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Effect of Physiologic Point-of-Care Cardiopulmonary Resuscitation Training on Survival With Favorable Neurologic Outcome in Cardiac Arrest in Pediatric ICUs
A Randomized Clinical Trial

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and Human Development Collaborative Pediatric Critical Care Research Network Investigator Groups

IMPORTANCE Approximately 40% of children who experience an in-hospital cardiac arrest survive to hospital discharge. Achieving threshold intra-arrest diastolic blood pressure (BP) targets during cardiopulmonary resuscitation (CPR) and systolic BP targets after the return of circulation may be associated with improved outcomes.

OBJECTIVE To evaluate the effectiveness of a bundled intervention comprising physiologically focused CPR training at the point of care and structured clinical event debriefings.

DESIGN, SETTING, AND PARTICIPANTS A parallel, hybrid stepped-wedge, cluster randomized trial (Improving Outcomes from Pediatric Cardiac Arrest—the ICU-Resuscitation Project [ICU-RESUS]) involving 18 pediatric intensive care units (ICUs) from 10 clinical sites in the US. In this hybrid trial, 2 clinical sites were randomized to remain in the intervention group and 2 in the control group for the duration of the study, and 6 were randomized to transition from the control condition to the intervention in a stepped-wedge fashion. The index (first) CPR events of 1129 pediatric ICU patients were included between October 1, 2016, and March 31, 2021, and were followed up to hospital discharge (final follow-up was April 30, 2021).

INTERVENTION During the intervention period (n = 526 patients), a 2-part ICU resuscitation quality improvement bundle was implemented, consisting of CPR training at the point of care on a manikin (48 trainings/unit per month) and structured physiologically focused debriefings of cardiac arrest events (1 debriefing/unit per month). The control period (n = 548 patients) consisted of usual pediatric ICU management of cardiac arrest.

MAIN OUTCOMES AND MEASURES The primary outcome was survival to hospital discharge with a favorable neurologic outcome defined as a Pediatric Cerebral Performance Category score of 1 to 3 or no change from baseline (score range, 1 [normal] to 6 [brain death or death]). The secondary outcome was survival to hospital discharge.

RESULTS Among 1389 cardiac arrests experienced by 1276 patients, 1129 index CPR events (median patient age, 0.6 [IQR, 0.2-3.8] years; 499 girls [44%]) were included and 1074 were analyzed in the primary analysis. There was no significant difference in the primary outcome of survival to hospital discharge with favorable neurologic outcomes in the intervention group (53.8%) vs control (52.4%); risk difference (RD), 3.2% (95% CI, −4.6% to 11.4%); adjusted OR, 1.08 (95% CI, 0.76 to 1.53). There was also no significant difference in survival to hospital discharge in the intervention group (58.0%) vs control group (56.8%); RD, 1.6% (95% CI, −6.2% to 9.7%); adjusted OR, 1.03 (95% CI, 0.73 to 1.47).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial conducted in 18 pediatric intensive care units, a bundled intervention of cardiopulmonary resuscitation training at the point of care and physiologically focused structured debriefing, compared with usual care, did not significantly improve patient survival to hospital discharge with favorable neurologic outcome among pediatric patients who experienced cardiac arrest in the ICU.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02837497

Visual Abstract

Supplemental content

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A study from 2019 estimated that more than 15 000 hospitalized children in the US experience a cardiac arrest and undergo cardiopulmonary resuscitation (CPR) each year.[1] More than 95% of these events occurred in an intensive care unit (ICU).[2] Survival outcomes after cardiac arrest have plateaued between 2010 and 2018, and approximately 60% of children who experience cardiac arrest do not survive to hospital discharge.[3] American Heart Association (AHA) CPR guidelines, which have historically focused on CPR mechanics such as compression depth and rate, currently highlight resuscitation training to intra-arrest and postarrest physiologic targets as a strategy to improve outcomes.[4]

In a single-center study,[5] a bundled intervention of CPR training at the point of care and post-cardiac arrest event debriefing improved survival to hospital discharge with favorable neurologic outcome in pediatric patients who underwent CPR in an ICU. The training and debriefing in this prior study[5] emphasized intra-arrest and postarrest physiologic targets, specifically diastolic blood pressure (DBP)[6] and end-tidal CO_2 ($ETCO_2$) during CPR,[7] and systolic blood pressure (SBP) in the postarrest period.[8] To prospectively evaluate the effectiveness of this intervention across multiple ICUs, this study was designed as a parallel, hybrid stepped-wedge, cluster randomized interventional trial (Improving Outcomes from Pediatric Cardiac Arrest—the ICU-Resuscitation Project [ICU-RESUS][9]) and was conducted at 18 pediatric ICUs at 10 sites in the US.

Key Points

Question Does a bundled intervention that emphasizes patient physiology during cardiopulmonary resuscitation (CPR) training and debriefing improve outcomes of pediatric patients who receive CPR in the intensive care unit (ICU)?

Findings In this parallel, hybrid stepped-wedge, cluster randomized trial that included 1129 pediatric patients with cardiac arrest who received CPR in an ICU, an intervention of physiologically focused CPR training at the point of care and clinical event debriefing vs usual care did not significantly improve survival to hospital discharge with favorable neurologic outcome (53.8% vs 52.4%, respectively).

Meaning Among patients in pediatric ICUs, a bundled intervention that emphasized physiologically focused CPR training and structured clinical event debriefing did not significantly improve patient survival to hospital discharge with favorable neurologic outcome.

