In-hospital versus out-of-hospital pediatric cardiac arrest: A multicenter cohort study*

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Objectives: To describe a large multicenter cohort of pediatric cardiac arrest (CA) with return of circulation (ROC) from either the in-hospital (IH) or the out-of-hospital (OH) setting and to determine whether significant differences related to pre-event, arrest event, early postarrest event characteristics, and outcomes exist that would be critical in planning a clinical trial of therapeutic hypothermia (TH).

Design: Retrospective cohort study.

Setting: Fifteen Pediatric Emergency Care Applied Research Network sites.

Patients: Patients aged 24 hours to 18 years with either IH or OH CA who had a history of at least 1 minute of chest compressions and ROC for at least 20 minutes were eligible.

Interventions: None.

Measurements and Main Results: A total of 491 patients met study entry criteria with 353 IH cases and 138 OH cases. Major differences between the IH and OH cohorts were observed for patient prearrest characteristics, arrest event initial rhythm described, and arrest medication use. Several postarrest interventions were used differently, however, the use of TH was similar (<5%) in both cohorts. During the 0–12-hour interval following ROC, OH cases had lower minimum temperature and pH, and higher maximum serum glucose recorded. Mortality was greater in the OH cohort (62% vs. 51%, $p = 0.04$) with the cause attributed to a neurologic indication much more frequent in the OH than in the IH cohort (69% vs. 20%; $p < 0.01$).

Conclusions: For pediatric CA with ROC, several major differences exist between IH and OH cohorts. The finding that the etiology of death was attributed to neurologic indications much more frequently in OH arrests has important implications for future research. Investigators planning to evaluate the efficacy of new interventions, such as TH, should be aware that the IH and OH populations differ greatly and require independent clinical trials. (Crit Care Med 2009; 37:2259–2267)

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

Cardiac arrest (CA) in childhood is often a catastrophic event that is associated with mortality or poor neurologic outcome in the in-hospital (IH) or out-of-hospital (OH) setting (1–19). Until recently, most studies of pediatric OH and IH CA with return of circulation (ROC) have been relatively small retrospective reports from single sites or geographical areas (5–19). Two contemporary reviews of the literature about OH pediatric CA have summarized available information and concluded that nonuniform data collection and inadequate outcome information exist for this setting (1, 2).

For CA in the IH setting, the American Heart Association's National Registry of Cardiopulmonary Resuscitation (NRCPR) database has addressed many of the limitations of small case series reports (3). It has been used extensively for quality improvement and research. The data collection for adults and pediatric cases has

been standardized and includes consistent data field definitions and data abstractor training for review of primary data sources at each site. At this time, however, there is no comparable data set for OH CA in children.

Because of the dismal neurologic outcomes associated with CA, especially in the OH setting, interventions to ameliorate hypoxic-ischemic encephalopathy following CA have been sought for decades. Until recently, no therapy had been demonstrated to improve outcome in any human population. In 2002, two randomized clinical trials (RCTs) of therapeutic hypothermia (TH) for adults with OH ventricular fibrillation or pulseless ventricular tachycardia reported improved survival with good neurologic outcome (20, 21). In 2005, three trials of TH in newborns with hypoxic-ischemic encephalopathy reported improved survival with good neurologic outcome (22–24). Clinical trials of TH in adult and pediatric populations with traumatic brain injury have not demonstrated benefit at this time (25, 26). A recently completed pediatric trial of traumatic brain injury observed a trend for lower survival in patients receiving TH (25). Clinical trials of TH for pediatric CA have not been conducted to date, although expert surveys have ranked the efficacy of TH for pediatric CA as an urgent research priority (27).

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 (28). The scope of both the Emergency Medical Services for Children and the PECARN research agenda includes the continuum of care from prehospital, emergency department, operating room, pediatric intensive care unit (PICU), through rehabilitation and discharge. This represents an ideal setting in which to study pediatric CA interventions and evaluate long-term outcomes. As part of the planning for a clinical trial to investigate the efficacy of TH and potentially other interventions to improve outcomes in children after CA, we conducted a National Institutes of Health–sponsored preclinical trial cohort study of IH and OH CA at 15 PECARN-associated hospitals. The current report is the first large multicenter cohort study of both IH and OH pediatric CA in the United States. This report 1) describes prearrest, arrest, early postarrest variables, and outcomes at hospital discharge for IH and OH co-

horts of pediatric patients with CA and ROC and 2) compares and contrasts the IH and OH cohorts of cases that might be eligible for an interventional trial of TH. We hypothesized that we would identify significant differences between children with CA and ROC in the IH and OH setting that would require either *a priori* planning to adjust for differences or performance of separate clinical trials for each setting.

