

Outcomes among neonates, infants, and children after extracorporeal cardiopulmonary resuscitation for refractory inhospital pediatric cardiac arrest: A report from the National Registry of Cardiopulmonary Resuscitation*

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LEARNING OBJECTIVES

After participating in this educational activity, the participant should be better able to:

1. Prepare the physician for assessing potential extracorporeal cardiopulmonary candidates in the setting of cardiac arrest/resuscitation.
2. Demonstrate the limitations of extracorporeal cardiopulmonary resuscitation in the setting of pediatric cardiac arrest/resuscitation.
3. Predict the impact of optimized cerebral perfusion using extracorporeal cardiopulmonary resuscitation rather than conventional extracorporeal cardiopulmonary resuscitation on functional outcome in pediatric patients after cardiopulmonary arrest.

Dr. Dalton has disclosed that she and her spouse/life partner are on the speaker's bureau for Brahm's-Thermo Fisher. The remaining authors have disclosed that they have no financial relationships with, or interests in, any commercial companies pertaining to this educational activity. The remaining authors' spouse(s)/life partner(s) (if any) have nothing to disclose.

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Objectives: Describe the use of extracorporeal cardiopulmonary resuscitation as rescue therapy in pediatric patients who experience cardiopulmonary arrest refractory to conventional resuscitation. We report on outcomes and factors associated with survival in children treated with extracorporeal cardiopulmonary resuscitation during cardiopulmonary arrest from the American Heart Association National Registry of CardioPulmonary Resuscitation.

Design: Multicentered, national registry of in-hospital cardiopulmonary resuscitation.

Setting: Two hundred eighty-five hospitals reporting to the registry from January 2000 to December 2007.

Patients: Pediatric patients <18 yrs of age who received extracorporeal membrane oxygenation during cardiopulmonary resuscitation for in-hospital cardiopulmonary arrest.

Interventions: None.

Measurements and Outcomes: Prearrest and arrest variables were collected. The primary outcome variable was survival to hospital discharge. The secondary outcome was neurologic status after extracorporeal cardiopulmonary resuscitation at hospital discharge. Favorable neurologic outcome was defined as Pediatric Cerebral Performance Categories 1, 2, 3, or no change from admission Pediatric Cerebral Performance Category.

Results: Of 6288 pediatric cardiopulmonary arrest events reported, 199 (3.2%) index extracorporeal cardiopulmonary resus-

citation events were identified; 87 (43.7%) survived to hospital discharge. Fifty-nine survivors had Pediatric Cerebral Performance Category outcomes recorded, and of those, 56 (94.9%) had favorable outcomes. In a multivariable model, the prearrest factor of renal insufficiency and arrest factors of metabolic or electrolyte abnormality and the pharmacologic intervention of sodium bicarbonate/tromethamine were associated with decreased survival. After adjusting for confounding factors, cardiac illness category was associated with an increased survival to hospital discharge.

Conclusions: Forty-four percent of pediatric patients who failed conventional cardiopulmonary resuscitation from in-hospital cardiopulmonary arrest and who were reported to the National Registry of CardioPulmonary Resuscitation database as treated with extracorporeal cardiopulmonary resuscitation survived to hospital discharge. The majority of survivors with recorded neurologic outcomes were favorable. Patients with cardiac illness category were more likely to survive to hospital discharge after treatment with extracorporeal cardiopulmonary resuscitation. Extracorporeal cardiopulmonary resuscitation should be considered for select pediatric patients refractory to conventional in-hospital resuscitation measures. (*Pediatr Crit Care Med* 2010; 11:362-371)

KEY WORDS: cardiopulmonary resuscitation; extracorporeal cardiopulmonary resuscitation; cardiac arrest; pediatrics; extracorporeal membrane oxygenation; survival

INTRODUCTION

The physician will be able to better select candidates for the use of extracorporeal cardiopulmonary resuscitation (E-CPR).

Cardiac arrest is not rare in pediatric patients, occurring in 2% to 6% of children admitted to a pediatric intensive care unit (1–4). Although successful resuscitation to return of spontaneous circulation after in-hospital cardiac arrest is achieved in approximately 43% to 67% of pediatric patients, survival to hospital discharge occurs in approximately 25% to 33% of these children (2, 5–8). If the patients have prolonged (>30 mins) conventional CPR, survival to hospital discharge is even lower (9, 10). Extracorporeal membrane oxygenation (ECMO) is being used as a resuscitation therapy in some pediatric and adult patients who experience cardiopulmonary arrest (CPA) that is refractory to conventional CPR (9, 11–19). The American Heart Association has recognized a role for E-CPR (or rescue ECMO) in the 2005 pediatric advanced life support guidelines for CPR and emergency cardiovascular care. These guidelines recommend consideration of E-CPR for in-hospital cardiac arrest that is refractory to initial resuscitation efforts when the cause of arrest is reversible or amenable to heart transplantation (20).

Although once considered an extreme measure, ECMO is increasingly used to provide blood flow and oxygenation to both cardiac and noncardiac patients when resuscitation is unsuccessful. Studies have shown improved outcomes for patients who were otherwise unresponsive to conventional resuscitation efforts and were treated with E-CPR (9, 12, 14–16, 18, 19). Prior studies reported 33% to 42% survival to discharge in patients who underwent E-CPR during active chest compressions for CPA (9, 12, 16, 19). In the most comprehensive review of E-CPR experience to date, Thiagarajan et al re-

ported data from the Extracorporeal Life Support Organization registry, which found 38% survival to discharge in 682 patients who were treated with E-CPR (16). This report provided greater insight into the types of patients being treated with E-CPR and the factors associated with mortality but was limited by the data present in the Extracorporeal Life Support Organization registry. The Extracorporeal Life Support Organization does not track any assessment of neurologic outcome. The registry does not record resuscitation measures, the presence of invasive monitoring or devices used at the time of the cardiac arrest, or post-resuscitation care. The neurologic outcome of these patients was not available through the Extracorporeal Life Support Organization registry, although favorable neurologic outcomes have been demonstrated in prior institution-specific case series reports (9, 10).