Methods

Trial Design

The design of this trial has been published,[9] and the protocol and statistical analysis plan are available in Supplement 1. The University of Utah central institutional review board approved the project. Pediatric patients with cardiac arrest and ICU clinicians were enrolled under a waiver of consent. A data and safety monitoring board (DSMB) was appointed by the National Heart, Lung, and Blood Institute.

To compare the intervention to usual care, a parallel, hybrid stepped-wedge, cluster randomized trial was conducted (eFigure 1 in Supplement 2). In this hybrid design, 3 ICUs were transitioned to treatment prior to patient enrollment, 3 ICUs remained as control for the duration of the study, and 12 ICUs transitioned every 7.3 months from control to intervention over the 4.5-year duration of the study. This trial design was selected because the study intervention was targeted to the ICU care environment and patient-level randomization would have led to contamination of the control group. A hybrid design was used instead of a traditional stepped-wedge design to improve statistical power.

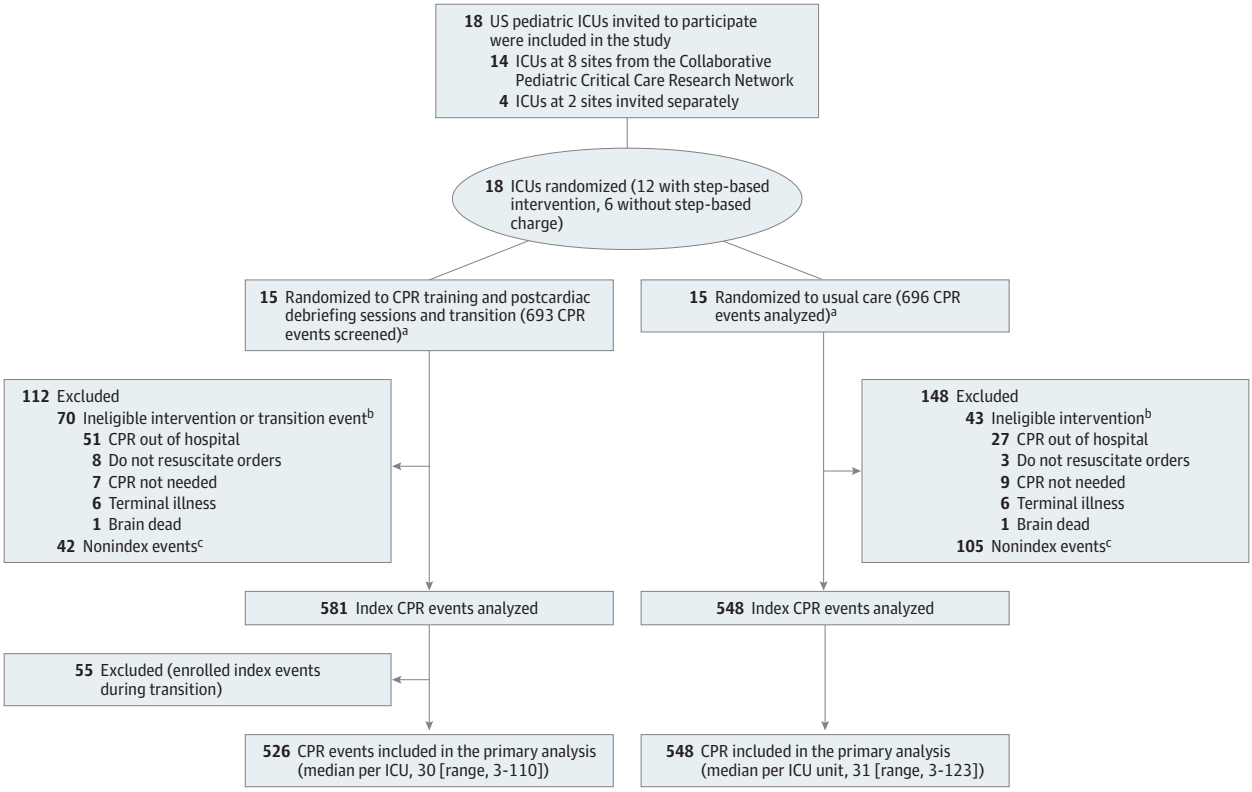
Trial Centers and Patient Inclusion Criteria

The trial was conducted in 18 ICUs—a mixture of 9 pediatric and 9 pediatric cardiac ICUs—across 10 clinical sites. Eight sites (14 ICUs) of the Collaborative Pediatric Critical Care Research Network (CPCCRN)[10] formed the core of this trial. Two additional sites (4 ICUs) were recruited prior to study start. All clinical sites committed to implementing the intervention when scheduled by the randomization process. Other resuscitation quality improvement (QI) initiatives were permitted in these ICUs if they were not identical to this study's intervention. A standardized survey was sent quarterly to each site's lead investigators to record start dates of other resuscitation QI initiatives (eg, huddles focused on prevention of or preparation for CPR). Patient inclusion criteria for this study were (1) age 37 weeks' corrected gestation or older and 18 years or younger and (2) CPR of any duration in the ICU. Patients were excluded, if prior to the arrest, they (1) had documented goals of care that limited aggressive ICU therapies; (2) were brain dead; or (3) had an out-of-hospital cardiac arrest associated with the current hospitalization. Race and ethnicity data, self-reported using fixed categories, were obtained from entries in the electronic medical record. These data were used to provide additional description of the enrolled patients and to allow for assessment of generalizability of the study findings.

