Extracorporeal Cardiopulmonary Resuscitation (E-CPR) During Pediatric In-Hospital Cardiopulmonary Arrest Is Associated With Improved Survival to Discharge

A Report from the American Heart Association's Get With The Guidelines–Resuscitation (GWTG-R) Registry

Javier J. Lasa, MD; Rachel S. Rogers, MS; Russell Localio, PhD; Justine Shults, PhD; Tia Raymond, MD; Michael Gaies, MD, MPH; Ravi Thiagarajan, MBBS, MPH; Peter C. Laussen, MBBS; Todd Kilbaugh, MD; Robert A. Berg, MD; Vinay Nadkarni, MD, MS; Alexis Topjian, MD, MSCE

Background—Although extracorporeal cardiopulmonary resuscitation (E-CPR) can result in survival after failed conventional CPR (C-CPR), no large, systematic comparison of pediatric E-CPR and continued C-CPR has been reported.

Methods and Results—Consecutive patients <18 years old with CPR events ≥10 minutes in duration reported to the Get With the Guidelines–Resuscitation registry between January 2000 and December 2011 were identified. Hospitals were grouped by teaching status and location. Primary outcome was survival to discharge. Regression modeling was performed, conditioning on hospital groups. A secondary analysis was performed with the use of propensity score matching. Of 3756 evaluable patients, 591 (16%) received E-CPR and 3165 (84%) received C-CPR only. Survival to hospital discharge and survival with favorable neurological outcome (Pediatric Cerebral Performance Category score of 1–3 or unchanged from admission) were greater for E-CPR (40% [237 of 591] and 27% [133 of 496]) versus C-CPR patients (27% [862 of 3165] and 18% [512 of 2840]). Odds ratios (ORs) for survival to hospital discharge and survival with favorable neurological outcome were greater for E-CPR versus C-CPR. After adjustment for covariates, patients receiving E-CPR had higher odds of survival to discharge (OR, 2.80; 95% confidence interval, 2.13–3.69; $P<0.001$) and survival with favorable neurological outcome (OR, 2.64; 95% confidence interval, 1.91–3.64; $P<0.001$) than patients who received C-CPR. This association persisted when analyzed by propensity score–matched cohorts (OR, 1.70; 95% confidence interval, 1.33–2.18; $P<0.001$; and OR, 1.78; 95% confidence interval, 1.31–2.41; $P<0.001$, respectively].

Conclusion—For children with in-hospital CPR of ≥10 minutes duration, E-CPR was associated with improved survival to hospital discharge and survival with favorable neurological outcome compared with C-CPR. **(*Circulation*. 2016;133:165-176. DOI: 10.1161/CIRCULATIONAHA.115.016082.)**

Key Words: cardiopulmonary resuscitation ■ extracorporeal circulation ■ heart arrest ■ mortality ■ pediatrics

Pediatric in-hospital cardiac arrest (IHCA) occurs in 1% to 3% of pediatric intensive care unit (ICU) admissions and up to 6% of children treated in cardiac ICUs.[1–12] Survival to hospital discharge after pediatric IHCA has improved over the last 25 years from 9% to 13.7%[2,13] to 35% (78.1% with a favorable neurological outcome).[14] Improvement in outcomes has been attributed in part to the impact of extracorporeal membrane oxygenation (ECMO) as a rescue strategy when prolonged conventional cardiopulmonary resuscitation (C-CPR) cannot restore spontaneous circulation. Pediatric patients who receive ECMO CPR (E-CPR) for refractory cardiac arrest have survival to hospital discharge rates ranging from 33% to 42% in general ICU patients[15–18] and from 23% to 55% in cardiac ICU patients.[17,19–22] Presumably, without E-CPR, many of these patients would have died during their resuscitation.

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However, the exact indications for and timing of E-CPR deployment remain unknown. Comparing E-CPR strategies with C-CPR to determine the relative effectiveness of either

Received April 7, 2015; accepted October 9, 2015.

From Texas Children's Hospital, Houston (J.J.L.); Children's Hospital of Philadelphia, PA (R.S.R., R.L., J.S., T.K., R.A.B., V.N., A.T.); Medical City Children's Hospital, Dallas, TX (T.R.); University of Michigan C.S. Mott Children's Hospital, Ann Arbor (M.G.); Boston Children's Hospital, MA (R.T.); and Toronto Sick Kids Hospital, Canada (P.C.L.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.016082/-/DC1.

Correspondence to Javier J. Lasa, MD, Assistant Professor, Department of Pediatrics, Sections of Critical Care Medicine and Cardiology, Texas Children's Hospital, 6621 Fannin St, West Tower, B6041, Houston, TX 77030. E-mail jjlasa@texaschildrens.org

approach poses a challenge. ECMO is not uniformly available at all hospitals, and select patient populations such as pediatric cardiac surgical patients are more likely to receive E-CPR than noncardiac patients.[17,23,24] For many reasons, including the impact of ECMO availability and clinician preference for ECMO use, conducting a randomized, controlled trial has not been feasible. Modeling based on propensity scores has been used to compare adults who received E-CPR with those who received C-CPR and shows increased survival among those treated with E-CPR.[25–28] To date, no multicenter investigation has been conducted comparing E-CPR and C-CPR in pediatric IHCA.

Our objective was to determine whether patients with prolonged in-hospital CPR (≥10 minutes) who received E-CPR were more likely to survive to discharge and survive with a favorable neurological outcome than those who received C-CPR alone.

Methods

We used 2 approaches in this analysis to confirm that results were consistent across methods of analysis. Because we sought to compare E-CPR and C-CPR, we used 2 modeling approaches stratified by hospital groups, just as a randomized, controlled trial of an intervention would stratify treatment assignment by hospital. To this end, we used both conditional logistic regression and propensity score–based matching to control for potential confounding in this observational study.