Our objective was to describe the types of pediatric patients treated with E-CPR, to report trends in the use of E-CPR, and to determine factors associated with survival after E-CPR with data abstracted from the American Heart Association National Registry of CardioPulmonary Resuscitation (NRCPR) database. The NRCPR is a large, multicenter database that prospectively and rigorously documents adult and pediatric in-hospital cardiac arrest (6–8, 21–27). We evaluated whether in-hospital mortality after E-CPR use was associated with facility characteristics, patient demographic data, pre-event data, and resuscitation event data. We hypothesized that children with pre-existing cardiac illness would have improved odds of survival to hospital discharge when compared with those without pre-existing cardiac illness. We further hypothesized that those patients who had a CPA event and maintained a pulse with poor perfusion (i.e., never became pulseless) would have improved odds of survival when compared with patients who became pulseless before being

placed on rescue ECMO. Additionally, patients surviving to hospital discharge would have favorable neurologic outcomes. The present study is the first multicenter report on neurologic outcomes after treatment with E-CPR for refractory pediatric in-hospital cardiac arrest.

METHODS

Design. The NRCPR is a multicenter registry of in-hospital cardiac arrest and resuscitation that uses a standardized form to report patient characteristics and conditions, details of the cardiac arrest event, and processes of care and outcomes. The NRCPR is sponsored by the American Heart Association and is the only national registry of in-hospital resuscitation events. Certified data abstractors from participating institutions record information about each CPA from medical charts and submit data to the NRCPR using a standardized form. Data are collected according to standardized Utstein definitions for cardiac arrest (28, 29). The six major categories of variables collected are facility data, patient demographic data, pre-event data, event data, outcome data, and quality improvement data.

Explicit operational definitions have been generated for every data element. “Facility type” was defined by the participating institution based on the primary patient population. “First documented rhythm” was defined as the first electrocardiographic rhythm documented at the time the patient required chest compressions and for those patients with unwitnessed/unmonitored arrests represents the first rhythm documented at the time a monitor is applied. Pulseless cardiac arrest was defined as cessation of cardiac mechanical activity determined by the absence of a palpable central pulse, unresponsiveness, and apnea. Pneumonia was defined as a documented diagnosis of active pneumonia, in which antibiotics have not yet been started or the pneumonia is still being treated with antibiotics. Renal insufficiency was defined as requiring ongoing dialysis or extracorporeal ultrafiltration therapy; if <30 kg oliguria (urine output <1 mL/kg/hr for >8 hrs) and creatinine >1 mg/dL within 24 hrs up to the time of the CPA event; or if >30 kg oliguria (urine output <0.5 mL/kg/hr for >8 hrs) and creatinine >2 mg/dL within 24 hrs up to the time of the CPA event. Septicemia was defined as a documented bloodstream infection in which antibiotics have not yet been started or the infection is still being treated with antibiotics. Metabolic/electrolyte abnormality was defined as any of the following within 4 hrs up to the time of the event: (pediatric) blood glucose <60 mg/dL, lactate >2.5 mmol/L, magnesium >4 mEq/L, arterial pH <7.3 or >7.5, potassium <2.5 or >6 mEq/L, or sodium <125 or >150 mEq/L. Hypotension was defined as

*See also p. 429.

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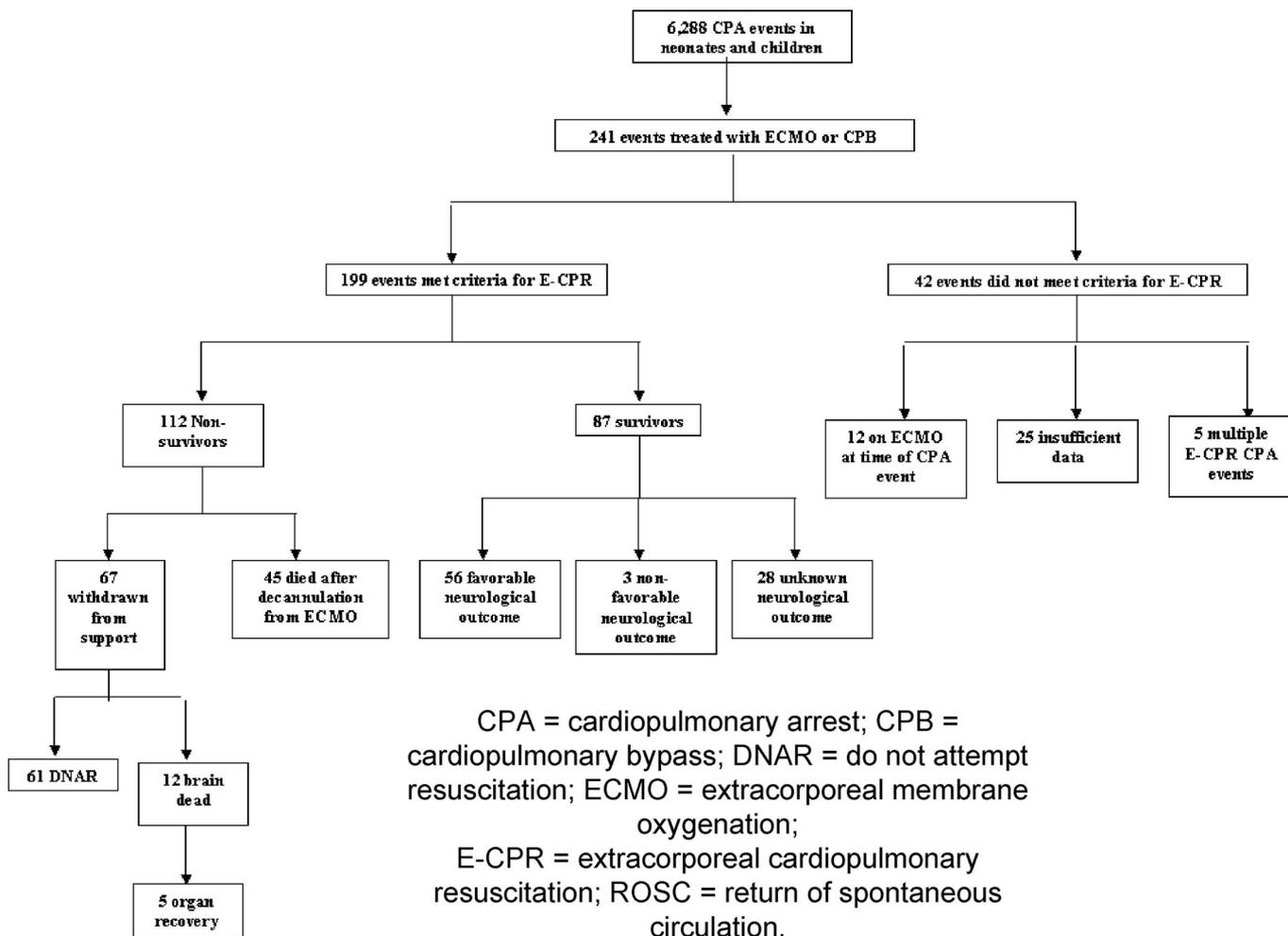