Randomization

Randomization was performed at the level of the hospital sites enrolled in the study (**Figure**). The assignment of hospitals to remain in either intervention or control for the duration of the study and the order of hospitals crossing over to the intervention in a stepped-wedge fashion was selected from all possible random computer-generated permutations of the 10 clinical sites that would result in balanced enrollment between intervention and control (<5% difference between groups). Sites were notified 3 months prior to transition to prepare for implementation of the intervention. The end of the transition period was delineated by the fourth ICU debriefing session, a milestone selected because the effect of the intervention on CPR quality and outcomes was not expected to be immediate. For the 3 ICUs randomized to remain in intervention for the duration of the study, implementation of the intervention occurred during the 3-month

Figure. Flow of Patients Through the ICU-RESUS Study



[a] Fifteen intensive care units (ICUs) contributed to both intervention and control based on the stepped-wedge design.

[b] Events could have been excluded for more than 1 reason.

[c] Nonindex refers to subsequent cardiopulmonary resuscitation (CPR) events after the first CPR event of a given hospitalization.

period prior to the study start date of October 1, 2016, with the goal of having these ICUs completely transition to intervention prior to collection of patient outcome data.

Treatment Groups

A description of the intervention has been published[9] and is available in Supplement 1. The intervention was a 2-part ICU QI bundle consisting of CPR training at the point of care on a manikin and structured physiologically focused postcardiac arrest debriefings. Oversight of the intervention implementation was the responsibility of the unit "physician-champion," an individual with specific-interest in resuscitation QI. The point-of-care CPR training sessions were less than 2 minutes in duration, and each ICU during the intervention period was expected to conduct 48 trainings per month. The point-of-care training program leaders included nurse educators and site physician-champions, depending on the ICU. The manikins used (Resusci Anne QCPR and Resusci Baby QCPR; Laerdal Medical) provided feedback on the quality of CPR mechanics targets such as CPR rate and depth of compressions (eFigure 2 in Supplement 2). Standardized cue cards highlighting intra-arrest CPR physiologic targets were reviewed at each training (eFigures 3 and 4 in Supplement 2). The debriefings were 1 hour in duration and held monthly. Case presentations emphasized physiologic CPR[6,7] and postarrest care[8] targets using arterial catheter pressure tracings and $ETCO_2$ waveforms. Other aspects of cardiac arrest care, such as early recognition of arrest[11] and important postarrest care goals[8,12-17] were targets of discussion (eFigure 5 in Supplement 2). The study team provided presentation slides (Microsoft PowerPoint) for use during debriefings via a secure cloud-based sharing software (eRoom; Open Text Corp) to ensure consistency across ICUs. Weekly report cards detailing CPR performance during recent pediatric ICU cardiac arrests were presented during the debriefings (eFigure 6 in Supplement 2). Usual care consisted of existing resuscitation practices at the enrolled pediatric ICUs. Due to the COVID-19 pandemic, the CPR training program was paused beginning March 1, 2020, and reinstated when state or local restrictions allowed. The monthly debriefing sessions continued uninterrupted but were transitioned to a virtual platform.

Data Collection

Standard cardiac arrest variables were collected by trained research coordinators in accordance with published in-hospital cardiac arrest guidelines.[18] All data including outcome assessments were based on the index cardiac arrest (ie, the first event during the ICU hospitalization). Patients

Table 1. Study Participant Characteristics by Treatment Group

	No. (%)	
	Intervention (n = 526)[a]	Control (n = 548)[a]
Demographic characteristics		
Age		
≤1 mo	60 (11.4)	111 (20.3)
1 mo to <1 y	220 (41.8)	236 (43.1)
1 y to <8 y	143 (27.2)	112 (20.4)
8 y to <19 y	103 (19.6)	89 (16.2)
Age, median (IQR), y	0.9 (0.3-5.8)	0.5 (0.1-2.4)
Weight, median (IQR), kg	8.0 (4.4-19.1)	6.0 (3.7-12.6)
Boy	287 (54.6)	288 (52.6)
Girl	239 (45.4)	260 (47.4)
Race[b]		
American Indian or Alaska Native	3/407 (0.7)	4/431 (0.9)
Asian	16/407 (3.9)	22/431 (5.1)
Black or African American	111/407 (27.3)	161/431 (37.4)
Multiracial	4/407 (1.0)	10/431 (2.3)
Native Hawaiian or Other Pacific Islander	1/407 (0.2)	3/431 (0.7)
White	272/407 (66.8)	231/431 (53.6)
Ethnicity[b]		
Hispanic or Latino	53/458 (11.6)	110/513 (21.4)
Not Hispanic or Latino	405/458 (88.4)	403/513 (78.6)
Diagnoses prior to cardiac arrest		
Respiratory insufficiency	451 (85.7)	477 (87.0)
Hypotension	309 (58.7)	367 (67.0)
Congenital heart disease	267 (50.8)	349 (63.7)
Pulmonary hypertension	90 (17.1)	84 (15.3)
Sepsis	80 (15.2)	98 (17.9)
Kidney disease	70 (13.3)	77 (14.1)
Pneumonia	68 (12.9)	70 (12.8)
Congestive heart failure	65 (12.4)	72 (13.1)
Malignancy	29 (5.5)	21 (3.8)
Trauma	21 (4.0)	11 (2.0)
Characteristics prior to cardiac arrest		
Illness category[c]		
Medical		
Cardiac	117 (22.2)	142 (25.9)
Noncardiac	215 (40.9)	172 (31.4)
Surgical		
Cardiac	154 (29.3)	207 (37.8)
Noncardiac	21 (4.0)	20 (3.6)
Trauma	19 (3.6)	7 (1.3)
PRISM, median (IQR)[d]	4.0 (0.0-10.0)	4.0 (0.0-11.0)
Vasoactive inotropic score [2 h prior], median (IQR)[e]	0.0 (0.0-5.0)	0.0 (0.0-8.0)
Baseline PCPC score[f]		
1: Normal	318 (60.5)	335 (61.1)
2: Mild disability	78 (14.8)	114 (20.8)
3: Moderate disability	59 (11.2)	51 (9.3)
4: Severe disability	65 (12.4)	42 (7.7)
5: Coma or vegetative state	6 (1.1)	6 (1.1)
Baseline FSS[f]	6.0 (6.0-10.0)	6.0 (6.0-10.0)

