmics	10 (20)	23 (27)	.37
Anticonvulsants	12 (24)	23 (27)	.71
Any inotrope or vasopressor	22 (45)	71 (85)	<.01
Dopamine	10 (20)	38 (45)	<.01
Dobutamine	2 (4)	15 (18)	.02
Epinephrine	19 (39)	57 (68)	<.01
Norepinephrine	0 (0)	5 (6)	.16
Milrinone or inamrinone	1 (2)	5 (6)	.41
Vasopressin	1 (2)	9 (11)	.09
Other inotrope or vasopressor	5 (10)	13 (15)	.39
Subsequent arrests w/in 24 hrs of initial cardiac arrest	5 (9)	26 (31)	<.01
Seizures (any time after arrest)	11 (22)	24 (29)	.33

[a]Unavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: intensive care unit intervention and monitoring devices (five) (except therapeutic hypothermia [0]) and drug therapies (five); [b]chi-square or Fisher's exact was used for comparison between survivors and nonsurvivors.

Table 5. Physiologic and laboratory values (0–12 hrs after arrest) and relationship to hospital survival[a]

	Survivors, n = 53		Nonsurvivors, n = 85		
Value	n	Median (Interquartile Range)	n	Median (Interquartile Range)	p^b
Minimum temperature, °C	52	35.5 (33.7, 36.2)	81	33.5 (32.3, 34.8)	<.01
Maximum temperature, °C	52	37.9 (37.1, 38.8)	81	37.5 (36.4, 39.0)	.70
Minimum pH	46	7.17 (7.08, 7.34)	77	6.90 (6.77, 7.06)	<.01
Maximum pH	46	7.40 (7.35, 7.46)	77	7.37 (7.27, 7.45)	.05
Maximum lactate, mmol/L	27	3.5 (2.1, 10.0)	49	10.4 (5.7, 14.8)	<.01
Minimum glucose, mg/dL	46	124 (100, 168)	80	143 (93, 250)	.35
Maximum glucose, mg/dL	46	215 (150, 294)	80	318 (249, 389)	<.01
Two responsive pupils [n (%)]	51	31 (60.8)	80	11 (13.8)	<.01

[a]Unavailable (missing) values were excluded from calculations of summary statistics; [b]for comparison between survivors and nonsurvivors, Chi-square test was used for categorical variables and Wilcoxon's rank sum test was used for continuous variables.

mortality. On clinical exam, the presence of bilateral reactive pupils in the immediate 12-hr period after ROC was associated with higher survival.

The only previous large U.S.-based report to describe both survival and neurologic 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 area of Los Angeles, CA. After cases that did not have ROC were excluded, 165 cases with OH cardiac arrest with ROC were described (1). Overall, 51 (31%) patients were discharged home alive, whereas 114 (69%) died during hospitalization. Of those who survived to hospital discharge, a good PCPC score (1 or 2) occurred in 16 of 51 (31%), no change from previously abnormal neurologic status in 11 of 51 (22%), and poor outcome (PCPC score of 3–5) occurred in 24 of 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 of 138) of cases died, whereas 38% (53 of 138) survived. Of survivors with available PCPC score information (n = 50), 27 (54%) had a PCPC score of 1 or 2 at hospital discharge; four (8%) had no change from a previously abnormal PCPC score, and 19 (38%) had a poor outcome (score 3–5). Approximately 50% of survivors of OH cardiac arrest did not receive epinephrine, similar to what was reported by Young et al (1).

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 two or three doses of epinephrine have been reported as such cut points in the past (1, 3). In 1996, Schindler et al (3) reported no survivors of pediatric cardiac arrest if more than two doses of epinephrine were required. Young et al (1) more recently reported in 2004 that more than three epinephrine doses were universally associated with poor survival outcome. In our cohort, 46 patients had more than three doses of epinephrine. Only seven of these 46 children survived with live hospital discharge. Six of the seven had normal PCPC scores reported before 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 an unknown baseline PCPC score and had mild disability (PCPC score of 2) at discharge. Overall, 44 of 46 (96%) had poor outcome defined as death or a PCPC score of more than 2. Therefore, a cut point of four or more doses of epinephrine was usually, but not always, associated with poor outcome in our experience. Finally, we believe caution is required as future interventions (i.e., TH) 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 VF/VT anytime during the arrest. Similar analyses were also performed with additional information available up to 12 hrs after

Table 6. Logistic regression models for hospital mortality[a,b]

Model	Variable	Odds Ratio	95% Confidence Interval	p
Model 1 (n = 121)	Epinephrine doses	1.44	1.12–1.86	<.01
	Atropine administered during arrest	3.47	1.25–9.66	.02
Model 2 (n = 115)	Preexisting lung or airway disease	.26	.07–.90	.03
	Etiology of arrest of drowning/asphyxia	.25	.08–.80	.02
	pH (.10 point change)	.73	.58–.92	.01
	Both pupils reactive	.18	.06–.59	<.01

Model 1 (prearrest and arrest variables only). If race (final p value = .10) was removed from the model selection process, then the variable for etiology of arrest drowning/asphyxia enters into the model instead. All other variables were unchanged. The c-statistic for the model with drowning/asphyxia was also .83.

Model 2 (adding in variables from 12 hrs postarrest). If race (final p value = .09) was removed from model selection process, then the final model was unchanged (that is, all variables were the same, except race was not included).

[a]Each model controlled for gender, age, race, and asystole or ventricular fibrillation/ventricular tachycardia ever documented during arrest; [b]area under the curve as estimated by c-statistic was .83 for model 1 and .86 for model 2.

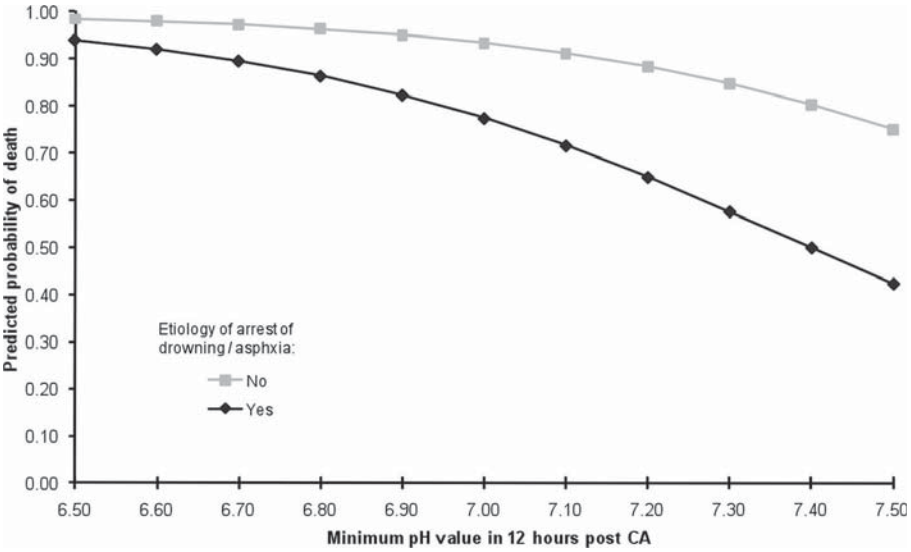

Figure 2. Predicted probabilities of death for lowest pH values within 12 hrs of return of circulation, which was based on logistic regression model 2 (including variables before, during, and up to 12 hrs after cardiac arrest [*CA*]). The predicted probabilities are based on an "average" cardiac arrest patient with median age (2.9 yrs), and values for all other variables are based on the most frequently observed in population, i.e., white male with asystole arrest rhythm and pupils not responsive at some point during the 12 hrs after arrest.

ROC. For variables available at the completion of the CPR (model 1), only the use of epinephrine and atropine was independently associated with reduced survival (area under curve .83). In a model with additional factors available out to 12 hrs 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 (area under curve .86).

A major limitation of the existing pediatric cardiac arrest literature concerns the long-term neurologic outcome of survivors. In our report, neurologic outcome could only be ascertained at hospital discharge with the simple clinical PCPC score (20). Optimally, outcome would be assessed at follow-up periods of at least 1 yr 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 a 12-month follow-up (26). Detailed neurobehavioral testing on a large number of cases has not been reported at 1-yr-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 IH 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 score 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 IH cardiac arrests reported missing first documented rhythm occurring in 22% of cases (28). In spite of the fact that most IH cardiac arrests occurred in monitored settings (PICU and emergency department) 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 (1), who reported arrest rhythms in 548 of 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 pulseless electrical activity (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 pediatric advanced life support guidelines were followed. Because we examined only cases with ROC for at least 20 mins, 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 newborn cardiac arrest cases (5%), whereas 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 because 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, patients up to 18 yrs of age were included, whereas Young et al (1) did not report data on patients of >40 kg or 12 yrs of age. Their population originated from two counties near Los Angeles, CA and may not be generalizable to the rest of the United States. Our 15 centers were widespread and well represented across the United States, 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. Because 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 mins. For this reason, comparison of our findings directly with other reports that often included cases without ROC would need to account for this difference. A recent literature review of OH cardiac arrest reported approximately 70% of OH arrests in children not to have ROC (17). Another difference is that we had study-specific inclusion and exclusion criteria. For example, because 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 <1 min of chest compressions, regardless of whether epinephrine or defibrillation was administered. Finally, we excluded patients of <1 day (24 hrs) of age (newborn) because TH studies have been and are being conducted in this population.

A simple requirement of a minimum of 1 min of chest compressions was used for our definition of cardiac arrest as inclusion criteria in planning a future randomized controlled trial of TH after cardiac arrest. We did not use the existing NRCPR definition of IH 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 pulse 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), and 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 more than three 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 hrs 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 available only up to ROC, the 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. Preclinical trial cohort studies may clarify such associations and assist in the planning of clinical trials.

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