Design and Setting

The American Heart Association's (AHA's) Get With the Guidelines–Resuscitation (GWTG-R) is a multicenter registry of IHCA that uses Utstein-style data reporting.[29–31] The design and reporting of GWTG-R have been described in detail previously (www.heart.org/resuscitation).[14,18,20,31–37] Participating hospitals are not required to obtain Institutional Review Board approval, although this study was approved by the Institutional Review Board of The Children's Hospital of Philadelphia. Quintiles is the data collection coordination center for the AHA/American Stroke Association's GWTG programs.

Operational definitions for the GWTG-R have been described in detail previously[20] and include 8 predefined illness categories that are based on patient characteristics at the time of CPR (medical cardiac, medical noncardiac, surgical cardiac, surgical noncardiac, newborn, trauma, obstetric, or other). Patients' circulatory status at the time of CPR initiation was categorized into pulse categories: pulseless, pulse present and then pulseless, or pulse present. First documented rhythm was defined as the first electrocardiographic rhythm documented during a CPR event. We included all patients with CPR events regardless of the presence of pulse and rhythm at the onset of CPR. Each patient's electrocardiographic status was described as asystole/pulseless electric activity, bradycardia, ventricular tachycardia/ventricular fibrillation, or other. Asystole and pulseless electric activity were grouped together because of previously published similarities in outcome.[32,36]

Arrest locations were grouped into the following categories: ICUs, inpatient areas, procedural areas (cardiac catheterization laboratory, diagnostic/interventional, operating room, postanesthesia recovery unit), emergency department, and other (ambulatory/outpatient, other).

Inclusion and Exclusion Criteria

Between January 1, 2000, and December 31, 2011, the GWTG-R registry identified a total of 13 814 patients <18 years of age with in-hospital CPR from 374 medical/surgical hospitals reporting pediatric data. All patients <18 years of age who received ≥10 minutes of CPR were selected. A CPR event was defined as an event that required chest compressions or defibrillation and terminated with either return of spontaneous circulation (sustained for >20 minutes with no further need for chest compression), placement of patient on extracorporeal life support during CPR (E-CPR), or death.[20] A C-CPR event was defined as any CPR event without the use of extracorporeal support. An E-CPR event was defined as a CPR event during which extracorporeal life support was used. Both ECMO and cardiopulmonary bypass were included in the definition of extracorporeal life support. For patients having multiple CPR events, only the first event ≥10 minutes was included. Any patient who received ≥10 minutes of C-CPR and subsequently received ECMO was classified as an E-CPR recipient, regardless of C-CPR duration. Therefore, each patient had only 1 event analyzed. Patients who were missing E-CPR status or survival status at discharge were excluded. CPR data from hospitals with no reported E-CPR cases were excluded from the primary analyses because there were no events for meaningful comparison with C-CPR patients. Patients were excluded if the CPR event occurred in a delivery room, rehabilitation/skilled nursing facility, or same-day surgery center. Obstetric and trauma patients were also excluded.

Multiple hospitals had small numbers of patients who received E-CPR, thus limiting the ability to match similar patients with E-CPR to those with C-CPR in the same hospital. Therefore, to address this limitation and to form patient matches that accounted for unobserved hospital-level differences in indications and preferences for E-CPR, we categorized hospitals into 10 groups, ranging from 1 to 6 institutions, based on teaching status (major and minor) and location. Two of the 10 groups had a single institution because the hospital had sufficient volumes of both E-CPR and C-CPR to support matching based on patient characteristics. The registry does not identify hospitals.

Outcomes

The primary outcome measure was survival to hospital discharge. The secondary outcome was survival with favorable neurological outcome at hospital discharge. Neurological outcome was determined with the use of the Pediatric Cerebral Performance Category (PCPC) scale, which was assigned after review of medical records 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.[38,39] Favorable neurological outcome was prospectively defined as a discharge PCPC score of 1, 2, or 3 or no change from admission PCPC score.[20] Nonsurvivors were included in the analysis as having an unfavorable neurological outcome. Neurological outcome was available for only 62% of subjects.

Statistical Analysis

Data were analyzed initially with conditional logistic regression to examine the effect of CPR type on survival to discharge and favorable neurological outcome, stratified by hospital groups. This analysis used only complete cases; subjects with incomplete covariate data were dropped. While controlling for patient-level factors, this analysis asks whether patients admitted to a hospital within the group of similar institutions fared better (or worse) when treated with E-CPR

Propensity Score Analysis

In contrast, the 2-step propensity score analysis allowed the inclusion of all data and was balanced on missing and complete data categories.[40] The approach also allowed us to consider contrasts between otherwise similar C-CPR versus E-CPR patients within hospital groups. With this approach, a first-stage logistic model of C-CPR versus E-CPR as the outcome examines treatment choice as a function of patient-level covariates. It then allows grouping of patients by their probability of receiving E-CPR. The second-stage logistic regression (response model) then modeled survival as a function of treatment received, adjusted for the probability of receiving E-CPR.[40]

For the first comparison (within hospital group), we implemented subclassification by propensity score to achieve balance in patient characteristics within each of the 10 hospital groups.[41–43] We first estimated a propensity score within each of the 10 hospital groups using logistic regression, observing the covariates of interest between the

patients who received C-CPR and those who received E-CPR. Missing data formed a separate covariate level and propensity score methods balance on all covariate levels, even those that represent missing values. From this initial logistic model, we then stratified patients into quintiles defined by the probability of E-CPR (Table I in the online-only Data Supplement). We compared patients within each of these 50 strata (5 strata within each of the 10 hospital groups) before and after stratification to determine whether balance was improved with the propensity score (Table II in the online-only Data Supplement). With the use of conditional logistic regression, the response model examined the association of outcome and C-CPR/E-CPR, stratified by 50 strata formed by propensity quintiles and the 10 hospital groups. The sample used for the response model consisted only of patients who demonstrated "common support" between the C-CPR/E-CPR propensity scores. Thus, only patients with overlapping C-CPR/E-CPR propensity values were represented in the response model.