(continued)

Table 1. Study Participant Characteristics by Treatment Group (continued)

	No. (%)	
	Intervention (n = 526)[a]	Control (n = 548)[a]
Interventions in ICU		
Peripheral venous catheter	473 (89.9)	504 (92.0)
Invasive mechanical ventilation	396 (75.3)	369 (67.3)
Central venous catheter	360 (68.4)	378 (69.0)
End-tidal CO_2 monitoring	341 (64.8)	333 (60.8)
Vasoactive infusion[g]	257 (48.9)	306 (55.8)
Arterial catheter	248 (47.1)	300 (54.7)
Noninvasive ventilation	73 (13.9)	125 (22.8)

Abbreviations: FSS, Functional Status Scale; ICU, intensive care unit; PCPC, Pediatric Cerebral Performance Category; PRISM, Pediatric Risk of Mortality.

[a] Number (%) of patients unless otherwise indicated.

[b] Race and ethnicity data, self-reported using fixed categories, were obtained from entries in the electronic medical record.

[c] Illness category refers to the primary diagnosis at the time of the event as determined by medical record review.

[d] Most abnormal value for each of the 17 physiological variables of the PRISM III was used to calculate the score during the time period from 2 to 6 hours prior to the event. Higher values indicate more severe illness (range, 0-74).

[e] Calculated from the following equation: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + nitroprusside dose (μg/kg/min) + (10 × milrinone dose [μg/kg/min]) + (100 × epinephrine dose (μg/kg/min)) + (100 × norepinephrine dose [μg/kg/min]) + (100 × phenylephrine dose [μg/kg/min]) + vasopressin dose (mU/kg/h).

[f] The PCPC and FSS scores were determined by medical record review. PCPC score ranges from 1 (normal) to 6 (brain death or death). Across the 6 domains of the FSS (mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status), a score from 1 (normal) to 5 (very severe dysfunction) was assigned. Total FSS score is the sum of the scores across the 6 domains (range, 6-30). Baseline PCPC and FSS represent subject status prior to the event leading to hospitalization.

[g] Vasoactive infusions include dobutamine, dopamine (>3 μg/kg/min), epinephrine, nitroglycerin, nitroprusside, norepinephrine, phenylephrine, and vasopressin.

still hospitalized at the end of the study period (March 31, 2021) were followed up for an additional 30 days. For the analyses, each CPR event was subdivided into 30-second epochs. Means for physiologic and CPR quality mechanics data were calculated for each epoch. A mean of all epochs was used in the survival analyses. Physiologic and CPR mechanics data extraction and analysis details can be found in Supplement 2.

Outcomes

The primary outcome was survival to hospital discharge with favorable neurologic outcome, defined as a Pediatric Cerebral Performance Category (PCPC) score[19,20] of 1 to 3 or no worse than baseline (score range, 1 [normal] to 6 [brain death or death]). The PCPC score was determined through chart abstraction by the trained research coordinators who were unblinded to the groups. The secondary outcome was survival to hospital discharge. Exploratory and post hoc outcomes highlighted as training targets included (1) adequate DBP during CPR (≥25 mm Hg for age <1 year, ≥30 mm Hg for older children[6]); (2) target $ETCO_2$ during CPR (≥20 mm Hg)[21]; and (3) postarrest systolic hypotension (<5th percentile for age, sex, and height).[8,14] Additional exploratory and post hoc outcomes are available in eTable 1 in Supplement 2.

Sample Size Calculation

A sample size of 1391 events was estimated to provide more than 80% power to detect an increase from 40% to 51% in survival with a favorable neurologic outcome. In a hybrid design, the study duration is prespecified. Extending the trial to achieve prespecified enrollment targets renders a priori sample size estimations invalid. For this study, an enrollment period of 4.5 years was conservatively selected a priori to attain adequate power based on historical enrollment of CPCCRN, resulting in a rigid study period from October 1, 2016, through March 31, 2021.[6,22] Additional parameters for estimation included a baseline CPCCRN primary outcome rate of 40%,[22] an absolute improvement of 11%, an estimate informed by the prior single-center study[5] and a concern about a ceiling effect (ie, based on previous literature, rates of survival with favorable neurologic outcome greatly exceeding 50% were considered unlikely[3,22,23]), and an intracluster correlation of 0.03.[24]

