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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 Registry (GWTG-R)

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Abstract

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

Methods and Results—Consecutive patients <18 years old with CPR events ≥ 10 minutes duration reported to GWTG-R 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 using propensity-score matching. Of 3,756 evaluable patients, 591 (16%) received E-CPR and 3,165 (84%) received C-CPR only. Survival to hospital discharge and survival with favorable neurologic outcome (Pediatric Cerebral Performance Category score of 1–3 or unchanged from admission) were greater for E-CPR [40% (237/591) and 27% (133/496)] versus C-CPR patients [27% (862/3,165) and 18% (512/2,840)]. Odds ratios for survival to hospital

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discharge and survival with favorable neurologic outcome were greater for E-CPR versus C-CPR. After adjusting for covariates, patients receiving E-CPR had higher odds of survival to discharge [OR 2.80, 95% CI 2.13–3.69, p <0.001] and survival with favorable neurologic outcome [OR 2.64, 95% CI 1.91–3.64, p < 0.001] than patient who received C-CPR. This association persisted when analyzed by propensity-score matched cohorts [OR 1.70, 95% CI 1.33–2.18, p < 0.001 and OR 1.78, 95% CI 1.31–2.41, p < 0.001 respectively].

Conclusions—For children with in-hospital CPR ≥ 10 minutes duration, E-CPR was associated with improved survival to hospital discharge and survival with favorable neurologic outcome when compared to C-CPR.

Keywords

cardiopulmonary resuscitation; extracorporeal circulation; cardiopulmonary bypass; pediatrics; cardiac arrest; mortality

Introduction

Pediatric in-hospital cardiac arrest (IHCA) occurs in 1–3% of pediatric intensive care unit (ICU) admissions and up to 6% of children treated in cardiac ICU's (CICU).[1–12] Survival to hospital discharge after pediatric IHCA has improved over the last 25 years from 9–13.7%[2,13] to 35% (78.1% with a favorable neurologic outcome).[14] Improvement in outcomes has been partially attributed to the impact of extracorporeal membrane oxygenation (ECMO) as a rescue strategy when prolonged conventional CPR (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 CICU patients.[17,19–22] Presumably, without E-CPR many of these patients would have died during their resuscitation.

However, the exact indications for and timing of E-CPR deployment remain unknown. Comparing E-CPR strategies to C-CPR to determine the relative effectiveness of either 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 non-cardiac patients[17,23,24]. For many reasons, including the impact of ECMO availability and clinician preference for ECMO utilization, conducting a randomized controlled trial has not been feasible. Modeling based on propensity scores has been used to compare adults who receive E-CPR to C-CPR, and shows increased survival among those treated with E-CPR.[25–28] To date, no multi-center 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 neurologic outcome than those who received C-CPR alone.

Methods

We used two approaches in this analysis to confirm results were consistent across methods of analysis. As we sought to compare E-CPR versus C-CPR, we used two 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) Get With the Guidelines®- Resuscitation (GWTG-R) is a multicenter registry of IHCA that utilizes Utstein-style data reporting.[29–31] The design and reporting of GWTG-R has 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 American Heart Association/American Stroke Association's Get With the Guidelines® programs.

Operational definitions for the GWTG-R have been described in detail previously[20] and include 8 predefined illness categories which are based on patient characteristics at the time of CPR (medical cardiac, medical non-cardiac, surgical cardiac, surgical non-cardiac, newborn, trauma, obstetrical, 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 electrical activity (PEA), bradycardia, ventricular tachycardia/ventricular fibrillation (VT/VF), or other. Asystole and PEA were grouped together due to previously published similarities in outcome.[32,36]

Arrest locations were grouped into the following categories: intensive care units, inpatient areas, procedural areas (cardiac catheterization lab, diagnostic/interventional, operating room, post-anesthesia recovery unit), emergency department, and other (ambulatory/outpatient, other).

Inclusion and Exclusion Criteria

Between January 1, 2000, and December 31, 2011, 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 that received ≥ 10 minutes of CPR were selected. A CPR event was defined as an event that required chest compressions and/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 utilization of extracorporeal support. An E-CPR event was defined as a CPR event during which extracorporeal life support was used. Both ECMO and/or 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 that received ≥ 10 minutes of conventional CPR and subsequently received ECMO was classified as an E-CPR recipient, regardless of conventional CPR duration. Therefore each patient had only one 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. Neurologic 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 neurologic outcome was prospectively defined as a discharge PCPC score of 1, 2, or 3, or no change from admission PCPC score.[20] Non-survivors were included in the analysis as having an unfavorable neurologic outcome. Neurologic outcome was only available for 62% of subjects.