A second propensity score modeling process attempted to compare similar C-CPR patients in 2 groups: those treated at hospitals that offered both C-CPR and E-CPR and those treated in hospitals that offered only C-CPR. This analysis sought to determine whether the patients who received E-CPR were selected by reason of better overall prognosis, leaving those with worse overall outlook to receive C-CPR, an unobserved selection bias. If that were the case, we hypothesized that C-CPR patients at hospitals offering both options would fare worse than similar patients at hospitals with only C-CPR available. Therefore, we used propensity score methods, similar to those outlined above, to compare C-CPR outcomes among similar patients at the 2 sets of hospitals. In this application, the outcome of the propensity score model at the first stage was hospital group (those that offered E-CPR versus those with only C-CPR) with the goal of balancing on patient-level characteristics across the 2 hospital groups.

Finally, we performed a sensitivity analysis using the method of Lin et al[44] to consider the potential for bias from unmeasured/unobserved confounders. All conditional logistic modeling was performed with the PROC logistic procedure (SAS Institute Inc). All *P* values are reported with a significance level set at <0.05. All analyses were performed with SAS software (version 9.2, SAS Institute Inc).

Results

Study Population

During the 11-year study period, 13 814 pediatric patients received in-hospital CPR and were reported in the registry. The patient selection process is displayed in the Figure. A total of 4856 patients underwent <10 minutes of CPR, with 3756 patients meeting inclusion criteria for analysis.

The prearrest characteristics of the E-CPR and C-CPR groups are given in Table 1. (Prearrest characteristics for variables not included in conditional logistic regression are listed in Table III in the online-only Data Supplement.) Children 1 month to 1 year of age made up the largest group of both C-CPR and E-CPR patients. Significant differences were seen in illness category type and CPR exposure, with a higher percentage of E-CPR patients having surgical cardiac illness and the majority of C-CPR patients categorized as medical noncardiac. More E-CPR patients had a first documented rhythm of asystole/pulseless electric activity (41% versus 32%), whereas more C-CPR patients had bradycardia as their first documented rhythm (49% versus 32%).

E-CPR patients were more likely to have pre-existing congestive heart failure and hypotension (Table 1). E-CPR patients were also more likely to receive vasoactive infusions, inhaled nitric oxide, sodium bicarbonate and calcium replacement, and more doses of epinephrine. The E-CPR group received a longer duration of CPR than the C-CPR group. There were no differences between groups for CPR event time of day (day versus night); however, E-CPR was less likely to have occurred during weekend hours compared with C-CPR (21% versus 29%).

Primary outcomes are presented in Table 2. Overall, 29% of patients survived to hospital discharge. Survival to hospital discharge was 27% for C-CPR patients compared with 40% in the E-CPR group. Survival with favorable neurological outcome data are also displayed in Table 2 (Survival and neurological outcome data for variables not included in final conditional regression are listed in Table IV in the online-only Data Supplement.) The discharge PCPC score was documented for 679 of the 1099 patients (62%) who survived to hospital discharge. Survival with favorable neurological outcome occurred in 18% of the C-CPR patients and 27% of the E-CPR patients.

Conditional Logistic Regression

The initial conditional regression analysis included 3756 patients (Table 3). After adjustment for illness category, hospital grouping, year of arrest, first documented rhythm, pre-existing conditions at the time of arrest (renal insufficiency, invasive

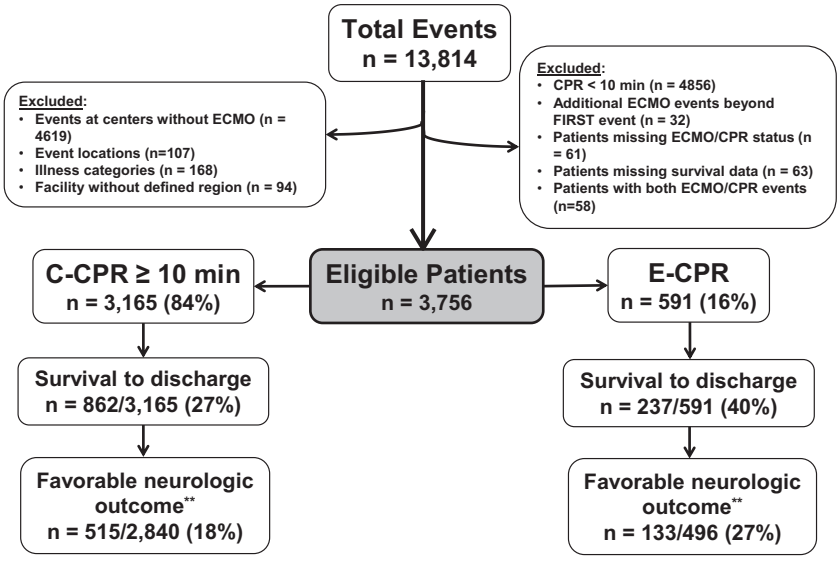

Figure. Patient selection flow diagram. **Pediatric Cerebral Performance Category score was available for 679 of 1099 survivors (62%). CPR indicates cardiopulmonary resuscitation; C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; and ECMO, extracorporeal membrane oxygenation.