Statistical Analysis

All analyses used the index ICU CPR event per hospitalization. Adjusted odds ratios (ORs) and *P* values for binary outcomes were based on multivariable logistic regression models with treatment group as the primary predictor, unit as a random effect, and the following fixed covariates: illness category,[25] age category,[26] Pediatric Risk of Mortality (PRISM) III score between 2 to 6 hours prior to arrest as a measure of pre-CPR illness severity to account for any potential practice changes in CPR use,[27] first documented rhythm,[28] a piecewise-linear spline of time since trial start to account for temporal trends unrelated to the intervention, and time of day (weekday vs night and weekend).[29] Adjusted risk differences (RDs) and 95% CIs were bootstrapped (n = 10 000) from the logistic regression model. Adjusted mean differences for continuous outcomes are reported based on multivariable linear regression models controlling for the same covariates. There were no missing data for the primary or secondary outcomes, and exploratory and

Table 2. Characteristics of Patient Cardiopulmonary Resuscitation Events

	No. (%)[a]	
	Intervention (n = 526)	Control (n = 548)
Event characteristics		
Location of CPR event		
Pediatric ICU	315 (59.9)	206 (37.6)
Pediatric cardiac ICU	211 (40.1)	342 (62.4)
CPR time[b]		
Weekday	281 (53.4)	286 (52.2)
Weeknight or weekend	245 (46.6)	262 (47.8)
Immediate cause of the CPR event[c]		
Respiratory decompensation	298 (56.7)	286 (52.2)
Hypotension as immediate cause of event	264 (50.2)	316 (57.7)
Arrhythmia	99 (18.8)	84 (15.3)
Cyanosis without respiratory decompensation	14 (2.7)	34 (6.2)
First documented rhythm		
Bradycardia with poor perfusion	267 (50.8)	285 (52.0)
Pulseless electrical activity or asystole	226 (43.0)	212 (38.7)
Ventricular fibrillation or tachycardia	33 (6.3)	51 (9.3)
Duration of CPR, min		
Median (IQR)	6.0 (2.0-21.0)	7.0 (2.0-26.0)
<1	10 (1.9)	17 (3.1)
1 to <6	246 (46.8)	222 (40.5)
6 to 15	105 (20.0)	110 (20.1)
16 to 35	78 (14.8)	103 (18.8)
>35	87 (16.5)	96 (17.5)
Pharmacological interventions during CPR		
Epinephrine	418 (79.5)	435 (79.4)
No. of epinephrine boluses, median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-6.0)
No. of patients	418	434
Epinephrine dosing interval, median (IQR), min	4.0 (3.0-5.7)	4.5 (3.3-7.0)
No. of patients	288	297
Minutes to first epinephrine bolus, median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-2.0)
No. of patients	418	429
Sodium bicarbonate	236 (44.9)	279 (50.9)
Calcium	218 (41.4)	218 (39.8)
Fluid bolus	110 (20.9)	167 (30.5)
Atropine	55 (10.5)	65 (11.9)
Lidocaine	18 (3.4)	23 (4.2)
Vasopressin	17 (3.2)	20 (3.6)
Amiodarone	16 (3.0)	21 (3.8)

Abbreviations: CPR, cardiopulmonary resuscitation; ICU, intensive care unit.

[a] Number of patients (%) unless otherwise indicated.

[b] Weekday is between 7 AM and 11 PM Monday through Friday; weeknight is after 11 PM Monday through Thursday; weekend is from 11 PM on Friday through 7 AM on the following Monday.

[c] Immediate cause of the CPR event was determined by electronic medical record review. Site primary investigators provided guidance to research coordinators when necessary. Patients could have more than 1 immediate cause of a CPR event.

post hoc outcomes were assessed using complete case analysis. Interim analyses for efficacy were performed by the DSMB at 2.5 and 3.5 years. No changes were made to the statistical significance threshold based on these interim analyses. For the final analysis of the primary outcome, as well as all secondary, exploratory, and post hoc analyses, a 2-sided *P* value <.05 was considered to indicate statistical significance. Because of the potential for type I error due to multiple comparisons, findings for secondary end points and analyses should be interpreted as exploratory. SAS software (version 9.4; SAS Institute Inc) was used for the statistical analyses.

Several post hoc exploratory analyses were performed. First, the primary analysis was repeated among (1) patients who received at least 1 minute of CPR, (2) patients who received at least 5 minutes of CPR, and (3) patients enrolled prior to COVID-19 restrictions (March 1, 2020). Second, an interaction between treatment and ICU was added to the model to assess the effect of the intervention at each ICU; homogeneity of treatment effect across ICUs was assessed by testing the significance of treatment by ICU interaction. Third, the underlying temporal trend in survival with favorable neurologic outcome, overall and by treatment group, was assessed by modeling interaction between time and treatment; homogeneity of treatment effect over time was assessed by testing the significance of this interaction. Fourth, changes in enrollment rate over time were assessed

Table 3. Effect of a Cardiopulmonary Resuscitation Training and Debriefing Intervention in Pediatric Intensive Care Units on Survival to Hospital Discharge After Cardiac Arrest

	No./total (%)		Risk differences (95% CI), %[a,b]			
	Intervention (n = 526)	Control (n = 548)	Unadjusted	Adjusted	OR (95% CI)[a,c]	*P* value
Primary outcome						
Survival to hospital discharge with favorable neurologic outcome[d]	283 (53.8)	287 (52.4)	1.4 (−4.5 to 7.4)	3.2 (−4.6 to 11.4)	1.08 (0.76 to 1.53)	.68
Post hoc analysis of primary outcome by length of CPR						
Among patients with ≥1 min of CPR	274/516 (53.1)	275/531 (51.8)	1.3 (−4.7 to 7.4)	3.0 (−5.0 to 11.5)	1.07 (0.75 to 1.53)	.72
Among patients with ≥5 min of CPR	123/300 (41.0)	146/339 (43.1)	−2.1 (−9.7 to 5.6)	2.3 (−7.4 to 12.4)	1.04 (0.68 to 1.58)	.87

Abbreviations: CPR, cardiopulmonary resuscitation; OR, odds ratio.

[a] Adjusted results are based on models that controlled for age, time since trial start, illness category, first documented rhythm, Pediatric Risk of Mortality, and time of CPR and unit.

[b] Adjusted risk differences and 95% CIs were bootstrapped (n = 10 000) from the logistic regression model.

[c] Odds of the outcome for the intervention group compared with the control group. ORs for binary outcomes are based on logistic regression models.

[d] Favorable neurologic outcome was defined as no more than moderate disability (1-3) or no worsening from baseline Pediatric Cerebral Performance Category.

with negative binomial regression, accounting for time, treatment, time × treatment interaction, and ICU (random effect).

Results

Participants

Among 1389 pediatric ICU patients who had a cardiac arrest between October 1, 2016, and March 31, 2021, 1129 index events (81%) were enrolled in this study. The primary and secondary outcomes were available for all enrolled patients. Fifty-five patients enrolled during the transition period prior to the fourth debriefing were excluded (Figure), leaving 1074 patients' index events included in the primary analysis. Among 548 patients with an arterial line in place at the time of cardiac arrest, 397 (72%) had analyzable arterial line data; among 674 patients with $ETCO_2$ monitoring in place at the time of cardiac arrest, 234 (35%) had analyzable $ETCO_2$ data. **Table 1** lists characteristics of the intervention group (526 CPR events) and control group (548 CPR events). Characteristics of CPR events are presented in **Table 2**. Hospital site-level patient characteristics are shown in eTable 2 in Supplement 2.

Intervention Fidelity

The mean (SD) length of the transition period was 104 (28) days (range, 77-185). A total of 21 323 CPR trainings at the point of care were completed. Excluding the approximately 4-month period when the training program was paused due to COVID-19 restrictions, the mean (SD) number of trainings completed per month was 51 (15). A total of 440 structured postcardiac arrest debriefings were performed, and the mean (SD) time between debriefings was 34 (20) days. Of the 15 sites included in the control period, 7 (47%) had at least 1 other resuscitation QI initiative active for at least 3 months. Descriptive analyses of CPR training are presented in eTable 3 (Supplement 2); debriefing, eTable 4 (Supplement 2); other QI initiatives, eTable 5 (Supplement 2); and depiction of intervention fidelity over time and in the context of the COVID-19 pandemic, eFigure 7 (Supplement 2).

Primary Outcome

There was no significant difference in the primary outcome of survival to hospital discharge with favorable neurologic outcome between the intervention (53.8%) and control group (52.4%); adjusted RD, 3.2%, (95% CI, −4.6% to 11.4%); adjusted OR, 1.08, (95% CI, 0.76 to 1.53). In post hoc analyses, there was also no significant difference between the intervention and control groups among patients who received CPR for at least 1 minute (adjusted OR, 1.07 [95% CI, 0.75 to 1.53; *P* = .72) or at least 5 minutes (adjusted OR, 1.04; 95% CI, 0.68 to 1.58; *P* = .87) (**Table 3**), or when the analysis excluded CPR events after COVID-19 restrictions (adjusted OR, 1.08; 95% CI, 0.72 to 1.64; *P* = .70; eTable 6 in Supplement 2).

Secondary Outcome

Survival to hospital discharge was not significantly different between the intervention (58.0%) and control groups (56.8%); RD, 1.6% (95% CI, −6.2% to 9.7%); adjusted OR, 1.03 (95% CI, 0.73 to 1.47, *P* = .85).

Exploratory Outcomes

CPR quality metrics did not differ significantly between the groups (**Table 4**). However, CPR events were significantly more likely to achieve intra-arrest DBP targets in the intervention group (90.9%) vs control (80.4%); RD, 8.5% (95% CI, −0.2% to 17.9%); adjusted OR, 2.18 (95% CI, 1.04 to 4.54, *P* = .04).

Post Hoc Analyses

Systolic hypotension was significantly less likely to occur between 0 and 24 hours after return of circulation in the intervention group (62.1%) vs the control group (71.4%); RD, −11.7% (95% CI, −20.4% to −3.7%); adjusted OR, 0.59 (95% CI, 0.37 to 0.93; *P* = .02) (eTable 7 in Supplement 2). Achievement of target $ETCO_2$ was not significantly different between the intervention group (58.1%) and the control group (54.3%); RD, −12.1% (95% CI, −32.2% to 6.7%); adjusted OR, 0.75 (95% CI, 0.30 to 1.88; *P* = .53). In the analysis of ICU-specific treatment effects, no significant differences were found in the primary outcome between the intervention and

Table 4. Exploratory Analyses of the Effect of a Cardiopulmonary Resuscitation Training and Debriefing Intervention in Pediatric Intensive Care Units

	No./total (%)		Risk/mean differences, % (95% CI)[a,b]			
	Intervention (n = 526)	Control (n = 548)	Unadjusted	Adjusted	OR (95% CI)[a,c]	*P* value
Patient outcomes						
Return of spontaneous circulation	379 (72.1)	362 (66.1)	6.0 (0.5 to 11.5)	7.1 (−0.3 to 14.7)	1.42 (0.96 to 2.11)	.08
Return of circulation	464 (88.2)	487 (88.9)	−0.7 (−4.5 to 3.2)	−0.3 (−5.3 to 4.8)	0.96 (0.62 to 1.50)	.87
Survival to hospital discharge with no new morbidities[d,e]	224 (42.6)	204 (37.2)	5.4 (−0.5 to 11.2)	2.7 (−5.4 to 10.4)	1.13 (0.80 to 1.59)	.50
New morbidity (survivors only)[d,e]	81/305 (26.6)	107/311 (34.4)	−7.8 (−15.1 to −0.6)	−3.2 (−12.4 to 6.9)	0.79 (0.52 to 1.19)	.25
Patient outcomes, median (IQR)						
Change from baseline to hospital discharge in PCPC[d,f]	1.0 (0 to 4.0)	1.0 (0 to 4.0)	−0.10 (−0.35 to 0.15)	−0.04 (−0.33 to 0.25)		.78
Change from baseline to hospital discharge in functional status of survivors [No.][d,f]	0 (0 to 3.0) [305]	1.0 (0 to 3.0) [311]	−0.61 (−1.17 to −0.05)	−0.40 (−1.06 to 0.25)		.23
Event quality outcomes						
Adequate SBP[g]	143/197 (72.6)	127/195 (65.1)	7.5 (−1.7 to 16.6)	8.1 (−4.3 to 21.1)	1.21 (0.71 to 2.06)	.48
Adequate DBP[h]	180/198 (90.9)	160/199 (80.4)	10.5 (3.7 to 17.3)	8.5 (−0.2 to 17.9)	2.18 (1.04 to 4.54)	.04
High-quality CPR with adequate SBP[i]	93/197 (47.2)	74/195 (37.9)	9.3 (−0.5 to 19.0)	6.4 (−7.4 to 20.5)	1.17 (0.70 to 1.94)	.55
High-quality CPR with adequate DBP[j]	112/198 (56.6)	89/199 (44.7)	10.8 (1.1 to 20.5)	7.5 (−5.8 to 21.2)	1.29 (0.69 to 2.40)	.42
Target compression depth[k]	28/114 (24.6)	11/66 (16.7)	7.9 (−4.1 to 19.9)	2.2 (−8.8 to 12.4)	1.28 (0.52 to 3.24)	.59
Target chest compression rate[l]	217/273 (79.5)	175/242 (72.3)	7.2 (−0.2 to 14.6)	4.7 (−6.6 to 16.3)	1.30 (0.65 to 2.63)	.46
Target chest compression fraction[m]	196/273 (71.8)	177/242 (73.1)	−1.3 (−9.1 to 6.4)	−2.7 (−12.6 to 7.6)	0.82 (0.51 to 1.33)	.42
Event quality outcomes, median (IQR) [No.]						
Mean compression depth, mm	37.3 (25.2 to 51.0) [114]	32.3 (27.5 to 47.0) [66]	1.94 (−3.99 to 7.87)	−0.97 (−5.69 to 3.74)		.68
Mean chest compression rate	119.8 (109.9 to 128.9) [198]	121.9 (112.9 to 131.2) [199]	−1.82 (−5.17 to 1.53)	1.81 (−3.69 to 7.31)		.51
Mean chest compression fraction	0.98 (0.92 to 1.00) [198]	0.96 (0.91 to 1.00) [199]	−0 (−0.02 to 0.01)	−0 (−0.03 to 0.03)		.95

Abbreviations: CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; ICU, intensive care unit; OR, odds ratio; PCPC, Pediatric Cerebral Performance Category; SBP, systolic blood pressure.

[a] Adjusted results are based on models that controlled for age, time since trial start, illness category, first documented rhythm, Pediatric Risk of Mortality, time of CPR, and unit.

[b] Adjusted risk differences (RDs) and 95% CIs were bootstrapped (n = 10 000) from the logistic regression model. Adjusted mean differences for continuous outcomes are reported based on multivariable linear regression models controlling for the same covariates.

[c] Odds of the outcome for the intervention group compared with the control group. ORs for binary outcomes are based on logistic regression models. Effect sizes for continuous outcomes are based on linear regression.

[d] The PCPC and functional status scale (FSS) scores were determined by electronic medical record review. PCPC score ranges from 1 (normal) to 6 (brain death or death). Across the 6 domains of the FSS (mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status), a score from 1 (normal) to 5 (very severe dysfunction) was assigned. Total FSS score is the sum of the scores across the 6 domains (range, 6 to 30). Baseline PCPC and FSS represent subject status prior to the event leading to hospitalization.

[e] A new morbidity is defined as an increase in FSS of 3 or greater from baseline to hospital discharge.

[f] A positive change indicates worsening.

[g] SBP is considered adequate if at 60 mm Hg or higher for patients younger than 1 year or 80 mm Hg for patients 1 year or older. All of the surgical noncardiac or trauma events reached adequate SBP. As a result, the adjusted results for adequate SBP are based on a model that controls for a collapsed illness category, collapsing medical noncardiac, surgical noncardiac, and trauma together.

[h] DBP is considered adequate if 25 mm Hg for patients younger than 1 year or 30 mm Hg or higher for patients 1 year or older.

[i] SBP, rate, and chest compression fraction targets all met.

[j] DBP, rate, and chest compression fraction targets all met.