Statistical Analysis

Data were analyzed initially using conditional logistic regression to examine the effect of CPR type on “survival to discharge” and “favorable neurologic 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

By contrast, the two-step propensity score analysis allowed for inclusion of all data and balanced on missing as well as 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 for 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 probability of receiving E-CPR.[40]

For the first comparison (within hospital group), we implemented sub-classification 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 vs. 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 (See Supplemental Table 1). 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 using the propensity score. (See Supplemental Table 2) Utilizing 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 that 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 two groups: those treated at hospitals that offered both C-CPR and E-CPR and those 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 just outlined above to compare C-CPR outcomes among similar patients at the two 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 two hospital groups.

Lastly, we performed a sensitivity analysis using the method of Lin et al to consider the potential for bias from unmeasured/unobserved confounders.[44] All conditional logistic modeling was performed with the PROC logistic procedure (SAS). All p-values are reported with a significance level set at < 0.05. All analyses were performed using SAS software (Version 9.2, Copyright, 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 Figure 1. A total of 4,856 patients underwent < 10 minutes of CPR, with 3,756 patients meeting inclusion criteria for analysis.

The pre-arrest characteristics of the E-CPR and C-CPR groups are displayed in Table 1. (Pre-arrest characteristics for variables not included in conditional logistic regression are listed in Supplemental Table 3.) Children aged 1 month to 1 year of age comprised 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 while the majority of C-CPR patients were categorized as medical non-cardiac. More E-CPR patients had a first documented rhythm of asystole/pulseless electrical activity (PEA) (41% vs. 32%), whereas more C-CPR patients had bradycardia as their first documented rhythm (49% vs. 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 vs. night); however, E-CPR was less likely to have occurred during weekend hours compared to C-CPR (21% vs 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 to 40% in the E-CPR group. Survival with favorable neurologic outcome data is also displayed in Table 2 (Survival and neurologic outcome data for variables not included in final conditional regression are listed in Supplemental Table 4.) The discharge PCPC score was documented for 679 of the 1,099 (62%) who survived to hospital discharge. Survival with favorable neurologic 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 3,756 patients (Table 3). After adjusting for illness category, hospital grouping, year of arrest, first documented rhythm, pre-existing conditions at time of arrest (renal insufficiency, invasive airway), pharmacologic 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 OR 2.76, 95% CI 2.08–3.65, p <0.0001), and survival with a favorable neurologic 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 excluding the surgical cardiac patient cohort, a

total of 1,915 patients were analyzed and those who received E-CPR continued to demonstrate an increased likelihood of survival to discharge and favorable neurologic outcome compared to C-CPR recipients (survival adjusted OR 3.1, 95% CI 1.98 – 4.71, p < 0.0001; favorable neurologic 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 two CPR groups was 2,178, and this number ranged from 108 to 306 across the ten hospital groups (See Supplemental Table 1). The primary analysis included 505 (23%) E-CPR patients and 1,673 (77%) C-CPR patients. Baseline and arrest characteristics are reported between the two 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 1,531 C-CPR patients with available data on neurologic outcomes, the E-CPR group had more survival with favorable neurologic status at discharge (adjusted OR 1.78, 95% CI 1.31–2.41, p < 0.001) for E-CPR than 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 the relative risk of survival to discharge for E-CPR compared to C-CPR is 2.0. Thus, to 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 patients' outcome at those hospitals that offered E-CPR to those 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 to 1.4).

Discussion

Among pediatric patients treated with at least 10 minutes of in-hospital cardiopulmonary resuscitation, those receiving E-CPR had greater odds of survival to discharge than patients who received continued conventional CPR in this large Get With The Guidelines®-Resuscitation in-hospital cardiac arrest database. Importantly, E-CPR patients also had greater survival with favorable neurologic outcome. These findings were demonstrable with two different *a priori* selected statistical methodologies intended to adjust for potential confounding factors.