Figure 1. Patient enrollment and outcomes.

within 4 hrs up to the time of the event: systolic blood pressure less than the fifth percentile for age, less than $[70 + 2 \times \text{age in years}]$ for age <10 , or mean arterial pressure less than the fifth percentile for age or vasopressor/inotropic requirement after volume expansion (except for dopamine $\leq 3 \mu\text{g}/\text{kg}/\text{min}$).

Each patient is given a unique code and deidentified data are then submitted to a central repository in compliance with the Health Insurance Portability and Accountability Act. The AHA provides oversight for data collection, integrity, analysis, and reporting through staff, a science advisory board, and an executive database steering committee. The NRCPR process for data collection and assimilation has been previously described in detail (6–8, 21, 22, 24–27). Although not required because the NRCPR database is a quality improvement database, the Institutional Review Board for the University of Texas Southwestern Medical Center approved this study.

Inclusion and Exclusion Criteria. Data were analyzed from 285 participating NRCPR hospitals that recorded CPAs of patients who were <18 yrs of age between January 1, 2000, and December 31, 2007. All patients who were

<18 yrs and experienced cardiopulmonary arrest requiring CPR at participating institutions were eligible for inclusion. A CPA was defined as an arrest that required chest compressions and/or defibrillation. An E-CPR event was defined as a CPA event in which extracorporeal life support was used during active CPR as identified in the database under “nondrug interventions.” Extracorporeal life support may have included ECMO or cardiopulmonary bypass. The end of the CPA event began with return of spontaneous circulation defined as the time the patient was placed on extracorporeal life support therapy. Arrest event duration was from the time chest compressions and/or defibrillation began to return of spontaneous circulation. Patients who were placed onto ECMO after return of spontaneous circulation were not included. For patients having multiple E-CPR events, only the index (first) E-CPR event was considered for analysis. One hundred ninety-nine patients meeting all inclusion criteria were identified (Fig. 1).

Outcome Measures. The prospectively selected primary outcome measure was survival to hospital discharge. Survival to hospital discharge was defined as discharge from the ECMO center to either home or another facil-

ity. Neurologic outcome at the time of hospital discharge was a secondary outcome measure. Neurologic outcome was determined by the Pediatric Cerebral Performance Category (PCPC) scale as follows: 1) normal age-appropriate neurodevelopmental function; 2) mild disability; 3) moderate disability; 4) severe disability; 5) coma or vegetative state; and 6) brain death (13, 15). Neurologic status before the arrest and at discharge was determined by chart review for NRCPR database abstraction. A favorable neurologic outcome was prospectively defined by a discharge PCPC score of 1, 2, or 3 or no change from admission PCPC score (8, 30). The NRCPR does not require that PCPC scores be recorded for each patient, and thus it is an optional variable that some facilities elect not to report.

In addition to listing specific pre-existing medical conditions, all patients were assigned to one of eight illness categories at the time of entry into the NRCPR database (medical–cardiac, medical–noncardiac, surgical–cardiac, surgical–noncardiac, newborn, trauma, obstetrical, or other). The categories represented in the study population included: medi-

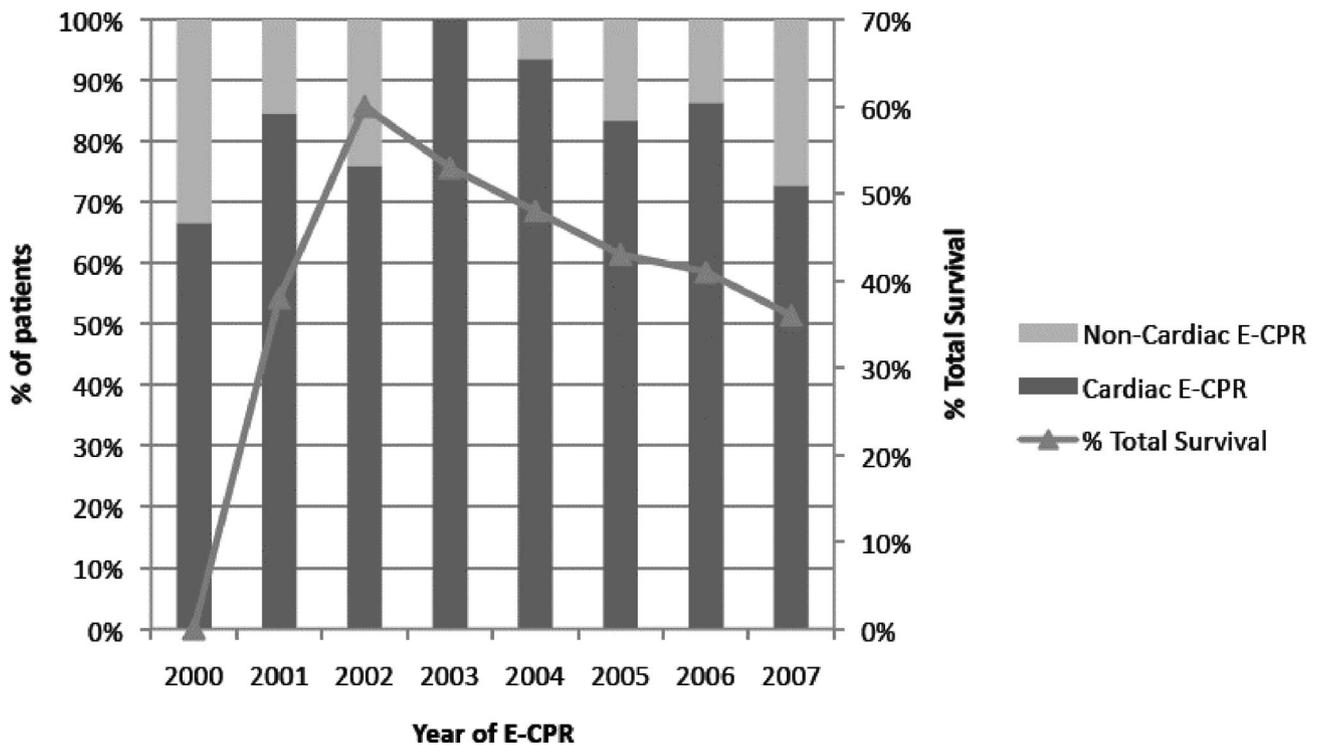


Figure 2. Trends in extracorporeal cardiopulmonary resuscitation (E-CPR) use and survival based on diagnostic groups from 2000 to 2007. There was no significant change in percent total E-CPR survival rate per year based on Cochran-Armitage trend test ($p = .62$).

cal-cardiac, medical-noncardiac, surgical-cardiac, surgical-noncardiac, and newborn. Each patient is assigned to a single category. Patients were first analyzed by illness category designation and for purposes of this study were then further classified into “cardiac” and “noncardiac” groups. Patients in medical-cardiac and surgical-cardiac illness categories were considered “cardiac” and medical-noncardiac, surgical-noncardiac, and newborn illness categories were designated “non-cardiac.” Survival trends were described comparing cardiac and noncardiac patients on a yearly basis. The NRCPR does not define “newborn” but rather allows each facility to designate a newborn by institution-specific criteria. For this study, we have defined a newborn/neonate as any patient ≤ 30 days of age.

Statistical Analysis. For patients with >1 E-CPR event, only the index (first) E-CPR event was included. Facility characteristics, patient demographic data, pre-event data, resuscitation event data, and postresuscitation care data were compared for survivors and nonsurvivors. The Mann-Whitney U test was used for continuous data, and categorical data were compared with the chi-square test. Fisher’s exact test was used when expected counts in $>20\%$ of cells were <5 . The associations of factors with inhospital mortality were evaluated by simple logistic regression and multivariate logistic regression. Candidate variables for inclusion in a multivariable logistic regression were chosen from the bivariate analysis, and the criterion for variable selection was set at $p \leq .1$. A forward-selection procedure was used for entry of variables into

the model, and a variable inclusion criterion was set at $p \leq .05$. Variables containing continuous values were only retained in the model if linearity assumption was met. Variables not meeting the linearity assumption were converted into categorical variables, and those categorical variables were included in the model. Two separate models were developed, one to identify prearrest variables associated with outcome, including demographic factors, and another model to evaluate both prearrest variables and arrest variables associated with outcome. Cochran-Armitage test was used to assess trend analysis of percent survival per year. SAS version 9.1.3 software (SAS Institute, Cary, NC) was used for the analysis. Data are reported as frequency (n) with proportion (%) of median values with interquartile ranges (25th percentile, 75th percentile). Statistical significance was set at probability value $<.05$.

RESULTS

From January 1, 2000, to December 31, 2007, there were 5069 pediatric and neonatal patients who had 6288 CPA events requiring CPR. We identified 203 (3.2%) pediatric and neonatal CPA events that met inclusion criteria for E-CPR while being resuscitated for in-hospital cardiac arrest. Four patients had two E-CPR events each, leaving 199 index E-CPR events (Fig. 1).

Trends in E-CPR Use. Trends in the use of E-CPR and survival are seen in

Figure 2. Since 2000, overall E-CPR use increased among both cardiac and noncardiac patients. However, since 2004, there has been a slight decline in the number of cardiac patients and an increase in the number of noncardiac patients using E-CPR. In 2007, cardiac patients accounted for approximately 73% of the total E-CPR patient cohort. Although the use of E-CPR has increased over the last few years, the survival rate has slowly trended downward from 60% in 2002 to 36% in 2007. Despite this, there was no significant change in survival over time based on trend analysis ($p = .62$).

Prearrest Characteristics of E-CPR Patients. Preatrest characteristics comparing survivors and nonsurvivors after E-CPR are described in Table 1. Age, weight, gender, age classification (neonate vs. pediatric), race, facility type (pediatric vs. mixed adult/pediatric), event time of day, and event day of week did not vary significantly between survivors and nonsurvivors after E-CPR. Overall, 87 patients (43.7%) survived to hospital discharge. In both survivors and nonsurvivors, respiratory insufficiency, congestive heart failure, and hypotension were the most common pre-existing conditions. The pre-existing conditions of pneumonia, renal insufficiency, and septicemia

Table 1. Prearrest characteristics of extracorporeal cardiopulmonary resuscitation patients

Characteristic	Survivors (n = 87)	Nonsurvivors (n = 112)	<i>p</i>
Age, months	2.5 (0, 13)	1.6 (0, 23)	.48
Weight, kg	4.3 (3.1, 11.1)	4.2 (2.7, 11.2)	.27
Gender			.51
Male	52 (60)	72 (64)	
Female	35 (40)	40 (36)	
Age classification			.18
Neonate (≤30 days)	33 (38)	53 (47)	
Pediatric	54 (62)	59 (53)	
Race			.28
White	56 (64)	70 (62)	
Black	16 (18)	14 (13)	
Others	15 (17)	28 (25)	
Facility type			.17
Pediatric	73 (84)	85 (76)	
Mixed (pediatric and adult)	14 (16)	27 (24)	
Event location			.70
All intensive care unit and operating room	74 (85)	93 (83)	
All others	13 (15)	19 (17)	
Event time of day			.79
Day/evening (7:00 AM–10:59 PM) ^b	61 (73)	78 (70)	
Night (11:00 PM–6:59 AM) ^b	23 (27)	32 (29)	
Event day of week			.07
Weekday (Mon 7:00 AM–Fri 10:59 PM)	65 (75)	95 (85)	
Weekend (Fri 11:00 PM–Mon 6:59 AM)	22 (25)	17 (15)	
Illness category ^a			.009
All cardiac	80 (92)	87 (78)	
All noncardiac and newborn	7 (8)	25 (22)	
Mode of discovery of event			.79
Witnessed	85 (98)	110 (98)	
Monitored by electrocardiogram/pulse oximetry/apnea	86 (99)	111 (99)	.86
Interventions in place at time of event			
Mechanical ventilation	64 (74)	81 (72)	.84
Arterial line	49 (56)	69 (62)	.45
Vascular access	84 (97)	106 (95)	.52
Vasoactive infusion	53 (61)	70 (63)	.82
Antiarrhythmic infusion	8 (9)	7 (6)	.44
Dialysis or extracorporeal therapies	2 (2)	3 (3)	1.00
Pacemaker	13 (15)	18 (16)	.83
Pre-existing conditions			
Arrhythmia	25 (29)	29 (26)	.65
Cardiac malformation, acyanotic	4 (5)	7 (6)	.62
Cardiac malformation, cyanotic	6 (7)	8 (7)	.95
Congestive heart failure, this admission	40 (47)	54 (49)	.77
Congestive heart failure, prior admission	32 (37)	39 (35)	.76
Hypotension	42 (49)	49 (44)	.51
Metabolic/electrolyte abnormality	9 (10)	22 (20)	.07
Pneumonia ^a	0 (0)	8 (7)	.01
Renal insufficiency ^a	2 (2)	12 (11)	.02
Respiratory insufficiency	47 (55)	73 (66)	.11
Septicemia ^a	3 (3)	13 (12)	.04

Data are reported as median (interquartile range) or n (%).

^a*p* < .05; ^bthe data were obtained from 194 patients.

were associated with an increased risk of mortality. Based on presence at the time of the E-CPR event, there were no survivors of the eight patients with pneumonia (*p* = .01), two of 12 survived with renal insufficiency (*p* = .02), and three of 13 survived with septicemia (*p* = .04). Patients with a cardiac illness category were more likely to survive to hospital discharge than those patients with a noncardiac illness category (*p* = .009).

Almost all of the patient population had witnessed CPA events (98%) and were being monitored by electrocardiogram and/or pulse oximetry and/or an apnea monitor (99%) at the time of the event. There were no differences between survivors and nonsurvivors based on the mode of discovery of the CPA event. The location of the CPA event and the interventions in place at the time of the CPA event did not vary significantly between

survivors and nonsurvivors. Of all patients, 167 (84%) arrested in an intensive care unit or operating room location. Thirty-two (16%) arrested in all other locations. After combining all intensive care unit and operating room locations into one category and comparing it to all nonintensive care unit/operating room locations, there was no difference in survival to hospital discharge. Pre-existing invasive monitoring (presence of an indwelling arterial line) was present in 118 (59%) patients at the time of the arrest event; however, survival did not differ between those patients with invasive arterial monitoring and those without (42% vs. 47%, *p* = .45).

Arrest Characteristics of E-CPR Patients. Arrest characteristics comparing survivors and nonsurvivors are described in Table 2. In both survivors and nonsurvivors, arrhythmia and hypotension were the most common immediate precipitating causes of the arrest; metabolic/electrolyte abnormalities were more commonly the immediate factors related to the arrest for patients who subsequently died compared with those who survived to hospital discharge. Survival did not differ based on the first documented rhythm or the state of the pulse during the CPA event (i.e., patients who were pulseless at any time during the arrest event and those who never became pulseless). There was a difference between survivors and nonsurvivors based on the first documented pulseless rhythm with an increased survival in patients with ventricular fibrillation and pulseless ventricular tachycardia compared with asystole and pulseless electrical activity (54% vs. 34%, *p* = .04). The duration of CPR as a continuous variable and at cut points (Fig. 3), time interval to CPR, defibrillation data, and epinephrine doses did not vary significantly between survivors and nonsurvivors. Although the median duration of CPR in survivors of 46 mins (range, 28–68 mins) was less than nonsurvivors at 57 mins (range, 38–71 mins), it was not associated with improved survival (*p* = .28). Receiving sodium bicarbonate or tromethamine during the arrest was the only pharmacologic intervention noted to be different in survivors compared with nonsurvivors, with nonsurvivors having a higher likelihood of receiving sodium bicarbonate or tromethamine (*p* = .02). There were no significant nonpharmacologic interventions that predicted survival to discharge.