[k] Target chest compression depth is 35 mm or more and 55 mm or less for patients younger than 1 year; 45 mm or more and 65 mm or less for patients older than 1 year. All of the surgical noncardiac or trauma CPR events reached target chest compression depth. As a result, the adjusted results for target chest compression depth are based on a model that controls for a collapsed illness category, collapsing medical noncardiac, surgical noncardiac, and trauma together.

[l] Target compression rate is 90 or more and 130 or less compressions per minute.

[m] Chest compression fraction is considered adequate if 90% or more.

control groups. There was also no significant heterogeneity of treatment effect across ICUs (P = .14, eTable 8 in Supplement 2) or over time (P = .94), and no underlying significant temporal changes in survival with a favorable neurologic outcome in the intervention group (P = .51), in the control group (P = .56), or overall (P = .39).

Discussion

In this multicenter study, CPR training at the point of care and physiologically focused postcardiac arrest debriefings in pediatric ICUs did not significantly improve survival to hospital discharge with favorable neurologic outcome among pediatric patients who received CPR. Among exploratory physiologic outcomes that were highlighted as training targets, intra-arrest DBP targets were more likely to be achieved during CPR during the intervention period when compared with control conditions. In post hoc analyses, postarrest systolic hypotension was less common in the intervention group than in the control group.

Survival rates of pediatric in-hospital cardiac arrest remain less than 50 percent.[3,23] Because more than 95% of pediatric CPR events occur in ICUs, invasive monitoring is frequently available to guide resuscitation.[2] Laboratory and clinical studies support shifting the focus of CPR from standardized targets, such as chest compression depth and rate, to patient-centric physiologic targets, such as blood pressure and $ETCO_2$, which are in the causal pathway from cardiac arrest to return of circulation and longer-term survival.[30-34] The AHA currently recommends tailoring training and postarrest care to physiologic targets[4] to improve outcomes. Although observational studies have demonstrated improved outcomes when clinicians report using physiologic data to guide resuscitation,[35] to our knowledge, no multicenter randomized clinical trials assessing the effectiveness of this approach in pediatric ICUs have been previously performed. Additional strengths of this trial include a novel hybrid design, a prepublished design and statistical analysis plan,[9] and excellent adherence to the bundle despite COVID-19 restrictions.

There are several possible explanations for failure of this intervention to improve patient survival to hospital discharge with a favorable neurologic outcome. First, in this study the rate of survival to discharge with a favorable neurologic outcome exceeded 50%, even in the control group, which is higher than was assumed in the study sample size estimates and is higher than any previous large-scale report of pediatric ICU CPR.[2,22] This may have resulted in limited ability to detect a significant improvement in outcomes, with a ceiling effect primarily due to the control group having incorporated physiologic-targeted CPR and postarrest care from previous CPCCRN physiologically focused in-hospital cardiac arrest studies,[6,7,36,37] AHA guideline publications,[4,38] or other unmeasured physiologically directed resuscitation QI interventions. In support of this theory, more than 80% of patients in the control group achieved the DBP targets thought to be a primary determinant of improved survival, nearly a 20% absolute improvement compared with previous CPCCRN data.[6] Second, it is possible that the high rate of adequate DBP in the control group led to event survival (≈ 89%), but other factors (eg, underlying illness) ultimately determined patient outcome. Third, there may be a need for more individualized DBP targets and additional investigation into optimal individualized BP targets may be warranted.

Limitations

This study has several limitations. First, the 18 enrolled sites were academic pediatric ICUs with an interest in physiologic resuscitation that may limit generalizability to other nonacademic pediatric ICUs or those with different staffing patterns or incidence of CPR. Second, unit-level interventions to prevent cardiac arrest may have rendered the initial sample size estimates invalid. A formal exploratory analysis did not find an association between rate of enrollment and the intervention or rate of enrollment and COVID-19 restrictions, but other initiatives to prevent cardiac arrest were active in some units (high-risk identification, watcher programs, and unit huddles).[39] Third, this study only enrolled 81% of planned patients, and it may have been underpowered to detect a potentially important difference in outcomes between groups, given the wide CIs around the ORs. Fourth, some differences in baseline characteristics existed between the groups, and there may be residual confounding despite adjustment for site-level differences. Fifth, this study was not designed to determine CPR utilization rates. Sixth, baseline rates of the primary outcome of survival to hospital discharge with favorable neurologic outcome were slightly higher in clinical sites randomized to remain in the control group for the duration of the study. Future trials using a hybrid stepped-wedge cluster randomized trial design should attempt to ensure that both enrollment and baseline primary outcomes rates are balanced between groups to strengthen study inferences. Seventh, although a hybrid design improves statistical power, because not all ICUs contributed to both control and intervention, this design may have also weakened the inferences that can be drawn from the study. Eighth, the study design may have underestimated the effect of study participation on usual care sites because the DBP targets of the intervention were derived from a previous CPCCRN study. Ninth, 4 ICUs implemented training at the point of care and/or debriefing during the control period, albeit at a reduced intensity as permitted by the protocol, which may have affected the study results. Tenth, the effect of the intervention on longer-term outcomes is unknown.[40]

Conclusions

In this randomized clinical trial conducted in 18 pediatric intensive care units, a bundled intervention of cardiopulmonary resuscitation training at the point of care and physiologically focused structured debriefing, compared with usual care, did not significantly improve patient survival to hospital discharge with favorable neurologic outcome among pediatric patients who experienced cardiac arrest in the ICU.

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