Initial small case series of successful rescue ECMO therapy during CPR for pediatric post-operative cardiac patients were reported in the 1980's 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 more than 30 minutes of in-hospital conventional 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 CHEER study, a single center prospective observational study evaluating adults receiving bundled care including early reperfusion with ECMO and hypothermia for refractory cardiac arrest, found that non-survivors had a longer time to ECMO cannulation and therefore longer duration of CPR.[50] While these data raise the question that earlier ECMO cannulation may impact outcomes, it remains unclear how the timing of ECMO initiation will impact a very heterogeneous population of adults and children suffering from in-hospital cardiac arrest.

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 conventional CPR was only 15.9% (survival for C-CPR receiving <15 minutes was 44.1%). Our analysis selected 10 minutes as a minimum amount of conventional CPR in order to define comparable CPR groups. This selection reflects a realistic time frame in which the decision to initiate E-CPR would be made while also including C-CPR patients with potential for survival and favorable neurologic outcomes comparable to prior E-CPR studies.[11,12,15–17,20,35,47,48] We sought to avoid biasing our results towards 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] Using two approaches, our data suggest that E-CPR is associated with better outcomes after adjusting 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 health care system-wide and complex bedside E-CPR decision-making continue to evolve as medical and technological advances continue to advance our understanding of cardiopulmonary resuscitation 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 amongst U.S. and international medical centers.[57] Financial, ethical, and logistical challenges must be considered as important factors influencing the utilization of E-CPR across health care 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 reported no significant difference in survival to hospital discharge between CPR groups.[58] 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) in comparison to the larger

C-CPR group (n=8,918) 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 (SIRS), 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 vs. 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 neurologic outcomes after in-hospital and out-of-hospital cardiac arrests.[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 conventional CPR. However, the studies were each limited by biases regarding their selection criteria for E-CPR.

The physiologic 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 post-resuscitation 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 conventional CPR duration prior to initiation of full flow extracorporeal support and its impact on survival and acceptable neurologic function at discharge remains unclear. A large study of pediatric in-hospital cardiac arrest from GWTG-R reported an inverse relationship between CPR duration and survival after conventional CPR[35] and found that survival and survival with favorable neurologic outcomes declined linearly with each 15-minute epoch of CPR. They also showed significant variability in survival outcomes among the various illness categories with approximately 25% of surgical cardiac patients surviving to discharge after > 35 minutes of conventional CPR compared to only 10% of medical non-cardiac patients surviving to discharge after a similar duration of conventional CPR.

Not surprisingly, our E-CPR group had a much longer median duration of CPR (45 minutes versus 27 minutes) than our conventional 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 conventional 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 when compared to patients receiving conventional CPR.[26,28] Ultimately, no clear

relationship exists between CPR duration and survival to discharge when comparing E-CPR and failed conventional CPR 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 neurologic 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 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, quality of administered CPR was not provided for either group. Therefore, we were not able to adjust for these important potentially confounding factors. Neurologic outcome data are also limited in this registry as PCPC scores are not available for all survivors. While survival data are almost always obtainable from the medical record, neurologic outcomes determined from chart review are often missing. Therefore, in cardiac arrest research, evaluating neurologic outcome can be more challenging as compared to short-term survival outcomes analyses.

Our registry data had missing values on potentially important covariates and, while 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 based on factors not included in the registry database.

Limitations also exist with regards to the statistical approach to our hypothesis. Although regression methods can reduce bias from confounding, the comparability of the two 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 observed covariates used in developing the propensity scores.

Conclusions

E-CPR for pediatric patients with in-hospital cardiac arrest requiring ≥ 10 minutes of CPR was associated with improved survival and favorable neurologic outcome at discharge compared to conventional CPR alone. E-CPR deployment might be considered in selected patients with IHCA in whom ROSC has not been established with conventional CPR for ≥ 10 minutes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

Get With The Guidelines-Resuscitation Investigators: Besides the authors Tia Raymond, MD, Michael Gaies, MD, MPH, Peter C. Laussen, MBBS, Vinay Nadkarni, MD, and Alexis

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Clinical Perspectives

Cardiopulmonary resuscitation 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, in order to further refine resuscitation practices across the spectrum of pediatric patient populations, a better understanding of the differences in outcomes between conventional CPR (C-CPR) and E-CPR is required. Our study of 3,756 pediatric patients from all illness categories undergoing ≥ 10 minutes of conventional CPR after in-hospital cardiac arrest (IHCA) found that survival to hospital discharge was 40% in E-CPR recipients compared to 27% for patients receiving continued C-CPR. This Get With the Guidelines – Resuscitation registry analysis also evaluated neurologic outcomes after IHCA and found higher levels of neurologic function for patients who received E-CPR. Our study evaluated patients with differing reasons for arrest and found that E-CPR improved survival and neurologic outcomes for all patients regardless of cause. Furthermore, this study demonstrated improved survival and favorable neurologic outcome even after excluding the surgical cardiac patient population. This analysis adds to previous studies that have found extracorporeal cardiopulmonary resuscitation to be an effective rescue therapy and expands this benefit to non-surgical cardiac patients as well as non-cardiac 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.