METHODS

Our retrospective cohort study of IH and OH CA was conducted between July 1, 2003 and December 31, 2004 at 15 sites associated with the PECARN. Patients aged 1 day (24 hours) to 18 years (inclusive) who experienced CA requiring at least 1 minute of chest compressions and who had a ROC for a minimum of 20 minutes were eligible for inclusion. Case classification as OH was assigned if chest compressions were initiated before hospital arrival. IH classification was assigned when

chest compressions were initiated in the emergency department or other hospital setting. Patients cared for in a neonatal ICU or who had planned CA in the operating room as part of congenital heart disease surgical repair were excluded. These criteria were selected to identify a cohort of pediatric patients similar to those who would be potentially eligible for a future TH trial.

Patients were identified by medical record International Classification of Diseases-9 codes (427.5 CA, 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., cardiopulmonary resuscitation committee or Quality Assurance committee), morbidity and mortality reviews, emergency department records, trauma records, Pediatric Risk of Mortality scores (29), and other site-specific mechanisms. If a patient experienced more than one CA during the study time period, only the first arrest meeting eligibility criteria was included. The study was approved with a waiver

Table 1. Comparison of patient demographic and preexisting conditions for in-hospital and out-of-hospital cardiac arrest cohorts[a]

	IH (n = 353), Median (IQR)	OH (n = 138), Median (IQR)	p^b
Age (yrs)	0.9 (0.2–6.1)	2.9 (0.6–11.4)	<0.01
Weight (kg)	7.4 (3.7–20.0)	15.0 (7.5–35.0)	<0.01
	n (%)	n (%)	
Gender (male)	202 (57)	94 (69)	0.02
Race			0.67
White	168 (48)	63 (46)	
Black	91 (26)	41 (30)	
Other/unknown	94 (27)	34 (25)	
Ethnicity			0.07
Hispanic	26 (7)	5 (4)	
Not Hispanic	117 (33)	59 (43)	
Unknown	210 (60)	74 (54)	
Insurance type			
Commercial	188 (56)	61 (47)	0.13
Medicaid	127 (38)	55 (42)	
Other insurance	22 (7)	14 (11)	
Any chronic preexisting condition	310 (88)	68 (49)	<0.01
Specific chronic preexisting conditions[c]			
Prenatal conditions or complications	46 (13)	17 (12)	0.83
Lung or airway disease	94 (27)	29 (21)	0.20
Congenital heart disease	176 (50)	14 (10)	<0.01
Acquired heart disease	43 (12)	6 (4)	0.01
Hematologic, oncologic, or immunologic	56 (16)	2 (1)	<0.01
Gastrointestinal	75 (21)	13 (9)	<0.01
Genetic/metabolic	54 (15)	6 (4)	<0.01
Endocrine	12 (3)	2 (1)	0.37
Renal	45 (13)	0 (0.0)	<0.01
Neurologic	82 (23)	30 (22)	0.72

IH, in hospital; OH, out of hospital; IQR, interquartile range.
[a]Unavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: age (1), weight (9), gender (3), insurance type (24); [b]for comparison between IH and OH arrests, chi-square or Fisher's exact was used for categorical variables and Wilcoxon's rank sum test was used for continuous variables; [c]for chronic preexisting conditions, a condition was assumed to be not present unless specifically noted otherwise.

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 accuracy was >96%. Data fields reviewed by the site investigator that did not match with those of the abstractor were flagged for site investigator review and 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, weight, sex, race, ethnicity, insurance type, and chronic preexisting conditions; 2) event characteristics, including location and timing of CA, first and subsequently monitored cardiac rhythms, presence and types of vascular access, endotracheal tube, monitoring devices and other interventions before arrest, use of defibrillation, and drugs administered during the arrest; 3) etiology of CA; 4) hospital course, including use of extracorporeal membrane oxygenation, TH, other intensive care–monitoring devices and interventions, drug therapies, and subsequent arrests and seizures; 5) physiologic and laboratory data, such as pupillary reflexes, body temperature, blood pH, glucose and lactate concentrations in the first 12 hours postarrest; 6) pediatric cerebral performance category (PCPC) scores before CA and at hospital discharge; and 7) survival to hospital discharge. Dates and times of important clinical events were recorded and related time intervals determined. Utstein-style definitions were used for most variables where such definitions exist (30, 31). PCPC scores (from 1–6) estimate cognitive function (1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative state, and 6 = death) (32, 33). Good neurologic outcome was defined as a PCPC score of 1 or 2 at hospital discharge, or no change in score from prearrest to hospital discharge. Two approaches were used to classify CA as day or night and weekday or weekend. Events were coded as day time if they occurred from 7:00 AM to 6:59 PM and as night time from 7 PM to 6:59 AM (Method 1). Weekday arrests were classified as Monday 12:00 AM to Friday 11:59 PM and weekend was defined as Saturday 12:00 AM

to Sunday 11:59 PM. We also described night and weekend time periods with night defined as interval from 11:00 PM to 6:59 AM and weekend classified from Friday 11:00 PM to Monday 6:59 AM (Method 2); Method 2 was described in a recent adult IH CA report (34).

Several steps were taken to prepare the data for analysis. We reviewed time intervals for invalid or extreme values. If a value was considered impossible (e.g., negative values) or extremely unlikely based on a valid range for that variable, it was set to missing for the analysis. Physiologic and laboratory data were collected as minimum and maximum values obtained from 0 to 6 hours and >6–12 hours. If there was only one value provided for a time interval, it was assigned to both the minimum and the maximum. To obtain minimum and maximum values for the first 12 hours, data from both time intervals were included; a

missing value was assigned only if it was missing across both 0–6 hours and >6–12 hours. For drugs administered during CA in the OH cohort, data were based on any documentation of drugs received either before hospital arrival or in the hospital.

Statistical Analyses. For the descriptive data analyses, medians with interquartile ranges are described for continuous variables and proportions depicted as percents for categorical variables. A nonparametric Wilcoxon's rank sum test was used for continuous univariate comparisons between groups, whereas a chi-square or Fisher's exact test was used for categorical variable comparisons between groups. The Cochran-Armitage test for trend was used for ordered categorical variables. A significance level of 0.05 was used for all analyses. Because this was an exploratory study to define factors that may differ in the OH and IH

Table 2. Comparison of cardiac arrest event characteristics for in-hospital and out-of-hospital cohorts[a]

	IH Overall (n = 353), n (%)	OH Overall (n = 138), n (%)	p^b
Day of arrest (if unavailable, using CPR, ROC, or arrival at hospital)			0.71
Weekday (Monday 12:00 AM to Friday 11:59 PM)	255 (72)	102 (74)	
Weekend (Saturday 12:00 AM to Sunday 11:59 PM)	98 (28)	36 (26)	
Time of arrest (if unavailable, using CPR, ROC, or arrival at hospital)			0.28
Day (7:00 AM to 6:59 PM)	190 (54)	80 (60)	
Night (7:00 PM to 6:59 AM)	160 (46)	54 (40)	
Day of arrest (if unavailable, using CPR, ROC, or arrival at hospital)			0.95
Weekday (Monday 7:00 AM to Friday 10:59 PM)	244 (70)	93 (69)	
Weekend (Friday 11:00 PM to Monday 6:59 AM)	106 (30)	41 (31)	
Time of arrest (if unavailable, using CPR, ROC, or arrival at hospital)			0.05
Day (7:00 AM to 10:59 PM)	252 (72)	108 (81)	
Night (11:00 PM to 6:59 AM)	98 (28)	26 (19)	
First monitored rhythm			<0.01
Asystole	55 (16)	64 (46)	
Bradycardia	173 (49)	14 (10)	
Pulseless electrical activity	31 (9)	14 (10)	
Ventricular fibrillation/tachycardia	35 (10)	9 (7)	
Other/unknown	59 (17)	37 (27)	
Asystole rhythm documented (any time)	101 (29)	71 (51)	<0.01
VF/VT rhythm documented (any time)	67 (19)	30 (22)	0.49
Drugs administered during arrest			
Fluid bolus	139 (42)	58 (43)	0.77
Atropine	124 (37)	67 (50)	0.01
Sodium Bicarbonate	203 (61)	56 (41)	<0.01
Calcium	174 (52)	10 (7)	<0.01
Vasopressin	18 (5)	2 (1)	0.06
Lidocaine	33 (10)	12 (9)	0.75
Procainamide	0 (0)	0 (0)	NA
Amiodarone	19 (6)	2 (1)	0.05
Epinephrine (any received)	293 (86)	96 (76)	0.01
Epinephrine doses administered, median (IQR)	2.0 (1.0–4.0)	3.0 (1.0–5.0)	0.28

IH, in hospital; OH, out of hospital; CPR, cardiopulmonary resuscitation; ROC, return of circulation; VF, ventricular fibrillation; VT, ventricular tachycardia; NA, not available. [a]Unavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: day of arrest (definition 2 only) (7), time of arrest (7), drugs administered (except epinephrine) (21), epinephrine administered (24); [b]for comparison between IH and OH arrests, chi-square or Fisher's exact was used for categorical variables and Wilcoxon's rank sum test was used for continuous variables.

cohort settings, statistical adjustment for multiple comparisons was not performed. We graphically summarized cumulative survival and discharged alive for the first 60 days post-arrest in each cohort. Patients discharged alive before day 60 were assumed alive through day 60. All analyses were performed using SAS 9.1 for Windows (Cary, NC).

RESULTS

Four hundred and ninety-three cases were included in this report of pediatric CA with ROC; 138 were OH and 353 were IH events. Table 1 describes demographic and preexisting conditions for both cohorts. Median age was older (2.9 vs. 0.9 years; $p < 0.01$) and gender more often male in the OH cohort (69% vs. 57%; $p = 0.02$). The frequency of a chronic preexisting condition was much less common for the OH cohort (49% vs. 88%; $p < 0.01$).

Table 2 describes CA event characteristics. The cohorts were similar with respect to proportion of weekend or night occurrence of the study eligible events using Method 1 definitions; with Method 2 definitions, there was a trend for more daytime events in the OH cohort ($p = 0.05$). The initial cardiac rhythms differed ($p < 0.01$); asystole was more commonly reported as the initial OH rhythm (46% vs. 16%), whereas bradycardia was the more frequent initial IH rhythm (49% vs. 10%). Asystole occurring anytime during an arrest event occurred more commonly in OH arrests than in IH arrests (51% vs. 29%; $p < 0.01$), whereas ventricular fibrillation or ventricular tachycardia at any time during an arrest occurred at a similar frequency of about one in five IH or OH arrests. The administration of Pediatric Advanced Life Support drugs during CA differed; atropine was more commonly administered during OH arrests, whereas sodium bicarbonate and calcium were administered much more frequently during IH events. Median number of epinephrine doses administered was similar for IH and OH arrests, whereas the proportion receiving any dose of epinephrine was higher in the IH cohort. The duration of cardiopulmonary resuscitation was shorter in the IH compared with OH cohort (median 9.0 [4.0–25.0] vs. 31 [18.0–50.0] minutes; $p < 0.01$); however, for the OH cohort, data were available for only 69 events.

Table 3 describes the etiology of the arrest events. There were important differences between the two cohorts; cardiac etiologies were much more frequently reported in IH arrests (congenital heart disease 37% vs. 4% and noncongenital heart disease 36% vs. 15%; both $p < 0.01$), whereas respiratory etiologies were more common in OH arrests (72% vs. 42%; $p < 0.01$).

Table 4 describes monitoring and interventions in the 12-hour postarrest period. Pulse oximetry and cardiac monitoring were nearly universal and the use of mechanical ventilation was >90% in both groups. Intraosseous catheters were used more commonly in OH cases, whereas central venous catheters (includes all central access catheters) and arterial catheters were more common in the IH cases. TH was infrequently used in either group (<5%). Extracorporeal membrane oxygenation and dialysis were used more commonly in IH cases. Anticonvulsant agents were administered more commonly in the OH group, whereas administration of one or more inotrope or vasopressor agents was more common in the IH group. An epinephrine infusion was the most frequently used inotrope/vasopressor agent; its use was similar in the cohorts. Dopamine, milrinone, vasopressin, steroids, and antimicrobial use were more common in IH cases, whereas mannitol was used more often following OH events.

Table 5 describes important physiologic and laboratory measurements in the 0–12-hour time period postarrest. In the OH cohort, the minimum body temperature recorded was lower than that for IH cases (median 34.1 vs. IH 35.3°C; $p < 0.01$). The maximum body temperature was also higher in the OH cohort. The minimum recorded pH was lower in OH arrests (median 7.03 vs. 7.20; $p < 0.01$), whereas maximum lactate measurements were similar (8.0 and 7.8 mmol/L). The maximum glucose was higher in the OH cohort, whereas the minimum glucose was lower in the IH cohort. Bilaterally reactive pupils were documented more often during the 12 hours following ROC in IH cohort. Seizures occurred after CA and before hospital discharge nearly twice as often in the OH cases. Subsequent CA within 24 hours occurred in about one of four cases in each group.

Table 6 depicts PCPC score changes in the two cohorts. Baseline PCPC was normal in 83% of OH cases and 66% of IH cases ($p < 0.01$). At hospital discharge, PCPC was unchanged in only 24% of OH

Table 3. Comparison of the etiology of cardiac arrest for in-hospital and out-of-hospital cohorts[a]

	IH Overall (n =353), n (%)	OH Overall (n = 138), n (%)	p^b
Cardiac (not congenital heart disease)	124 (36)	20 (15)	<0.01
Arrhythmia	42 (12)	13 (9)	
Hypovolemic shock	19 (5)	2 (1)	
Septic shock	28 (8)	2 (1)	
Cardiomyopathy	8 (2)	1 (1)	
Other	41 (12)	4 (3)	
Congenital heart disease	130 (37)	6 (4)	<0.01
Arrhythmia	69 (20)	4 (3)	
Low cardiac output	38 (11)	1 (1)	
Hypoxemia	15 (4)	2 (1)	
During postoperative course	52 (15)	1 (1)	
Tamponade	4 (1)	0 (0)	
Other	9 (3)	2 (2)	
Respiratory	145 (42)	98 (72)	<0.01
Acute life-threatening event	3 (1)	22 (16)	
Endotracheal tube displacement	19 (5)	2 (1)	
Respiratory failure	112 (32)	37 (27)	
Airway obstruction	8 (2)	5 (4)	
Drowning/asphyxia	0 (0)	43 (31)	
Other	8 (2)	4 (3)	
Neurologic	8 (2)	5 (4)	0.53
Drug overdose/ingestion	3 (1)	4 (3)	0.10
Trauma	22 (6)	15 (11)	0.09
Electrolyte imbalance	30 (9)	4 (3)	0.03
Terminal condition	12 (3)	1 (1)	0.12

IH, in hospital; OH, out of hospital.

[a]Patients could have multiple categories identified for etiology of arrest. There was one OH and six IH arrests with no information documented for etiology of arrest. These records were excluded from percentage calculations; [b]chi-square or Fisher's exact test was used for comparison between IH and OH arrests.

Table 4. Postarrest hospital course (0–12 hrs) for in-hospital and out-of-hospital cohorts[a]

	IH Overall (n =353), n (%)	OH Overall (n = 138), n (%)	p^b
ICU interventions and monitoring devices			
Cardiac monitor	350 (100)	130 (98)	0.07
Pulse oximeter	350 (100)	130 (98)	0.07
Peripheral intravenous catheter	256 (73)	116 (87)	<0.01
Intraosseous access	20 (6)	31 (23)	<0.01
Central venous catheter/CVP	307 (87)	100 (75)	<0.01
Arterial catheter	281 (80)	90 (68)	<0.01
Mechanical ventilation	335 (95)	122 (92)	0.11
ECMO	58 (17)	3 (2)	<0.01
Dialysis	19 (5)	0 (0)	0.01
Intracranial pressure monitor	9 (3)	1 (1)	0.30
Therapeutic hypothermia	13 (4)	3 (2)	0.57
Drug therapies			
Antiarrhythmics	66 (19)	33 (25)	0.14
Anticonvulsants	54 (15)	35 (26)	0.01
Any inotrope or vasopressor	293 (83)	93 (70)	<0.01
Dopamine	180 (51)	48 (36)	<0.01
Dobutamine	50 (14)	17 (13)	0.68
Epinephrine	216 (62)	76 (57)	0.38
Norepinephrine	27 (8)	5 (4)	0.12
Milrinone or amrinone	117 (33)	6 (5)	<0.01
Vasopressin	54 (15)	10 (8)	0.02
Other inotrope or vasopressor	49 (14)	18 (14)	0.90
Antimicrobials	257 (73)	73 (55)	<0.01
Steroids	87 (25)	7 (5)	<0.01
Mannitol	8 (2)	11 (8)	<0.01
Hypertonic saline	3 (1)	1 (1)	1.00

IH, in hospital; OH, out of hospital; ICU, intensive care unit; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation.

[a]Unavailable (missing) values were excluded from calculations of percentages and summary statistics for the following variables: ICU intervention and monitoring devices (7) [except therapeutic hypothermia (0)], drug therapies (7).

Table 5. Comparison of physiologic and laboratory values (0–12 hrs after ROC) for in-hospital versus out-of-hospital cohorts[a]

	IH Overall (n = 353)		OH Overall (n = 138)		
	n	Median (IQR)	n	Median (IQR)	p^b
Minimum body temperature (°C)	338	35.3 (34.2–36.3)	133	34.1 (32.5–35.6)	<0.01
Maximum body temperature (°C)	338	37.1 (36.5–38.0)	133	37.8 (36.7–38.8)	<0.01
Minimum pH	328	7.20 (7.04–7.33)	123	7.03 (6.80–7.20)	<0.01
Maximum pH	328	7.46 (7.36–7.53)	123	7.37 (7.31–7.46)	<0.01
Maximum lactate (mmol/L)	230	7.8 (3.1–14.0)	76	8.0 (4.1–13.8)	0.74
Minimum glucose (mg/dL)	313	113 (82–172)	126	135 (97–203)	<0.01
Maximum glucose (mg/dL)	313	195 (120–291)	126	291 (188–346)	<0.01
		n (%)		n (%)	
Two responsive pupils	313	235 (75)	131	42 (32)	<0.01
Seizures postarrest (before hospital discharge)	346	50 (14)	133	35 (26)	<0.01
Subsequent arrests within 24 hrs of initial CA	353	98 (28)	138	31 (22)	0.23

ROC, return of circulation; IH, in hospital; OH, out of hospital; IQR, interquartile range.

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

cause of death differed markedly ($p < 0.01$); death was attributed to neurologic futility or brain death much more frequently in the OH cohort (69% vs. 20%), whereas cardiovascular causes occurred more commonly in the IH cohort (50% vs. 22%).

Figure 1 highlights differences in the percentage surviving and discharged alive for the first 60 days following the CA. Trends differed remarkably between cohorts, with survival in the OH cohort falling below 50% within the first 5 days postarrest. Survival at 10 days postarrest was 42% in the OH cohort compared with 63% in the IH arrest group. Discharged alive was similar between the two groups at approximately day 15; the durations of PICU and hospital stay postarrest were longer for the IH compared with the OH cohort (median 7.0 [1.0–20.0] vs. 3.0 [1.0–7.0] and median 12.0 [2.0–27.0] vs. 3.0 [1.0–11.0]; $p < 0.01$ in both cases).

DISCUSSION

This is the first multicenter cohort study conducted in a US population of children with CA and ROC that compares and contrasts major clinical features of IH and OH CA. This study was performed to provide information needed to plan an interventional RCT of TH after pediatric CA. An essential prerequisite for evaluation of new therapies in these patients is information about whether there are differences that preclude combining IH and OH cases in clinical trials. Our analyses demonstrate that there are important differences between the IH and OH CA patients who would be eligible for an interventional clinical trial of TH to improve neurobehavioral outcome.

There were five major differences between the OH and IH cohorts: 1) prearrest baseline neurologic status (based on PCPC) was more frequently normal in OH cases (83% vs. 66%); 2) chronic preexisting conditions were nearly twice as common in the IH cohort (88% vs. 49%); 3) etiology was predominately respiratory for the large majority of the OH cohort (72% vs. 42%) and cardiac for the IH cohort; 4) neurologic status at hospital discharge was unchanged from baseline nearly twice as often in the IH cohort (44% vs. 24%); and 5) most important for an interventional trial of TH, the attributed cause for death was neurologic injury in the majority in the OH cohort, whereas uncommon in the IH cohort (69% vs. 20%). These findings strongly

cases compared with 44% of IH cases ($p < 0.01$). Good neurologic outcome (defined as PCPC equal to 1 or 2, or no change in baseline PCPC) occurred in 24% of the OH cohort compared with 47% in the IH cohort ($p < 0.01$). Mortality rate was higher in the OH cohort (62% vs. 51%, $p = 0.04$). The primary

Table 6. Prearrest PCPC and hospital outcomes for children with in-hospital versus out-of-hospital arrest[a]

	IH Overall (n = 353), n (%)	OH Overall (n = 138), n (%)	p[b]
Baseline PCPC			<0.01
Normal	187 (66)	105 (83)	
Mild disability	42 (15)	9 (7)	
Moderate disability	35 (12)	7 (6)	
Severe disability	16 (6)	5 (4)	
Vegetative	4 (1)	1 (1)	
Hospital d/c PCPC			0.01
Normal	89 (27)	23 (17)	
Mild disability	27 (8)	6 (4)	
Moderate disability	19 (6)	5 (4)	
Severe disability	11 (3)	12 (9)	
Vegetative	0 (0)	6 (4)	
Dead	181 (55)	85 (62)	
No change in PCPC	124 (44)	30 (24)	<0.01
Good neurologic outcome[c]	132 (47)	31 (24)	<0.01
Death (includes cases with missing PCPC data)	181 (51)	85 (62)	0.04
Cause of death			<0.01
Neurologic	36 (20)	59 (69)	
Cardiovascular	90 (50)	19 (22)	
Other	54 (30)	7 (8)	

PCPC, pediatric cerebral performance category; IH, in hospital; OH, out of hospital.

[a]Unavailable (missing) values were excluded from percentage calculations for the following variables: baseline PCPC (69 IH, 11 OH), PCPC at hospital discharge (26 IH, 1 OH), change in PCPC and neurologic outcome (74 IH, 11 OH cases), cause of death (1 IH); [b]cochran-Armitage trend test was used for comparison between IH and OH arrests for ordered categorical variables (i.e., baseline and hospital d/c PCPC). Chi-square test was used for all other variables; [c]good neurologic outcome defined as either no change in PCPC from baseline to hospital discharge or a PCPC of normal or mild disability at hospital discharge.
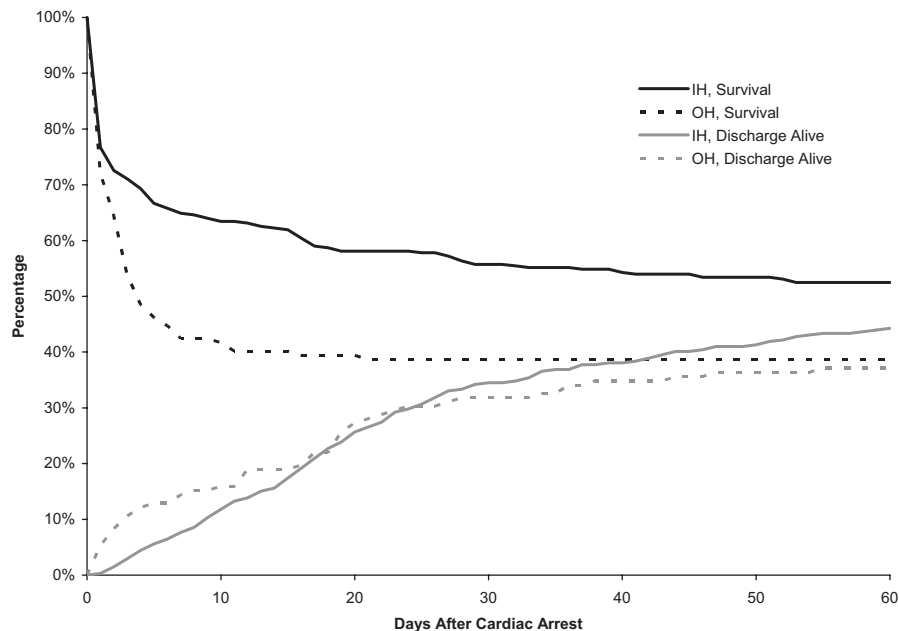
Figure 1. Overall survival (patients discharged alive before day 60 were assumed alive through day 60) and discharged alive proportion among cases with in-hospital and out-of-hospital cardiac arrest and return of circulation.

suggest that combining OH and IH cases in a single clinical trial would be ill advised, especially for interventions designed to improve neurobehavioral outcomes after pediatric CA.

Several other cohort differences merit comment. Baseline characteristics of the IH and OH cases differed with respect to age and sex. OH cases were older and more likely to be male. Specific arrest event–associated factors also were dissimilar between IH and OH cases. For example, the initial cardiac rhythm documented after start of chest compressions was bradycardia for IH arrests and asystole for OH arrests. This is not surprising given that most IH CA occur in monitored settings (i.e., PICU) where early rhythm and heart rate changes would be optimally identified, whereas OH arrests most likely documented the onset of the arrest and initial rhythm at a much later time when monitoring equipment was available (3). The use of Pediatric Advanced Life Support medications during resuscitations differed. Epinephrine use was reported in a somewhat higher proportion of IH cases, but this could reflect poor documentation or unavailable records from the prehospital setting in the OH group. The use of calcium in >50% of IH cases but only 7% of OH cases is quite notable. Calcium administration is not generally recommended for children in the IH setting, and its use may be associated with poorer outcomes (35).

Supportive therapies and monitoring used during the first 12 hours following ROC for OH and IH cohorts were dissimilar in some respects. Central venous and arterial catheters were documented more commonly in IH cases; in some cases, they may have been placed before the arrest. The higher use of IO catheters in OH cases is not surprising because this route is recommended when intravenous access cannot be established rapidly. Extracorporeal membrane oxygenation was used more commonly in IH cases where rapid response to an arrest event would be possible compared with OH arrests. It is noteworthy that the use of TH was very low in both groups (<5%), even though the study period followed publication of the adult hypothermia RCTs (20, 21). The low use is likely due to absence of pediatric RCTs and protocols to guide use; this suggests equipoise exists for TH at our PECARN sites. Equipoise was also described in a recent survey report (27).

Figure 1 depicts the large difference in the time courses of survival and live discharge between OH and IH cohorts. Mortality peaked rapidly (survival declined most) in the first 5 days in the OH cohort, which may reflect greater multiorgan hypoxic-ischemic injury compared with the IH cohort. This interpretation is supported by the lower minimum pH measured within 12 hours of ROC in the OH cohort. Seizures were reported and

treated nearly twice as often in the OH as the IH cohort, whereas bilateral reactive pupils were present less than half as often in the OH cohort. Both observations are congruent with greater neurologic injury sustained in the OH survivors, and the much higher proportion of deaths due to neurologic injury in the OH group.

For the planning of a TH RCT, it was important to determine the range of temperatures observed in the early post-ROC period. For the 12 hours immediately following OH arrest, the median for lowest temperature reported was 34.1°C and median maximum temperature was 37.8°C. This lowest temperature is very close to the range of hypothermia used in adult RCTs (32–34°C) and neonatal clinical trials (20, 21, 23, 24). This suggests a goal temperature in the 32–34°C range could be achieved quickly and easily in this group. The mildly elevated maximum temperatures observed in the OH group were an unexpected finding that could have been the result of overaggressive warming. Thus, rigorous monitoring will be necessary to avoid hyperthermia in the control groups of future hypothermia trials (36, 37). For the IH group, median recorded lowest temperature was higher (35.3°C); this likely reflects preexisting or early placement of temperature monitoring and warming equipment in the PICU or monitored setting.

Comparison of findings from our study to existing information in the literature may be limited. Our study population had unique characteristics related to our goal to delineate explicit inclusion and exclusion criteria for future pediatric TH trials. For example, a minimum requirement for inclusion was duration of chest compressions for at least 1 minute followed by ROC for at least 20 minutes; this time interval was selected to capture a population at some risk for adverse neurologic outcome. Patients receiving shorter durations of chest compression, whether they received defibrillation, epinephrine, or other Pediatric Advanced Life Support medications, were excluded. Also, we excluded cases that did not survive the initial resuscitation event (no ROC for at least 20 minutes) because our long-term goal was to plan an interventional clinical trial of hypothermia. This limits direct comparison of our results with studies that included cases without ROC. A recent review reported that about 70% of OH arrests did not have ROC and the NRCPR reported that approximately 50% of IH arrests do not have ROC (3, 4).

Additionally, we did not use the exact NRCPR definition of IH CA, which emphasizes documentation in the medical record of the absence of a palpable pulse or a rhythm not associated with a pulse. Pulse detection is an extremely unreliable and problematic physical finding to accurately measure in adults under optimal conditions; trained pediatric caregivers perform poorly as well (38–40). An American Heart Association–affiliated expert group recently proposed a different "pragmatic definition" for OH CA to include "receives chest compressions by EMS personnel" (41). A criterion of chest compressions for at least a minute (or other duration) could be applicable for clinical trials in both the OH and the IH settings. We suspect that few cases with a minute or more of chest compressions would actually be associated with a clinically detectable pulse and cases classified as bradycardia in our study would have been likely classified as pulseless electrical activity using the NRCPR algorithm. This is indirectly supported by mortality rates observed in our cohorts. For example, our IH cohort mortality was very similar to a recent NRCPR report containing pediatric cases with ROC (49%) (3), and our OH cohort mortality was similar to the largest report to date that used Utstein criteria (66%) (4).

A limitation of our report common to other reports on pediatric CA is missing data for some variables. For example, we observed missing initial rhythm data in 20% for IH and OH events, which is similar to a NRCPR report with 22% missing data for this variable. Another limitation, which is shared with most other reports on pediatric CA survivors, is the classification of neurologic outcome, both with respect to early timing at hospital discharge and reliance on relatively crude measures like PCPC. Although a few reports indicate that status of children at hospital discharge is largely unchanged at 1 year follow-up (42, 43), detailed neurobehavioral testing at 1 year or more after the CA event is needed to confirm these initial reports and to delineate the impact of the event on more subtle areas of neurobehavioral function (44, 45).

A major strength of our report is that the 15 sites were supported by a federally funded research network (PECARN) with a data coordinating center (CDMCC). A standard data collection tool and training were used by all sites and the CDMCC systematically verified data. The entire spectrum of pediatric CA cases, including IH, OH, and transfers from another facility, was captured. The participating clinical sites had at least 12 PICU beds and were distributed across most large geographical areas of the United States, except southern states. In contrast, most prior U.S. reports were from single sites or geographical areas. The notable exception is the NRCPR registry, which is currently limited to IH CA.

In summary, this study demonstrates global differences between pediatric CA in the OH and IH settings. The most important differences in the context of planning a clinical trial of TH to improve neurobehavioral outcome relate to neurologic issues. Patients from the OH setting are much more likely than IH cases to have normal baseline PCPC scores, whereas IH survivors are much more likely than OH survivors to have good PCPC outcomes at hospital discharge. Our most important new finding is that mortality was attributed to neurologic factors in nearly 70% of OH cases, in significant contrast to only 20% of IH cases. Other important differences were that etiology of CA was respiratory in the majority of the OH cohort and preexisting conditions were much more common in IH cohort. These findings provide a compelling rationale for implementation of separate clinical trials of TH for pediatric CA in the two groups.

ACKNOWLEDGMENTS

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