Table 2. Arrest characteristics of extracorporeal cardiopulmonary resuscitation patients

Characteristic	Survivors (n = 87)	Nonsurvivors (n = 112)	p
Immediate factors related to event			
Acute respiratory insufficiency	42 (48)	54 (48)	.99
Arrhythmia	57 (66)	70 (63)	.66
Hypotension	56 (64)	84 (75)	.10
Metabolic/electrolyte abnormality ^d	3 (3)	17 (15)	.006
State of pulse during event			
Pulse absent throughout event	36 (41)	57 (51)	.40
Pulse initially present, subsequently absent	27 (31)	30 (27)	
Pulse present throughout event	24 (28)	25 (22)	
First documented rhythm			
Pulseless rhythm	36 (41)	57 (51)	.18
Pulse with poor perfusion rhythm	51 (46)	55 (49)	
First documented pulseless rhythm ^{a,b}			
Asystole	11 (17)	32 (37)	.02
Pulseless electrical activity	20 (32)	28 (32)	
Ventricular fibrillation	13 (21)	15 (17)	
Pulseless ventricular tachycardia	7 (11)	2 (2)	
Unknown or not documented	12 (19)	10 (11)	
First documented pulseless rhythm (two levels) ^{a,b}			
Asystole and pulseless electrical activity	31 (61)	60 (78)	.04
Ventricular fibrillation and pulseless ventricular tachycardia	20 (39)	17 (22)	
Duration of cardiopulmonary resuscitation, mins (continuous variable) ^c			
Interval to cardiopulmonary resuscitation, mins ^d	0 (0–0)	0 (0–0)	.68
Interval to invasive airway, mins ^e	5 (2–11)	8 (2–13)	.29
Any VF/pulseless VT	27 (31)	39 (35)	.57
Defibrillation attempted	22 (81)	33 (85)	.73
Interval to first defibrillation, mins ^f	0 (0–2)	0 (0–2)	.77
Number of defibrillations	3 (1–4)	3 (1–4)	.42
Interval to first epinephrine dose, mins ^g	0 (0–3)	1 (0–5)	.60
No. of epinephrine doses (continuous variable)	4 (2–6)	4 (2–7)	.40
No. of epinephrine doses (categorized)			
1–2	24 (28)	25 (22)	.79
3–5	27(31)	36 (32)	
6–9	12 (14)	19 (17)	
10+	7 (8)	13 (11)	
Unknown	17 (20)	19 (17)	
Pharmacologic interventions			
Fluid bolus	33 (38)	56 (50)	.09
Sodium bicarbonate or tromethamine ^a	65 (75)	98 (88)	.02
Vasopressin ^h	8 (10)	4 (4)	.10
Vasopressor	34 (39)	45 (40)	.88
Atropine	25 (29)	29 (26)	.65
Calcium chloride or calcium gluconate	59 (66)	79 (71)	.68
Nonpharmacologic interventions			
Central venous line insertion	4 (5)	8 (7)	.45
Echocardiogram	4 (5)	11 (10)	.17
Pacemaker, transvenous/transcutaneous/epicardial	8 (9)	19 (17)	.11
Ice to head	6 (7)	15 (13)	.14

Data are reported as median (interquartile range) or n (%).

^ap < .05; ^bthe data were obtained from 128 patients; ^cthe data were obtained from 187 patients; ^dthe data were obtained from 189 patients; ^ethe data were obtained from 41 patients; ^fthe data were obtained from 43 patients; ^gthe data were obtained from 171 patients; ^hthe data were obtained from 179 patients.

Postarrest Characteristics of E-CPR Patients. The admission and discharge PCPC score were recorded and available for 59 of the 87 (68%) patients who survived to hospital discharge. Of those survivors with recorded categories, 56 (95%) had favorable neurologic outcomes. Of those patients with favorable outcomes,

37 were functioning normally (PCPC 1), 15 had mild neurologic disability (PCPC 2) and four had moderate disability (PCPC 3). The three patients with unfavorable neurologic outcomes had severe disability (PCPC 4). Overall, 112 patients (56%) did not survive to hospital discharge. Of these patients, 11 (10%) died

within the first 24 hrs of being treated with E-CPR. Sixty-one (54%) had “do not attempt resuscitation” orders enacted before death and 67 (60%) died after medical support was voluntarily withdrawn. Twelve (11%) were reported to have met criteria for brain death. Organs were recovered for transplant in five patients (4%).

Multivariate Logistic Regression Models Predicting Survival in E-CPR Patients. Multivariate logistic regression models predicting survival in E-CPR patients are described in Table 3. The adjusted odds ratio for inhospital mortality was lower for patients with a cardiac illness category than for patients with a noncardiac illness category in each model. In addition, the pre-existing condition of renal insufficiency was associated with an increased adjusted odds of inhospital mortality in each model. The pre-existing condition of metabolic or electrolyte abnormality was associated with an increased adjusted odds of inhospital mortality after controlling for prearrest factors in model 1 as well as after controlling for both prearrest and arrest variables in model 2. In addition, the pharmacologic intervention of sodium bicarbonate or tromethamine was also associated with an increased adjusted odds of inhospital mortality after controlling for prearrest and arrest variables.

DISCUSSION

In this cohort of neonates and children experiencing cardiopulmonary arrest, E-CPR was used as a resuscitation measure in those who were refractory to conventional resuscitation efforts. After the institution of extracorporeal life support during active chest compressions, 44% of cohort patients survived to hospital discharge and the vast majority of these patients with reported neurologic outcomes had favorable neurologic function. These patients had failed conventional CPR and would likely have died without treatment with E-CPR. Overall survival in this report is similar to the results of other recent studies (9, 12, 14, 16, 19) and supports the use of E-CPR as an adjunct to conventional CPR in select pediatric patients.

As hypothesized, we found that patients with pre-existing cardiac disease, defined as an illness category of cardiac-medical or cardiac-surgical had improved odds of surviving to hospital dis-

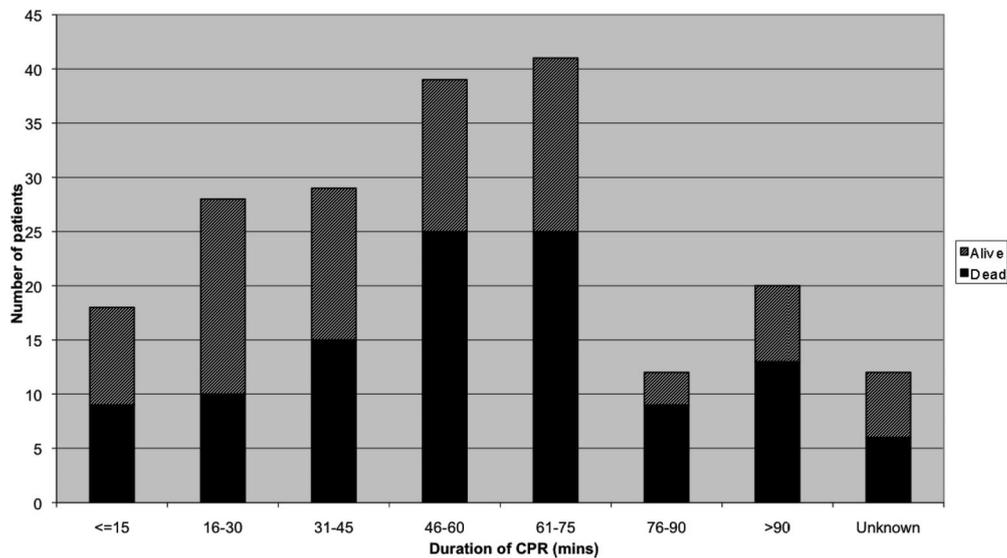


Figure 3. Duration of cardiopulmonary resuscitation (CPR) and the number of surviving patients managed with extracorporeal CPR. The duration of CPR was defined as the time from cardiac arrest until the extracorporeal membrane oxygenation pump was started. There was no association with the duration of CPR and survival based on time cut points ($p = .12$).

Table 3. Multivariate regression model of variables associated with survival in extracorporeal cardiopulmonary resuscitation patients

Variable	Odds Ratio	95% Confidence Interval	p
Model I: Candidate variables associated with survival in E-CPR patients, including pre-event arrest data			
Illness category			
Cardiac disease	3.55	1.45–8.72	.006
Pre-existing conditions			
Renal insufficiency	0.17	0.04–0.80	.02
Model II: Candidate variables associated with survival in E-CPR patients including pre-event arrest data and arrest event data			
Illness category			
Cardiac disease	5.82	2.08–16.29	.0008
Pre-existing conditions			
Renal insufficiency	0.16	0.03–0.84	.03
Metabolic/electrolyte abnormality	0.25	0.07–0.91	.04
Immediate factors related to event			
Metabolic/electrolyte abnormality	0.28	0.08–1.05	.05
Pharmacologic interventions			
Sodium bicarbonate or tromethamine	0.25	0.10–0.63	.003

E-CPR, extracorporeal cardiopulmonary resuscitation.

The overall model fit statistic measured by c statistic is .611 and .689 for models 1 and 2, respectively.

charge when compared with patients without pre-existing cardiac illness. Of those patients classified in cardiac categories, 48% survived to hospital discharge. These findings are consistent with previous studies that found improved survival in cardiac patients (9, 12, 16, 18, 19). Specific diagnoses are not known for these patients, but medical-cardiac conditions treated with E-CPR have included cardiomyopathy, myocarditis, and unrepaired congenital cardiac disease. Extracorporeal life support may

have provided the time and stabilization these patients required before proceeding to heart transplantation or surgical repair. Patients with primary cardiac disease frequently have diminished cardiopulmonary reserve and may be subject to increased risk of sudden CPA as a result of transient conditions of coronary hypoperfusion or respiratory insufficiency. These patients may have less dysfunction of other organ systems at the time of arrest and therefore may be more likely to survive after treatment with E-CPR.

Although return of circulation is essential for survival from cardiac arrest, meaningful neurologic survival represents the most clinically relevant outcome measure for CPR. To our knowledge, this study is the largest to date to report neurologic outcomes in pediatric patients after E-CPR. The majority of survivors with reported neurologic outcomes had favorable neurologic prognosis at the time of hospital discharge with at least 64% of all survivors having favorable outcomes. Twenty-eight patients had no PCPC score recorded at the time of admission or discharge so their neurologic outcome is unknown. Of those 59 patients with known outcomes, 95% were favorable. These findings are consistent with a previous study that found favorable neurologic outcomes in ten of 11 E-CPR survivors (91%) at follow-up (10). These data and prior data suggest that of those patients who survive to discharge after E-CPR, the majority have favorable neurologic outcomes (12, 14).

We hypothesized that those patients who maintained a pulse with poor perfusion (i.e., never became pulseless) would have improved odds of survival when compared with those who became pulseless before treatment with E-CPR. However, survival did not differ based on the first documented rhythm or between patients who were pulseless at any time during the arrest event vs. those who never became pulseless. This E-CPR cohort further confirms prior data that the first documented pulseless rhythm in

children is more likely to be asystole or pulseless electrical activity, but ventricular tachycardia and ventricular fibrillation are not rare in pediatric patients with 37.3% of this cohort having a shockable rhythm at some point during the E-CPR event (6, 8). Interestingly, there was a statistically significant difference between survivors and nonsurvivors based on the first documented pulseless rhythm with increased survival in patients with ventricular fibrillation and pulseless ventricular tachycardia compared with asystole and pulseless electrical activity (29.2% vs. 24.6%); however, this did not reach statistical significance (6).

Acid base and electrolyte abnormalities are commonly seen during and after recovery from cardiac arrest. These include, but are not limited to, metabolic acidosis resulting from lactic acidosis and nonanion gap acidosis usually resulting from renal tubular injury. Metabolic acidosis is often present before arrest as a sign of inadequate oxygen delivery and is further exacerbated by tissue hypoxia and ischemia occurring during the low-flow arrest state (31). Specific details regarding the metabolic/electrolyte abnormality as documented in the NRCPR database are not known, because this variable can be defined as an abnormality of blood glucose, lactate, magnesium, arterial pH, potassium, or sodium. Consistent with prior reports, our data support that pre-existing renal insufficiency and metabolic/electrolyte abnormalities are associated with worse survival to discharge after cardiac arrest. De Mos reported that renal failure in the 24 hrs before cardiac arrest is associated with increased mortality after pediatric intensive care unit cardiac arrest (10). Similarly, in a study of in-hospital pediatric ventricular fibrillation, pre-existing renal insufficiency was associated with decreased survival (8). In studies of rescue ECMO for pediatric cardiac arrest, nonsurvivors had higher plasma lactate levels (14) and persistent metabolic acidosis despite ECMO being associated with an increased incidence of death (16).

Sodium bicarbonate or tromethamine is often given during and after cardiac arrest to correct metabolic acidosis, although the usefulness remains contro-

versial. Because severe acid base disturbances may adversely affect cardiac function, it is important to recognize and correct acid base and electrolyte abnormalities promptly in the postarrest state to minimize the risk for arrhythmias, poor cardiac contractility, altered vascular resistance, and ongoing neurologic damage. The use of sodium bicarbonate in adults experiencing out-of-hospital cardiac arrest remains controversial (32–34). In a large multicenter trial, earlier and more frequent use of sodium bicarbonate was associated with higher early survival rates and with better long-term outcome suggesting that sodium bicarbonate may be beneficial in some circumstances (33). Other studies showed no benefit from administration of sodium bicarbonate or calcium during and after cardiac arrest (35–37). Consistent with our data, other pediatric studies of in-hospital cardiac arrest have associated the administration of sodium bicarbonate with decreased survival to discharge (survival 19% sodium bicarbonate vs. 37% no sodium bicarbonate) (7, 8).

It is unclear whether survival and acceptable neurologic outcome in patients rescued by E-CPR is dependent on the duration of CPR. Morris et al found no significant difference between survivors and nonsurvivors regarding length of CPR before E-CPR cannulation (9), and a case report by Kelly et al documented acceptable neurologic outcome in a 4-yr-old who sustained cardiac arrest requiring CPR for 176 mins before initiation of ECMO (17). In addition, Parra et al found no significant difference between CPR duration less than or >20 mins and survival; however, only a portion of these children received E-CPR (3). In contrast, a recent report by Chen and colleagues on adult in-hospital E-CPR documented that significantly more patients survived E-CPR if their CPR duration was <60 mins. Our data support no difference in survival to discharge based on CPR duration and further support that good neurologic outcome can occur after prolonged CPR rescued with ECMO. Seven of the survivors in this cohort had CPR for >90 mins with five of the seven having good neurologic outcomes at discharge (PCPC 1 = three patients; PCPC 2 = two patients; PCPC unknown = two). In fact, two patients had CPR for 196 mins and 220 mins with good neurologic outcome.

This study has several important limitations. It has the inherent limitation of a retrospective cohort study. A retrospec-

tive study can estimate measures of association and relative risk but cannot determine causality. E-CPR remains a rare occurrence so there are relatively few patients, even in multicenter registries such as the NRCPR. This cohort may lack a sufficient number of subjects to delineate some associations and significant differences among outcome variables, and some variables may include missing data for some subjects. Included in this missing data are the neurologic outcomes for 28 survivors, which may represent a “reporting bias” among patients with neurologic injury. Missing from the analysis are the important postresuscitation factors of temperature and glucose. The NRCPR did not request reporting of these postresuscitation factors until after the release of the 2005 Guidelines, and for this reason, these important factors have >20% “missing data” and could not be included in the multivariate analysis. Interpretation of the metabolic/electrolyte abnormality data must take into account the broad definition for this variable and that lactate and arterial pH are two of six possible variables that could meet criteria for metabolic/electrolyte abnormality according to the database. Another limitation is the lack of data on ECMO support details such as mode of cannulation and complications associated with ECMO. Like with all multicenter registries, analysis of the data may be limited by the data integrity and validation issues at multiple sites. The rigorous abstractor certification process, uniform data collection, consistent definitions, scientific advisory board reabstraction process, and large sample size were intended to minimize these sources of bias. In addition, the neurologic outcome was determined at hospital discharge with no long-term neurocognitive follow-up. However, previous studies indicate that neurologic status at discharge is not substantially different from status at 6 months and 1 yr postarrest (5, 38–40). The designated illness categories make it possible to compare groups, but specific diagnoses might allow more precise comparisons among subjects. It must also be pointed out that much of these data were collected before the 2005 CPR Guidelines being widely adopted, and recent clinical studies have demonstrated an improvement in outcomes resulting from implementation of the new guidelines (41–43). Currently, the NRCPR database does not allow for the assessment of the quality of CPR performed. Future studies must ac-

count for how differences in quality of CPR might affect outcome. Finally, inclusion of validated severity-of-illness scores in the NRCPR database would allow for more meaningful intergroup comparisons.

CONCLUSIONS

Although once considered an extreme measure, ECMO is increasingly used to provide blood flow and oxygenation to the patient when resuscitation is unsuccessful. Although unable to support the efficacy of E-CPR as a result of the observational, nonrandomized study design, the data do provide associations that may contribute information supportive of the effectiveness in treating select pediatric patients with E-CPR who have sustained CPA refractory to conventional resuscitation measures. The vast majority of survivors in this cohort with reported neurologic outcomes were favorable. Patients with pre-existing cardiac disease were more likely to survive after E-CPR and they continue to represent the majority of reported cases of E-CPR as noted in prior series. The hospital location, presence of invasive monitoring, event time of day, event day of week, and duration of CPR did not affect survival. The data further support that patients with pre-existing renal insufficiency and metabolic or electrolyte abnormalities should have careful consideration for the use of E-CPR as a result of increased mortality. When used in appropriate patients, E-CPR should be considered a viable adjunct to conventional resuscitation measures.

The physician will gain the knowledge that E-CPR is a potential therapeutic option for patients with refractory cardiac arrest and that the use of E-CPR appears to produce its maximal beneficial effects in the setting of cardiac arrest from a cardiac etiology.

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