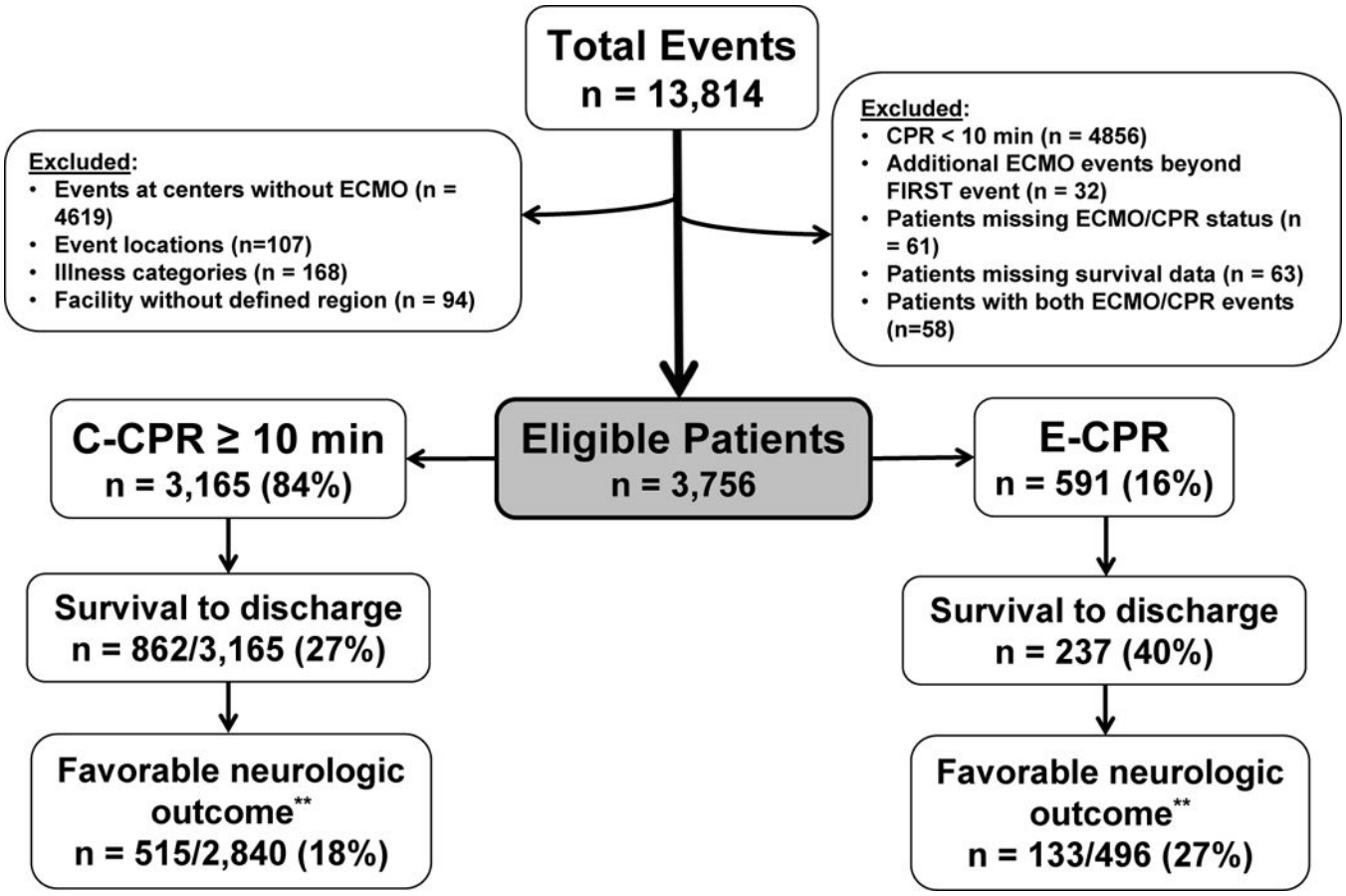

Figure 1.