Table 1. Baseline and Arrest Characteristics for the Initial Cohort and Propensity-Matched E-CPR and C-CPR Patients

	All Patients (n=3756), n (%)		Propensity-Matched Patients (n=2178), n (%)		
	C-CPR (n=3165)	E-CPR (n=591)	C-CPR (n=1673)	E-CPR (n=505)	*P* Value
Age groups					
0–1 mo	667 (21)	123 (21)	320 (19)	91 (18)	0.002
1 mo–1 y	1688 (53)	331 (56)	914 (55)	297 (59)	
1–8 y	788 (25)	126 (21)	434 (26)	109 (22)	
>8 y	22 (<1)	11 (2)	5 (<1)	8 (2)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Sex					
Male	1742 (55)	344 (58)	937 (56)	306 (61)	0.063
Female	1418 (44)	246 (41)	735 (44)	198 (39)	
Missing	5 (<1)	1 (<1)	1 (<1)	1 (<1)	
Year					
2000	73 (2)	10 (2)	40 (2)	9 (2)	0.16
2001	97 (3)	15 (3)	53 (3)	10 (2)	
2002	139 (4)	28 (5)	68 (4)	26 (5)	
2003	142 (5)	23 (4)	68 (4)	22 (4)	
2004	164 (5)	34 (6)	102 (6)	31 (6)	
2005	288 (9)	33 (5)	156 (9)	32 (6)	
2006	325 (10)	46 (8)	163 (10)	45 (9)	
2007	313 (10)	42 (7)	149 (9)	37 (7)	
2008	349 (11)	74 (12)	193 (12)	61 (12)	
2009	451 (14)	87 (15)	253 (15)	71 (14)	
2010	331 (11)	102 (17)	188 (11)	78 (15)	
2011	321 (10)	71 (12)	170 (10)	62 (12)	
2012	172 (6)	26 (4)	70 (4)	21 (4)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Illness category					
Medical, cardiac	491 (16)	119 (20)	325 (19)	106 (21)	<0.0001
Medical, noncardiac	1258 (40)	86 (15)	589 (35)	83 (16)	
Surgical, cardiac	628 (20)	349 (59)	496 (30)	282 (56)	
Surgical, noncardiac	282 (9)	18 (3)	114 (7)	16 (3)	
Newborn	506 (16)	19 (3)	149 (9)	18 (4)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
First documented rhythm					
Asystole/PEA	1021 (32)	243 (41)	657 (39)	204 (40)	0.005
Bradycardia	1563 (49)	192 (32)	691 (41)	173 (34)	
VT/VF	187 (6)	58 (10)	142 (8)	51 (10)	
Other	117 (4)	47 (8)	63 (4)	34 (7)	
Unknown/not documented	277 (9)	51 (9)	120 (7)	43 (9)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Preexisting conditions at time of arrest					
Metabolic/electrolyte abnormality					
Yes	478 (15)	96 (16)	303 (18)	81 (16)	0.29
No	2261 (71)	478 (81)	1270 (76)	409 (81)	
Missing	426 (13)	17 (3)	100 (6)	15 (3)	

(*Continued*)

Table 1. Continued

	All Patients (n=3756), n (%)		Propensity-Matched Patients (n=2178), n (%)		
	C-CPR (n=3165)	E-CPR (n=591)	C-CPR (n=1673)	E-CPR (n=505)	*P* Value
Renal insufficiency					
Yes	324 (10)	52 (9)	190 (11)	43 (9)	0.015
No	2415 (76)	522 (88)	1383 (83)	447 (86)	
Missing	426 (13)	17 (3)	100 (6)	15 (3)	
Respiratory insufficiency					
Yes	1826 (57)	337 (57)	1017 (61)	293 (58)	0.033
No	913 (29)	237 (40)	556 (33)	197 (39)	
Missing	426 (13)	17 (3)	100 (6)	15 (3)	
Interventions in place at time of arrest					
Invasive airway					
Yes	2071 (65)	441 (75)	1171 (70)	374 (74)	0.023
No	1094 (35)	150 (25)	502 (30)	131 (26)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Cause of arrest					
Hypotension/hypoperfusion					
Yes	1540 (49)	417 (71)	988 (59)	347 (69)	<0.001
No	1323 (49)	168 (28)	628 (28)	152 (30)	
Missing	302 (10)	6 (1)	57 (3)	6 (1)	
Pharmacological interventions					
Sodium bicarbonate administration					
Yes	1992 (63)	456 (77)	1177 (70)	387 (77)	0.002
No	1173 (37)	134 (23)	496 (30)	118 (23)	
Missing	0 (0)	1 (<1)	0 (0)	0 (0)	
Doses of epinephrine, median (IQR), n	4.0 (2.0–6.0)	5.0 (2.0–9.0)	4.0 (3.0–7.0)	5.0 (3.0–9.0)	0.092
Duration of CPR, median (IQR), min	24.0 (15.0–39.0)	43.0 (25.0–63.0)	27.0 (17.0–44.0)	41.0 (23.0–59.0)	<0.0001
Length of stay, median (IQR), d	13.0 (1.0–41.0)	24.0 (9.0–49.0)	13.0 (1.0–39.0)	23.0 (8.0–47.0)	<0.0001

C-CPR indicates conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; IQR, interquartile range; PEA, pulseless electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

airway), pharmacological interventions (sodium bicarbonate administration, calcium administration), cause of arrest (hypotension/hypoperfusion), number of doses of epinephrine, and duration of CPR, patients who received E-CPR had a higher odds of survival to hospital discharge (adjusted odds ratio [OR], 2.76; 95% confidence interval [CI], 2.08–3.65; $P<0.0001$) and survival with a favorable neurological outcome (adjusted OR, 2.64; 95% CI, 1.91–3.67; $P<0.0001$) than patients who received C-CPR. We sought to minimize any potential bias related to the high percentage of surgical cardiac patients receiving E-CPR in this registry and performed a secondary sensitivity analysis that excluded all surgical cardiac patients. After exclusion of the surgical cardiac patient cohort, a total of 1915 patients were analyzed, and those who received E-CPR continued to demonstrate an increased likelihood of survival to discharge and favorable neurological outcome compared with C-CPR recipients (survival adjusted OR, 3.1; 95% CI, 1.98–4.71; $P<0.0001$; favorable neurological outcome adjusted OR, 2.8; 95% CI, 1.69–4.66; $P<0.0001$).

Propensity Score Analysis

The number of patients per hospital who had propensity scores that overlapped between the 2 CPR groups was 2178, and this number ranged from 108 to 306 across the 10 hospital groups (Table I in the online-only Data Supplement). The primary analysis included 505 E-CPR patients (23%) and 1673 C-CPR patients (77%). Baseline and arrest characteristics are reported between the 2 groups (Table 1). Patients who received E-CPR had greater odds of survival to hospital discharge (adjusted OR, 1.70; 95% CI, 1.33–2.18; $P<0.001$). Of the 421 E-CPR and 1531 C-CPR patients with available data on neurological outcomes, the E-CPR group had more survival with favorable neurological status at discharge (adjusted OR, 1.78; 95% CI, 1.31–2.41; $P<0.001$) than the patients who received C-CPR (Table 4).

In a sensitivity analysis that explored the potential effect of an unmeasured/unobserved confounder, we found that our results would remain statistically significant even if an unmeasured/unobserved confounder had a10% prevalence for the outcome and assuming that the relative risk of survival to discharge for E-CPR compared with C-CPR is 2.0. Thus, to

Table 2. Survival to Discharge and Neurological Outcome: Summary Statistics for Conditional Logistic Regression Cohort

	Survival to Discharge, n (%) (n=3756)		Neurological Outcome, n (%) (n=3336)	
	No (n=2657)	Yes (n=1099)	Unfavorable (n=2688)	Favorable (n=648)
CPR group				
C-CPR	2303 (87)	862 (78)	2325 (87)	515 (79)
E-CPR	354 (13)	237 (22)	363 (14)	133 (21)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Age groups				
0–1 mo	572 (21)	218 (20)	574 (21)	100 (15)
1 mo–1 y	1381 (52)	638 (58)	1399 (52)	391 (60)
1–8 y	679 (26)	235 (21)	690 (26)	153 (24)
>8 y	25 (<1)	8 (<1)	25 (<1)	4 (<1)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Sex				
Male	1466 (55)	620 (56)	1485 (55)	367 (57)
Female	1186 (44)	478 (43)	1198 (45)	281 (43)
Missing	5 (<1)	1 (<1)	5 (<1)	0 (0)
Year				
2000	60 (2)	23 (2)	61 (2)	15 (2)
2001	76 (3)	36 (3)	79 (3)	27 (4)
2002	112 (4)	55 (5)	116 (4)	40 (6)
2003	117 (4)	48 (4)	121 (4)	33 (5)
2004	151 (6)	47 (4)	151 (6)	34 (5)
2005	225 (9)	96 (9)	231 (9)	59 (9)
2006	276 (10)	95 (9)	277 (10)	66 (10)
2007	272 (10)	83 (8)	274 (10)	52 (8)
2008	303 (11)	120 (11)	306 (11)	77 (12)
2009	357 (13)	181 (16)	360 (13)	114 (18)
2010	284 (11)	149 (14)	287 (11)	61 (10)
2011	259 (10)	133 (12)	260 (10)	54 (8)
2012	165 (6)	33 (3)	165 (6)	16 (3)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Illness category				
Medical, cardiac	419 (16)	191 (17)	427 (16)	121 (19)
Medical, noncardiac	1026 (39)	318 (29)	1037 (39)	190 (29)
Surgical, cardiac	603 (23)	374 (34)	612 (34)	231 (36)
Surgical, noncardiac	209 (8)	91 (8)	212 (8)	55 (8)
Newborn	400 (15)	125 (11)	400 (15)	51 (8)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
First documented rhythm				
Asystole/PEA	989 (37)	275 (25)	1002 (37)	181 (28)
Bradycardia	1183 (45)	572 (52)	1193 (33)	308 (48)
VT/VF	151 (6)	94 (9)	154 (6)	62 (10)
Other	200 (4)	64 (6)	101 (4)	42 (6)
Unknown, not documented	234 (9)	94 (9)	238 (9)	55 (8)
Preexisting conditions at time of arrest				
Metabolic/electrolyte abnormality				
Yes	461 (17)	113(10)	464 (17)	83 (13)
No	1866 (70)	873 (79)	1894 (70)	549 (85)
Missing	330 (12)	113 (10)	330 (12)	16 (2)

(*Continued*)

Table 2. Continued

	Survival to Discharge, n (%) (n=3756)		Neurological Outcome, n (%) (n=3336)	
	No (n=2657)	Yes (n=1099)	Unfavorable (n=2688)	Favorable (n=648)
Renal insufficiency				
Yes	321 (12)	55 (5)	322 (12)	36 (6)
No	2006 (76)	931 (85)	2036 (76)	596 (92)
Missing	330 (12)	113 (10)	330 (12)	16 (2)
Respiratory insufficiency				
Yes	1557 (59)	606 (55)	1577 (59)	392 (60)
No	770 (30)	380 (35)	781 (29)	240 (37)
Missing	330 (12)	113 (10)	330 (12)	16 (2)
Interventions in place at time of arrest				
Invasive airway				
Yes	1875 (71)	637 (58)	1890 (70)	388 (60)
No	782 (29)	462 (42)	798 (30)	260 (40)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Cause of arrest				
Hypotension/hypoperfusion				
Yes	1489 (56)	468 (43)	1501 (56)	290 (45)
No	946 (36)	545 (50)	965 (36)	349 (54)
Missing	222 (8)	86 (7)	222 (8)	9 (2)
Pharmacological interventions				
Sodium bicarbonate administration				
Yes	1882 (71)	565 (51)	1911 (71)	334 (52)
No	773 (29)	534 (49)	776 (29)	314 (48)
Missing	1 (<1)	0 (0)	1 (<1)	0 (0)
Doses of epinephrine, median (IQR), n	4.0 (2.0–7.0)	3.0 (1.0–5.0)	4.0 (2.0–7.0)	3.0 (1.0–4.0)
Duration of CPR, median (IQR), min	28.0 (17.0–46.0)	22.0 (14.0 – 36.0)	28.0 (17.0–46.0)	23.0 (14.0–37.0)
Length of stay, median (IQR), d	6.0 (1.0–26.0)	38.0 (20.0–73.0)	7.0 (1.0–27.0)	35.0 (18.0–69.0)

As a result of missing neurological outcome data, the total number for neurological outcome is different from the number for survival to discharge. See text for details. CPR indicates cardiopulmonary resuscitation; C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; IQR, interquartile range; PEA, pulseless electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

change our reported results, an unmeasured/unobserved confounder would have to be common (>10%) and strongly associated with both CPR types and outcome (relative risk of >2.0).

When we compared C-CPR patient outcomes at those hospitals that offered E-CPR with the outcomes of patients at hospitals that did not offer C-CPR (stratified by propensity scores representing combined patient-level characteristics), we found that similar C-CPR patients had a 20% improved odds of survival if they received C-CPR at hospitals that offered both C-CPR and E-CPR (OR for survival, 1.2; 95% CI, 1.1–1.4).

Discussion

Among pediatric patients treated with at least 10 minutes of in-hospital CPR, those receiving E-CPR had greater odds of survival to discharge than patients who received continued C-CPR in this large GWTG-R IHCA database. Importantly, E-CPR patients also had greater survival with favorable neurological outcome. These findings were demonstrable with 2 different statistical methodologies selected a priori that were intended to adjust for potential confounding factors.

Initial small case series of successful rescue ECMO therapy during CPR for pediatric postoperative cardiac patients were reported in the 1980s and 1990s.[45–47] Larger series confirmed that children with prolonged CPR could survive with E-CPR when C-CPR was unsuccessful.[11,12,15–17,20,47,48] More recent studies indicate that both adults and children can survive after >30 minutes of in-hospital C-CPR.[35,49] Therefore, some investigators have questioned whether E-CPR has been provided prematurely for patients who may have been successfully resuscitated with more prolonged and effective C-CPR. Contrary to this view, recent data from the Mechanical *C*PR, *H*ypothermia, *E*CMO and *E*arly *R*eperfusion (CHEER) study, a single-center, prospective, observational study evaluating adults receiving bundled care, including early reperfusion with ECMO and hypothermia for refractory cardiac arrest, showed that nonsurvivors had a

Table 3. Final Multivariable Conditional Logistic Regression Model for Survival to Discharge and Favorable Neurological Outcome

	Survival to Discharge (n=2649)			Favorable Neurological Outcome (n=2427)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
CPR group						
C-CPR	1.00	…	…	1.00	…	…
E-CPR	2.76	2.08–3.65	<0.0001	2.64	1.91–3.67	<0.0001
Age groups						
0–1 mo				1.00	…	…
1 mo–1 y				1.72	1.20–2.47	0.003
1–8 y				1.31	0.87–1.98	0.20
>8 y				0.96	0.25–3.66	0.95
Year						
2000	1.00	…	…	1.00	…	…
2001	0.99	0.44–2.28	0.99	1.12	0.43–2.93	0.81
2002	1.64	0.74–3.62	0.22	2.81	1.12–7.07	0.028
2003	2.15	0.92–5.06	0.079	4.04	1.46–11.17	0.007
2004	1.63	0.69–3.89	0.27	3.43	1.22–9.68	0.020
2005	1.68	0.74–3.80	0.22	2.47	0.92–6.62	0.073
2006	1.61	0.71–3.63	0.26	2.67	0.99–7.15	0.051
2007	1.26	0.54–2.90	0.59	2.37	0.87–6.43	0.091
2008	1.83	0.81–4.16	0.15	3.92	1.46–10.52	0.007
2009	1.96	0.87–4.39	0.10	3.61	1.37–9.56	0.010
2010	2.22	0.98–5.02	0.055	2.96	1.09–8.03	0.033
2011	2.14	0.95–4.83	0.068	2.74	1.01–7.43	0.048
2012	0.71	0.29–1.76	0.46	1.12	0.36–3.46	0.84
Illness category						
Medical, cardiac	1.00	…	…	1.00	…	…
Medical, noncardiac	0.62	0.46–0.84	0.002	0.59	0.41–0.84	0.003
Surgical, cardiac	1.26	0.94–1.69	0.12	1.22	0.87–1.70	0.26
Surgical, noncardiac	0.99	0.64–1.52	0.96	1.02	0.63–1.67	0.92
Newborn	0.38	0.25–0.58	<0.0001	0.35	0.21–0.59	<0.001
First documented rhythm						
Asystole/PEA	1.00	…	…	1.00	…	…
Bradycardia	1.53	1.22–1.91	<0.0.001	1.46	1.13–1.91	0.005
VT/VF	1.60	1.09–2.35	0.018	1.57	1.01–2.45	0.046
Other	2.12	1.37–3.29	0.001	1.99	1.20–3.30	0.001
Preexisting conditions at time of arrest						
Metabolic/electrolyte abnormality	0.71	0.53–0.95	0.019			
Renal insufficiency	0.45	0.31–0.66	<0.0001	0.47	0.30–0.74	0.001
Respiratory insufficiency				0.71	0.55–0.91	0.007
Interventions in place at time of arrest						
Invasive airway	0.67	0.54–0.83	<0.001			
Cause of arrest						
Hypotension/hypoperfusion	0.66	0.53–0.82	<0.001	0.61	0.48–0.78	<0.0001
Pharmacological interventions						
Sodium bicarbonate administration	0.70	0.57–0.88	0.002	0.61	0.47–0.80	<0.001
Doses of epinephrine	0.95	0.90–0.96	<0.0001	0.91	0.88–0.94	<0.0001
Duration of CPR	0.99	0.98–1.00	<0.001	0.99	0.99–1.00	0.084
Length of stay	1.01	1.01-1.01	<0.0001	1.01	1.01-1.01	<0.0001

Empty cells reflect a lack of inclusion of the variable in the final model for either survival to discharge or favorable neurological outcome. Because of missing neurological outcome data, the total number of neurological outcomes is different from the number for survival to discharge. See text for details. CI indicates confidence interval; CPR, cardiopulmonary resuscitation; C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; OR, odds ratio; PEA, pulseless electric activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 4. Mode of CPR and Survival to Discharge and Favorable Neurological Outcome: Results From Subclassification on the Propensity Score

	Survival to Discharge (n=2178)					Favorable Neurological Outcome (n=1952)				
E-CPR/C-CPR	No (n=1539), n (%)	Yes (n=639), n (%)	OR	95% CI	*P* Value	No (n=1558), n (%)	Yes (n=394), n (%)	OR	95% CI	*P* Value
C-CPR	1233 (80)	440 (69)	1	…	…	1244 (80)	287 (73)	1	…	…
E-CPR	306 (20)	199 (31)	1.70	1.33–2.18	<0.0001	314 (20)	107 (27)	1.78	1.31–2.41	<0.001

CI indicates confidence interval; CPR, cardiopulmonary resuscitation; C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; and OR, odds ratio.

longer time to ECMO cannulation and therefore longer duration of CPR.[50] Although these data raise the question that earlier ECMO cannulation may affect outcomes, it remains unclear how the timing of ECMO initiation will affect a very heterogeneous population of adults and children suffering an IHCA.

Historically, pediatric CPR was considered futile beyond 20 minutes' duration or >2 doses of epinephrine.[13,51] A recent report from the AHA's GWTG-R analyzed the relationship between CPR duration and survival to hospital discharge after pediatric IHCA.[35] Survival rates fell linearly over the first 15 minutes of CPR, yet patients who received E-CPR had no difference in survival across CPR durations. Survival for patients receiving >35 minutes of C-CPR was only 15.9% (survival for patients receiving C-CPR for <15 minutes was 44.1%). Our analysis selected 10 minutes as a minimum amount of C-CPR to define comparable CPR groups. This selection reflects a realistic time frame in which the decision to initiate E-CPR would be made while including C-CPR patients with potential for survival and favorable neurological outcomes comparable to prior E-CPR studies.[11,12,15–17,20,35,47,48] We sought to avoid biasing our results toward worse outcomes for C-CPR patients by including patients with up to 30 minutes of CPR, although many adult studies of OHCA consider this amount to be the definition of refractory cardiac arrest.[25,26,50,52,53]

Retrospective studies are challenged by the many biases related to patient treatment selection. Attempts to prospectively randomize extracorporeal mechanical support after cardiac arrest present ethical and logistical difficulties.[23,25,26,54,55] Therefore, to address these challenges, we used alternative methods to account for known confounders.[40–43] With the 2 approaches, our data suggest that E-CPR is associated with better outcomes after adjustment for known confounding factors. In addition, our analysis across hospital groups (those that offered both E-CPR and C-CPR and those with only C-CPR) tends to negate the possibility of selection of patients for E-CPR based on better prognosis.

Both healthcare system–wide decision making and complex bedside E-CPR decision making continue to evolve as medical and technological advances continue to advance our understanding of CPR strategies and outcomes. Although E-CPR use has increased over the past decade,[56] E-CPR continues to have an uncertain risk-benefit profile and unequal distribution of care among US and international medical centers.[57] Financial, ethical, and logistical challenges must be considered as important factors influencing the use of E-CPR across healthcare systems. Although registry analyses are unable to capture all factors associated with E-CPR initiation, temporal trends in E-CPR may help to better understand the evolution of physician practice. The challenges of including all measurable determinants of patient selection for E-CPR have been reported by similar resuscitation studies. Using an administrative data and matching methods, Lowry and colleagues[58] reported no significant difference in survival to hospital discharge between CPR groups. Notably, their definition of E-CPR was "ECMO used on the same day as CPR." Furthermore, the size discrepancy of the E-CPR cohort (n=82) compared with the larger C-CPR group (n=8918) limited their ability to appropriately propensity match cohorts. Pre-existing conditions evaluated in their study included the presence of acute renal failure, acute cerebrovascular disease, hepatic disease, sepsis/systemic inflammatory response syndrome, and several other conditions that overlap with our current evaluation. However, hospital size and location were not included in the analysis, potentially ignoring confounders such as hospital group differences in extracorporeal support cannulation practices. In our GWTG-R study, the more precise definition of E-CPR, size of the E-CPR population, analytic approaches that explicitly control for the potential confounding by hospital location (ECMO center versus non-ECMO center), temporal trends in E-CPR use and outcomes, and event location might lead to more appropriate comparisons of E-CPR and C-CPR.

Several adult cardiac arrest investigations have evaluated survival and neurological outcomes after IHCA and out-of-hospital cardiac arrest.[25,26,28,50,52,54,55,59–61] These single-center investigations have demonstrated promise for E-CPR as a rescue modality after failed C-CPR. However, each of the studies was limited by biases in selection criteria for E-CPR.

The physiological derangements notable during and after cardiac arrest include acid-base and electrolyte abnormalities among others. These alterations can be significantly exacerbated by pre-existing renal insufficiency, ultimately contributing to postresuscitation morbidity and mortality. Several prior reports of pediatric cardiac arrest patients have demonstrated this association between pre-existing renal insufficiency and worse survival to discharge after IHCA.[3,33,37] Consistent with prior reports, our study also found pre-existing renal insufficiency to be significantly associated with mortality for both CPR groups, yet a higher percentage of C-CPR patients were found to have pre-existing renal insufficiency. Renal insufficiency at the time of IHCA may affect the decision to initiate or withhold mechanical support for these patients, especially in light of recent reports demonstrating worse outcomes for neonates and children with acute kidney injury requiring ECMO.[62–64]

Our understanding of C-CPR duration before the initiation of full-flow extracorporeal support and its impact on survival and acceptable neurological function at discharge remains

unclear. A large study of pediatric IHCA from GWTG-R reported an inverse relationship between CPR duration and survival after C-CPR [35] and found that survival and survival with favorable neurological outcomes declined linearly with each 15-minute epoch of CPR. It also showed significant variability in survival outcomes among the various illness categories, with ≈25% of surgical cardiac patients surviving to discharge after >35 minutes of C-CPR compared with only 10% of medical noncardiac patients surviving to discharge after a similar duration of C-CPR.

Not surprisingly, our E-CPR group had a much longer median duration of CPR (45 versus 27 minutes) than our C-CPR group. Other adult investigations have also suggested that E-CPR can extend the time window of effective resuscitation beyond the presently accepted duration of C-CPR.[25,26,28,55,59] These authors report improved survival rates for E-CPR patients, most pronounced for patients receiving >21 to 30 minutes of CPR, compared with patients receiving C-CPR.[26,28] Ultimately, no clear relationship exists between CPR duration and survival to discharge when E-CPR and failed C-CPR are compared in the pediatric population. Our study demonstrated longer CPR times for E-CPR patients while also demonstrating a higher likelihood of survival to discharge and favorable neurological outcomes for E-CPR recipients. Because the role of E-CPR in patients with brief CPR durations remains uncertain, recognizing patients who may benefit from ECMO early after the initiation of CPR requires further investigation.

Our registry-based analysis has several limitations. All studies of multicenter registries are limited by the challenges of ensuring data integrity at multiple sites. These limitations were minimized by the rigorous abstractor certification process, uniform data collection, and use of consistent Utstein definitions. The GWTG-R database did not capture the physician- and systems-based variables influencing ECMO cannulation. In addition, the quality of administered CPR was not provided for either group. Therefore, we were not able to adjust for these important potentially confounding factors. Neurological outcome data are also limited in this registry because PCPC scores are not available for all survivors. Although survival data are almost always obtainable from the medical record, neurological outcomes determined from chart review are often missing. Therefore, in cardiac arrest research, evaluating neurological outcome can be more challenging compared with short-term survival outcomes analyses.

Our registry data had missing values on potentially important covariates, and although we implemented methods to overcome the challenges of missing data, no analytic approach can completely compensate for missingness. These retrospective data also cannot address selection bias if, for example, providers did not offer E-CPR to patients at higher risk on the basis of factors not included in the registry database.

Limitations also exist with regard to the statistical approach to our hypothesis. Although regression methods can reduce bias from confounding, the comparability of the 2 groups remains for further analysis based on more complete data. Propensity score–based methods do not balance on unmeasured covariates unless those unmeasured factors are strongly associated with the observed covariates used in developing the propensity scores.

Conclusions

E-CPR for pediatric patients with IHCA requiring ≥10 minutes of CPR was associated with improved survival and favorable neurological outcome at discharge compared with C-CPR alone. E-CPR deployment might be considered in selected patients with IHCA in whom return of spontaneous circulation has not been established with C-CPR for ≥10 minutes.

Disclosures

Part of the content of this manuscript was presented in oral abstract format at the AHA's Scientific Sessions, November 18, 2013, Dallas, TX. The Scientific Advisory Board of the AHA provided review and approval of the manuscript, and the Executive Database Steering Committee of the AHA provided additional peer review of the manuscript before submission. Dr Thiagarajan reports being a paid consultant for Bristol Myer Squibb for a clinical trial and co-chair of the ECMO registry of the Extracorporeal Life Support Organization. The other authors report no conflicts.

Appendix

Besides Drs Raymond, Gaies, Laussen, Nadkarni, and Topjian, members of the GWTG-R Pediatric Task Force include Emilie Allen, MSN, RN, CCRN, Parkland Health & Hospital System; Melania Bembea, MD, MPH, Johns Hopkins University School of Medicine; Ericka Fink, MD, University of Pittsburgh School of Medicine; Elizabeth Foglia, MD, MA, and Robert Sutton, MD, The Children's Hospital of Philadelphia; Anne-Marie Guerguerian, MD, PhD, and Chris Parshuram, MB ChB, DPhil, The Hospital for Sick Children; Monica Kleinman, MD, Boston Children's Hospital; Lynda J. Knight, RN, CCRN, CPN, Stanford Children's Health Hospital; Taylor Sawyer, DO, MEd, Seattle Children's Hospital; and Stephen M. Schexnayder, MD, Arkansas Children's Hospital.

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CLINICAL PERSPECTIVE

Cardiopulmonary resuscitation (CPR) modalities that include the use of extracorporeal membrane oxygenation (E-CPR) have been shown to improve survival for cardiac arrest in select populations of pediatric cardiac arrest patients. However, to further refine resuscitation practices across the spectrum of pediatric patient populations, a better understanding of the differences in outcomes between conventional CPR and E-CPR is required. Our study of 3756 pediatric patients from all illness categories undergoing ≥10 minutes of conventional CPR after in-hospital cardiac arrest found that survival to hospital discharge was 40% in E-CPR recipients compared with 27% for patients receiving continued conventional CPR. This Get With the Guidelines–Resuscitation registry analysis also evaluated neurological outcomes after in-hospital cardiac arrest and found higher levels of neurological function for patients who received E-CPR. Our study evaluated patients with differing reasons for arrest and found that E-CPR improved survival and neurological outcomes for all patients regardless of cause. Furthermore, this study demonstrated improved survival and favorable neurological outcome even after exclusion of the surgical cardiac patient population. This analysis adds to previous studies that have found E-CPR to be an effective rescue therapy and expands this benefit to nonsurgical cardiac patients and noncardiac patients. This study will serve to encourage the use of E-CPR as a rescue strategy after failed conventional CPR and provides information for investigators eager to expand our understanding of extracorporeal support in resuscitation.