Patient selection flow diagram. **Pediatric Cerebral Performance Category score available for 679/1,099 (62%) of survivors.

Table 1

Baseline and arrest characteristics for initial cohort and propensity-matched E-CPR and C-CPR patients.

	All Patients (n=3,756)		Propensity Matched Patients (n =2,178)		
	C-CPR (n=3,165) n (%)	E-CPR (n=591) n (%)	C-CPR (n=1,673) n (%)	E-CPR (n=505) n (%)	p-value
Age Groups					
0 – 1 month	667 (21)	123 (21)	320 (19)	91 (18)	0.002
1 month – 1 year	1,688 (53)	331 (56)	914 (55)	297 (59)	
1 year – 8 years	788 (25)	126 (21)	434 (26)	109 (22)	
> 8 years	22 (<1)	11 (2)	5 (<1)	8 (2)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Gender					
Male	1,742 (55)	344 (58)	937 (56)	306 (61)	0.063
Female	1,418 (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)	

	All Patients (n=3,756)		Propensity Matched Patients (n =2,178)		
	C-CPR (n=3,165) n (%)	E-CPR (n=591) n (%)	C-CPR (n=1,673) n (%)	E-CPR (n=505) n (%)	p-value
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Illness Category					<0.0001
Medical, cardiac	491 (16)	119 (20)	325 (19)	106 (21)	
Medical, non-cardiac	1,258 (40)	86 (15)	589 (35)	83 (16)	
Surgical, cardiac	628 (20)	349 (59)	496 (30)	282 (56)	
Surgical, non-cardiac	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					0.005
Asystole/PEA	1,021 (32)	243 (41)	657 (39)	204 (40)	
Bradycardia	1,563 (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)	
Pre-existing Conditions at time of Arrest					
Metabolic/Electrolyte Abnormality					0.29
Yes	478 (15)	96 (16)	303 (18)	81 (16)	
No	2261 (71)	478 (81)	1270 (76)	409 (81)	
Missing	426 (13)	17 (3)	100 (6)	15 (3)	
Renal Insufficiency					0.015
Yes	324 (10)	52 (9)	190 (11)	43 (9)	
No	2415 (76)	522 (88)	1383 (83)	447 (86)	
Missing	426 (13)	17 (3)	100 (6)	15 (3)	
Respiratory insufficiency					

	All Patients (n=3,756)		Propensity Matched Patients (n =2,178)		
	C-CPR (n=3,165) n (%)	E-CPR (n=591) n (%)	C-CPR (n=1,673) n (%)	E-CPR (n=505) n (%)	p-value
Yes	1,826 (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	2,071 (65)	441 (75)	1,171 (70)	374 (74)	0.023
No	1,094 (35)	150 (25)	502 (30)	131 (26)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Cause of Arrest					
Hypotension/Hypoperfusion					
Yes	1,540 (49)	417 (71)	988 (59)	347 (69)	<0.001
No	1,323 (49)	168 (28)	628 (28)	152 (30)	
Missing	302 (10)	6 (1)	57 (3)	6 (1)	
Pharmacologic Interventions					
Sodium Bicarbonate Administration					
Yes	1,992 (63)	456 (77)	1,177 (70)	387 (77)	0.002
No	1,173 (37)	134 (23)	496 (30)	118 (23)	
Missing	0 (0)	1 (<1)	0 (0)	0 (0)	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	
Number of Doses-Epinephrine	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 (minutes)	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 in Days	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

Key: C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; PCPC, Pediatric Cerebral Performance Category; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia

** P-value for Admission PCPC score does not include missing group.

Table 2

Survival to discharge and neurologic outcome: summary statistics for conditional logistic regression cohort.

	Survival to Discharge (n=3,756)		Neurologic Outcome (n=3,336)	
	No (n=2,657) n (%)	Yes (n=1,099) n (%)	Unfavorable (n=2,688) n (%)	Favorable (n=648) n (%)
CPR Group				
C-CPR	2,303 (87)	862 (78)	2,325 (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 month	572 (21)	218 (20)	574 (21)	100 (15)
1 month – 1 year	1,381 (52)	638 (58)	1,399 (52)	391 (60)
1 year – 8 years	679(26)	235 (21)	690 (26)	153 (24)
> 8 years	25 (<1)	8 (<1)	25 (<1)	4 (<1)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
Gender				
Male	1,466(55)	620 (56)	1,485 (55)	367 (57)
Female	1,186 (44)	478 (43)	1,198 (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, non-cardiac	1,026 (39)	318 (29)	1,037 (39)	190 (29)
Surgical, cardiac	603 (23)	374 (34)	612 (34)	231 (36)
Surgical, non-cardiac	209 (8)	91 (8)	212 (8)	55 (8)

	Survival to Discharge (n=3,756)		Neurologic Outcome (n=3,336)	
	No (n=2,657) n (%)	Yes (n=1,099) n (%)	Unfavorable (n=2,688) n (%)	Favorable (n=648) n (%)
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)	1,002 (37)	181 (28)
Bradycardia	1,183 (45)	572 (52)	1,193 (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)
Pre-existing 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)
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	1,557 (59)	606 (55)	1,577 (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	1,875 (71)	637 (58)	1,890 (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	1,489 (56)	468 (43)	1,501 (56)	290 (45)
No	946 (36)	545 (50)	965 (36)	349 (54)
Missing	222 (8)	86 (7)	222 (8)	9 (2)
Pharmacologic Interventions				
Sodium Bicarbonate Administration				

	Survival to Discharge (n=3,756)		Neurologic Outcome (n=3,336)	
	No (n=2,657) n (%)	**Yes (n=1,099) n (%)**	**Unfavorable (n=2,688) n (%)**	**Favorable (n=648) n (%)**
Yes	1,882 (71)	565 (51)	1,911 (71)	334 (52)
No	773 (29)	534 (49)	776 (29)	314 (48)
Missing	1 (<1)	0 (0)	1 (<1)	0 (0)
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Number of Doses-Epinephrine	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 (minutes)	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 in Days	6.0 (1.0 – 26.0)	38.0 (20.0 – 73.0)	7.0 (1.0 – 27.0)	35.0 (18.0 – 69.0)

Key: C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; PCPC, Pediatric Cerebral Performance Category; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia

** P-value for Admission PCPC score does not include missing group.

Note: Due to missing neurologic outcome data, the total n for neurologic outcome is different than survival to discharge numbers. See text for details.

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Table 3

Final multivariable conditional logistic regression model for survival to discharge and favorable neurologic outcome.

	Survival to Discharge (n=2,649)			Favorable Neurologic Outcome (n=2,427)		
	Odds Ratio	**95% CI**	**p-value**	**Odds Ratio**	**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 month				1.00	–	–
1 month – 1 year				1.72	1.20–2.47	0.003
1 year – 8 years				1.31	0.87–1.98	0.20
> 8 years				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, non-cardiac	0.62	0.46–0.84	0.002	0.59	0.41–0.84	0.003

	Survival to Discharge (n=2,649)			Favorable Neurologic Outcome (n=2,427)		
	Odds Ratio	**95% CI**	**p-value**	**Odds Ratio**	**95% CI**	**p-value**
Surgical, cardiac	1.26	0.94–1.69	0.12	1.22	0.87–1.70	0.26
Surgical, non-cardiac	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	<.0.001	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
Pre-existing 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
Pharmacologic Interventions						
Sodium Bicarbonate Administration	0.70	0.57–0.88	0.002	0.61	0.47–0.80	<0.001
Number of Doses-Epinephrine	0.95	0.90–0.96	<0.0001	0.91	0.88–0.94	<0.0001
Duration of CPR (minutes)	0.99	0.98–1.00	<0.001	0.99	0.99–1.00	0.084
Length of Stay in Days	1.01	1.01–1.01	<0.0001	1.01	1.01–1.01	<0.0001

Key: C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation;; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia

Note: Empty cells reflect a variable's lack of inclusion in the final model for either survival to discharge or favorable neurologic outcome. Due to missing neurologic outcome data, the total n neurologic outcome is different than survival to discharge numbers. See text for details.

Table 4

Mode of CPR and survival to discharge and favorable neurological outcome. Results from sub-classification on the propensity score.

	Survival to Discharge (n=2,178)					Favorable Neurologic Outcome (n=1,952)				
E-CPR/C-CPR	No (n=1,539) n (%)	Yes (n=639) n (%)	Odds Ratio	95% CI	p-value	No (n=1,558) n (%)	Yes (n=394) n (%)	Odds Ratio	95% CI	p-value
C-CPR	1,233 (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

Key: C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation